

SARS
Society of Academic and Research Surgery



Yearbook 2011

Dublin

www.surgicalresearch.org.uk



SARS Council ending 6th January 2011

From left to right

Back Row: *Dion Morton, Andrew Bradley, Bijan Moderai, Sarah King, Alun Davies, Frank Smith*

Front Row: *Rob Sayers, Dileep Lobo, Norman Williams, Marilena Loizidou, Daryll Baker*

THE CONSTITUTION OF THE SARS COUNCIL

UP TO 6PM, JANUARY 6TH 2011

<i>Executive Committee</i>	<i>Name</i>	<i>Demits*</i>
President	Professor N Williams	2011
President-Elect	Professor A Bradley	2011
Honorary Secretary	Mr F C T Smith	2012
Honorary Treasurer	Professor D Morton	2012
Editorial Secretary	Mr D M Baker	2012

Sub Committees and Chairmen

Programme Chair	Professor R Sayers	2011
Membership Chair	Mr R Vohra	2011
Education/Professional Development Chair	Mr D Lobo	2012

Committee Members

Council Member	Professor P R O'Connell	2011
Council Member	Professor A Davies	2012
Council Member	Professor J Reynolds	2012
Co-opted Clinical Scientist	Dr M Loizidou	2013
Non-clinical Scientist	Dr S Watts	2013
NIHR Academic Surgeon in Training	Mr B Modarai	2012
BAUS Rep	Professor K Mellon	2012

FROM 6PM, JANUARY 6TH 2011

President	Professor A Bradley	2013
President-Elect	Professor C Shearman	2013

CONTENTS LIST

The Constitution of the SARS Council	1
Welcome from the President	3
Foreword by Local Organiser	4
Programme at a glance	5
Profiles of SARS Council Members	7
Full Meeting Programme	13
Burns and Plastic Surgery Section Meeting Programme	30
BAUS Section of Academic Urology Meeting Programme	33
Guest Speaker Profiles	37
Annual General Meeting Agenda	43
Honorary Secretary's Report	44
Honorary Treasurer's Report	45
Annual SARS Accounts Year End 2008	46
Prize Recipients	47
Past Presidents and Honorary Secretaries	48
Past Meetings	49
Constitution of SARS	50
Abstracts Index	52
Abstracts	
Patey Prize Presentations	53
Oral Presentations	62
Posters	134
Burns & Plastics Section	148
BAUS Section of Academic Urology Abstracts	158

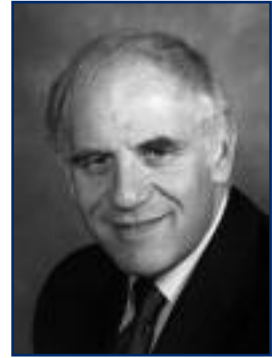
SARS SECRETARIAT

Society of Academic and Research Surgery
The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields
London WC2A 3PE
Tel: 020 7869 6640
Fax: 020 7869 6644
Email: sars@rcseng.ac.uk
www.surgicalresearch.org.uk

Designed and Printed by CPL Associates, London
Compiled and edited by Sarah King and Frank Smith

WELCOME FROM THE PRESIDENT

The 59th Annual meeting of SARS, to be held in Dublin at the Royal College of Surgeons of Ireland, promises to be exceptional. The quality of surgical science emanating from Ireland has always been superb and for many years the Irish academic surgical community has “punched well above its weight”. I have no doubt they will be well represented in the meeting. They will be joined however, by contributions from many other leading centres from the UK and beyond, thus ensuring that the annual SARS meeting lives up to its reputation as being the premier society for academic surgical science. SARS attempts to embrace the academic components of all surgical specialties. Since 2008 we have been joined by our urological colleagues and once again BAUS will run a satellite meeting and present their best papers in the Patey Prize sessions. Over the last few years under the direction of successive Presidents we have continued to foster close ties with ASiT who now are very much a part of SARS. ASiT will once more hold a joint symposium within the body of the meeting. This year we are delighted to welcome colleagues from the British Burns Association (BBA) who will also run a satellite session. Slowly but surely, we are expanding and very much wish to embrace all specialties who have a serious desire to extend their academic horizons. There are common themes that all can learn and benefit from thus enriching their own specialty.



The set piece SARS' lectures are always highlights and this year is no exception. The British Journal of Surgery Lecture will be given by Professor Stefan Post from Mannheim, Germany, his title is Defining Surgical Research which I am sure will be philosophical yet practical, and knowing Stefan, will be entertaining. The John Farndon Lecture will be given by Professor Freddie Hamdy, a leading urologist who has recently moved from Sheffield to take up the Nuffield Chair in Surgery at Oxford. Freddie leads one of the largest surgical inspired clinical trials which has ever been mounted. His insights into how this was achieved will, I know, be fascinating as well as illuminating. Professor René Adam, a leading French academic surgeon will provide new insights in the downsizing of liver metastases when he gives the RCSI lecture. We are also fortunate that Zaed Hamady has chosen to give his Royal College of Surgeons of England Hunterian Lecture at SARS. In addition the BBA guest lecture will be given by Sir John Temple, author of the recent Temple report on training in the era of EWTR, which is proving to be highly influential. We believe that his lecture will be of great interest to all trainers and trainees and we have therefore cleared the programme so that all delegates can listen to Sir John.

Professor Arnie Hill, the local organiser, ably assisted by Rob Sayers, Programme Director and Frank Smith, Honorary Secretary have worked tirelessly to ensure the success of the meeting and we do hope as many of the surgical academic community as possible will be there. In addition to all trainees and fellows engaged in surgical research, we are particularly keen to see their senior supervisors, scientific and clinical, contributing to the meeting.

The tide in medical research is changing. In the recent past the RAE, whilst delivering certain benefits has led to a diminution in applied clinical research, particularly in the craft specialties. However with the establishment of NIHR, and a greater emphasis on translational research, there is much greater opportunity to undertake the type of research that surgeons excel in. The responsibility is, in large measure, ours, to grasp the opportunities that are now available. SARS very much sees itself as a focal organisation to unlock these opportunities. The more individuals and societies that join us, the more influential we can become. I do encourage all surgical academics to join SARS and help in ensuring that surgical research is restored to its rightful place in the academic medical hierarchy.

I am enormously grateful to the support of all members of Council and particular thanks go to our administrative staff, Sarah King and Linda Slater. It has been a privilege to serve as your President over the last two years. I believe I leave a healthy and vibrant society which, under the direction of the next President, Professor Andrew Bradley, will I am sure go from strength to strength.

Norman Williams
President

FOREWORD BY LOCAL ORGANISER, DUBLIN 2011

It is with great pleasure that we invite you to the 2011 Annual Meeting of the Society of Academic and Research Surgery (SARS), to be hosted by the Department of Surgery in Royal College of Surgeons in Ireland, Dublin.

We have organised a full and exciting programme. We have kept the meeting to the highly successful 2-day format pioneered 2 years ago. The packed scientific programme includes symposia on 'Surgical Training' and 'Translational trials that have influenced clinical practice'. We are delighted to continue as hosts for the Association of Surgeons in Training (ASIT) symposia, the Section of Academic Urology of BAUS and the academic section of the British Burns Association. The prestigious Patey Prize sessions will take place over the 2 days of the meeting. There will be presentations of prize-winning papers from our sister surgical research societies from the USA, South Africa and Europe.

The BJS Lecture is entitled "Defining Surgical Research" and will be given by Professor Dr Stefan Post from Mannheim University. The John Farndon Memorial Lecture entitled 'Surgical Research – closing the loop in prostate cancer' will be given by Professor Freddie Hamdy, Nuffield Professor of Surgery and Professor of Urology. We are very pleased to be able to join the BBA session for their Guest Lecture which will be given by Professor Sir John Temple. Professor René Adam will give the RCSI lecture entitled "How is neoadjuvant treatment used optimally for downsizing unresectable colorectal liver metastases?"

Dublin is a vibrant and cosmopolitan city. It has the great advantage of combining city, country and sea, giving visitors a great variety of activities: from golf to museums, from fishing to sailing, delegates can finally combine business and pleasure! The Royal College of Surgeons in Ireland is located within the heart of the city. Founded in 1784, originally to train surgeons, today it provides extensive education and training in the healthcare professions at both undergraduate and postgraduate level. RCSI operates the largest Medical School in Ireland and also provides undergraduate courses in pharmacy and physiotherapy. The College provides an extensive range of postgraduate training and education programmes in the medical sciences, surgery, medical and nursing specialties, international health, tropical medicine and leadership and healthcare management. The RCSI Research Institute is one of Ireland's foremost research centres.

We look forward to welcoming you to Dublin. We have the makings of an outstanding scientific meeting, with opportunities to meet old friends and to make new ones.

Professor Arnie Hill
Local Organiser



PROGRAMME AT A GLANCE

WEDNESDAY 5 JANUARY	Location
---------------------	----------

SARS Programme *see full programme on page 13 for further details*

07.30	Registration	The Concourse
08.20	Welcome	O'Flanagan Lecture Theatre
08.30	Symposium 1 – Surgical Training	O'Flanagan Lecture Theatre
09.15	Parallel Oral Presentations 1A	Cheyne Lecture Theatre
09.15	Parallel Oral Presentations 1B	Houston Lecture Theatre
09.15	Parallel Oral Presentations 1C	O'Flanagan Lecture Theatre
10.55	Coffee and Trade Exhibition	Exam Hall
11.25	Plenary Session 1 for the Patey Prize	Cheyne Lecture Theatre
12.35	Lunch and Trade Exhibition	Exam Hall
12.35	Lunchtime GI Symposium (pre-booking required)	Houston Lecture Theatre
13.50	Parallel Oral Presentations 2A	Cheyne Lecture Theatre
13.50	Parallel Oral Presentations 2B	Houston Lecture Theatre
14.50	SUS,SARS (SA) and ESSR Prize Winners' Presentations	Cheyne Lecture Theatre
15.20	Tea and Trade Exhibition	Exam Hall
15.50	Parallel Oral Presentations 3A	Cheyne Lecture Theatre
15.50	Parallel Oral Presentations 3B	Houston Lecture Theatre
16.50	Hunterian Lecture	Cheyne Lecture Theatre
17.20	BJS Lecture	Cheyne Lecture Theatre
17.50	AGM	Cheyne Lecture Theatre

BAUS Programme *see full programme on page 33 for further details*

13.30	Registration	The Concourse
13.55	Introduction and Welcome	Albert Lecture Theatre
14.00	Paper session 1	Albert Lecture Theatre
15.30	Tea and Trade Exhibition	Exam Hall
15.50	Paper session 2	Albert Lecture Theatre
16.50	Hunterian Lecture (SARS main programme)	Cheyne Lecture Theatre
17.20	BJS Lecture (SARS main programme)	Cheyne Lecture Theatre

THURSDAY 6 JANUARY	Location
--------------------	----------

SARS Programme *see full programme on page 22 for further details*

08.00	Symposium 3 Translational trials that have influenced clinical practice	Cheyne Lecture Theatre
09.00	BBA Guest Lecture – open to all delegates	O'Flanagan Lecture Theatre
09.30	Parallel Symposium 4A SARS/ASiT symposium 4	TR4
09.30	Parallel Oral Presentations 4A	Cheyne Lecture Theatre
09.30	Parallel Oral Presentations 4B	Houston Lecture Theatre
11.00	Coffee and Trade Exhibition	Exam Hall
11.30	Parallel Oral Presentations 5A	Cheyne Lecture Theatre
11.30	Parallel Oral Presentations 5B	Houston Lecture Theatre
13.00	Lunchtime Symposium 5 (pre-booking required)	Houston Lecture Theatre
14.00	Plenary Session 2 for Patey Prize	Cheyne Lecture Theatre
15.10	Tea and Trade Exhibition	Exam Hall
15.40	John Farndon Lecture	Cheyne Lecture Theatre
16.10	RCSI Guest Lecture	Cheyne Lecture Theatre
16.40	Presentation of Prizes	Cheyne Lecture Theatre

PROGRAMME AT A GLANCE CONTINUED

THURSDAY 6 JANUARY	Location
--------------------	----------

BAUS Programme *see full programme on page 35 for further details*

09.00	BBA Guest Lecture – open to all delegates	O’Flanagan Lecture Theatre
09.30	Symposium on screening	Albert Lecture Theatre
10.15	Paper session 3	Albert Lecture Theatre
11.15	Coffee and Trade Exhibition	Exam Hall
11.30	Hunterian Lecture	Albert Lecture Theatre
12.10	Guest lecture	Albert Lecture Theatre
13.00	Lunch and Trade Exhibition	Exam Hall
14.00	Plenary Session 2 for the Patey Prize	Cheyne Lecture Theatre
15.10	Tea and Trade Exhibition	Exam Hall
15.40	John Farndon Lecture	Cheyne Lecture Theatre
16.10	RCSI Guest Lecture	Cheyne Lecture Theatre
16.40	Presentation of Prizes	Cheyne Lecture Theatre

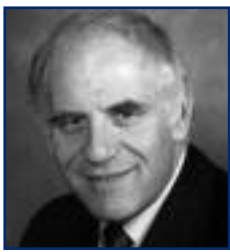
BBA Programme *see full programme on page 30 for further details*

08.00	Registration	Concourse
08.50	Welcome	O’Flanagan Lecture Theatre
09.00	Guest Lecture	O’Flanagan Lecture Theatre
09.45	Jackson Prize section	TR1
11.00	Coffee and Trade Exhibition	Exam Hall
11.30	Gibson Prize section	TR1
13.00	Lunch and Trade Exhibition	Exam Hall

BBA delegates are able to join the main SARS programme for the afternoon

14.00	Patey Prize Session	Cheyne Lecture Theatre
15.10	Tea and Trade Exhibition	Exam Hall
15.40	John Farndon Lecture	Cheyne Lecture Theatre
16.10	RCSI Guest Lecture	Cheyne Lecture Theatre
16.40	Presentation of Prizes	Cheyne Lecture Theatre

PROFILES OF SARS COUNCIL MEMBERS 2010



PROFESSOR NORMAN S WILLIAMS

PRESIDENT

Norman Williams is the Professor and Director of the Centre for Academic Surgery at Barts and The London School of Medicine and Dentistry, from where he originally qualified. His early surgical and academic training was in London and Bristol, before moving to Leeds General Infirmary as a Research Fellow, and subsequently Lecturer and Senior Lecturer. He is a colorectal surgeon and his main clinical interests are sphincter preservation, reconstructive surgery and functional bowel disorders and his scientific interests are now concentrated on neurogastroenterology. During his Lecturer years, he went as a Fullbright Scholar to the University of California, Los Angeles (UCLA), and gained particular expertise in gastrointestinal motility. He has won the Patey Prize of the Surgical Research Society, the Moynihan Fellowship of the Association of Surgeons and the BUPA Society of Authors' Prize (Jointly) for the textbook "Surgery of the Anus, Rectum and Colon". He was awarded the Nessim Habib Prize for Surgery in 1995 and the Galen Medal in Therapeutics in recognition of the advances made in colorectal surgery in 2002. He was elected as a Fellow of the Academy of Medical Sciences in 2004. He has been President of European Digestive Surgery, Vice-Chairman of the Editorial Board of the British Journal of Surgery, Chairman of the UKCCCR Committee on Colorectal Cancer, and a member of the National Cancer Research Network Steering Group. He was President of the Ileostomy and Internal Pouch Support Group of Great Britain (1992-2008), President of The International Surgical Group (2006-7) and is an elected member of the Council of The Royal College of Surgeons of England (2005-11) and is now Chairman of its Academic and Research Board and the Invited Review Mechanism (IRM). In 2008 he was made an Honorary Fellow of The American Surgical Association.



PROFESSOR J ANDREW BRADLEY

PRESIDENT ELECT

Professor Andrew Bradley is Professor of Surgery and Head of the Department of Surgery at the University of Cambridge. He is an Honorary Consultant Surgeon and Clinical Director of Transplantation at Addenbrooke's Hospital Cambridge. After qualifying MB ChB in Leeds (1975), he undertook surgical training in Leeds and Glasgow where he completed a PhD before appointment as a NHS Consultant Surgeon at the Western Infirmary, Glasgow. In 1994 he was appointed Professor of Surgery and Immunology at the University of Glasgow, before moving to the Chair of Surgery in Cambridge in 1997. He is a Fellow and past Member of Council of the Academy of Medical Sciences, Past President of the British Transplantation Society and the British Society of Histocompatibility and Immunogenetics, and past secretary and treasurer of the International Transplantation Society. He is a Trustee of Kidney Research UK and of the Roche Organ Transplant Foundation. His research interests range from basic aspects of transplant immunology to the clinical evaluation of novel immunosuppressive agents and investigation of the donor and recipient factors that influence outcome after kidney transplantation. He is Editor of the journal Transplantation and Associate Editor of the American Journal of Transplantation and chairs the Kidney Transplantation Advisory Group at NHS Blood and Transplant.



MR FRANK SMITH

HONORARY SECRETARY

Mr Frank CT Smith is Reader in Surgical Education and Honorary Consultant Vascular Surgeon at the University of Bristol and Bristol Royal Infirmary. After graduating from Birmingham University, he trained in Edinburgh, the West Midlands, Exeter and Bristol. He was awarded Peter Clifford and RCS Edinburgh Travelling Fellowships in 1996, undertaking further vascular training in Boston, Denver, Los Angeles and Seattle. Research interests have encompassed systemic effects of reperfusion injury in aortic aneurysm surgery, in distal bypass surgery and in intermittent claudication and the pathology and attenuation of myointimal hyperplasia. He has specific interests in medical education. He has been an elected member of Council and of the Education & Training Committee of the Vascular Society of GB & Ireland and is a past Intercollegiate Basic Surgical Skills Tutor at the Royal College of Surgeons of England. He is currently a member of the SAC for General Surgery, Programme Director of the Confidential Reporting System for Surgery (CORESS), assessor and examiner for the Intercollegiate MRCS and examiner for the European Boards of Vascular Surgery.



PROFESSOR DION MORTON

HONORARY TREASURER

Professor Dion Morton is the Professor of Colorectal Surgery in the Academic Department of Surgery at the University of Birmingham. He is a Colorectal Surgeon and his main clinical interests are in colorectal cancer treatment and prevention and the surgical treatment of inflammatory bowel disease. His early research interests were in the field of inherited colorectal cancer. This more recent research interest has also encompassed chemo prevention of sporadic colorectal cancer and the molecular biology of early colorectal tumourigenesis. He is leading a number of national and international trials in the field of colorectal cancer. He is a member of the NCRI colorectal clinical subgroup, and is the Chairman of the Surgical Subcommittee. He is currently a member of the Clinical Trials Advisory and Awards Committee (CTAAC) for Cancer Research UK and is Experimental Cancer Medicine Centre (ECMC) Network Lead for Birmingham.



MR DARYLL M BAKER

EDITORIAL SECRETARY

Mr Baker read medicine at Oriel College, Oxford and trained in surgery in Nottingham and London. He gained his PhD from the University of Wales. He is presently a Consultant Vascular Surgeon in the Department of Surgery at the Royal Free Hospital and Honorary Senior Lecturer at University College London Medical School. His research focuses on the effects of ischaemia on skeletal muscle.



PROFESSOR ROBERT D SAYERS

CHAIRMAN, PROGRAMME COMMITTEE

Professor Robert D Sayers is a Professor in Vascular Surgery at the University of Leicester. He qualified with Honours from the University of Birmingham in 1984 but did most of his vascular training as a Lecturer in Surgery in Leicester and Adelaide, South Australia. His research interests include clinical studies into endovascular aneurysm repair and basic science research investigating the genetic factors that lead to pathogenesis and expansion of aneurysms. He is a founding member of the recently formed AAA consortium that has attracted £1 million funding from The Wellcome Trust for a genome wide association study into the causes of aortic aneurysms.



MR RAJIV VOHRA

CHAIRMAN, MEMBERSHIP COMMITTEE

Mr Rajiv Vohra is a Consultant Vascular Surgeon at the Queen Elizabeth Hospital Birmingham, University Hospital Birmingham Foundation NHS Trust. He held the post of Associated Divisional Director for the Outpatients for the Trust from 07-09 and has been appointed Associate Medical Director for Courses Development in his Trust this year. His clinical interests include carotid surgery, femoro-distal reconstructions and vascular surgical training. He has supervised 9 research fellows and has over 100 publications and book chapters to his credit.

He held the office of in-charge of Basic Surgical Skills Courses in India on behalf of The RCS Edinburgh 02-05. He has organised 11 femoro-distal reconstruction courses attracting 88 vascular trainees and consultants. Mr Vohra has served on the council of The Vascular Society of Great Britain and Ireland, 05-07 and also held the post of Chairperson of the South Birmingham Research and Ethics Committee, 04-09.

He currently is an Intercollegiate MRCS Examiner, Intercollegiate FRCS (Exit) Examiner, member Editorial Board of European Journal of Vascular and Endovascular Surgery, Programme Director General Surgery Birmingham/Black Country West Midlands Deanery and a member of General Surgery Specialist Advisory Committee. He also represents the Vascular Society of Great Britain & Ireland as a Specialist Advisor to NICE and as co-chair of the Vascular Specialist Library. The Vascular Societies of India and Egypt have honoured him with honorary fellowships.



MR DILEEP LOBO

CHAIR, EDUCATION/PROFESSIONAL DEVELOPMENT

Mr Dileep Lobo is an Associate Professor and Reader in Gastrointestinal Surgery and Consultant Hepatopancreaticobiliary Surgeon at Queen's Medical Centre, Nottingham, UK. He qualified from Bangalore University, India and has trained as a surgeon in Chandigarh, Nottingham and Leicester. He was awarded a DM degree with distinction by the University of Nottingham for his work on fluid and electrolytes and is a recipient of the Sir David Cuthbertson Medal for his contributions to the field of Nutrition and Metabolism. He has received research awards and grants from the Surgical Research Society, the British Journal of Surgery Society, the Intensive Care Society, the European Society for Clinical Nutrition and Metabolism, the British Society of Gastroenterology and the Royal College of Surgeons of England. He has recently been awarded the prestigious James IV Society of Surgeons Traveller's Award and the Moynihan Fellowship. His clinical interests focus surgery of the liver, pancreas and biliary tree and laparoscopic surgery. His research interests include surgical nutrition and metabolism, fluid and electrolyte balance and pancreatic cancer. He is also keen on postgraduate surgical education and is responsible for the higher surgical teaching programme in the mid-Trent region. Dileep is the local Special Interest Group Lead in Surgery for the UK Comprehensive Clinical Research Network. He is an Associate Editor of the European Journal of Clinical Nutrition and has over 120 publications in peer-reviewed journals. He has lectured both nationally and internationally. He has been awarded the Fellowship of the American College of Surgeons in 2010 and is a member of the Scientific committees of the European Society for Clinical Nutrition and Metabolism and the International Society for Surgical Metabolism and Nutrition.



PROFESSOR P RONAN O'CONNELL

COUNCIL MEMBER

Professor P Ronan O'Connell is Professor of Surgery at University College Dublin and formally Consultant Senior Lecturer at the London Hospital and later Consultant Surgeon at the Mater Hospital, Dublin. He is a fellow of ACPGIBI, ASCRS and ASGIBI. He is secretary of ESCP. He is an elected member of the Society of Pelvic Surgeons, the ESA and ISG. A former winner of the Patey Prize (1985), Professor O'Connell has published widely in the areas of inflammatory bowel disease, pelvic floor physiology and continence. He has been an editor of BJS (1999 -2006) and DCR (since 2001).



PROFESSOR ALUN DAVIES

COUNCIL MEMBER

Professor Alun Davies is Professor of Vascular Surgery and Honorary Consultant Surgeon at Imperial College, Charing Cross Campus, London. He trained in Cambridge, Oxford, Plymouth, Boston (USA) and Bristol, prior to taking up a Senior Lecturer appointment in 1994. Professor Davies has been a Hunterian Professor and Arris & Gale Lecturer at the Royal College of Surgeons and Abdol Islami Scholar at the American College of Surgeons. He is the Editor in Chief of Phlebology and Venous Times. He is Past - President of the European Venous Forum, President of UK Venous Forum, Past Council member of Vascular Society of Great Britain and Ireland, Member of the American Venous Forum, the American College of Phlebology, The Venous Forum at The Royal Society of Medicine, European Society of Vascular Surgery. His main research interests are clinical trials and basic science research related to venous disease and carotid artery disease. He has written/edited 21 books, 56 chapters and over 230 research papers on many aspects of vascular disease and has lectured in many parts of the world on a wide range of vascular topics. He examines for the Intercollegiate Board of RCS and the European Board of Vascular Surgery.



PROFESSOR J REYNOLDS

COUNCIL MEMBER

Professor John V Reynolds is Professor of Surgery and Head of the Department of Clinical Surgery, Trinity College Dublin. He is also the Scientific Director of the Cancer Clinical Trials Office at St. James's Hospital. He currently is the Regional Director of the Cancer Strategy Group for the HSE South Western Area and has managed Cancer Audit Systems and the development of clinical guidelines and promotional efforts for cancer care. He has formerly held Fellowship positions with the University of Pennsylvania and Wistar Institute in Philadelphia and at the Memorial Sloan-Kettering Cancer Centre in New York. He was a Senior Lecturer at St. James's University Hospital in Leeds and at St Mary's Hospital and Imperial College, London. Professor Reynolds has obtained numerous research awards and has published widely in cancer research. His hospital base is at St. James's Hospital, Dublin. His clinical interest is in cancers of the oesophagus, and stomach, and in Barrett's oesophagus and GIST tumours. His research interest is in using modern molecular biology techniques to uncover pathways of cancer development in the oesophagus, in obesity and cancer, in the inflammatory and procoagulant response to major surgery, and in understanding why patients with oesophageal cancer respond or are resistant to chemotherapy and radiation therapy.



DR MARILENA LOIZIDOU

CO-OPTED CLINICAL SCIENTIST

Dr M Loizidou is a non-clinical Senior Lecturer in the Division of Surgery and Interventional Science, UCL Medical School, Royal Free Campus. Previously she worked in the Academic Department of Surgery, Southampton University. She trained as a biochemist and a pharmacologist first in Canada and later in the UK. She has been involved in academic surgical training throughout her career. She has supervised more than 30 postgraduate surgeons working towards higher research degrees and has contributed extensively to the design and ongoing delivery of the MSc in Surgical Science at UCL. She has recently designed and is director of the intercalated BSc in Surgical Science, UCL and the MSc in Nanotechnology and Regenerative Medicine, UCL. Her research programme focuses on aspects of colorectal cancer and liver metastases, from the basic underlying biology to experimental therapeutics. Additional research areas include multidrug resistant breast and bladder cancer. She is assistant Editor for colorectal cancer for Oncology News.

DR SARAH WATTS

NON-CLINICAL SCIENTIST

Dr Sarah Watts is a Principal Scientist in the Biomedical Sciences Department at Dstl, Porton Down. She graduated from the Royal Veterinary College, University of London in 1994 and is a member of the Royal College of Veterinary Surgeons. She spent 3 years working in a mixed veterinary practice before returning to RVC to undertake a PhD, which was awarded in 2001. She has worked at Dstl since 2000 and has been an academic lead for a research programme that addresses the current and emerging research requirements in combat casualty care for the Surgeon Generals Department since 2003. She also supervises and mentors military surgical trainees registered for higher research degrees.



MR BIJAN MODARAI

NIHR ACADEMIC SURGEON IN TRAINING AND ASIT REPRESENTATIVE

Mr Bijan Modarai is a Clinical Lecturer in Vascular Surgery at King's College London and Guy's and St Thomas' NHS Foundation Trust. He completed his Basic Surgical Training in London before being awarded a British Heart Foundation Clinical PhD Studentship in 2002. He graduated with a PhD in Biochemistry in 2006 and won the Patey Prize for his research work in 2007. He began his Higher Surgical Training on the South East Thames rotation before taking up his current post, part of the integrated academic training initiative funded by The National Institute for Health Research. His research interests include angiogenesis in tissue remodelling, angiogenic cell therapy and novel imaging techniques applied to vascular disease.



PROFESSOR KILIAN MELLON

BAUS SECTION OF ACADEMIC UROLOGY REPRESENTATIVE

Kilian Mellon is Professor of Urology at the University of Leicester. He qualified from Queens University Belfast in 1983 and subsequently trained in Urology in Newcastle upon Tyne. He was appointed to the Foundation Chair in Urology at the University of Leicester in 2001. His principal research interests focus on the molecular mechanisms of tumour invasion and metastasis in bladder and prostate cancer. His main clinical interests are the surgical management of urological cancer. He is a former member of the SAC in Urology and the Editorial Board of the BJU International. He is currently Chairman of the BAUS Section of Academic Urology and Chairman of the Scientific and Education Committee of The Urology Foundation. He is a former elected member of the BAUS Section of Oncology. In 2004 he was awarded the Karl Storz – Harold Hopkins Golden Telescope award by the British Association of Urological Surgeons.



PROFESSOR CLIFF P SHEARMAN

PRESIDENT-ELECT FROM 6PM, 6TH JANUARY 2011

Cliff Shearman is a Professor of Vascular Surgery at the University of Southampton and Consultant Vascular Surgeon, Southampton University Hospitals NHS Trust. He qualified from Guys Hospital Medical School London University and trained in vascular surgery in Birmingham. He was appointed as a senior lecturer/consultant vascular surgeon at the Queen Elizabeth Hospital, Birmingham in 1990. In 1994 he moved to Southampton as a NHS Consultant Vascular Surgeon and in 1999 was appointed to the Chair of Vascular Surgery at the University of Southampton.

He currently works in a busy vascular unit which undertakes most vascular and endovascular treatments of arterial and venous disease. The unit serves a local population of 1.2 million people. His research programme is largely directed at determining factors that promote the progression of vascular disease, both environmental and genetic, and how these might be modified particularly in diabetes. He is currently Associate Medical Director for R and D. He was on the Council and Chairman of the Training and Education Committee of the Vascular Society of Great Britain and Ireland, and President of the Society (2009-10). He was appointed Head of the Wessex Post Graduate School of Surgery in 2007.

SARS Full Meeting Programme

WEDNESDAY 5 JANUARY 2011

07.30-08.20	REGISTRATION AND COFFEE
08.20-08.30	WELCOME - O'Flanagan Lecture Theatre Professor Arnold Hill and Professor Norman Williams
08.30-09.15	SYMPOSIUM 1 - O'Flanagan Lecture Theatre SURGICAL TRAINING <i>Chairs:</i> Professor Alun Davies and Mr Daryll Baker
09.00-09.15	Role of Research - Professor Michael Kerin
09.15-09.30	Competency based progression - can we deliver? - Professor Sean Tierney
09.30-09.45	Discussion
09.15-10.55	PARALLEL ORAL PRESENTATIONS 1A (14 Papers) (5 min + 2 min) <i>Cheyne Lecture Theatre</i> GENERAL <i>Chairs:</i> Professor Karim Brohi and Professor Paul Redmond
09.15-09.22	O15 INVESTIGATING HMGB1 AS A POTENTIAL MEDIATOR IN BRAIN DEATH INDUCED LUNG DAMAGE Vallance AE, Walden HR, Karamanou DM, Fox CR, Rostron AJ, Kirby JA, Simpson AJ, Dark JH, Fisher AJ Institute of Cellular Medicine, Newcastle University
09.22-09.29	O16 THE EFFECT OF SENSORY INPUT FROM A COCHLEAR IMPLANT ON BALANCE Karagama YG, Rashid M, Agarwal L, Elliott C, Johnson IJM ENT Department, Tameside Hospital
09.29-09.26	O17 DEVELOPMENT AND CHARACTERISATION OF A COMPOSITE BIOENGINEERED NOSE FOR RECONSTRUCTION POST RHINECTOMY USING A NOVEL POSS-NANOCOMPOSITE POLYMER Adelola O. Oseni ¹ , Leila N. Nayyer ¹ , Peter M. Butler ³ , Alexander M. Seifalian ^{1,2} University College London: ((1) Centre for Nanotechnology and Regenerative Medicine, Division of Surgery and Interventional Science 2 Centre for Stem Cells and Regenerative Medicine). 3 Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital
09.36-09.43	O18 OBJECTIVE ASSESSMENT OF SURGICAL TRAINEES IN SELECTION FOR HIGHER SURGICAL TRAINING: THE ROLE OF FUNDAMENTAL APTITUDE TESTING Emmeline Nugent ¹ , Dara O'Keeffe ¹ , Hazem Hseino ¹ , Borislav D Dimitrov ² , Arthur Tanner ¹ , Paul Neary ³ , Oscar Traynor ¹ (1) National Surgical Training Centre, Royal College of Surgeons in Ireland, Dublin 2. 2 Department of General Practice, Royal College of Surgeons in Ireland, Dublin 2. 3 Division of Colorectal Surgery, The Adelaide and Meath Hospital Incorporating the National Children's Hospital, Dublin 24 & Trinity College Dublin.
09.43-09.50	O19 PARADOXICAL ENHANCEMENT OF ENDOTHELIAL PROGENITOR CELLS AND ENDOTHELIAL REGENERATION IN MICE HEMIZYGOUS FOR DELETION OF THE TYPE 1 INSULIN-LIKE GROWTH FACTOR RECEPTOR S. Tawqeer Rashid, Nadira Yuldasheva, Matthew Kahn, Mark T Kearney, D. Julian A Scott & Stephen B Wheatcroft Division of Cardiovascular & Diabetes Research, University of Leeds, United Kingdom

- 09.50-09.57 O20 **THE EFFECTS OF RESISTANCE TRAINING AND NEUROMUSCULAR ELECTRICAL STIMULATION IN KNEE OSTEOARTHRITIS - A RANDOMISED CONTROL TRIAL**
R.A. Bruce-Brand¹, N.M. Moyna², J.M. o'Byrne¹
1 Cappagh National Orthopaedic Hospital, Dublin, Ireland; 2 Department of Health & Human Performance, Dublin City University, Ireland
- 09.57-10.04 O21 **POINT OF CARE DIAGNOSTICS FOR THE RAPID IDENTIFICATION OF ACUTE TRAUMATIC COAGULOPATHY AND PREDICTION OF MASSIVE TRAUMA HAEMORRHAGE**
Ross Davenport¹, Joanna Manson¹, Henry De'Ath¹, Sean Platten², Amy Coates¹, Shubha Allard², Daniel Hart², Rupert Pearse⁴, K. John Pasi⁵, Peter MacCallum², Simon Stanworth³, Karim Brohi¹
(1)Trauma Clinical Academic Unit, Blizzard Institute of Cell & Molecular Science & 4 William Harvey Research Institute, Bart's and the London School of Medicine and Dentistry, Queen Mary University of London, UK.2 Department of Haematology, Bart's and the London NHS Trust, UK 3 NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK⁵Pathology Group, Blizzard Institute of Cell & Molecular Science
- 10.04-10.11 O22 **CARDIAC DYSFUNCTION AFTER TRAUMA: A REAL AND PRESENT DANGER**
Henry D I De'Ath, Claire Rourke, Ross Davenport, Joanna Manson, Jane McNeill, Ceri Davies, Ian Renfrew, Martin Rothman, Karim Brohi
Trauma Clinical and Academic Unit, The Royal London Hospital
- 10.11-10.18 O23 **NOVEL HYBRID RESUSCITATION IN TRAUMA IMPROVES COAGULOPATHY AND OUTCOME**
C M Doran^{1,3}, C A Doran³, T Woolley², M Midwinter¹, P F Mahoney², S Watts³, E Kirkman³
Academic Departments of Military Surgery & Trauma 1 & Military Anaesthesia & Critical Care 2, RCDM, Birmingham, Dstl Porton Down³, Salisbury
- 10.18-10.25 O24 **ROTEM INDICES OF PLATELET FUNCTION IN ACUTE TRAUMATIC COAGULOPATHY**
Spoors C, Rourke C, Manson J, De'Ath H, Raza I, Khan S, Davenport R, Brohi K
Trauma Clinical Academic Unit, Royal London Hospital, Whitechapel, London
- 10.25-10.32 O25 **TIMING OF MESENCHYMAL STEM CELL TRANSPLANTATION INTO AN AREA OF ACUTE MYOCARDIAL INFARCTION APPEARS TO BE CRUCIAL FOR SUCCESSFUL REPAIR**
M DaCosta^{1,3}, A Flynn¹, A Duffy², P Nash^{1,3}, F Barry^{2,3}, T O'Brien^{1,2,3}
Galway University Hospital, Regenerative Medicine Institute, National University of Ireland Galway
- 10.32-10.39 O26 **IMPROVING PATIENT SAFETY BY PREVENTING SURGICAL INFECTION - RESULTS OF A TWO YEAR INITIATIVE**
McHugh SM¹, Corrigan MA¹, Dimitrov BD², Tierney S¹, Cowman³, Hill ADK¹, Humphreys HH^{4,5}
1. Department of Surgery, RCSI, 2. Department of General Practice, RCSI, 3. Faculty of Nursing and Midwifery, RCSI, 4. Department of Microbiology, Beaumont Hospital, Dublin 9. 5. Department of Clinical Microbiology, RCSI
- 10.39-10.46 O27 **IS THE INCREASE IN CARDIAC-DEATH ORGAN DONORS IN THE UK CONTRIBUTING TO A DECLINE IN BRAIN-DEATH DONORS?**
D.M.Summers^{1,2}, C.Counter², R.J.Johnson², P.Murphy², J.Neuberger², J.A.Bradley¹
(1) Department of Surgery, University of Cambridge. 2 NHS Blood and Transplant
- 10.46-10.53 O28 **REDUCED LEVELS OF SOLUBLE UROKINASE RECEPTOR (SUPAR) FRAGMENT DII-III PREDICTS VENOUS ULCERS THAT FAIL TO HEAL**
Anwar Ahmad¹, Matthew Waltham¹, Gunilla Høyer-Hansen², Tine Thurison Sørensen², Katherine Mattock¹, Prakash Saha¹, Bijan Modarai¹, Hany Zayed³, Alberto Smith¹
1 King's College London, London, UNITED KINGDOM, 2Finsen Laboratory, Copenhagen, DENMARK, 3 Guy's & St Thomas' NHS Foundation Trust, London, UNITED KINGDOM
-
- 09.15-10.55 **PARALLEL ORAL PRESENTATIONS 1B** (14 Papers) (5 min + 2 min) - *Houston Lecture Theatre COLORECTAL/SEPSIS*
Chairs: Professor John MacFie and Professor Calvin Coffey
- 09.15-09.22 O29 **ADIPOCYTES ARE CAPABLE OF PRESENTING ANTIGEN IN A MHC CLASS II-DEPENDENT MANNER AND ACTIVATING NAÏVE CD4+ T CELLS**
Joanne Lysaght, Emma Allott, Suzanne Doyle, Graham P Pidgeon John V Reynolds
Institute of Molecular Medicine and Trinity College Dublin

- 09.22-09.29 O30 **CELLULAR REPROGRAMMING BY BACTERIAL LIPOPROTEIN RESCUES ST2-DEFICIENT MICE FROM LETHAL SEPSIS**
Andrew Coveney, Juliette M. Buckley, Jing Hua Liu, H. Paul Redmond, Jiang Huai Wang
Department of Academic Surgery, University College Cork, Cork University Hospital, Cork, Ireland.
- 09.29-09.36 O31 **INDUCTION OF GRAM-POSITIVE BACTERIAL LIPOPROTEIN TOLERANCE UP-REGULATES GENES THAT ARE INVOLVED IN ANTI-MICROBIAL FUNCTION WHILE DOWN-REGULATES GENES RESPONSIBLE FOR PROINFLAMMATORY RESPONSE**
DP Power, JH Wang, HP Redmond
Department of Academic Surgery, University College Cork, Cork University Hospital, Ireland
- 09.35-09.13 O32 **UNRAVELLING A NOVEL ROLE OF MYELOID-RELATED PROTEINS 8/14 (MRP8/14) IN SELF TOLERANCE AND CROSS TOLERANCE TO GRAM NEGATIVE AND GRAM POSITIVE BACTERIA**
Andrew Coveney, Jiang Huai Wang, H. Paul Redmond
Department of Academic Surgery, University College Cork, Cork University Hospital, Cork, Ireland.
- 09.43-09.50 O33 **BOWEL BIOFEEDBACK TREATMENT IN PATIENTS WITH MULTIPLE SCLEROSIS: PSYCHOLOGICAL AND DISABILITY FACTORS, NOT PHYSIOLOGICAL VARIABLES, PREDICT SUCCESS**
G.Preziosi, C.R.G. Cohen, A.C.J Windsor, P. Boulos, A.V. Emmanuel
University College London Hospital
- 09.50-09.57 O34 **MOLECULAR PROFILING OF COLORECTAL CANCER: DOES IT APPLY CLINICALLY?**
EAH Kheirelseid, N Miller, KH Chang, OJ McAnena, M Regan, MJ Kerin
Department of Surgery, National University of Ireland, Galway
- 09.57-10.04 O35 **PERISTEEN TRANSANAL IRRIGATION IN PATIENTS WITH MULTIPLE SCLEROSIS**
G.Preziosi, C.R.G. Cohen, A.C.J Windsor, P. Boulos, A.V. Emmanuel
University College London Hospital
- 10.04-10.11 O36 **A RANDOMISED CONTROLLED TRIAL COMPARING EARLY HOME BIOFEEDBACK PHYSIOTHERAPY WITH PELVIC FLOOR EXERCISES FOLLOWING REPAIR OF THIRD DEGREE OBSTETRIC TEARS**
C Peirce¹, C Murphy², M Cassidy², M Fitzpatrick², PR O'Connell¹, C O'Herlihy^{1,2}
(1) School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4, Ireland. 2 Department of Obstetrics and Gynaecology, National Maternity Hospital, Holles Street, Dublin 2, Ireland.
- 10.11-10.18 O37 **AUTOPHAGY PROTECTS COLON CANCER CELLS AGAINST STRESS-INDUCED DEATH**
Aleksandra Bartnik, Shi Yu Yang, Anur Miah, Yi Wei Chen and Marc Winslet
University College London
- 10.18-10.25 O38 **THE ROLE OF P38 MAPK PATHWAY IN HUMAN COLON CANCER CELL RESISTANCE TO 5-FLUOROURACIL**
Yi-Wei Chan, Anur Miah, Ola Bartnik, Barry Fuller, Marc Winslet, Shi-Yu Yang
Division of Surgery and Interventional Science, Royal Free Hospital and University College London Medical School, London
- 10.25-10.32 O39 **REGIONAL VARIATION IN UREA TRANSPORTER EXPRESSION IN HUMAN COLON- A NOVEL CONTRIBUTION TO BACTERIAL SYMBIOSIS?**
D Collins^{1,2}, AM Hogan^{1,2}, E Ryan^{1,2}, AW Baird¹, GS Stewart¹, DC Winter²
1 University College Dublin, 2 St. Vincent's University Hospital, Dublin
- 10.32-10.39 O40 **MICRORNAS ARE DIFFERENTIALLY EXPRESSED IN THE CIRCULATION OF COLORECTAL CANCER PATIENTS COMPARED TO HEALTHY CONTROLS**
M Nugent, KH Chang, EAH Kheirelseid, N Miller, OJ McAnena, M Regan, MJ Kerin
University Hospital Galway
- 10.39-10.46 O41 **PARAMETRIC SURVIVAL ANALYSIS AND PREDICTIVE MODELS FOR PROPHYLACTIC SURGERY IN FAMILIAL ADENOMATOUS POLYPOSIS**
A Sinha¹, PP Tekkis², RKS Phillips¹, SK Clark¹
1 Polyposis Registry, St Marks Hospital & Imperial College, London 2 Royal Marsden Hospital & Imperial College, London

- 10.46-10.53 O42 **GENOME-WIDE METHYLATION PROFILING OF RECTAL TUMOURS IDENTIFIES NOVEL MARKERS OF EARLY STAGE DISEASE**
KJ Leong^{1,2}, LA Tannahill¹, W Wei¹, GM Caldwell¹, CE Jones¹, GM Matthews¹, DG Morton^{1,2}, SP Bach^{1,2}
1 School of Cancer Sciences, University of Birmingham, Birmingham, UK 2 Academic Department of Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, UK.
-
- 09.15-10.55 **PARALLEL ORAL PRESENTATIONS 1C** (14 Papers) (5 min + 2 min) - *O'Flanagan Lecture Theatre ONCOLOGY*
Chairs: Professor John Primrose and Mr Karl Sweeney
- 09.15-09.22 O43 **DISRUPTION OF MICRORNA EXPRESSION TIPS CELLULAR REGULATION TOWARDS A CARCINOGENIC PHENOTYPE**
A.C.Lee, I. Bhatti, C.Tufarelli, M. Larvin and J.N. Lund
University of Nottingham
- 09.22-09.29 O44 **PATIENTS WITH OESOPHAGEAL CARCINOMA AGED LESS THAN 50 YEARS HAVE IMPROVED SURVIVAL**
CL Donohoe, E McGillicuddy, JV Reynolds
Dept of Surgery, Trinity Centre for Health Sciences/St James' Hospital, Dublin
- 09.29-09.36 O45 **NANOPARTICLES FOR CANCER TREATMENT: APPLICATION OF LECTIN (GLYCOPROTEIN) IN THE DELIVERY OF CARBON NANOTUBES TO THE BREAST CANCER CELL**
Yazdan Madani¹, Sana Khan¹, Miriam Dwek², Alexander Seifalian¹
1 University College London 2 University of Westminster
- 09.35-09.13 O46 **IN-VITRO CHARACTERISTICS OF DESMOID TUMOUR CELLS IN FAMILIAL ADENOMATOUS POLYPOSIS**
A Sinha¹, RKS Phillips¹, C Linge², I Kill³, SK Clark¹
(1) Polyposis Registry, St Marks Hospital & Imperial College, London 2 RAFT Institute of Plastic Surgery, Mount Vernon Hospital, London³ Brunel University, London
- 09.43-09.50 O47 **ONCOLYTIC VIROTHERAPY IN AN IN VIVO MODEL OF ISOLATED LIMB PERFUSION FOR ADVANCED EXTREMITY SARCOMA**
Tim Pencavel^{1,2}, Kevin Harrington², Andrew Hayes¹
1 Sarcoma/Melanoma Unit, Dept of Academic Surgery, Royal Marsden Hospital. 2 Targeted Therapy Team, The Institute of Cancer Research
- 09.50-09.57 O48 **HUNTINGTIN INTERACTING PROTEIN 1 (HIP1) INDUCES EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT) IN PROSTATE CANCER CELLS**
Rao R B, Wang J, Ittmann MM, Neal D, Mills IG
CRUK Cambridge Research Institute
- 09.57-10.04 O49 **C-MYC INDUCTION OF HES6 ACTIVATES A DISTINCT TRANSCRIPTIONAL NETWORK DRIVING ANDROGEN INSENSITIVE PROSTATE CANCER**
Alastair Lamb*, Antonio Ramos-Montoya*, Maria Vias, Helen Scott, Ian Mills†, David Nealt
CRUK Uro-Oncology Research Group, Cambridge Research Institute
- 10.04-10.11 O50 **THICK MELANOMA - ARE WE DOING THE RIGHT THING?**
J Kelly & HP Redmond
Cork University Hospital
- 10.11-10.18 O51 **THE RS10993994 RISK ALLELE FOR PROSTATE CANCER RESULTS IN CLINICALLY RELEVANT CHANGES IN MICROSEMINOPROTEIN-BETA EXPRESSION IN TISSUE AND URINE**
Hayley C. Whitaker^{1†}, Zsofia Kote-Jarai², Helen Ross-Adams¹, Anne Y. Warren³, Rosalind Eeles², David E. Neal¹
1 Uro-Oncology Research Group, Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE, 2 The Institute of Cancer Research, 15 Cotswold Rd, Belmont, Sutton, Surrey, SM2 5NG, 3 Department of Pathology, Addenbrookes Hospital, Cambridge, CB2 0QQ.

- 10.18-10.25 O52 **PROGESTERONE RECEPTOR STATUS IN BREAST CANCER PATIENTS: ASSOCIATION WITH DISEASE CHARACTERISTICS AND PATIENT SURVIVAL**
Coll J, Healy NA, Coyne J, Malone C, McLaughlin R, Sweeney K, Kerin MJ
Department of Surgery, National University of Ireland, Galway
- 10.25-10.32 O53 **THE INHIBITION OF GLYCOLYSIS USING A PYRUVATE DEHYDROGENASE KINASE II INHIBITOR INDUCES APOPTOSIS AND SENSITISES MELANOMA CELLS TO TEMOZOLOMIDE**
O'Leary DP, Hallihan P, Wang JH, Redmond HP
Cork University Hospital
- 10.32-10.39 O54 **IMMUNOHISTOCHEMISTRY CONFIRMS DOWNREGULATION OF PROTEIN MARKERS ASSOCIATED WITH RESISTANCE TO RADIOTHERAPY**
Dalia ELFadl^{1,2}, Victoria Hodgkinson², Ervine Long³, Andrew W Beavis^{2,4}, Philip J Drew^{2,5} Michael J Lind^{2,4,5} and Lynn Cawkwell^{2,5}
1. Academic Surgical Unit, University of Hull, UK. 2. Cancer Biology Proteomics Group, Post Graduate Medical Institute, University of Hull, UK. 3. Histopathology Department, Hull Royal Infirmary, Hull, UK. 4. Queens Centre for Oncology and Haematology, Castle Hill Hospital, Hull, UK. 5. Hull York Medical School, UK
- 10.39-10.46 O55 **PRE-OPERATIVE NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC INDICATOR IN URINARY BLADDER CANCER**
J. S. Rai, P. Ravindra, S.A.Thomas, H. L. Ratan
Royal Derby Hospital, Derby, UK
- 10.46-10.53 O56 **A POTENTIAL ROLE FOR IRON AND HAEM IN BREAST CANCER**
Thomas Roe, Fiona Hoar, Chris Tselepis
Birmingham University Institute for Cancer Sciences
-
- 10.55-11.25 **COFFEE AND TRADE EXHIBITION** - Exam Hall
-
- 11.25-12.35 **PLENARY SESSION 1 FOR THE PATEY PRIZE** (7 Papers) (7 min+ 3 min) - *Cheyne Lecture Theatre*
Chairs: Professor Norman Williams and Professor J Andrew Bradley
- 11.25-11.35 O1 **EICOSAPENTAENOIC ACID (EPA) FREE FATTY ACID REDUCES POLYP BURDEN IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP): RESULTS OF A RANDOMISED, PLACEBO-CONTROLLED TRIAL**
N. J. West^{1,4}, S. K. Clark¹, A. Belluzzi², J. M. Hutchinson³, M. A. Hull³, R. J. Leicester⁴, R. K. S. Phillips¹
1 Polyposis Registry, St Mark's Hospital, Harrow, UK, 2 Gastroenterology, S. Orsola Hospital, Bologna, Italy 3 Leeds Institute of Molecular Medicine, St James' University Hospital, Leeds, UK, 4 Endoscopy, St George's Hospital, London, UK
- 11.35-11.45 O2 **INSULIN-LIKE GROWTH FACTOR 1 AND ITS RECEPTOR CORRELATES WITH OBESITY STATUS IN OESOPHAGEAL ADENOCARCINOMA TUMOURS**
Claire L. Donohoe, Suzanne L. Doyle, Joanne Lysaght, Graham P. Pidgeon, John V. Reynolds
Dept of Surgery, Trinity Centre for Health Sciences, St James' Hospital, Dublin, Ireland
- 11.45-11.55 O3 **WHOLE TRANSCRIPTOME PROFILING OF PERIPHERAL BLOOD IN ABDOMINAL AORTIC ANEURYSM DISEASE**
Butt HZ, Salem M, Ehsan S, Wright B, Choke E, London NJ, Sayers RD, Bown MJ
Vascular Surgery Group, University of Leicester
- 11.55-12.05 O4 **NANOCOMPOSITE CONTAINING BIOACTIVE PEPTIDES ENHANCES BOTH SCHWANN CELL PROLIFERATION AND NEURITE OUTGROWTH: AN IN VITRO EVALUATION**
Tina Sedaghati¹, Shiyu Yang¹, Peter Butler², Ash Mosahebi², Alexander M. Seifalian¹
1 Centre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional Sciences, University College London, London, UK, 2 Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London, UK
- 12.05-12.15 O5 **MULTI-ANALYTE PROFILING AND PATHWAY ANALYSIS REVEALS A PREDOMINANCE OF PRO-INFLAMMATORY M1-TYPE MACROPHAGE POLARISATION AND EVIDENCE OF IL17/TH17 SIGNALLING IN SYMPTOMATIC HUMAN CAROTID ATHEROSCLEROSIS**
Joseph Shalhoub, Amanda Cross, David M Allin, Ian J Franklin, Claudia Monaco, Alun H Davies
Imperial College London

- 12.15-12.25 06 **ATB-346, A HYDROGEN SULPHIDE RELEASING DERIVATIVE OF NAPROXEN, REDUCES ISCHAEMIA REPERFUSION INJURY (IRI) IN A PORCINE MODEL OF DONATION-AFTER-CARDIAC-DEATH (DCD) KIDNEY TRANSPLANTATION**
Mohamed IH, Hosgood SA, Nicholson ML
Department of Infection, Immunity and Inflammation, Transplant Surgery Group, University of Leicester, Leicester General Hospital
- 12.25-12.35 07 **TUMOUR PAI-1 OVEREXPRESSION CORRELATES WITH VISCERAL OBESITY AND IS AN INDEPENDENT PROGNOSTIC FACTOR IN OESOPHAGEAL ADENOCARCINOMA.**
Allott, E.H.¹, Lysaght, J.¹, Cathcart, M.C.¹, Cummins, R.³, Howard, J.², Reynolds, J.V.^{1,2}, Pidgeon, G.P.¹
1 Trinity College Dublin, 2 St James Hospital, 3 Beaumont Hospital
-
- 12.35-13.50 **LUNCH AND TRADE EXHIBITION** - Exam Hall
Poster Judging Professor Pierce Grace
-
- 12.35-13.50 **LUNCHTIME SYMPOSIUM** (Pre-Booked places only) - *Houston Lecture Theatre*
Chairs: Mr Gordon Watson and Mr Denis Evoy
- 12.35-13.05 **Dr Mark Pegram**
Medical Oncologist, Director of Translational Research, Braman Breast Cancer Institute, University of Miami Hospital, Florida
New therapeutic strategies targeting HER2 in breast cancer
- 13.05-13.35 **Dr Henz Josef Lenz**
Professor of Medicine & Professor of Preventative Medicine, Division of Medical Oncology, Keck School of Medicine, University of Southern California
- 13.35-13.50 **Discussion**
-
- 13.50-14.50 **PARALLEL ORAL PRESENTATIONS 2A** (8 Papers) (5 min + 2 min) - *Cheyne Lecture Theatre*
VASCULAR
Chairs: Professor R Sayers and Professor Julian Scott
- 13.50-13.57 057 **PERSISTENT ELEVATION OF CYSTATIN C FOLLOWING ENDOVASCULAR ANEURYSM REPAIR (EVAR)**
MF Abdelhamid^{1,2}, RSM Davies², RK Vohra², AW Bradbury¹, DJ Adam¹.
1. University Department of Vascular surgery, Birmingham Heartland Hospital. 2. University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham.
- 13.57-14.04 058 **NEGOTIATING TORTUOUS ILIAC ARTERIES IN ENDOVASCULAR ANEURYSM REPAIR**
Gokani VJ, Choke E, Dennis MJ, McCarthy MJ, Nasim A, London NJ, Naylor AR, Sayers RD, Bown MJ
Leicester Royal Infirmary
- 14.04-14.11 059 **IDENTIFYING NOVEL CANDIDATE GENES IN UNSTABLE CAROTID ATHEROSCLEROTIC PLAQUES**
MK Salem, HZ Butt, E Choke, RD Sayers, AR Naylor, MJ Bown
Vascular Surgery Group, Department of Cardiovascular Sciences, University of Leicester
- 14.11-14.18 060 **VO2 PEAKS BUT ANAEROBIC THRESHOLD IS EXHAUSTED IN THE PREOPERATIVE ASSESSMENT OF PATIENTS WITH ABDOMINAL AORTIC ANEURYSM**
Kordowicz AGR¹, Sohrabi S^{1,2}, Foster K², Howell SJ³, Scott DJA^{1,2}
1 Leeds Vascular Institute, The General Infirmary at Leeds 2 Division of CardioVascular and Diabetes Research, University of Leeds 3 Academic Unit of Anaesthesia, The General Infirmary at Leeds
- 14.18-14.25 061 **DISCOVERY OF PLAUSIBLE "CANDIDATE BIOMARKERS OF AAA" AT PROTEIN LEVEL: A PILOT STUDY**
S Ehsan¹, SE Slade², G Balls, DJL Jones, HZ Butt, NJM London, RD Sayers, MJ Bown
1 University of Leicester 2 The University of Warwick
- 14.25-14.32 062 **PREDICTING INDIVIDUAL PATIENT MORTALITY RISK IN ELECTIVE AAA SURGERY**
Grant SW¹, Grayson AD², Purkayastha D¹, Wilson S¹, McCollum CN¹ on behalf of the VGNW participants
1Academic Surgery Unit, University Hospital of South Manchester 2 Southport & Ormskirk NHS Hospitals

- 14.32-14.39 O63 **RATES OF SPONTANEOUS EMBOLISATION IN ACUTELY SYMPTOMATIC PATIENTS WITH CAROTID ARTERY DISEASE**
MK Salem, APWW Watts, RD Sayers, MJ Bown, AR Naylor
Vascular Surgery Group, Department of Cardiovascular Sciences, University of Leicester
- 14.39-14.46 O64 **IDENTIFYING THE RISK OF RENAL FAILURE FOLLOWING ELECTIVE AAA REPAIR**
Grant SW¹, Grayson AD², Sekhar H¹, Purkayastha D¹, Wilson S¹, McCollum CN¹ on behalf of the VGNW participants
1 Academic Surgery Unit, University Hospital of South Manchester 2 Southport & Ormskirk NHS Hospitals
-
- 13.50-14.50 **PARALLEL ORAL PRESENTATIONS 2B** (8 Papers) (5 min + 2 min) - *Houston Lecture Theatre HEPATOBILIARY/PANCREATIC*
Chairs: Mr John Simpson and Mr Kevin Conlon
- 13.50-13.57 O65 **TRANSLATION OF SIMULATION TRAINING TO THE OPERATING THEATRE**
Kennedy AM, Al-Akash M, Hill AD, Traynor O
National Surgical Training Centre, Royal College of Surgeons in Ireland, Dublin 2
- 13.57-14.04 O66 **IDENTIFICATION OF DIFFERENTIALLY EXPRESSED PROTEINS IN HILAR CHOLANGIOCARCINOMA USING A LABEL FREE SHOTGUN PROTEOMIC APPROACH**
SG Farid^{1,2}, RA Craven¹, A Zougman¹, DA Cairns¹, PJ Selby¹, RE Banks¹, KR Prasad²
1 Cancer Research UK Clinical Centre, St James University Hospital, Leeds UK 2 Department of HPB Surgery, St James University Hospital, Leeds UK
- 14.04-14.11 O67 **THE ROLE OF MULTISLICE COMPUTERISED TOMOGRAPHIC ARTERIAL PORTOGRAPHY IN THE DETECTION OF COLORECTAL LIVER METASTASES, AND THE FACTORS INFLUENCING PERFUSION DEFECTS**
C Jones¹, SA Badger¹, BE Kelly², M Love², PT Kennedy²
Department of Hepatobiliary Surgery, Mater Hospital, Belfast¹, Department of Radiology, Royal Victoria Hospital, Belfast²
- 14.11-14.18 O68 **UPREGULATED MICRO-RNA 21 TARGETS PDCD4 INHIBITING PANCREATIC CANCER PROLIFERATION**
I Bhatti¹, A Lee¹, C Tufarelli¹, JN Lund¹, RI Hall², DN Lobo³, M Larvin¹
1 Division of Surgery, University of Nottingham School of Graduate Entry Medicine, Royal Derby Hospital, Derby DE22 2DN; 2 Surgical Directorate, Royal Derby Hospital, Derby DE22 2DN; 3 Division of Gastrointestinal Surgery, Nottingham Digestive Diseases Centre NIHR Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH.
- 14.18-14.25 O69 **PATHOGENESIS OF CHEMOTHERAPY ASSOCIATED LIVER INJURY PRIOR TO MAJOR HEPATIC RESECTION**
Robinson SM^{1,2}; Mann J¹, Burt AD¹, Manas DM², Mann DA¹, White SA^{1,2}
1 Liver Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; 2 Department of HPB Surgery, Freeman Hospital, Newcastle upon Tyne, UK
- 14.25-14.32 O70 **THE ROLE OF A NOVEL SEMI-SYNTHETIC FLAVONOID (MONOHER) IN PREVENTING MONOCROTALINE INDUCED SINUSOIDAL OBSTRUCTION SYNDROME IN RATS**
Tarek M Ezzat, Dipok Dhar, Massimo Malago, Steven WM Olde Damink
HPB and Liver transplantation surgery, Royal Free Hospital, University College London
- 14.32-14.39 O71 **THE ROLE OF THE BONE MARROW AND NOTCH SIGNALLING IN THE STROMAL MICROENVIRONMENT IN CHOLANGIOCARCINOMA**
AJ Robson^{1,2}, K Samuel¹, A Pellicoro¹, OJ Garden², SJ Wigmore^{1,2}, JP Iredale¹, SJ Forbes¹
1 Centre for Inflammation Research and Department of Surgery 2 University of Edinburgh
- 14.39-14.46 O72 **MOLECULAR MECHANISMS OF L-ARGININE INDUCED EXPERIMENTAL ACUTE PANCREATITIS**
O.Masood^{1,2}, A.K Siriwardena¹ & J.Bruce²
1 Hepatobiliary Unit, Manchester Royal Infirmary. 2 Faculty of Life Sciences, University Of Manchester.

-
- 14.50-15.20 **SUS, SRS (SA) AND ESSR PRIZE WINNERS' PRESENTATION** (7 minute presentation + 3 minute discussion) - *Cheyne Lecture Theatre*
Chairs: Professor Gordon Carlson and Mr Paul Ridgeway
- 14.50-15.00 **SRS (SA) 2010**
Dr Gayla Chinnery - Risk factors for early rebleeding and death in alcoholic cirrhotic patients with acute variceal haemorrhage treated with emergency endoscopic injection sclerotherapy.
- 15.00-15.10 **SUS Award Winner**
Dr. Allison Nauta - Silencing Prolyl Hydroxylase Domain-2 Gene in Mesenchymal Stem Cells Accelerates Wound Healing".
- 15.10-15.20 **ESSR Walter Brendel Award**
Nikolaos Bonaros - Secretoneurin gene- therapy improves cardiac function in a model of myocardial infarction in-vivo and induces angiogenesis in cardiac cells via VEGF expression in-vitro
-
- 15.20-15.50 **TEA AND TRADE EXHIBITION** - Exam Hall
-
- 15.50-16.50 **PARALLEL ORAL PRESENTATIONS 3A** (8 Papers) (5 min + 2 min) - *Cheyne Lecture Theatre*
WOUNDS AND TISSUES
Chairs: Mr Paul Balfe and Mr Michael Sugrue
- 15.50-15.57 O73 **TISSUE ENGINEERED TRACHEA DEVELOPMENT USING A NOVEL NANOCOMPOSITE MATERIAL**
Claire Crowley^{1,2}, Martin Birchall², Alexander Seifalian¹
1 UCL Division of Surgery & Interventional Science, 2 The Royal National Throat, Nose and Ear Hospital and UCL Ear Institute
- 15.57-16.04 O74 **THE EFFICACY OF ANTIMICROBIAL WOUND DRESSINGS USED IN THE MANAGEMENT OF MILITARY COMPLEX EXTREMITY INJURY: A PRE-CLINICAL RANDOMIZED CONTROLLED TRIAL**
WGP. Eardley^{1,2}, KR. Martin¹, E. Kirkman¹, JC. Clasper², SA. Watts¹
1 Department of Biomedical Sciences, Defence Science and Technology Laboratory, Porton Down, Salisbury, Wiltshire, United Kingdom. 2 Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine, Vincent Drive, Edgbaston, Birmingham, United Kingdom
- 16.04-16.11 O75 **EVALUATION OF THE BIOCOMPATIBILITY OF HUMAN GRADE CHITOSAN DERIVATIVE, HUMAN SKIN ALLOGRAFT AND INTEGRA IMPLANT IN RATS**
SJ Mohd. Yussof, AS Halim, SN Saifuddin, WR Wan Mokhtar, WS Wan Kasim, H Jaafar
Reconstructive Sciences Unit, Universiti Sains Malaysia Health Campus, Kubang Kerian, Kelantan, Malaysia
- 16.11-16.18 O76 **TRAUMA: CHARACTERISING THE CYTOKINE RESPONSE TO TISSUE DAMAGE**
J.Manson, R.Davenport, A.Coates, H.De'Ath, C.Spoors, S.Khan, I.Raza, C.Rourke, P.Vulliamy, K.Brohi
Trauma Clinical Academic Unit, Royal London Hospital and QMUL
- 16.18-16.25 O77 **TORSION OF MONOFILAMENT AND POLYFILAMENT SUTURES UNDER TENSION DECREASES SUTURE STRENGTH AND INCREASES RISK OF SUTURE FRACTURE**
Hennessey DB¹, Carey E², Simms CK³, Hanly A¹, Winter DC¹
1 Department of General and Colorectal Surgery, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland 2 School of Chemical and Bioprocess Engineering, University College Dublin, Belfield, Dublin 4, Ireland 3 Trinity Centre for Bioengineering and Department of Mechanical Engineering, Trinity College Dublin, Dublin 2, Ireland

- 16.25-16.32 O78 **ENHANCED HAEMOCOMPATIBILITY OF POSS NANOCOMPOSITE: A MATERIAL OF CHOICE FOR CARDIOVASCULAR APPLICATION**
 Hossein Ghanbari^{1,2}, Maqsood Ahmed¹, Brian G. Cousins¹, George Hamilton³, Alexander M. Seifalian^{1,3}
 1 Centre for Nanotechnology & Regenerative Medicine, Division of Surgery & Interventional Sciences, University College University College London, London, United Kingdom; 2 Nanotechnology Research Centre, Tehran University of Medical Sciences, Tehran, Iran; 3 Royal Free Hampstead NHS Trust Hospital, London, United Kingdom.
- 16.32-16.39 O79 **HUR AND ITS ROLE IN WOUND HEALING**
 Bosanquet DC, Harding KG, Jiang WG
 Departments of Wound Healing and Surgery
- 16.39-16.46 O80 **THE ROLE OF EHM2 IN WOUND HEALING**
 Bosanquet DC, Ye L, Harding KG, Jiang WG
 Departments of Wound Healing and Surgery
-
- 15.00-16.50 **PARALLEL ORAL PRESENTATIONS 3B** (8 Papers) (5 min + 2 min) - *Houston Lecture Theatre UPPER GI*
Chairs: Professor Derek Alderson and Mr Criostoir O Suilleabhain
- 15.50-15.57 O81 **MICRORNA-31 MODULATES TUMOUR SENSITIVITY TO RADIATION IN OESOPHAGEAL CANCER**
 Niamh Lynam-Lennon¹, John V. Reynolds^{1,2}, Graham P. Pidgeon¹, Stephen G. Maher¹
 1 Trinity College Dublin 2 St James Hospital
- 15.57-16.04 O82 **A POTENTIAL PATHOLOGICAL ROLE FOR OMENTAL CD8+ T CELLS IN OESOPHAGEAL ADENOCARCINOMA.**
 Joanne Lysaght, Emma Allott, Claire Donohoe, Julia Howard, Narayamasamy Ravi, Graham P Pidgeon, John V Reynolds
 Institute of Molecular Medicine, Trinity College Dublin
- 16.04-16.11 O83 **PRO-INFLAMMATORY AND PRO METASTATIC PATHWAYS ARE ACTIVATED BY OBESITY IN BARRETT'S METAPLASIA**
 R Casey, N Ravi, JV Reynolds, G Pidgeon
 Trinity College Dublin
- 16.11-16.18 O84 **PRE-TREATMENT COMPLEMENT SYSTEM SERUM PROTEIN LEVELS PREDICT RESPONSE TO NEOADJUVANT CHEMORADIATION FOR OESOPHAGEAL CANCER**
¹Stephen G. Maher, ¹Dermot T. McDowell, ¹Sinead A. Murphy, ²Ben C. Collins, ³Cian Muldoon, ²William M. Gallagher, ¹John V. Reynolds
 Departments of 1 Surgery and 3 Histopathology, Institute of Molecular Medicine, Trinity Centre for Health Science, Trinity College Dublin, St. James's Hospital, Dublin 8; 2 Proteome Research Core, Conway Institute for Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin 4.
- 16.18-16.25 O85 **OMENTAL ADIPOSE TISSUE INCREASES OESOPHAGEAL AND COLORECTAL TUMOUR GROWTH THROUGH A VEGF-MEDIATED MECHANISM**
 Eric P. van der Stok^{1,2}, Emma Allot¹, Julia Howard¹, Claire L. Donohoe¹, Joanne Lysaght¹, Rob Cummins³, Elaine Kay³, John V. Reynolds¹, Graham P. Pidgeon¹
 1 Dept. Surgery, Institute of Molecular Medicine, Trinity Centre for Health Sciences, St. James's Hospital Dublin. 2 Dept. Surgery, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands. 3 Dept. Pathology, Beaumont Hospital, Royal College of Surgeons Ireland, Dublin
- 16.25-16.32 O86 **PROGNOSTIC IMPACT OF P53 EXPRESSION IN OESOPHAGEAL ADENOCARCINOMA**
 Coats MV^{1,2}, Walsh SV¹, Baker L², Jordan L¹, Thompson AM^{1,2}, Exon DJ²
 1 NHS Tayside, Ninewells Hospital, Dundee 2 University of Dundee, Ninewells Hospital, Dundee
- 16.32-16.39 O87 **INCREASED BMI DOES NOT ADVERSELY AFFECT VASCULAR FUNCTION MEASURED IN VITRO IN OBESE PATIENTS**
 Hye-Chung Kwak¹, Mike Larvin^{1,2}, Saoirse O'Sullivan¹
 1 School of Graduate Entry Medicine, University of Nottingham; 2 Trent Regional Bariatric Surgical Service, Derby Hospitals

PATEY ABSTRACTS

01 EICOSAPENTAENOIC ACID (EPA) FREE FATTY ACID REDUCES POLYP BURDEN IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP): RESULTS OF A RANDOMISED, PLACEBO-CONTROLLED TRIAL

N. J. West^{1,4}, S. K. Clark¹, A. Belluzzi², J. M. Hutchinson³, M. A. Hull³, R. J. Leicester⁴, R. K. S. Phillips¹

(1) Polyposis Registry, St Mark's Hospital, Harrow, UK, (2) Gastroenterology, S. Orsola Hospital, Bologna, Italy, (3) Leeds Institute of Molecular Medicine, St James' University Hospital, Leeds, UK, (4) Endoscopy, St George's Hospital, London, UK.

Introduction

Epidemiology suggests omega-3 fish oils may be protective against development of colorectal cancer. We report the effects of eicosapentaenoic acid as the free fatty acid (EPA-FFA) on polyp burden in subjects with FAP in a single-centre RCT.

Methods

Adult subjects with FAP, previous colectomy and IRA, were randomised to 6 months EPA-FFA 2g/day or placebo (PLA). A focal area of rectum (containing ≥ 3 polyps) was tattooed at baseline endoscopy. Focal area photographs (0 and 6 months) were analysed for polyp numbers and diameters. Videos of randomised endoscopies were scored by a 5-member expert panel (0 and 6 months).

Results

58 subjects were randomised 1:1. There was statistically significant difference between groups for change in polyp numbers (0-6 months) in the tattooed area (EPA-FFA mean [\pm SD] number of polyps 4.13 [2.47] at baseline decreased to 3.61 [2.31] at 6 months; PLA 4.50 [2.63] at baseline increased to 5.05 [3.30]; $p=0.0046$), net difference of -22.4% [95%CI -39.6 to 5.1] ($p=0.0122$). There were corresponding reductions in total polyp diameters (reduction of -29.8% [95%CI -56.1 to -3.6] for EPA-FFA vs PLA; $p=0.027$). These findings were corroborated by the video panel scores (EPA-FFA +0.09 [95%CI -0.14 to +0.32] vs PLA -0.34 [95%CI 0.56 to -0.11]; $p=0.011$). Rectal mucosal levels of EPA increased significantly (+159%) in the EPA-FFA group compared to PLA (+78%; $p=0.0179$). EPA-FFA was well-tolerated.

Conclusion

EPA-FFA, exhibited anti-neoplastic activity in subjects with FAP, with reductions in rectal polyp number and size and improvements in endoscopic appearance. EPA-FFA has potential as a safe and effective chemopreventative agent.

Take-home message

The omega-3, eicosapentaenoic acid as the free fatty acid demonstrates anti-neoplastic activity in FAP, which additionally is a human model for sporadic colorectal carcinogenesis. It has potential as a chemopreventative agent for colorectal cancer.

02 INSULIN-LIKE GROWTH FACTOR 1 AND ITS RECEPTOR CORRELATES WITH OBESITY STATUS IN OESOPHAGEAL ADENOCARCINOMA TUMOURS

Claire L. Donohoe, Suzanne L. Doyle, Joanne Lysaght, Graham P. Pidgeon, John V. Reynolds

Dept of Surgery, Trinity Centre for Health Sciences, St James' Hospital, Dublin, Ireland

Introduction

Obesity has been strongly implicated in the pathogenesis of oesophageal adenocarcinoma. In this context, the insulin-like growth factor (IGF-1) axis warrants exploration.

Methods

Samples from 100 patients diagnosed with oesophageal adenocarcinoma with prospective clinicopathological, follow-up and obesity status data were collected. Adipocyte conditioned media (ACM) was created by co-culture of oesophageal cancer patient's omental or subcutaneous fat in media for 72 hours. ELISA was used to measure levels of free IGF-I in ACM ($n=55$) and serum ($n=100$) and of circulating total IGF-I levels using an acid precipitation pre-treatment ($n=24$). mRNA expression of IGF-IR and IGF-I was determined by qPCR in resected tumour samples ($n=70$). Immunohistochemistry (IHC) determined IGF-1R expression in human tumour sections ($n=40$) and tissue microarrays ($n=200$).

Results

ACM is a source of IGF-1. There was a significantly increased total IGF-I level in the serum of overweight patients but free IGF-1 was unchanged. Gene expression analysis revealed positive significant correlations between IGF-IR and IGF-I in tumours and obesity status ($p<0.05$). IGF-I levels correlated moderately with IGF-IR expression ($\rho=0.465$, $p=0.001$). In

resected oesophageal tumour IHC sections, no statistical difference between intensity of IGF-1R expression and obesity or stage was observed. However, higher intensity IGF-1R staining was observed in the leading edge of adenocarcinomas. This was replicated in tissue microarray immunohistochemistry.

Conclusion

This study suggests an important role for the IGF axis in oesophageal adenocarcinoma and a relationship between the IGF axis and obesity status. Phase I trials of IGF axis inhibitors may be indicated in these patients.

Take-home message

Obesity has been strongly implicated in the pathogenesis of oesophageal adenocarcinoma in epidemiological studies. These data show correlations between the IGF-1 axis and obesity status of oesophageal adenocarcinoma patients at circulating and tumour levels.

03 WHOLE TRANSCRIPTOME PROFILING OF PERIPHERAL BLOOD IN ABDOMINAL AORTIC ANEURYSM DISEASE

Butt HZ, Salem M, Ehsan S, Wright B, Choke E, London NJ, Sayers RD, Bown MJ

Vascular Surgery Group, University of Leicester

Objective

Whole genome microarray-based expression profiling is a powerful tool that can determine disease progression in many common cancers and inflammatory diseases. The aim of this study was to determine expression profiles of individuals with abdominal aortic aneurysms (AAA) compared to screened controls.

Methods

Blood samples were obtained from 12 males with AAAs of mean diameter 6.25cm (SD 0.6) and 12 healthy age-sex matched controls with aortas <2.5cm (cases 71.3 years \pm SD 0.6, controls 73.25 \pm SD 7, $p=0.45$). High quality RNA was extracted (mean RIN 9.18 \pm 0.52) and samples hybridised to Illumina HT-12 arrays, each containing probes representing 37846 genes. Results were analysed with GeneSpring (v11.0).

Results

Gene expression analysis inclusive of multiple testing correction (5% false discovery rate) revealed 48 genes to be significantly differentially expressed in AAA against controls ($p<0.05$). Gene ontology (GO) analysis revealed that 'translation' was the most overrepresented biological process in AAA ($P=0.003$). Eleven genes were upregulated including CARD8 and CASP2 which related to GO categories involving positive regulation of caspase and endopeptidase activity, Il-1 and Il-1 β secretion and regulation of apoptosis. Thirty-seven genes including PSMB10, SIVA and PUF60 were downregulated and collectively involved in regulation of immune system processes and apoptosis.

Conclusion

This study demonstrates differential expression of several transcripts with functional characteristics (pro-proteolytic, pro-inflammatory, apoptosis regulation) previously implicated in AAA pathogenesis. These transcripts have not been previously described in transcriptomic studies of AAA (blood and tissue studies) and therefore further validation to define their role will be beneficial.

Take-home message

The use of novel whole transcriptome profiling has allowed this study to identify significantly differentially expressed genes of interest (previously unidentified) involved in biological processes including apoptosis and proteolysis known to be involved in AAA onset. These genes may therefore also be involved in AAA pathophysiology.

04 NANOCOMPOSITE CONTAINING BIOACTIVE PEPTIDES ENHANCES BOTH SCHWANN CELL PROLIFERATION AND NEURITE OUTGROWTH: AN IN VITRO EVALUATION

Tina Sedaghati¹, Shiyu Yang¹, Peter Butler², Ash Mosahebi², Alexander M. Seifalian¹

(1) Centre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional Sciences, University College London, London, UK, (2) Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London, UK

Introduction

The commercially available nerve conduits do not support nerve regeneration in relatively large gaps (>3cm in length and >2.5mm in diameter). Thus, there is a high clinical demand for new smart biomaterials which stimulate neuronal cell proliferation, migration, and increase cell-material interaction to facilitate nerve regeneration across these critical sized defects. The present study aimed to bio-functionalise the surface of the POSS-PCL, a novel nanocomposite biopolymer developed and patented by our group, using RGD peptide and investigate SC behaviour on RGD-coated and unmodified (control) surfaces.

Methods

POSS-PCL surface topography was characterised by AFM. SCs metabolic activity was assessed by AlamarBlue assay. Assessment of cell phenotype, morphology, and neurite extension was performed by immunochemical staining of S-100, SC specific cell marker, and hematoxylin staining. Western blot analysis of GFAP expression was undertaken to evaluate cell differentiation.

Results

AFM revealed a 'pebble stone' structure of POSS-PCL. AlamarBlue assay confirmed that both control and RGD-coated POSS-PCL samples were not cytotoxic with no statistical difference in SC proliferation compared to TCP. However, SC differentiation and increased migration was achieved on the RGD-coated POSS-PCL by S-100 immunochemical staining and this was confirmed with hematoxylin staining and Western blot analysis.

Conclusion

Both unmodified and RGD bio-functionalised POSS-PCL nanocomposite polymers support SC attachment and proliferation, important aspects for peripheral nerve regeneration. However, RGD bio-functionalised POSS-PCL nanocomposite demonstrated a significant improvement on the SC spreading, migration, and differentiation ($p < 0.05$) and can be considered as a potential alternative for the current clinical options of the peripheral nerve regeneration.

Take-home message

A novel surface modified nanocomposite biopolymer has been developed and investigated as a potential alternative for the current clinical options of the peripheral nerve regeneration.

05 MULTI-ANALYTE PROFILING AND PATHWAY ANALYSIS REVEALS A PREDOMINANCE OF PRO-INFLAMMATORY M1-TYPE MACROPHAGE POLARISATION AND EVIDENCE OF IL17/TH17 SIGNALLING IN SYMPTOMATIC HUMAN CAROTID ATHEROSCLEROSIS

Joseph Shalhoub, Amanda Cross, David M Allin, Ian J Franklin, Claudia Monaco, Alun H Davies
Imperial College London

Introduction

Molecular and cellular characterisation of vulnerable atherosclerosis is necessary for targeting functional imaging and plaque-stabilising therapeutics. Quantification of cytokine and MMP protein production in carotid plaques allowed mapping of the pro-inflammatory milieu responsible for instability.

Methods

Research Ethics Committee approval was obtained (08/H0706/129). Carotid endarterectomies from symptomatic ($n=35$) and asymptomatic ($n=32$) patients were enzymatically dissociated producing mixed macrophage-rich, atheroma cell suspensions which were cultured for 24 hours. Supernatants were interrogated with a 45-analyte panel using Luminex 100. Analyte inter-relationships were described statistically via Spearman correlation. Resulting sets were analyzed via Ingenuity Pathways Analysis v7.6. A 1.5-fold cut-off was set, and right-tailed Fisher's exact test determined significance (p -value) of protein over-representation compared to the result expected by a random protein set.

Results

Tumour necrosis factor- α , IL-1 α , IL-1 β , IL-6, IL-10, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, CCL2, CCL5, CCL20, CXCL9, CXCL10, MMP1, MMP3, MMP8 and MMP9 levels were significantly higher in symptomatic than asymptomatic plaques ($p < 0.05$). A number of inter-related analyte 'clusters' were identified. Ingenuity-identified top-ranked biological pathways associated with differences between symptomatic and asymptomatic data sets focused on the interplay between innate and adaptive immunity, nuclear factor- κ B and MAPK signalling, hypercytokinemia in inducing pathology and matrix degradation, and IL17 signalling.

Conclusion

The inflammatory milieu within human unstable plaque indicates a predominance of M1-type macrophages with signatures of interferon- γ and IL17 signalling. The novel finding in symptomatic atherosclerosis of elevated CCL20 is further supportive of this T helper 17/IL17 signalling. Abbreviations IL, interleukin; MMP, matrix metalloproteinase.

Take-home message

The inflammatory milieu within human unstable plaque indicates a predominance of M1-type macrophages with signatures of interferon- γ and IL17 signalling. The novel finding in symptomatic atherosclerosis of elevated CCL20 is further supportive of this T helper 17/IL17 signalling.

06 ATB-346, A HYDROGEN SULPHIDE RELEASING DERIVATIVE OF NAPROXEN, REDUCES ISCHAEMIA REPERFUSION INJURY (IRI) IN A PORCINE MODEL OF DONATION-AFTER-CARDIAC-DEATH (DCD) KIDNEY TRANSPLANTATION

Mohamed IH, Hosgood SA, Nicholson ML

Department of Infection, Immunity and Inflammation, Transplant Surgery Group, University of Leicester, Leicester General Hospital

Introduction

Hydrogen sulphide has been demonstrated to improve renal function and oxidative damage. Its administration is complicated by its short half-life and need for a donor. A novel hydrogen sulphide releasing drug, ATB-346, a derivative of Naproxen (NSAID), may address these problems. The objective of the study was to investigate its effects in reducing IRI.

Method

Porcine kidneys retrieved by electrocution and exsanguination were subjected to 25 minutes of warm ischaemia and 18 hours of static cold storage. These were reperfused with autologous blood using an isolated organ preservation system at 39°C and mean arterial pressure of 85 mmHg for 3 hours. Kidneys were randomised to 3 groups: control (n=6), ATB-346 (10µmol/l) (n=6) and Naproxen only (10µmol/l) (n=6). ATB-346 and Naproxen were added during priming of the circuit prior to ex-vivo perfusion. Functional parameters, serum and urine were measured. 3-way ANOVA measures with post-test comparisons were used.

Results

ATB-346 improved renal function with greater creatinine fall, with a significantly lower AUC (ATB-346 (2063±143) versus Control (2261±169) versus Naproxen (2258±117) µmol/l.h; P=0.0112) and greater total urine output (P=0.0227). Kidneys receiving ATB-346 demonstrated reduced renal blood flow (AUC P=0.0123).

Discussion

ATB-346 ameliorates IRI with improved creatinine fall and total urine output. The reduced renal blood flow suggests that protection may also be conferred other than from its haemodynamic effects. As such, hydrogen sulphide releasing drugs shows promise in alleviating IRI.

Take-home message

ATB-346, a hydrogen sulphide releasing derivative of Naproxen shows promise in reducing renal ischaemia reperfusion injury.

07 TUMOUR PAI-1 OVEREXPRESSION CORRELATES WITH VISCERAL OBESITY AND IS AN INDEPENDENT PROGNOSTIC FACTOR IN OESOPHAGEAL ADENOCARCINOMA.

Allott, E.H.¹, Lysaght, J.¹, Cathcart, M.C.¹, Cummins, R.³, Howard, J.², Reynolds, J.V.^{1,2}, Pidgeon, G.P.⁽¹⁾

1: Trinity College Dublin, 2: St James Hospital, 3: Beaumont Hospital

Introduction

Oesophageal adenocarcinoma (OAD) is associated with poor survival due to early tumour dissemination. Pathways in metastasis are therefore of great importance. Obesity is an independent risk factor. The 50% rise in OAD in Ireland over the last decade mirrors recent trends in obesity. Elucidation of shared pathways in obesity and OAD could uncover novel therapeutic targets for OAD treatment.

Methods

Altered gene expression in OE33 following co-culture with adipose tissue was investigated using Cancer-Profiler Arrays and validated by qPCR and Western analysis. The effect of ACM on OE33 proliferative, migratory and invasive capacity was examined by BrdU and migration and invasion kits. Tumour biopsy gene expression was investigated by qPCR and corresponding protein expression by IHC in tissue microarrays. Expression alterations were correlated with visceral fat area (VFA), survival, tumour differentiation and pathological tumour stage.

Results

PAI-1 and MMP9, involved in tumour metastasis, were up-regulated 10 (p<0.001) and 4,000 fold (p<0.01), respectively, following co-culture with adipose tissue. Tumour suppressors and cell-cycle regulators p53 and ATM were down-regulated twofold (p<0.05). Adipose-conditioned media increased proliferative, invasive and migratory phenotype of OE33. High tumour PAI-1 and MMP9 correlated significantly with VFA (p<0.05). PAI-1 significantly correlated with poor prognosis (p<0.05). High MMP9 and low p53 significantly correlated with poor tumour differentiation (p<0.05).

Conclusion

Obesity is associated with PAI-1 and MMP9 overexpression in OAD. High PAI-1 expression is prognostic in OAD. High MMP9 and low p53 are associated with poor tumour differentiation. These results highlight a novel association between visceral obesity and OAD metastasis.

Take-home message

Oesophageal adenocarcinoma (OAD) is an aggressive disease with poor survival due to early tumour metastasis. Visceral obesity is associated with OAD but molecular pathways responsible are poorly understood. We identify for the first time that visceral obesity is associated with tumour overexpression of MMP9 and PAI-1, genes involved in pathways of tumour invasion and metastasis. Increased expression of MMP9 and PAI-1 and decreased expression of tumour suppressor p53 correlate with aggressive tumour biology and PAI-1 is an independent prognostic factor in OAD. These results highlight a novel association between visceral obesity and OAD metastasis.

08 BLADDER REGENERATION WITH DECELLULARISED XENOGRAFTS IN AN ANIMAL MODEL

NF Davis^{1,2}, A Huber³, HD Flood¹, SF Badylak³, TM McGloughlin²

1. Department of Urology, Mid-Western Regional Hospital, Dooradoyle, Co. Limerick, Ireland. 2. Centre for Applied Biomedical Engineering and Research, University of Limerick, Castletroy, Limerick, Ireland. 3. McGowan Institute for Regenerative Medicine, Pittsburgh, U.S.A.

Introduction

Patients with end-stage bladder disease are commonly treated with cystoplasty using autogenous gastrointestinal tissue. The presence of mucus secreting epithelium within the genitourinary tract is associated with debilitating long-term complications. We explored an alternative approach for replacing bladder tissue by applying decellularised porcine xenografts for reconstructive purposes.

Methods

A partial cystectomy was performed on female Sprague-Dawley rats under sterile conditions. The cystectomy defect was replaced with decellularised porcine urinary bladder matrix (UBM) scaffolds and constructive tissue remodelling was evaluated by gross histology at 0, 3, 5 and 7 days. Additionally, immunohistochemistry was performed to assess the scaffold's potential to form a mature endothelium and smooth muscle layer. Cell apoptosis and tissue necrosis was determined by TUNEL staining.

Results

All UBM scaffolds were successfully implanted into each cystectomy defect. At days 0, 1 and 3 cellular infiltration was confined to the periphery of the implanted scaffold. However, the scaffold's centre stained positive for urothelial and smooth muscle cells at day 5. Histological evaluation at day 7 demonstrated a confluent monolayer of urothelial cells along the luminal surface of the scaffold and disorganised smooth muscle cells infiltrating the abluminal surface.

Conclusion

Implantation of tissue-engineered xenogenic scaffolds into the urinary bladder is technically feasible and may prove a viable surgical alternative to gastrointestinal tissue for bladder augmentation and replacement purposes

Take-home message

In the near future, tissue-engineered xenogenic scaffolds may replace autogenous gastrointestinal tissue as the gold-standard surgical treatment for neurogenic bladder.

09 THE CONTRIBUTION OF THE RNA-BINDING PROTEIN RNPC1 TO P21-MEDIATED CELL CYCLE ARREST AND RADIATION SENSITIVITY IN OESOPHAGEAL CANCER.

Gijsbert Hotte^{1,2}, Stephen G. Maher¹, John V. Reynolds¹

(1) Department of Surgery, Institute of Molecular Medicine, Trinity Centre for Health Sciences, Trinity College Dublin, St. James's Hospital, Dublin 8, Ireland and (2) Department of Surgery, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands.

Background

Recently, we identified that the RNPC1 gene was upregulated in the tumours of oesophageal cancer patients who had a poor response to neoadjuvant CRT. RNPC1 encodes an RNA-binding protein that is required for maintaining the stability of p21, which regulates cell cycle transition from G1 to S phase. Overexpression of the RNPC1 protein has been shown to induce cell cycle arrest through G1 phase accumulation. As cells are most resistant to radiation in the G1 phase, we hypothesize that the observed upregulation of RNPC1 contributes to resistance to radiation therapy through a p-21-mediated mechanism.

Methods & Materials

OE33 adenocarcinoma cells were stably transfected with a plasmid (pCMV6-AC-GFP) encoding a C-terminal GFP-tagged RNPC1 and overexpression (relative to an empty vector control (expressing GFP only)) was confirmed by qPCR. p21 transcript levels and RNPC1/p21 association were assessed by qPCR and protein/RNA co-immunoprecipitation, respectively. Cell cycle phase distribution was measured by propidium iodide staining and flow cytometry. Radiosensitivity was assessed by clonogenic assay.

Results

In a pre-treatment setting, RNPC1 is overexpressed in the tumours of oesophageal cancer patients who are subsequently unresponsive to neoadjuvant CRT. In OE33 cells, overexpression of RNPC1-GFP mRNA resulted in increased levels of the p21 transcript levels, G0/G1 cell cycle arrest and enhanced sensitivity to radiation.

Conclusion

Our patient and in vitro data suggest that RNPC1 contributes to resistance to radiotherapy, which likely occurs through a p21-mediated G0/G1 arrest mechanism. Therefore, RNPC1 may represent a potential therapeutic target for enhancing tumour sensitivity to ionising radiation.

Take-home message

The RNPC1 protein may mediate resistance to radiation in oesophageal tumours. It may represent a therapeutic target for enhancing tumour radiosensitivity.

010 A P-SELECTIN POLYMORPHISM IS ASSOCIATED WITH THE DEVELOPMENT OF CANCER CACHEXIA: RESULTS OF A CANDIDATE GENE ASSOCIATION STUDY

Benjamin H.L. Tan¹, Torill Fladvad², Vickie E. Baracos³, D.A. Christopher Deans¹, Frank Skorpen², Kenneth C.H. Fearon¹

1 University of Edinburgh, Clinical and Surgical Sciences (Surgery), Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK 2 Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway 3 Department of Oncology (Division of Palliative Care Medicine), University of Alberta, Edmonton, Alberta, Canada

Introduction

Polymorphisms in genes that play a role in the development of cancer cachexia have potential as susceptibility biomarkers.

Methods

We analysed 129 SNPs in 80 genes for association with cachexia based on degree of weight loss (>5, >10, >15%) with or without the presence of systemic inflammation (CRP >10mg/l). 775 cancer patients from three centres were recruited at first presentation to a surgical or oncology clinic. Percentage weight loss was calculated from weight measured at recruitment and pre-morbid weight recalled. A validation association study was performed on an independently recruited cohort (n=101) of cancer patients from one centre.

Results

21 SNPs had significant associations with cachexia phenotypes. However, only the C allele (minor allele frequency 10.7%) of the rs6136 (SELP) SNP was found to be associated with weight loss >10% both in the main study (OR 0.52, 95%CI 0.29 - 0.93, p=0.026) and the validation study (OR 0.09, 95%CI 0.01 - 0.98, p=0.035). Gene-group analysis was performed based on functional similarity according to gene ontology in the main study patients. Gene groups regulating appetite, glucocorticoid signalling, and mitogen activated protein kinases (MAPK) activity were associated with both weight loss >15% and CRP >10mg/l (p=0.0008, p=0.018, and p=0.026 respectively), which suggests that they may have central roles in the pathogenesis of cancer cachexia.

Conclusion

Individuals who carry the C-allele of the rs6136 polymorphism are at reduced risk of developing cachexia and this finding may prove useful in the risk stratification of pre-cachectic cancer patients.

Take-home message

The study suggests that multiple pathways are likely to be involved in the pathogenesis of cancer cachexia and, in particular, appetite regulation, glucocorticoid signalling, and MAPK activity regulation may have central roles in this process and should be further investigated. Individuals with the C-allele of the rs6136 P-selectin polymorphism appear to be at reduced risk of developing cachexia and this information may eventually prove useful in the risk stratification of pre-cachectic cancer patients.

011 THE CCL28 CHEMOKINE IS DIFFERENTIALLY EXPRESSED IN RESPONSE TO BILE ACID ACROSS THE BARRETT'S OESOPHAGUS TO ADENOCARCINOMA SEQUENCE.

Sarah Picardo¹, Gary Sommerville², Stephen Maher¹, John Reynolds¹

Department of Surgery(1) and Histopathology (, Institute of Molecular Medicine, Trinity College Dublin , St. James' Hospital & Molecular Medicine Ireland, Dublin 8, Ireland

Background

Chronic exposure to bile and acid is a major risk factor for Barrett's oesophagus and oesophageal adenocarcinoma development. The CCL28 chemokine is not expressed by normal oesophageal tissue, but is constitutively expressed by columnar epithelium and is inducible in vitro, in response to IL-1 β and TNF- α . We previously identified CCL28 mRNA as being upregulated in oesophageal tumours.

Aim

To examine expression of CCL28, IL-1 β and TNF- α in normal, Barrett's and tumour tissue explants and cell lines in response to bile acid. Methods and Materials: An ex vivo tissue explant model was established. Tissue explants from normal, Barrett's and tumour tissue were treated with 100uM deoxycholic acid (DCA), as were oesophageal cancer cell lines. TNF- α , IL-1 β and CCL28 mRNA was quantified by qPCR and protein expression was investigated using Western blotting and ELISA.

Results

IL-1 β and CCL28 mRNA was significantly upregulated in Barrett's tissue compared with normal tissue. The adenocarcinoma cell lines also showed increased IL-1 β and CCL28 mRNA and protein expression with DCA treatment, with a stronger induction after a 1h pulse treatment. ELISA demonstrated increased CCL28 protein in Barrett's tissue treated with DCA.

Conclusion

This study is the first to show expression of CCL28 in Barrett's tissue and adenocarcinoma cell lines. CCL28 expression may result from direct stimulation with bile acid, or as a secondary consequence of signalling via bile-acid induced TNF- α and IL-1 β . CCL28 may alter the tissue's immune profile to promote a microenvironment favourable to progression to Barrett's oesophagus and adenocarcinoma, which is under further investigation.

Take-home message

Expression of the chemokine CCL28 is increased in Barrett's oesophagus and oesophageal adenocarcinoma, which may result either from direct stimulation by bile acid, or via the bile-acid induced cytokines TNF- α and IL-1 β . CCL28 may alter the immune microenvironment of the oesophagus to promote progression to Barrett's oesophagus and adenocarcinoma.

012 A RANDOMISED CONTROLLED TRIAL OF OMEGA-3 CONTAINING TOTAL PARENTERAL NUTRITION. THE IMPACT ON INFLAMMATORY RESPONSE.

O. S. Al-Taan, J. Stephenson, D. Al-Leswas, W.-Y. Chung, C. Pollard, M. Metcalfe, A. Dennison

Hepatobiliary Department, Leicester General Hospital, Leicester, UK

Introduction

Total parenteral nutrition (TPN) is often required for critically ill patients. Conventional TPN contains only Omega-6 fatty acids and the arachidonic acid (AA) which is a substrate for many cytokines that drive the inflammatory reaction. Omega-3 fatty acids (n-3FA) have shown profound anti-inflammatory properties in clinical trials. We investigated if n-3FA addition to TPN has an effect on systemic inflammatory response.

Methods

We randomised 20 patients to receive a 72 hour infusion of TPN compounded with or without n-3FA. Circulating serum cytokine levels were measured at 9 time points from baseline to 2 hours after TPN infusion using ELISA.

Results

There was a significant increase in pro-inflammatory cytokines IL2, 6, 8, 13, EGF & TNFa ($p = <0.05$, Wilcoxon signed rank test) in response to TPN infusion in the control group. Maximal changes occurred at 6 hours for IL2, 8, 13 & TNFa, and 66 hours for IL6 and EGF. The same inflammatory cytokines did not show the rise in the study group and when compared were significantly lower values for IL-2 (0.018), IL-6 (0.012), IL-8 (0.043), IL-13 (0.018), EGF (0.008) & TNFa (0.018)

Conclusion

The addition of n-3FAs to TPN seems immunomodulate the inflammatory response. effect on production of inflammatory cytokines. In patients with uncontrolled or chronic inflammation requiring TPN the addition of n-3FAs to TPN is likely to be beneficial in curbing additional inflammatory response from infusion of parenteral lipid emulsions.

Take-home message

Addition of Omega-3 fatty acids into TPN has an immuno-stabilising effect. Omega-3 fatty acids will become an essential part of the TPN in the future.

O13 ACTIVATION OF THE WNT SIGNALLING PATHWAY SYNERGISES WITH EITHER PI3K OR MAPK ACTIVATION TO LEAD TO UROTHELIAL CELL CARCINOMAS (UCC) WITH DIFFERING TREATMENT REQUIREMENTS

I Ahmad, OJ Sansom, HY Leung

The Beatson Institute for Cancer Research, Glasgow

Summary

Although deregulation of the Wnt signalling pathway has been implicated in UCC, the functional significance is unknown. Data from clinical UCC demonstrate a significant correlation between high levels of β -catenin and pAKT (and low levels of PTEN) in resected bladder UCC ($p < 0.001$, $n=80$). Interestingly there was also a significant correlation between high levels of nuclear β -catenin and pERK1/2 ($p < 0.001$, $n=80$), but no correlation between high β -catenin /pAKT and β -catenin /pERK1/2 tumours, suggesting they are mutually exclusive groups.

As a result we expressed an activated form of β -catenin in the murine urothelium, leading to formation of localised hyperproliferative lesions, which did not progress to malignancy. Furthermore these lesions showed marked upregulation of the PTEN tumour suppressor protein, a consequence of activating Wnt signalling in the bladder. We therefore combined PTEN deficiency with β -catenin activation, resulting in rapid formation of UCC. These tumours had increased pAKT signalling and were dependent on mTOR (as demonstrated by Rapamycin treatment). Similarly Ras mutation in isolation did not lead to UCC, however in combination with activated α -catenin these mice rapidly developed UCC. In contrast these tumours exhibited high pERK1/2 and low pAKT and were dependent on MAPK signalling as a reduction in size and proliferation was observed upon treatment with a MEK1/2 inhibitor.

Taken together, we are first to examine the causative role of Wnt signalling in the formation of UCC in vivo and provide definitive evidence that activating mutations in the Wnt pathway promote UCC when combined with other tumour suppressor mutations.

Take home message

Our studies would suggest in those patients where tumours had activation of the Wnt and PI3K pathways, the combination of mTOR and Wnt inhibition may be particularly efficacious, whereas the patients with high levels of Wnt and MAPK signalling, the combination of MEK1/2 and Wnt inhibition may be more appropriate.

O14 CREATING A TISSUE ENGINEERED PROSTHESIS FOR STRESS URINARY INCONTINENCE AND PELVIC ORGAN PROLAPSE, WHICH SCAFFOLD?

A Mangera, AJ Bullock, S MacNeil, CR Chapple

Sheffield Teaching Hospitals/ University of Sheffield

Introduction

Many materials are used in surgery for stress urinary incontinence (SUI) and pelvic organ prolapse (POP) but none have so far delivered long term success. Current materials have poor biocompatibility, biomechanical mismatching with native tissues and failure to stimulate fibrosis. Against this background we compared four scaffold materials as candidates for producing autologous tissue engineered repair materials.

Methods

Fibroblasts were obtained from oral biopsies and 800 000 cells were seeded onto 2cm² of the four different materials; cadaveric dermis (CD), polypropylene (PPL), porcine small intestinal submucosa (SIS) and thermoannealed poly(L)lactic acid (Th PLA). Cells were cultured for two weeks in 10% DMEM medium. The tissue engineered constructs were then assessed for:

- 1) Cell attachment using AlamarBlue (vital stain) and DAPI (nuclear stain)
- 2) Cell mediated contraction by serial photographs
- 3) Mechanical properties; including ultimate tensile strength, strain and Young's modulus using a Bose electroforce instrument
- 4) Collagen production by Sirius red staining

Results

Of the 4 materials, SIS and Th PLA were promising in terms of supporting fibroblast adhesion, metabolic activity and new collagen production. The biomechanical properties of Th PLA and SIS were also closest to native tissue. There was

approximately 16% contraction of the tissues over 2 weeks of culture. In contrast CD and PPL were poor at supporting cellular ingrowth and hence did not achieve new collagen synthesis.

Conclusions

SIS and Th PLA are clear front runners and will be taken forward for further evaluation.

Take home message

Small intestinal submucosa and poly(L)lactic acid show good mechanical properties, collagen production and cell attachment which makes them good candidate materials for a tissue engineered prosthesis for SUI or POP.

ORAL PRESENTATIONS 1A GENERAL

O15 INVESTIGATING HMGB1 AS A POTENTIAL MEDIATOR IN BRAIN DEATH INDUCED LUNG DAMAGE

Vallance AE, Walden HR, Karamanou DM, Fox CR, Rostron AJ, Kirby JA, Simpson AJ, Dark JH, Fisher AJ

Institute of Cellular Medicine, Newcastle University

Summary

Donor lung inflammation which occurs following induction of brain death (BD) is associated with poor post-transplant outcomes. Donor LPS pre-conditioning significantly ameliorates lung inflammation after BD suggesting TLR-4 ligation following BD contributes to donor lung inflammation, even in the absence of LPS. We hypothesised that the alarmin HMGB1, a known TLR-4 ligand, may act as an inflammatory mediator in BD induced lung injury. Broncho-alveolar lavage (BAL), serum and lung tissue were retrieved from a rat model of BD and sham operated controls rats. The HMGB1 concentration in the rat serum and BAL was measured by ELISA. Real-time PCR was used to assess HMGB1 mRNA expression in lung tissue following BD. HMGB1 immunolocalisation studies were performed on rat and human lung tissue from BD and non BD groups. The BAL HMGB1 concentration was significantly higher in the BD group ($965 \pm 302 \text{ ng/ml}$) than the sham group ($655 \pm 274 \text{ ng/ml}$) ($p=0.0172$). There was no difference in HMGB1 gene expression. HMGB1 positive staining was dispersed throughout the rat and human lung at a greater density around the bronchioles. There was a significantly higher area of positive staining in BD than sham rat lung tissue ($p=0.0345$). In conclusion, HMGB1 is likely to be released from cells in the lung suffering sustained damage during BD. As HMGB1 gene transcription is unchanged up to 5 hours following BD, lung tissue is most likely releasing presynthesised HMGB1. This study provides evidence of the presence of an alarmin which is likely to potentiate inflammation in the donor lung via the TLR-4 pathway.

Take-home message

The alarmin HMGB1 is present following brain death, this is likely to potentiate inflammation in the donor lung via the TLR-4 pathway resulting in increased transplant recipient morbidity and mortality.

O16 THE EFFECT OF SENSORY INPUT FROM A COCHLEAR IMPLANT ON BALANCE

Karagama YG, Rashid M, Agarwal L, Elliott C, Johnson IJM

ENT Department, Tameside Hospital

Objective

To find out whether sensory input generated by cochlear implant has any effect on balance in patients fitted with cochlear implants.

Method

In this prospective cohort study, 12 cochlear implant patients all 10 years old and above were tested with a sway magnetometer with eyes open and then closed with the implant on and then repeated with the device off in a vestibular test room. The degree of sway was recorded in terms of body sway pathlength via bodyworn magnets with subsequent vector analysis using a computer software program.

Results

Mean sway with eyes open and implant open: 135.5mm. Eyes open and implant off: 138mm. Eyes closed and implant on: 175mm and eyes closed and implant off 154mm. Upper limit in normal subjects; eyes open: 140mm, eyes closed 200mm.

Conclusion

The results of this study show that body sway measurements in cochlear implant patients are comparable to the body sway in healthy normal subjects. The small reduction in body sway with eyes open suggests that the cochlear implant might actually improve balance. The small sample size precludes any definitive comment on the favourable effect on balance. The authors would advocate the need for a laboratory study in order to establish the evidence of cochlear implants on balance.

Take-home message

The results of this study show that body sway measurements in cochlear implant patients are comparable to the body sway in healthy normal subjects.

017 DEVELOPMENT AND CHARACTERISATION OF A COMPOSITE BIOENGINEERED NOSE FOR RECONSTRUCTION POST RHINECTOMY USING A NOVEL POSS-NANOCOMPOSITE POLYMER

Adelola O. Oseni¹, Leila N. Nayyer¹, Peter M. Butler³, Alexander M. Seifalian^{1,2}

University College London: ((1) Centre for Nanotechnology and Regenerative Medicine, Division of Surgery and Interventional Science (2) Centre for Stem Cells and Regenerative Medicine). (3) Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital

Introduction

Reconstructing the nose from autologous cartilage and bone has limitations, namely donor site morbidity and insufficient or inadequate donor material. Tissue engineering has been suggested as a source of functional replacement cartilage for nasal reconstructive surgery. We have therefore fabricated a whole nasal construct using an in house novel nanocomposite polymer (POSS-PCU), incorporating a titanium L-Strut for support of the nasal tip and dorsum and studied the polymer's ability to support cartilaginous growth.

Methods

The mechanical suitability of the nasal replica for nasal reconstruction was assessed using biomechanical compression and tensile strength testing. The chondrogenic potential of the polymer was assessed by seeding flat sheets of POSS-PCU polymer with naso-septal chondrocytes (Negative controls included monolayer culture and PCU sheets seeded with chondrocytes). Scaffold architecture, cell attachment, and morphology were studied for 21 days with scanning electron microscopy (SEM). Cell viability and functionality were also assessed using fluorescent nucleic acid staining and RT-PCR. Results: The nasal construct was deemed mechanically superior on both compressive resistance and tensile strength compared with tests on animal and human noses ($p < 0.01$). Cytotoxicity studies showed good chondrocytic growth on the POSS PCU polymer with the POSS modification enhancing chondrocyte growth on PCU ($p < 0.05$). On POSS-PCU, markers of chondrogenesis, Coll II, Aggrecan increased during the 21 day incubation period ($p < 0.05$).

Conclusion

We can develop a mechanically stable, cytocompatible bioengineered nose using a novel nanocomposite polymer for application in nasal reconstruction.

Take-home message

POSS-nanocomposite is a suitable polymer for developing a mechanically stable and cytocompatible bioengineered nose for nasal reconstruction.

018 OBJECTIVE ASSESSMENT OF SURGICAL TRAINEES IN SELECTION FOR HIGHER SURGICAL TRAINING: THE ROLE OF FUNDAMENTAL APTITUDE TESTING

Emmeline Nugent¹, Dara O'Keeffe¹, Hazem Hseino¹, Borislav D Dimitrov², Arthur Tanner¹, Paul Neary³, Oscar Traynor¹

(1) National Surgical Training Centre, Royal College of Surgeons in Ireland, Dublin 2. (2) Department of General Practice, Royal College of Surgeons in Ireland, Dublin 2. (3) Division of Colorectal Surgery, The Adelaide and Meath Hospital Incorporating the National Children's Hospital, Dublin 24 & Trinity College Dublin.

Background

In order to ensure consultant surgeons of the future are the best we can produce, assessment of how we select our trainees is vital. We report the experience of RCSI with the use of fundamental aptitude testing as part of a novel selection process.

Methods

We performed a retrospective analysis of a prospectively collected database consisting of 146 candidates that were shortlisted for further assessment in application for a place on higher surgical training (HST) between the years 2007 - 2009. Thirty-six medical students were separately recruited. All had visual-spatial, psychomotor and depth perception aptitude assessed. The primary aim of our study was to determine whether the aptitude of the shortlisted candidates had an association with selection for HST. Secondary aims were whether aptitude levels were similar in distribution across all surgical specialities and whether aptitude of the shortlisted surgical trainees differed from baseline controls.

Results

There was a significant difference in visual-spatial ($p = 0.027$) and depth perception ($p = 0.001$) aptitude between the medical students and trainee surgeons, with the surgeons scoring higher. Aptitude across the different surgical specialities assessed was similar. There was no significant difference found in aptitude between successful applicants and those that were not.

Conclusion

We have demonstrated that the shortlisted trainees throughout all specialities assessed were of the highest calibre. No candidate was excluded from HST based on aptitude alone. Selection of surgical trainees for HST needs to be objective and transparent. Aptitude testing is another tool to aid this process.

Take-home message

Fundamental aptitude testing of trainees applying for higher surgical training is an additional tool that should be considered as part of a transparent and objective selection process.

O19 PARADOXICAL ENHANCEMENT OF ENDOTHELIAL PROGENITOR CELLS AND ENDOTHELIAL REGENERATION IN MICE HEMIZYGOUS FOR DELETION OF THE TYPE 1 INSULIN-LIKE GROWTH FACTOR RECEPTOR

S. Tawqeer Rashid, Nadira Yuldasheva, Matthew Kahn, Mark T Kearney, D. Julian A Scott & Stephen B Wheatcroft

Division of Cardiovascular & Diabetes Research, University of Leeds, United Kingdom

Introduction

EPCs participate in endothelial regeneration following vascular injury. IGF-1 is implicated in metabolic homeostasis and contributes to vascular endothelial function by increasing nitric oxide bioavailability. Signalling via the IGF1R has been suggested to have favourable effects on EPCs. However, the contribution of IGF1R signalling to endothelial repair in vivo remains unexplored. Our laboratory has shown mice hemizygous for deletion of IGF1R (IGF1R^{+/-}) are IGF1-resistant but insulin-sensitive. We used IGF1R^{+/-} mice to investigate the effect of downregulation of IGF1 signalling on endothelial repair.

Methods

We assessed circulating, spleen and bone marrow-derived EPCs and endothelial regeneration, using Evans blue staining following denuding femoral artery wire-injury, in IGF1R^{+/-} mice and littermate WT controls (days 0/4/7).

Results

Peripheral blood Sca-1⁺/VEGFR-2⁺ EPCs, measured by flow cytometry, declined immediately post-injury in WT but not IGF1R^{+/-} mice ($p=0.03$). Endothelial regeneration was significantly enhanced in IGF1R^{+/-} mice compared to WT (day 4 post-injury re-endothelialised area $31.0 \pm 7.6\%$ vs. $17.7 \pm 8.6\%$; $P=0.02$). Interestingly, culture of mononuclear cells from peripheral blood and bone marrow but not spleen revealed significantly fewer EPCs at baseline in IGF1R^{+/-} mice compared to WT ($p<0.05$).

Conclusion

These novel data confirm that IGF1R signalling plays a critical role in endothelial repair in vivo. However, downregulation of IGF1Rs results in paradoxical enhancement of endothelial repair. Complex interactions between IGF1R and insulin receptors influencing insulin sensitivity may be implicated in this response. These findings support the hypothesis that insulin resistance may promote atherosclerosis by impairing the capacity to repair sites of endothelial damage. Abbreviations: EPC = endothelial progenitor cell IGF1 = type 1 insulin-like growth factor R = receptor WT = wild type

Take-home message

Downregulation of type 1 insulin-like growth factor receptors hastens endothelial repair possibly through enhanced endothelial progenitor cell levels. This may be through compensatory enhanced insulin receptor activity and could serve as a means to alleviate the ill effects of insulin resistance on atherosclerotic damage.

O20 THE EFFECTS OF RESISTANCE TRAINING AND NEUROMUSCULAR ELECTRICAL STIMULATION IN KNEE OSTEOARTHRITIS - A RANDOMISED CONTROL TRIAL

R.A. Bruce-Brand¹, N.M. Moyna², J.M. O'Byrne¹

(1) Cappagh National Orthopaedic Hospital, Dublin, Ireland; (2) Department of Health & Human Performance, Dublin City University, Ireland

Summary

The purpose of this study was to assess the effects of 6-week home-based resistance training (RT) and neuromuscular electrical stimulation (NMES) programs on self-reported disability, functional capacity, quadriceps strength and cross-sectional area (CSA) in older persons with moderate to severe knee osteoarthritis (OA). 39 patients, aged 55 to 75 with arthroscopically or radiographically confirmed moderate to severe knee OA were recruited and randomised to either a 6-week home RT program, a 6-week NMES program, or a control group receiving standard care. The RT group performed supervised quadriceps femoris strengthening exercises 3 times per week, while the NMES group used a portable garment

stimulator for 20 minutes 5 times per week at the maximum intensity comfortably tolerated. The primary outcome measure was self-reported disability, measured using the Short Form Health Survey (SF-36) score. Secondary outcome measures were functional capacity (25m walk test, chair rise test, stair climb test), peak isometric and isokinetic quadriceps torque, quadriceps CSA, expression of myosin heavy chain isoforms and of 2 ubiquitin-protein ligases implicated in quadriceps atrophy (MuRF and MAFbx). These measures were assessed at baseline, post-intervention and at 6-weeks post-intervention. Both intervention groups showed significant improvements in SF-36 score, functional tests and quadriceps CSA immediately post-intervention. These benefits were maintained 6 weeks post-intervention. Home-based NMES is an acceptable alternative to physical therapy, and is especially appropriate for patients who have difficulty complying with an exercise program.

Take-home message

Both a 6-week home RT program and a 6-week NMES program produce significant improvements in physical and mental health and functional performance for subjects with moderate to severe knee OA. Home-based NMES is an acceptable alternative to physical therapy, and is especially appropriate for patients who have difficulty complying with an exercise program.

O21 POINT OF CARE DIAGNOSTICS FOR THE RAPID IDENTIFICATION OF ACUTE TRAUMATIC COAGULOPATHY AND PREDICTION OF MASSIVE TRAUMA HAEMORRHAGE

Ross Davenport¹, Joanna Manso¹, Henry De'Ath¹, Sean Platton², Amy Coates¹, Shubha Allard², Daniel Hart², Rupert Pearce⁴, K. John Pasi⁵, Peter MacCallum², Simon Stanworth³, Karim Brohi¹

(1) Trauma Clinical Academic Unit, Blizard Institute of Cell & Molecular Science & (4) William Harvey Research Institute, Bart's and the London School of Medicine and Dentistry, Queen Mary University of London, UK. (2) Department of Haematology, Bart's and the London NHS Trust, UK (3) NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK (5) Pathology Group, Blizard Institute of Cell & Molecular Science

Introduction

Resuscitation targeted to correct ATC may improve survival but requires early activation for optimal effect. Prediction of ATC from clinical parameters is unreliable and laboratory-based clotting tests have logistic issues limiting their utility in acute care. We wished to identify an appropriate diagnostic tool for the early diagnosis of ATC and validate this through prediction of transfusion requirements in trauma haemorrhage.

Methods

Single centre, prospective, cohort study of trauma patients (<15 years) presenting directly to a MTC. Exclusion criteria were arrival in ED >2 hours after injury; >2000ml of intravenous fluid before arrival and burns >5% of TBSA. Blood was collected on arrival for ROTEM analysis. Prothrombin Time (PT) ratio was calculated for both laboratory and PoC PT.

Results

Laboratory PT results were available after a median of 78 (62-103) minutes. Correlation between PoC PT and laboratory results was good ($r=0.676$, $p<0.001$) for normal values. ATC has a specific ROTEM trace which is identifiable within 5 minutes by a 42% reduction in clot strength (CA5 normal vs ATC, $p<0.001$). Patients with CA5 ≤ 35 mm had greater PRBC transfusion requirements (4 vs 1 units, $p<0.001$) and more likely to receive FFP (47% vs 12%, $p<0.001$). A normal CA5 (>35mm) had a NPV of 99% for massive transfusion (10+ units).

Conclusion

In trauma haemorrhage laboratory clotting times are not available within clinically useful timeframes. A functional definition of ATC (CA5 ≤ 35 mm) can identify patients at 5 minutes and accurately predict the need for massive transfusion.

Take-home message

Laboratory based clotting screens are unable to identify ATC early enough to activate massive haemorrhage protocols. ROTEM is a valid method by which to rapidly diagnosis ATC and predict transfusion requirements in major trauma haemorrhage.

O22 CARDIAC DYSFUNCTION AFTER TRAUMA: A REAL AND PRESENT DANGER

Henry D I De'Ath, Claire Rourke, Ross Davenport, Joanna Manson, Jane McNeill, Ceri Davies, Ian Renfrew, Martin Rothman, Karim Brohi

Trauma Clinical and Academic Unit, The Royal London Hospital

Introduction

Cardiac dysfunction has been demonstrated in experimental models of trauma haemorrhage. The existence and relevance of trauma induced cardiac dysfunction in the clinical setting remains unclear.

Methods

Prospective cohort study of adult trauma patients admitted to a Level I trauma centre. Blood for Troponin I, BNP and H-FABP was collected on arrival to the emergency department and 24 hours after admission. Patients not requiring critical care were retrospectively excluded. Demographics, cardiac arrhythmias and clinical outcomes were recorded.

Results

135 patients were recruited over 24 months. H-FABP levels were highest on admission but Troponin I and BNP peaked at 24 hours. At both time points, Troponin I levels were higher in patients who died compared to survivors (Hour 0: 1.22 vs. 0.09ng/ml; $p<0.04$) (Hour 24: 7.34 vs. 0.35; $p=0.003$). BNP was correlated with survival at both Hour 0 (581 vs. 489pg/ml; $p=0.01$) and Hour 24 (1369 vs. 694pg/ml; $p<0.001$). In patients who developed arrhythmias, BNP was elevated on arrival (440 vs. 693pg/ml; $p<0.001$) while H-FABP was raised at 24 hours (56 vs. 101ng/ml; $p=0.03$). 52 (39%) patients had no thorax injury and there was no association between thoracic trauma and biomarker elevation or cardiac dysfunction.

Conclusion

Trauma induced cardiac dysfunction is present early after trauma and is associated with worse outcomes. Troponin I and BNP levels are positively correlated with mortality and there is an association between BNP and H-FABP with cardiac arrhythmia. Further research is required to characterise the extent, mechanism and long-term implications of cardiac dysfunction.

Take-home message

Trauma can cause cardiac dysfunction even in the absence of direct thoracic trauma. In patients who die, a rise in Troponin I and BNP is seen both at Hour 0 and 24, and there is an association between H-FABP and BNP levels and arrhythmia.

023 NOVEL HYBRID RESUSCITATION IN TRAUMA IMPROVES COAGULOPATHY AND OUTCOME

C M Doran^{1,3}, C A Doran³, T Woolley², M Midwinter¹, P F Mahoney², S Watts³, E Kirkman³

(1)Academic Departments of Military Surgery & Trauma & (2) Military Anaesthesia & Critical Care, (3)RCDM, Birmingham, Dstl Porton Down, Salisbury

Introduction

Acute trauma coagulopathy in seriously injured casualties may be initiated by tissue hypoperfusion. NH resuscitation was developed to overcome poor tissue oxygen delivery associated with prolonged Hypot .

Methods

Under the Animals (Scientific Procedures) Act 1986, terminally anaesthetised Large White pigs were divided into 4 groups (n=6). Groups 1 & 2 received blast injury (BI) and 3 & 4 no blast (Sham). All were given a controlled haemorrhage (35% blood volume) and an uncompressed Grade IV liver injury. 5 min later all were resuscitated with 0.9% saline to a systolic arterial pressure (SBP) of 80 mmHg. After 60 min the NH groups (1 & 3) were resuscitated to a SBP (110 mmHg) while Hypot groups (2 & 4) continued with SBP 80 mmHg for up to 8h from onset of resuscitation.

Results

Mean survival time was shorter in Group 2 (258 min) compared to 1, 3 & 4 (452, 448, 369 min). By the end of the study Hypot was associated with a significantly greater PT (1.73 ± 0.10 and 1.87 ± 0.15 times baseline, Groups 2 & 4) compared to NH (1.44 ± 0.09 and 1.36 ± 0.06 , Groups 1 & 3, $P=0.001$). Blast vs sham had no significant effect on PT ($P=0.56$). Arterial base excess was significantly lower with Hypot (-18.4 ± 2.7 and -12.1 ± 3.2 mM) vs NH (-3.7 ± 2.8 and -1.8 ± 1.8 mM, $P=0.0001$). Haematocrit was not significantly different between groups ($P=0.16$)

Conclusion

NH significantly attenuates the development of trauma coagulopathy, with improved tissue perfusion and reduced metabolic acidosis. NH, Novel Hybrid; Hypot, Hypotensive resuscitation; PT, Prothrombin Time

Take-home message

Prolonged hypotensive resuscitation after major trauma leads to coagulopathy and adverse outcomes which can be ameliorated by a novel hybrid (hypotensive, then normotensive) resuscitation strategy.

O24 ROTEM INDICES OF PLATELET FUNCTION IN ACUTE TRAUMATIC COAGULOPATHY

Spoors C, Rourke C, Manson J, De'Ath H, Raza I, Khan S, Davenport R, Brohi K

Trauma Clinical Academic Unit, Royal London Hospital, Whitechapel, London

Introduction

Platelets are integral to coagulation, providing a physical framework, cellular control and feedback. Acute traumatic coagulopathy (ATC) is endogenous and caused by severe trauma and shock. Our group has previously used EXTEM CA5 (clot amplitude at 5 mins) <36 mm as an indicator of ATC. The function of platelets in ATC is unclear. This study examines thromboelastometric indices of platelet function and ATC.

Methods

With ethics committee approval, blood samples were obtained from trauma patients within 20 minutes of ED arrival. Samples were analysed using rotational thromboelastometry (ROTEM). Patients were classified as coagulopathic if the EXTEM CA5 was <36m. The EXTEM MCF (maximum clot firmness) - FIBTEM MCF were compared between groups using an unpaired t-test.

Results

442 patients were analysed. 13 were excluded because of thrombocytopenia (<120 x 10⁹/L), and 23 due to incomplete data. Mean platelet count was 195 (± 53) x 10⁹/L in the coagulopathic group, versus 248 (± 62) x10⁹ in the non-coagulopathic group (p<0.001). The mean EXTEM MCF - FIBTEM MCF in the coagulopathic group was 41.7 (±6.9) mm, versus 45.5 (±6.4) mm in the non-coagulopathic group (p<0.001).

Conclusion

EXTEM clots comprise platelets and fibrin; the FIBTEM assay produces primarily fibrin clot. The difference in MCF between EXTEM and FIBTEM represents platelets' contribution to the EXTEM clot. While a relative thrombocytopenia was observed in the coagulopathic group, a count of >120 x 10⁹/L should be adequate for coagulation if platelet function is normal. ROTEM indices indicate likely platelet dysfunction in ATC.

Take-home message

Primary platelet dysfunction is likely to contribute to the acute traumatic coagulopathy phenotype.

O25 TIMING OF MESENCHYMAL STEM CELL TRANSPLANTATION INTO AN AREA OF ACUTE MYOCARDIAL INFARCTION APPEARS TO BE CRUCIAL FOR SUCCESSFUL REPAIRM DaCosta^{1,3}, A Flynn¹, A Duffy², P Nash^{1,3}, F Barry^{2,3}, T O'Brien^{1,2,3}

Galway University Hospital, Regenerative Medicine Institute, National University of Ireland Galway

Background

Myocardial infarction may result in significant tissue loss ultimately causing heart failure. Stem cell therapies have been suggested as an approach to diminish the extent of tissue loss and thus prevent the development of heart failure. While there has been a substantial number of publications on the use of unfractionated bone marrow cells on cardiac repair, individual cell types have been studied to a lesser extent. We have explored the effect of intramyocardial delivery of bone marrow derived Mesenchymal Stem Cells (MSCs) in an animal model of acute myocardial infarction. Methods: In a rat model of total ligation of the LAD, 4 million MSCs cells were delivered to the infarct border zone by direct injection at 10 minutes and 24 hours after inducing myocardial infarction. The endpoints assessed were ejection fraction and histological infarct size 4 weeks later.

Results

When cells were delivered 10 minutes after LAD ligation, there was no improvement in ejection fraction or infarct size. In contrast, when cells were delivered 24 hours after LAD ligation, there was a significant improvement in ejection fraction without a change in infarct size.

Conclusion

Intramyocardial delivery of bone marrow derived mesenchymal stem cells in the setting of acute myocardial infarction has beneficial effects on cardiac function but the timing of administration appears to be crucial. Although the mechanism whereby ejection fraction improves without a corresponding decrease in infarct size is unclear, this has significant implications for clinical application.

Take-home message

A specific subgroup of stem cells, such as bone marrow MSCs may be more effective at cardiac repair in the setting of acute myocardial infarction, but timing of delivery appears to be crucial for success.

O26 IMPROVING PATIENT SAFETY BY PREVENTING SURGICAL INFECTION - RESULTS OF A TWO YEAR INITIATIVE

McHugh SM¹, Corrigan MA¹, Dimitrov BD², Tierney S¹, Cowman³, Hill ADK¹, Humphreys HH^{4,5}

1. Department of Surgery, RCSI, 2. Department of General Practice, RCSI, 3. Faculty of Nursing and Midwifery, RCSI, 4. Department of Microbiology, Beaumont Hospital, Dublin 9. 5. Department of Clinical Microbiology, RCSI

Introduction

Surgical site infection accounts for 20% of all healthcare associated infection. We audited aspects of surgical practice to inform the development of an educational programme geared for surgeons.

Methods

The audit was carried out in Beaumont Hospital in 2009. An educational website was developed targeting deficiencies highlighted in the audit as part of a blended approach incorporating traditional initiatives such as posters and lectures. Interactive clinical cases were constructed using PHP coding. PowerPoint tutorials were produced as online 'flash' audiovisual movies and an online repository of streaming videos demonstrating best practice were made available. Weekly podcasts were made available on the iTunes® store. Use of the e-learning programme was assessed quantitatively by independent commercial monitoring and a repeat audit was carried out in July 2010 following implementation of the educational initiative.

Results

Since going online the SurgInfection website has been viewed over 18,000 times. Visitors from Ireland have accounted for 79% of site users. Interactive clinical cases have been the most popular site resource, accounting for 31% of page views. Significant improvements in surgical practice have been recorded, e.g. adherence to guidelines on surgical prophylaxis pre-incision increased to 64.3% ($p < 0.05$). The incidence of unnecessary peripheral venous catheters decreased to 25.7% from 38.9% ($p < 0.05$) and the duration of indwelling peripheral venous catheters also improved; only 3.5% in situ > 72 hours, compared with 10.6% previously ($p < 0.05$).

Conclusion

Our educational initiative has significantly improved aspects of surgical practice. Incorporating e-learning as part of a blended learning approach allows for greater accessibility and transferability.

Take-home message

By identifying key deficiencies in patient care, and providing an educational initiative purely for surgical trainees and targeting these deficiencies we can improve the quality and safety of patient care by increasing adherence to best practice guidelines.

O27 IS THE INCREASE IN CARDIAC-DEATH ORGAN DONORS IN THE UK CONTRIBUTING TO A DECLINE IN BRAIN-DEATH DONORS?

D.M.Summers^{1,2}, C.Counter², R.J.Johnson², P.Murphy², J.Neuberger², J.A.Bradley¹

(1) Department of Surgery, University of Cambridge. (2) NHS Blood and Transplant

Introduction

Organ donation after brain-death (DBD) has declined in the UK whereas donation after cardiac-death (DCD) has increased markedly. We sought to understand the reasons for the decline in DBD donation and determine whether the rise in DCD donation was a major factor.

Methods

The UK Transplant Registry was analysed to determine trends in organ donation. Data from the "Potential Donor Audit", an audit of all patients aged < 76 years who died in non-cardiothoracic UK intensive care units (ICU), was analysed to identify trends in clinical demographics and management, and to determine whether potential donors (DBD and DCD) were identified and appropriate steps taken to enable organ donation.

Results

There were 7,589 (12.8 pmp) deceased organ donors in the UK from 1999-2009. The total number of deceased donors increased by 16% (to 14.9 pmp) but DBD donors fell from 744 to 612 and the overall increase in donors was due to an 8-fold rise in DCD donors (33 in 1999/2000, 288 in 2008/9). Analysis of the PDA over the 5-year period 2004/5- 2008/9 showed that the number of patients dying in ICU who were possibly brain-stem dead (comatose, apparently apnoeic with unresponsive pupils) fell from 1,929 in 2004/5 to 1,495 in 2008/9 (22.5% reduction). The proportion of potential DBD donors who became donors increased from 45% to 51%.

Conclusion

There is no evidence that the rise in DCD donors has contributed directly to the decline in DBD donation which reflects a fall in the number of patients with braindeath.

Take-home message

There is no evidence that the rise of cardiac-death organ donation has directly contributed to the decline in brain-death organ donation in the UK.

028 REDUCED LEVELS OF SOLUBLE UROKINASE RECEPTOR (SUPAR) FRAGMENT DII-III PREDICTS VENOUS ULCERS THAT FAIL TO HEAL

Anwar Ahmad¹, Matthew Waltham¹, Gunilla Høyer-Hansen², Tine Thurison Sørensen², Katherine Mattock¹, Prakash Saha¹, Bijan Modarai¹, Hany Zayed³, Alberto Smith¹

(1) King's College London, London, UNITED KINGDOM, (2) Finsen Laboratory, Copenhagen, DENMARK, (3) Guy's & St Thomas' NHS Foundation Trust, London, UNITED KINGDOM

Introduction

The plasminogen system has an important role in wound healing. Soluble uPAR contains 3 domains (DI, DII and DIII). Cleavage between DI and DII exposes a chemotactic peptide on DII-III that is a potent inducer of cell migration. This study compares levels of soluble uPAR (suPAR) and its fragments DI and DII-III in exudates from healing and covered(non-healing venous ulcers).

Methods

Exudates were aspirated from Opsite ulcers at recruitment. Acute wound exudates (AWE) were collected from donor sites of split skin grafts. Patients were treated with standard compression dressings and prospectively followed for healing (defined as complete re-epithelialisation within 6 months). Levels of suPAR and its fragments were measured in the exudates by time-resolved fluorescence immunoassays. Statistical analysis was carried out using unpaired t test.

Results

Exudates were collected from 25 patients with venous ulcers (12 males; median age 68 yrs, range 34-92yrs) and 7 AWEs (3 males; median age 78yrs, range 47-88yrs). Nine patients had healed ulcers. Exudates from non-healers had lower levels of suPAR (8+/-1fmol/mg) than healers (19+/-5fmol/mg, p<0.05) and AWEs (32+/-3fmol/mg, p<0.05). Healers had higher levels of DII-III (138+/-19fmol/mg) than non-healers (47+/-7fmol/mg, p<0.0001) and AWEs (41+/-19fmol/mg, p<0.005). Conclusions: This is the first study to show that suPAR and its fragments are present in wound exudates. Levels of suPAR and DII-III in exudates can differentiate between healing and non-healing venous ulcers. Measurement of these fragments could be used to stratify patients in whom early skin grafting would be beneficial. DII-III may represent a novel target to promote venous ulcer healing.

Take-home message

Soluble uPAR fragment DII-III can differentiate between healing and non-healing venous ulcers. This fragment may be used to promote ulcer healing.

ORAL PRESENTATIONS 1B

COLORECTAL/SEPSIS

O29 ADIPOCYTES ARE CAPABLE OF PRESENTING ANTIGEN IN A MHC CLASS II-DEPENDENT MANNER AND ACTIVATING NAÏVE CD4+ T CELLS.

Joanne Lysaght, Emma Allott, Suzanne Doyle, Graham P Pidgeon John V Reynolds
Institute of Molecular Medicine and Trinity College Dublin

Introduction

The omentum is a multicellular organ comprising mostly of adipocytes but also a range of immune cells, including T cells. It is also believed to be a site of extra-thymic T cell differentiation, with an important role in microbial infections, autoimmunity and cancer. T cell activation requires the interaction with an antigen presenting cell. As previous work from our unit has shown that T cells in the human omentum are activated, this study examined the interactions between adipocytes and T cells.

Methods

An adipocyte cell line, SGBS, and primary omental adipocytes were screened for the expression of co-stimulatory and antigen presenting molecules by qPCR arrays. Naïve CD4+ T cells were isolated from peripheral blood and co-cultured with SGBS cells in the presence of a super-antigen, staphylococcal enterotoxin A (SEA) for 72hrs, after which T cell activation was determined by flow cytometry.

Results

Both the SGBS cell line and primary omental adipocytes express co-stimulatory and antigen presenting molecules including CD80, CD86, CD40, CCR7, MHC class I and II at the mRNA level. The SGBS cell line was capable of presenting SEA to and activating naïve CD4+ T cells in a MHC class II-dependent manner, as assessed by CD69 expression. Upregulation of CD69 was not detected in cells treated with anti-MHC class II.

Conclusion

This is the first study of its kind to identify the potential of adipocytes to interact with and activate T cells, allowing the omentum to play an important immunological role in controlling abdominal inflammation, injury and infection.

Take-home message

Adipocytes express co-stimulatory and antigen presenting molecules and are capable of activating naïve CD4+ T cells via MHC class II.

O30 CELLULAR REPROGRAMMING BY BACTERIAL LIPOPROTEIN RESCUES ST2-DEFICIENT MICE FROM LETHAL SEPSIS

Andrew Coveney, Julliette M. Buckley, Jing Hua Liu, H. Paul Redmond, Jiang Huai Wang
Department of Academic Surgery, University College Cork, Cork University Hospital, Cork, Ireland.

Introduction

ST2, a member of the Toll-IL-1 receptor (TIR) superfamily, negatively regulates both TLR2 and TLR4 signaling which trigger an innate immune response to bacterial infection. This study examines this phenomenon and how it is affected by bacterial lipoprotein (BLP) tolerance.

Methods

Bone marrow derived macrophages isolated from ST2 deficient and wild type mice were stimulated in vitro with gram negative and gram positive bacteria. Bacterial killing and phagocytosis was compared. This was repeated in BLP tolerised macrophages. In vivo, ceacal ligation and perforation was performed to induce polymicrobial sepsis in ST2 deficient and wild type mice. Survival, bacterial clearance and pro-inflammatory cytokine levels were compared between both groups.

Results

ST2-deficient mice were more susceptible to polymicrobial sepsis when compared to wild-type mice, with an increased release of proinflammatory cytokines. ($p < 0.05$). Bacterial clearance following polymicrobial infection was significantly delayed in ST2-deficient mice compared to wild type mice ($p < 0.05$). This was associated with a reduced antimicrobial response and impaired phagosome maturation characterized in ST2-deficient phagocytes. Cellular reprogramming by BLP tolerisation protected ST2-deficient mice against polymicrobial sepsis-related lethality and abrogated the pro-inflammatory effect of ST2-deficiency. Moreover, bacterial clearance was accelerated in BLP-tolerised, ST2-deficient mice, with substantially enhanced bacterial uptake, phagocytosis and killing, and accelerated phagosome maturation in BLP-tolerised, ST2-deficient phagocytes.

Conclusion

ST2-deficient mice exhibit an increased susceptibility to polymicrobial infection, and cellular reprogramming by BLP rescues ST2-deficient mice from lethal sepsis by attenuating the overwhelming proinflammatory response, and simultaneously accelerating bacterial clearance via enhanced phagosome maturation and bactericidal activity.

Take-home message

BLP tolerisation eliminates the increased susceptibility to bacterial sepsis in ST2 deficient mice..

031 INDUCTION OF GRAM-POSITIVE BACTERIAL LIPOPROTEIN TOLERANCE UP-REGULATES GENES THAT ARE INVOLVED IN ANTI-MICROBIAL FUNCTION WHILE DOWN-REGULATES GENES RESPONSIBLE FOR PROINFLAMMATORY RESPONSE

DP Power, JH Wang, HP Redmond

Department of Academic Surgery, University College Cork, Cork University Hospital, Ireland

Aims

Inflammation and sepsis cause morbidity. Dysregulated inflammation can lead to various pathological outcomes including SIRS, septic shock or death. Current understanding of inflammation and its regulation remains incomplete. The inflammatory response is stimulated chiefly at the level of Toll-like receptors (TLRs), which induce transcriptional activation of thousands of genes. However, these genes encompass a wide scope of activity. We hypothesise that additional, more specific mechanisms exist to regulate these genes.

Methods

Mouse bone marrow macrophages were divided into two arms containing control and treatment groups, and stimulated with gram-positive BLP or gram-negative LPS as appropriate. RNA was extracted. RNA gels and spectrometry ensured quality. DNA microarray analysis (Affymetrix 430 2.0 mouse genome arrays) and sub-group analysis was performed using the NCBI database.

Results

45,101 genes examined. In the BLP arm, 9,401 genes were significantly up- or down-regulated (18,972 in LPS arm), significance defined as a 1.5 fold change in expression or greater. Down-regulated genes tended to code for pro-inflammatory effects. Up-regulated genes coded for anti-microbial effects. The top 50 genes were further sub-classified according to their function. One difference observed between the BLP and LPS arms was the number of up-regulated genes involved in pathogen recognition, with ~3 fold greater in BLP arm than LPS arm ($p < 0.05$). We further confirmed these changes by real-time PCR.

Conclusion

Our results indicate that TLRs do not completely account for all inflammatory regulation. Therefore, additional component specific regulation must exist in the inflammatory process. BLP also induces more potent anti-microbial activity than LPS.

Take-home message

Inflammation and sepsis are a leading cause of morbidity and mortality on surgical wards. Our understanding of inflammation & its regulation remain incompletely understood.

032 UNRAVELLING A NOVEL ROLE OF MYELOID-RELATED PROTEINS 8/14 (MRP8/14) IN SELF TOLERANCE AND CROSS TOLERANCE TO GRAM NEGATIVE AND GRAM POSITIVE BACTERIA.

Andrew Coveney, Jiang Huai Wang, H. Paul Redmond

Department of Academic Surgery, University College Cork, Cork University Hospital, Cork, Ireland.

Summary

This study examines the ability of myeloid-related protein 8/14, an endogenous protein complex and its two subunits to induce self-tolerance and cross-tolerance to BLP and LPS. Murine peritoneal and bone marrow derived macrophages (BMMs) from C3H/HeN mice were stimulated with increasing doses of murine Mrp8 for 18hrs, washed and re-stimulated with 5 μ g/ml of Mrp8 for 6 hrs. TNF- α levels of supernatants from naïve macrophages and pre-stimulated macrophages were compared. Mrp8 tolerised macrophages were re-stimulated with BLP and LPS to investigate for cross-tolerance. The experiment was repeated with TLR2 $^{-/-}$ and TLR4 $^{-/-}$ mice and also in human monocytes from healthy volunteers. Mrp8 stimulation triggers TNF- α release. Prestimulation with Mrp8 attenuates this TNF- α release, in both murine macrophages and human monocytes. The tolerance effect is both dose and time dependent. TLR4 is essential but TLR2 also contributes to the tolerising effects of Mrp8. Pre-stimulation of murine macrophages with 1 μ g/ml of Mrp8 leads to a 26% reduction in TNF- α release when cells are stimulated with 100ng/ml of BLP ($p < 0.002$) confirming cross tolerance with BLP. Human

monocytes were much more sensitive than murine macrophages to the tolerising effects of Mrp8 with a prestimulation dose of 0.1 µg/ml of Mrp8 leading to an 85% reduction in TNF- α release compared to naive cells, when both cells were re-stimulated with 1 µg/ml Mrp8 ($p < 0.005$). The Mrp14 subunit also demonstrated tolerising effects. Mrp8 induces self-tolerance and cross-tolerance to BLP, and LPS in a dose and time dependent manner in murine macrophages and human monocytes identifying a potential mechanism for attenuating the inflammatory response.

Take-home message

Prestimulation of macrophages with Mrp8/14, an endogenous protein, attenuates the inflammatory response to subsequent gram negative and gram positive bacterial stimulation.

O33 BOWEL BIOFEEDBACK TREATMENT IN PATIENTS WITH MULTIPLE SCLEROSIS: PSYCHOLOGICAL AND DISABILITY FACTORS, NOT PHYSIOLOGICAL VARIABLES, PREDICT SUCCESS

G.Preziosi, C.R.G. Cohen, A.C.J Windsor, P. Boulos, A.V. Emmanuel

University College London Hospital

Introduction

Bowel dysfunction in MS is common. Small studies showed that bowel biofeedback can be successful. In non-neurological patients biofeedback improves behavioural and mood dysfunction associated with bowel symptoms. We hypothesized that successful biofeedback is related to disability and psychological variables, not ARP changes.

Materials and Methods

We prospectively studied 39 patients with MS and bowel symptoms, measured with Wexner scores; the HAD questionnaires and EDSS were performed in all patients at baseline and immediately after completion of biofeedback. At these same time points standard ARP tests were undertaken.

Results

22/39 (56%) patients improved Wexner scores (fall to < 10) after biofeedback (Responders). Comparing Responders with non-Responders, baseline variables that differed were EDSS (3.6 ± 1.8 vs 6.3 ± 1.9 resp, $p < 0.0001$), HAD-anxiety (3.2 ± 2.8 vs 7.3 ± 5.3 resp, $p = 0.004$) and HAD-depression (5.4 ± 3.8 vs 10.2 ± 5.6 , $p = 0.003$), but not ARP. Responders with Incontinence improved anal squeeze and pressure (66 ± 42 vs 76 ± 35 mmHg, $p = 0.03$) and 5-second endurance squeeze (36 ± 29 vs 55 ± 23 , $p < 0.0001$). Responders with Constipation improved threshold volume (55 ± 23 vs 49 ± 10 mls, $p = 0.0002$) and anal electro-sensitivity (10.2 ± 4.4 vs 8.9 ± 3.5 mAmp $p = 0.0265$). Responders reduced HAD-anxiety (3.2 ± 2.8 to 2 ± 1.4 , $p = 0.0260$) and HAD-depression (5.4 ± 3.8 to 3.8 ± 2.6 , $p = 0.0103$).

Conclusion

MS patients with less disability were the most likely to improve with biofeedback. Low HAD scores also predicted good outcome, unlike ARP tests. Also HAD scores improved with successful treatment, as did measures of external anal sphincter function in incontinent patients and ano-rectal sensation in constipated patients. Abbreviations MS: Multiple Sclerosis; ARP: Ano-Rectal Physiology; HAD: Hospital Anxiety and Depression questionnaire; EDSS: Expanded Disability Status Scale.

Take-home message

There is a behavioural component for bowel symptoms in Multiple Sclerosis. Tests of Ano-rectal physiology only offer a crude measurement of function, not underlying pathophysiology in ano-rectal disturbances; better tests are needed

O34 MOLECULAR PROFILING OF COLORECTAL CANCER: DOES IT APPLY CLINICALLY?

EAH Kheirelseid, N Miller, KH Chang, OJ McAnena, M Regan, MJ Kerin

Department of Surgery, National University of Ireland, Galway

Introduction

Despite developments in diagnosis and treatment, 20% of colorectal cancer (CRC) patients present with metastatic disease and 30% of cases recur after curative surgery. Furthermore, the molecular factors involved in prognosis and response to therapy in CRC are poorly understood. The objectives of this study were to examine the expression patterns of candidate miRNAs in CRC in order to identify molecular biomarkers for disease classification and prognostication.

Methods

Expression patterns of candidate miRNA and mRNA species were determined in FFPE and fresh-frozen colorectal tumour and normal tissue using a combined microarray and real-time PCR approach. Statistical analysis and correlation with clinicopathological data was performed using SPSS software.

Results

Reduced expression levels of CXCL12 ($p=0.000$), CDH17 ($P=0.026$), MUC2 ($p=0.000$), L-FABP ($p=0.000$) and PDCD4 ($p=0.000$) and increased IL8 ($p=0.000$) were observed in tumours compared to normal colorectal tissue. Significantly associated expression patterns were observed between certain miRNAs and their mRNA targets (miR21:PDCD4, miR-31: CXCL12 and miR-145:IL8). Moreover, significant associations of gene expression levels and clinicopathological variables including tumour size (CXCL12, CXCR7, CXCR4 & CDH17), grade (CXCL12, CXCR4 & IL8), invasion (CXCL12) and lymph node status (CXCL12, IL8 & TGFBR2) were identified.

Conclusion

We identified a comprehensive list of markers with highly differential expression patterns in colorectal cancer that could serve as molecular markers to complement existing histopathological factors in diagnosis, follow up and therapeutic strategies for individualised care of patients. The significant miRNA:mRNA correlations highlight important novel mechanisms in CRC initiation and progression.

Take-home message

Clinical applications of molecular profiling in colorectal cancer are both visible and achievable

O35 PERISTEEN TRANSANAL IRRIGATION IN PATIENTS WITH MULTIPLE SCLEROSIS

G.Preziosi, C.R.G. Cohen, A.C.J Windsor, P. Boulos, A.V. Emmanuel

University College London Hospital

Introduction

Bowel symptoms in MS are common, but management is empirical because of the lack of evidence-based treatments. We evaluated the effectiveness of Peristeen transanal irrigation in MS, and also examined possible predictors of success.

Materials and Methods

19 patients with MS who failed maximal medical treatment and biofeedback for bowel symptoms were entered in the study. 8 had rr MS, 3 pp and 8 sp. Symptoms were quantified with Wexner constipation and incontinence questionnaires. Standard ano-rectal physiology and rectal compliance (with barostat) were measured at baseline. Patients were followed up at 3 months, and classified as Responders or non-Responders on the basis of reduction to below 10 in the relevant Wexner score.

Results

10 patients (52%, 3 rr, 2 pp and 5 sp) were Responders, and had higher Wexner incontinence scores compared to non-Responders (12.8 ± 4.3 vs 7.4 ± 9 $p=0.0290$), but similar Wexner constipation scores (13.8 ± 4 vs 11.6 ± 6.2 $p=0.3792$). Sphincter function was similar between the groups. Responders had a higher Maximum tolerated volume to balloon distension (230 ± 98 vs 115 ± 89 ml, $p=0.0296$) but similar ano-rectal electrosensitivity to non-Responders. Rectal compliance was significantly higher in Responders (17.5 ± 4.2 vs 11.264 ± 9 ml/mmHg $p=0.0337$).

Conclusion

Peristeen-TAI is a viable option for patients with MS who have failed to respond to maximal medical treatment and biofeedback for bowel symptoms. A highly compliant and capacious rectum and high baseline incontinence scores are a positive predictive factor for successful treatment.

Abbreviations

MS: Multiple Sclerosis, TAI: transanal irrigation, rr: relapsing remitting, pp: primary progressive, sp: secondary progressive

Take-home message

Trans-anal irrigation is a promising conservative measure to treat bowel symptoms. This study provides much needed evidence for the treatment of bowel dysfunction in MS

O36 A RANDOMISED CONTROLLED TRIAL COMPARING EARLY HOME BIOFEEDBACK PHYSIOTHERAPY WITH PELVIC FLOOR EXERCISES FOLLOWING REPAIR OF THIRD DEGREE OBSTETRIC TEARS

C Peirce¹, C Murphy², M Cassidy², M Fitzpatrick², PR O'Connell¹, C O'Herlihy^{1,2}

(1) School of Medicine and Medical Science, University College Dublin, Belfield, Dublin 4, Ireland. (2)

Department of Obstetrics and Gynaecology, National Maternity Hospital, Holles Street, Dublin 2, Ireland.

Introduction

Women who sustain third degree anal sphincter tears have increased risk of developing faecal incontinence. Optimal treatment following repair of the tear remains unknown. Pelvic floor exercises (PFEs) are standard. Altered continence is initially addressed with intensive physiotherapy including biofeedback. This study aimed to determine whether women receiving home biofeedback physiotherapy had superior anal manometry and continence scores compared with women performing PFEs following a third degree tear.

Methods

120 women who sustained a primary third degree tear were randomised (1 to 3 ratio) to either early home biofeedback physiotherapy (n=30) or PFEs (n=90). Follow up was 3 months postpartum where anorectal manometry, endoanal ultrasound, symptom score and Rockwood continence questionnaire were completed.

Results

The mean anal resting pressure was 39 ± 13 mmHg in the biofeedback group and 43 ± 17 mmHg in the PFE group. The mean anal squeeze pressure was 64 ± 17 mmHg in the biofeedback group and 62 ± 23 mmHg in the PFE group. There was no significant difference in anal resting and squeeze pressure values between the groups ($p=0.123$ and $p=0.68$ respectively, unpaired Student's t-test). Symptom and continence scores were similar between the groups.

Conclusion

This study demonstrates no added value using early home biofeedback physiotherapy in the management of third degree tears. Poor compliance may have contributed as patients found it difficult to designate time to using the biofeedback machine. Thus, biofeedback physiotherapy should remain a first treatment option for women with new, ongoing or worsening symptoms at follow up at 3 months postpartum.

Take-home message

Home biofeedback therapy is an important tool in the treatment of postpartum third degree tears, although compliance is an issue and is often dependent on symptom severity.

037 AUTOPHAGY PROTECTS COLON CANCER CELLS AGAINST STRESS-INDUCED DEATH

Aleksandra Bartnik, Shi Yu Yang, Anur Miah, Yi Wei Chen and Marc Winslet
University College London

Introduction

Autophagy is a cellular process of auto-digestion, which involves recycling of excess proteins and destruction of old organelles. It serves maintenance of homeostasis and acts as an alternative cell death mechanism. Increased autophagy has been observed in several cancers including colorectal. However, the role of autophagy in cancer growth remains unclear. Here we show that induction of autophagy by cellular stress in colon adenocarcinoma cells has a pro-survival effect.

Methods

HT-29 cells were subjected to cellular stress by treatment with p38 inhibitor in DMSO* solution alone and in combination with autophagy inhibitor, Bafilomycin A1. Dose-dependent and time-dependent effects were investigated. Proliferation, morphology and expression of autophagic marker LC3 were examined using CellTiter-Blue® cell viability assay, electron microscopy and immunocytochemistry, respectively.

Results

Electron microscopy showed dose-dependent and time-dependent induction of autophagy in response to cellular stress. Autophagy was identified by the appearance of characteristic vacuoles in the cytoplasm. Increasing vacuole size correlated with reduced volume of the cytoplasm and reduced number of mitochondria. Electron microscopy findings correlated with expression of the autophagic marker. In the absence of biological stress, inhibition of autophagy conferred a significant growth advantage to the cells ($p<0.0005$). In contrast, in cells subjected to biological stress, inhibition of autophagy markedly reduced cell viability compared to control ($p<0.001$). Conclusion: We demonstrate a dual role of autophagy in colon cancer cells, pro-survival under biological stress and pro-death under normal conditions. *DMSO - dimethyl sulfoxide

Take-home message

Targeting of autophagy for anticancer therapy is a viable perspective and requires further investigation.

038 THE ROLE OF P38 MAPK PATHWAY IN HUMAN COLON CANCER CELL RESISTANCE TO 5-FLUOROURACIL

Yi-Wei Chan, Anur Miah, Ola Bartnik, Barry Fuller, Marc Winslet, Shi-Yu Yang

Division of Surgery and Interventional Science, Royal Free Hospital and University College London Medical School, London

Introduction

Although 5-fluorouracil (5-FU) has been widely used in the treatment of patients with advanced colon cancer, its therapeutic effect is often constrained by various chemoresistance mechanisms. Recent evidence suggests that the stress-activated p38 mitogen-activated protein kinase (MAPK) pathway is involved in oncogenic behaviour of colon cancer cells and may therefore be used as a target to potentiate 5-FU effect.

Methods

5-FU sensitive SW620 and 5-FU resistant HT29 cells were treated with p38 MAPK inhibitor (SB203580) as a single agent or in combination with 5-FU and then evaluated using CellTiter Blue Cell Viability Assay, inverted microscopy, immunofluorescence and Western blot.

Results

We found that inhibition of p38 MAPK alone tended to increase SW620 cell growth but reduced HT29 cell survival. In combination therapy, p38 MAPK inhibitor suppressed the inhibitory action of 5-FU in SW620 cells by 17.6% ($P=0.029$) but was able to enhance the effect of 5-FU in HT29 cells with an additional gain in inhibition of 19.7% ($P=0.005$). Furthermore, autophagy was significantly induced in p38 MAPK inhibitor-treated HT29 cells and seems to be a possible mechanism of sensitisation to 5-FU.

Conclusion

Taken together, our results suggest that p38 MAPK is involved in colon cancer cell homeostasis following 5-FU treatment, and manipulation of the p38 MAPK pathway can augment colon cancer cell sensitivity to 5-FU treatment.

Take-home message

p38 MAPK is involved in colon cancer cell resistance to 5-FU treatment and manipulation of the p38 MAPK pathway can improve the efficacy of 5-FU in killing colon cancer cells.

O39 REGIONAL VARIATION IN UREA TRANSPORTER EXPRESSION IN HUMAN COLON- A NOVEL CONTRIBUTION TO BACTERIAL SYMBIOSIS?

D Collins^{1,2}, AM Hogan^{1,2}, E Ryan^{1,2}, AW Baird¹, GS Stewart¹, DC Winter²

(1) University College Dublin, (2) St. Vincent's University Hospital, Dublin

Background

Differences between the right and left colon extend beyond that of an alternative embryological origin. Mechanisms of ion transport and composition of bacterial populations differ along the colon, however, the functional relevance of these findings have yet to be elucidated. Urea provides a nitrogen source for commensal bacteria enabling them to produce important nutrients for the host ("urea-nitrogen salvaging process").

Aims

We hypothesised that the higher bacterial populations found in proximal colon are due to increased availability of urea on the right side. Methods: A combination of immunohistochemistry and immunoblot analysis for the facilitative urea transporter UT-B and Ussing chamber experiments to measure urea flux were used to determine differences between proximal and distal colon in ex vivo human tissue.

Results

The 35 kDa UT-B transporter was predominantly located in plasma membrane-enriched samples ($P < 0.001$, $N = 6$) with greater expression in right colon ($P < 0.01$, $N = 3$). At the cellular level, UT-B transporters were located throughout colonocytes situated in the upper portion of colonic crypts. Bidirectional trans-epithelial urea transport was significantly higher in right colon ($P < 0.05$, $N = 6$). In addition, UT-B inhibition significantly reduced urea transport in the right colon ($P < 0.05$, $N = 6$) but had no effect in the left colon (NS, $N = 6$).

Conclusion

This study identifies regional differences in urea transport and receptor expression in human colon such that the majority of urea transport occurs in the ascending colon where bacterial populations are highest.

Take-home message

This study identifies regional differences in urea transport and receptor expression in human colon such that the majority of urea transport occurs in the ascending colon where bacterial populations are highest. Colonic UT-B transporters may therefore represent a potential target to manipulate colonic bacterial populations in health and disease.

O40 MICRORNAS ARE DIFFERENTIALLY EXPRESSED IN THE CIRCULATION OF COLORECTAL CANCER PATIENTS COMPARED TO HEALTHY CONTROLS

M Nugent, KH Chang, EAH Kheirleiseid, N Miller, OJ McAnena, M Regan, MJ Kerin

University Hospital Galway

Introduction

Mi(cro)RNA expression profiles have been shown to differ between tumour and normal tissue in colorectal cancer. Recent work has shown that circulating miRNAs in breast cancer reflect these alterations, however there are few reports regarding miRNAs in the circulation of colorectal cancer patients. In view of the limited sensitivity and specificity of available tumour markers for colorectal cancer, there is a need for new non-invasive biomarkers. The aim of this study was to investigate the differential expression of 8 miRNAs in the circulation of colorectal cancer patients compared to controls.

Methods

Blood samples were collected from 63 patients and 45 controls. Candidate miRNAs (miR-10b, miR-143, miR-145, miR-21, miR-30a-3p, miR-31, miR-34a, miR-92) were selected based on previously demonstrated expression profiles in colorectal cancer tissues and expression was measured using RQ-PCR. MiRNA expression data was correlated with clinicopathological data and statistical analysis was performed.

Results

Analysis of mean expression levels revealed significant ($p=0.001$) overexpression of miR-21 in the cancer cohort compared to controls. MiR-21 levels were greater in those with more advanced disease, although this did not reach statistical significance. In addition there was a trend towards lower levels of miR-34a in the cancer group ($p=0.063$).

Conclusion

This study demonstrates significant differential expression of miR-21 in the circulation of colorectal cancer patients compared to controls. In addition, this is the first report of altered expression levels of the colorectal cancer specific miR-34a in the circulation which may have diagnostic, screening and therapeutic implications.

Take-home message

Circulating miRNA levels in colorectal cancer patients are altered compared to controls. This may have diagnostic, screening and therapeutic implications.

041 PARAMETRIC SURVIVAL ANALYSIS AND PREDICTIVE MODELS FOR PROPHYLACTIC SURGERY IN FAMILIAL ADENOMATOUS POLYPOSIS

A.Sinha¹, PP Tekkis², RKS Phillips¹, SK Clark¹

(1) Polyposis Registry, St Marks Hospital & Imperial College, London (2) Royal Marsden Hospital & Imperial College, London

Introduction

Colectomy and ileo-rectal anastomosis (IRA) or restorative proctocolectomy (RPC) are performed for prophylaxis in familial adenomatous polyposis (FAP). Post-IRA patients may require proctectomy for worsening polyposis or rectal cancer. Outcomes post-IRA was evaluated and predictive models developed, identifying patients at risk of progressive rectal disease.

Methods

Parametric survival analysis was used to identify predictors of progressive rectal disease and develop the model. Hazard ratios (HR) were calculated for phenotype, genotype, gender, age at surgery and presence of colonic cancer.

Results

427 patients underwent IRA, 48(11%) developed rectal cancer and 77(18%) required proctectomy for worsening polyposis over a median follow-up of 15(7-25) years. 50% retained a healthy rectum at age 60. Rectal polyp count >20 (HR3.1, 95% CI 1.6-6.0, $p<0.0001$), APC mutation codon 1250-1450 (HR3.9, 95%CI 1.5-10.5, $p=0.007$), colonic polyp count >500 (HR2.2, 95%CI 1.2-3.8, $p=0.006$) and age at surgery <25 (HR2, 95%CI 1.2-3.4, $p=0.011$) were independent predictors of progressive rectal disease. The rectal retention index (RRI) yields a maximum score of 5 based on these variables. The genotype model awards 1 point for codon 1250-1450 mutation, 1 point for age at surgery <25 and 0,2,3 points for rectal polyp count <5, 5-20 or >20 respectively. Where mutation analysis is unavailable, the phenotype model is applied and 1 point awarded for colonic polyp count >500. A RRI >3 was associated with a significantly worse rectal outcome.

Conclusion

The RRI identifies FAP patients at high risk of proctectomy or rectal cancer post-IRA based on genotype, phenotype and age at surgery and can inform surgical decision making.

Take-home message

1. The rectal retention index, an evidence-based model determined by patient genotype, phenotype and age at surgery, can inform the surgical decision making process for prophylaxis in familial adenomatous polyposis. 2. Patients with rectal retention index of 3 or less, have good rectal survival and are better served by IRA. Patients scoring 5, require an RPC. Patients with a score of 4, could have an IRA but are at an increased risk of requiring secondary proctectomy.

O42 GENOME-WIDE METHYLATION PROFILING OF RECTAL TUMOURS IDENTIFIES NOVEL MARKERS OF EARLY STAGE DISEASE

KJ Leong^{1,2}, LA Tannahill¹, W Wei¹, GM Caldwell¹, CE Jones¹, GM Matthews¹, DG Morton^{1,2}, SP Bach^{1,2}

(1) School of Cancer Sciences, University of Birmingham, Birmingham, UK. (2) Academic Department of Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, UK.

Background

Aberrant DNA methylation could predict disease progression in rectal cancer, enabling personalised therapy to be developed. Using three quantitative platforms to characterise DNA methylation during tumourigenesis, we correlated methylation patterns with clinicopathological indices of disease progression.

Methods

The study consisted of 115 rectal samples (19 normal controls, 10 adenomas, 35 tissues adjacent to tumour and 51 adenocarcinomas). Genome-wide screening was performed using the Nimblegen promoter array in a subgroup of rectal samples and validated by bisulphate Pyrosequencing. Differentially methylated genes were identified using the two-step TileMap approach. Methylation of 24 tumour suppressor genes was then quantified using the methylation-specific multiplex ligation-dependent probe assay (MS-MLPA) and correlated with clinicopathological features.

Results

1324 genes were hypermethylated in neoplasia compared to normal controls. 523 genes were hypermethylated uniquely in adenoma; 218 in early and 286 in advanced tumours ($p < 0.01$). The number of hypermethylated genes preserved during transformation of adenoma to early and advanced tumour was reduced in a stepwise manner (773/107/81, $p < 0.01$). 5 genes identified to be hypermethylated in neoplasia was confirmed by Pyrosequencing ($p < 0.01$). Using MS-MLPA, ESR1, CDH13, CHFR, APC and RARB were found hypermethylated in tumour compared to adjacent tissue and normal controls ($p < 0.05$). Hypermethylation of ≥ 2 of APC, RARB, TIMP3, CASP8 and GSTP1 was associated with node-negativity and absent distant metastasis ($p < 0.05$).

Conclusion

DNA methylation is more prevalent in early disease. We have described a panel of tumour suppressor genes that is associated with localised disease. This may select for biologically indolent tumours, enabling selection for local surgery.

Take-home message

Molecular markers that provide biological information of rectal tumour may guide selection of surgical options.

ORAL PRESENTATIONS 1C ONCOLOGY

O43 DISRUPTION OF MICRORNA EXPRESSION TIPS CELLULAR REGULATION TOWARDS A CARCINOGENIC PHENOTYPE

A.C.Lee, I. Bhatti, C.Tufarelli, M. Larvin and J.N. Lund

University of Nottingham

Introduction

MicroRNAs (miRs) are short RNAs which regulate translation. Aberrant miR expression has been reported in all carcinomas studied. Individual miRs target a large repertoire of genes and the disruption of miR expression often impinges on cellular processes such as proliferation and death. The challenge ahead is to elucidate the targets of aberrantly expressed miRs and their contribution to carcinogenesis.

Methods

Expression of miR-31, -143, -145, -21 and -191 were examined in 15 colorectal tumours, matched controls and 4 cell lines by real-time PCR. The effects of aberrant miR expression were determined using inhibitors of miR-21 and artificial RNA to mimic miR-143 in cells. We then quantified the expression of PDCD4 and DNMT3B targets of miR -21 and -143 respectively. To control for total miR activity we depleted TNRC6A, (required for miR function) by shRNA.

Results

Colorectal tumours and cell lines demonstrated upregulation of miR-21, whilst miR-143, 145 and 191 were downregulated. In contrast, miR-31 expression was variable. Inhibition of miR-21 increased expression of PDCD4, as did depletion of TNRC6A, confirming PDCD4 is targeted by miRs, specifically miR-21. PDCD4 promotes cell death, thus increased miR-21 expression may enhance cell survival a tumorigenic characteristic. Mimicry of miR-143, decreased DNMT3B expression. Depletion of TNRC6A increased DNMT3B expression confirming DNMT3B is also regulated by miRs, specifically -143. DNMT3B elicits gene silencing, thus miR-143 likely impacts upon an additional mechanism linked with carcinogenesis.

Conclusion

Our data demonstrates modulation of miR expression affects the complement of cellular proteins likely impacting cell regulation, potentially contributing to carcinogenesis.

Take-home message

Modulating microRNA expression in the cell can impact on carcinogenic phenotypes.

O44 PATIENTS WITH OESOPHAGEAL CARCINOMA AGED LESS THAN 50 YEARS HAVE IMPROVED SURVIVAL

CL Donohoe, E McGillicuddy, JV Reynolds

Dept of Surgery, Trinity Centre for Health Sciences, St James' Hospital, Dublin

Introduction

It is not known whether patients diagnosed with oesophageal carcinoma aged younger than fifty years have a more aggressive disease phenotype and thus poorer outcomes following treatment.

Methods

Prospectively maintained database records of oesophageal carcinoma patients (n= 2129) over a twenty year period (1990-2009) were analysed. Patients aged less than fifty years at diagnosis (n= 170) were compared to those over fifty years.

Results

Patients were more likely to be male (77.4 versus 64.7%, p=0.001), diagnosed with an oesophagogastric junction tumour (p=0.002) and to have symptoms for a longer period prior to diagnosis (24.0 versus 17.8 weeks, p=0.03) if aged less than fifty years. There were no significant differences in clinicopathological staging. Younger patients were more likely to be treated with curative rather than palliative intent (66.9 versus 51.1%, p<0.001). The disease-specific survival of patients younger than 50 years treated with curative intent is significantly greater than older patients (median 35 versus 21 months, p=0.04). A subset of patients aged less than 35 years (n=18) had poorer outcomes than those 35-50 years and over 50 years. Multivariate analysis revealed independent factors related to the difference in survival observed between the age groups included advanced T stage, nodal metastases and perineural invasion (p<0.05), although age itself was not an independent variable.

Conclusion

A proportion of oesophageal cancer patients are diagnosed aged less than 50 years old. With an aggressive approach to management, survival is significantly greater than in the older cohort, although outcomes are poorer in those aged under 35 years.

Take-home message

Patients aged less than 50 years, treated aggressively, have improved survival compared to those over 50 years, which may relate to differences in biological parameters between the groups. Those aged less than 35 years have poorer outcomes than older groups.

O45 NANOPARTICLES FOR CANCER TREATMENT: APPLICATION OF LECTIN (GLYCOPROTEIN) IN THE DELIVERY OF CARBON NANOTUBES TO THE BREAST CANCER CELL

Yazdan Madani¹, Sana Khan¹, Miriam Dwek², Alexander Seifalian¹

(1) University College London, (2) University of Westminster

Introduction

Carbon Nanotubes (CNT) have novel properties that make them potentially useful in cancer treatment, such as the ability to absorb the NIR light and convert the absorbed energy into the heat as well as drug delivery applications. The aim of this experiment is to investigate the ability of Lectin on the deliver of the CNT to the Breast Cancer Cells.

Method

CNT was functionalised by refluxing these materials in 1:3(HNO₃/H₂SO₄) at 120°C for a period of 120minutes. TEM, FTIR and NIR light were used to determine the functionalisation of the CNT. F-CNTS were conjugated to the FITC-Lectin and the Confocal Microscopy images were used to determine the conjugation. Interaction of the Lectin only and Lectin with F-CNT to the breast cancer cells were measured by using Quartz Crystal Microbalance technique.

Results

A thin layer on the CNT showed by the TEM images, confirmed the functionalisation of the CNT. In the FTIR experiment, Succinic acid(containing -COOH group), Succinic Acid with F-CNT and pure CNT were analyzed. Results determined high intensity of the (-COOH) group on the Succinic acid with F-CNT. Also the temperature increase of the supernatant part of the F-CNT following the exposure to NIR light was far greater than the normal CNT. QCM results showed that the interactions of the Lectin to the breast cancer cells were not significantly altered by its attachment to the CNT.

Conclusion

Lectin would be a suitable candidate for the delivery of the F-CNT to the breast cancer cell.

Abbreviations

CNT: CARBON NANO TUBES F-CNT: FUNCTIONALISED CARBON NANOTUBES QCM: QUARTZ CRYSTAL MICROBALANCE TEM: TRANSMISSION ELECTRON MICROSCOPY

Take-home message

Carbon nanotubes could be used for the treatment of cancer by thermal treatment or delivering the anticancer drugs to the site of action.

O46 IN-VITRO CHARACTERISTICS OF DESMOID TUMOUR CELLS IN FAMILIAL ADENOMATOUS POLYPOSIS

A SINHA¹, RKS PHILLIPS¹, C LINGE², I KILL³, SK CLARK¹

1. Polyposis Registry, St Marks Hospital & Imperial College, London 2. RAFT Institute of Plastic Surgery, Mount Vernon Hospital, London 3. Brunel University, London

Introduction

Desmoid tumours (DT) are non-metastatic, locally infiltrative, monoclonal proliferations occurring in familial adenomatous polyposis (FAP). They display a variable clinical course, 10% grow causing mortality. This study established primary desmoid cell cultures and identified markers of aggressive disease.

Methods

Primary DT cell cultures were established using explant tissue culture technique. Following ethical approval, DT cell lines (n=5) were established and compared to mesenteric FAP fibroblast cell lines (n=2) and non-FAP human foreskin fibroblast (n=1). Immunocytochemistry panel, including β -catenin and α -smooth muscle actin (SMA) was performed. Cellular senescence was studied using proliferative markers Ki-67 and PCNA. Cellular traits were characterised using cell based migration and contraction assays.

Results

Increased nuclear accumulation of β -catenin in DT cells (mean78.6 \pm SD8.86%) compared with FAP fibroblasts (10.5 \pm 5.23%) and non-FAP fibroblasts (12.2 \pm 4.84%) was seen ($p < 0.0001$). Increased cytoplasmic α -SMA was detected in DT cells (80.1 \pm 8.47%) compared with FAP fibroblasts (14.9 \pm 1.95%) and non-FAP fibroblasts (11.4 \pm 3.41%) ($p < 0.0001$).

DT cells displayed aberrant migration response compared with controls. Over passages, a greater proportion of DT cells were in the growth phases of the cell cycle compared to controls, demonstrating immortality in culture. PCNA over-expression was associated with aggressive DT phenotype ($p < 0.0001$).

Conclusion

This study provides a robust in-vitro model for studying DT tumourigenesis. It confirms that DT cells harbour second hit APC mutation leading to aberrant Wnt signalling and nuclear β -catenin accumulation. The ubiquitous expression of α -SMA confirms the myofibroblastic nature of DT cells. DT, like cancer cells, display an escape from cellular senescence in-vitro.

Take-home message

1. An in-vitro model of desmoid tumour cells is described, previous attempts have proven difficult.
2. Beta-catenin and alpha-smooth muscle actin are ubiquitous in desmoid tumour cells. PCNA expression could predict aggressive phenotype.
3. Desmoid tumour cells are immortal in culture.

047 ONCOLYTIC VIROTHERAPY IN AN IN VIVO MODEL OF ISOLATED LIMB PERFUSION FOR ADVANCED EXTREMITY SARCOMA

Tim Pencavel^{1,2}, Kevin Harrington², Andrew Hayes¹

1: Sarcoma/Melanoma Unit, Dept of Academic Surgery, Royal Marsden Hospital. (2) Targeted Therapy Team, The Institute of Cancer Research

Introduction

Isolated Limb Perfusion (ILP) allows for limb salvage in patients with advanced extremity sarcoma. However it has no effect on distant disease. Oncolytic viral therapy displays tumour response and immune priming in preclinical models but systemic administration is problematic due to attenuation of administered viruses.

Methods

We have previously described the establishment of the ILP model. To this we have added oncolytic Vaccinia virus (VV), alone and in combination with standard ILP agents (TNF- α /melphalan). Tumour response is assessed by direct calliper measurement with an endpoint of time to severity limit. Tumour and organ samples were taken to establish the biodistribution characteristics of the virus after ILP.

Results

Untreated animals have a median survival time of 10 days, with a non-significant increase to 11 days after non-therapeutic ILP. The addition of 1×10^7 plaque-forming units of VV increases median survival to 17.5 days ($p < 0.001$). Perfusion with melphalan and VV further increases survival, to a median time of 21 days ($p < 0.001$). Tumour growth rates are also inhibited. Biodistribution assays using X-gal staining and qPCR for viral DNA show virus consistently within the perfusion field at 24, 48 and 72 hours, and at significantly lower levels systemically at 48 hours, a likely reflection of intratumoural viral replication and consequent haematogenous dissemination of virus.

Conclusion

Tumours respond to oncolytic VV, and are consistently infected with VV post-operatively. Future work will focus on the role of TNF in the setting of tumour-associated vasculature and microscopic residual disease models, as well as evaluating other oncolytic agents.

Take-home message

In a microscopic residual disease (MRD) model:

- Survival time is significantly prolonged
- Tumours grow more slowly
- Combination treatment with melphalan and virus is more efficacious than virus alone Virus is recoverable from the perfusion field:
- At titres that indicate successful viral replication
- With minimal systemic spread

048 HUNTINGTIN INTERACTING PROTEIN 1 (HIP1) INDUCES EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT) IN PROSTATE CANCER CELLS

Rao R B, Wang J, Ittmann MM, Neal D, Mills IG

CRUK Cambridge Research Institute

Background

HIP1, an adaptor protein classically involved in clathrin mediated endocytosis, is overexpressed in prostate cancer (CaP) and believed to drive fibroblast and prostate epithelial cell transformation by perturbing growth factor signalling. It also translocates to the nucleus and has a role as an androgen receptor coactivator.

Methods

To explore its role in CaP we used HIP1 overexpressing (HIP1+) PNT1a and LNCaP cell lines in functional assays, gene expression arrays, and real-time PCR.

Results

HIP1 overexpression in PNT1a, an immortalised epithelial cell-line, induced transformation as determined in an anchorage independent growth assay. HIP1 overexpression in LNCaP cells, an androgen-dependent CaP cell-line, resulted in significantly increased adhesion to fibronectin. These observations suggest HIP1 overexpression induces mesenchymal transition. Epithelial-to-Mesenchymal Transition (EMT) is associated with increased propensity for cell migration, invasion, and metastasis. EMT markers such as Wnt7b, Snail, and Vimentin were >2 fold upregulated in HIP1+ lines. HIP1+ lines also showed significant upregulation of GDF15- a secreted TGF β superfamily member. GDF15 has been implicated in drug resistance and as a biomarker for CaP prognosis. LNCaPs cultured in conditioned media from HIP1+ LNCaP showed significantly increased growth compared to controls, which was abrogated by a GDF15 antibody. HIP1+ PNT1a cell lines also showed taxol resistance in soft agar colony formation assays.

Conclusion

We believe HIP1 overexpression causes GDF15 upregulation which contributes to CaP progression and drug resistance through the induction of EMT. Future work will assess whether HIP1 and GDF15 are co-expressed in clinical samples and whether HIP1 expression is a predictor of chemoresistance.

Take-home message

Huntingtin interacting protein 1(HIP1) expression may be used as a marker for predicting chemoresistance in prostate cancer.

O49 C-MYC INDUCTION OF HES6 ACTIVATES A DISTINCT TRANSCRIPTIONAL NETWORK DRIVING ANDROGEN INSENSITIVE PROSTATE CANCER

Alastair Lamb*, Antonio Ramos-Montoya*, Maria Vias, Helen Scott, Ian Mills†, David Nealt
CRUK Uro-Oncology Research Group, Cambridge Research Institute

Summary

Castrate resistant prostate cancer (CRPC) has been shown to exhibit a state of altered differentiation, which may involve acquisition of 'stem-like' properties, or possibly a neuroendocrine phenotype, with expression of notch pathway related basic helix-loop-helix transcription factors (bHLH) in both human tissue and mouse models. c-Myc is a well known oncogene in prostate cancer and induces survival of androgen-dependent LNCaP cells in androgen deprived conditions. In normal tissues, c-Myc induces stem cell differentiation into specific lineages. The lineages of the normal prostate are now characterised and it is becoming clear that CRPC does not display the typical "luminal phenotype". We have now shown using quantitative PCR and chromatin immunoprecipitation that expression of bHLH transcription factor, Hes6, is up-regulated in response to activated c-Myc. Furthermore, cell growth assays show that like c-Myc it can deliver androgen-independence in androgen-dependent LNCaP cells, a finding that is being followed up in vivo. Expression profiling of these androgen-independent LNCaP-Hes6 cells reveals increased levels of transcripts regulating cell-cycle progression such as AURKA/B, CDK1, PLK1, MELK, and UBE2C. This signature exquisitely clusters aggressive and poor outcome human disease. Given that normal prostate cancer cells rely on the androgen receptor (AR) promoting G1-S cell cycle transition and progression, identification of these targets suggests that Hes6 acts by 'priming' cell cycle progression, creating a phenotype that is independent of standard AR signalling for continued growth. This raises the possibility that pharmacological inhibition of these Hes6 cell cycle targets could rescue AR dependence and augment standard androgen blockade.

Take-home message

c-Myc upregulates Hes6 to evoke a distinct transcriptional phenotype in prostate cancer cells that is partially responsible to androgen insensitive prostate cancer.

O50 THICK MELANOMA - ARE WE DOING THE RIGHT THING?

J Kelly & HP Redmond
Cork University Hospital

Aims

To evaluate the role, if any, of sentinel lymph node mapping (SLNM) with biopsy (SLNB) in patients with thick cutaneous melanoma.

Methods

Consecutive patients with thick (Breslow \geq 4mm) cutaneous melanoma, undergoing SLNB were identified from a departmental database comprising 550 patients in total from 2000-2010. Factors examined included demographic data, histological subtype, site and depth of lesion, percentage of positive SLNs, regional recurrence in the setting of a negative SLNB result (false-negative rate), complications, further lymphadenectomy, and follow-up (disease free and overall survival), where available.

Results

Sixty-four patients (37 men, 27 women) underwent primary excision and SLNM. Median patient age was 59 years (range 8-82 years). Mean Breslow depth was 7mm (range 4-19 mm). Thirty melanomas were located on the limbs, 19 on the head and neck and 15 on the trunk. Twenty-three (35%) were ulcerated. Of the 57 patients, 18 (31%) had metastatic melanoma identified. The mean survival time for patients with a negative SLN was 79 months versus 18 months for those with a positive node (log rank $p < 0.001$). Patients with a negative SLN have a 5 year disease free survival of 79% versus 11% ($p < 0.001$) and an overall 5 year survival rate of 85% versus 32% when compared to node positive patients.

Conclusion

The status of the SLN is predictive of disease recurrence and overall survival in patients with a thick primary cutaneous melanoma. This modality should be employed routinely in this cohort of patients.

Take-home message

The status of the sentinel node is predictive of disease recurrence and overall survival in patients with a thick primary cutaneous melanoma.

O51 THE RS10993994 RISK ALLELE FOR PROSTATE CANCER RESULTS IN CLINICALLY RELEVANT CHANGES IN MICROSEMINOPROTEIN-BETA EXPRESSION IN TISSUE AND URINE

Hayley C. Whitaker^{1†}, Zsofia Kote-Jarai², Helen Ross-Adams¹, Anne Y. Warren³, Rosalind Eeles², David E. Neal¹

1 Uro-Oncology Research Group, Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE, 2 The Institute of Cancer Research, 15 Cotswold Rd, Belmont, Sutton, Surrey, SM2 5NG, 3Department of Pathology, Addenbrookes Hospital, Cambridge, CB2 0QQ.

Background

Microseminoprotein-beta (MSMB) regulates apoptosis and using genome-wide association studies the rs10993994 single nucleotide polymorphism in the MSMB promoter has been linked to an increased risk of developing prostate cancer. The promoter location of the risk allele, and its ability to reduce promoter activity, suggested that the rs10993994 risk allele could result in lowered MSMB in benign tissue leading to increased prostate cancer risk.

Methodology/principle findings

MSMB expression in benign and malignant prostate tissue was examined using immunohistochemistry and compared with the rs10993994 genotype. Urinary MSMB concentrations were determined by ELISA and correlated with urinary PSA, the presence or absence of cancer, rs10993994 genotype and age of onset. MSMB levels in prostate tissue and urine were greatly reduced with tumourigenesis. Urinary MSMB was better than urinary PSA at differentiating men with prostate cancer at all Gleason grades. The high risk allele was associated with heterogeneity of MSMB staining and loss of MSMB in both tissue and urine in benign prostate.

Conclusion

These data show that some high risk alleles discovered using genome-wide association studies produce phenotypic effects with potential clinical utility. We provide the first link between a low penetrance polymorphism for prostate cancer and a potential test in human tissue and bodily fluids. There is potential to develop tissue and urinary MSMB for a biomarker of prostate cancer risk, diagnosis and disease monitoring.

Take-home message

These data show that some high risk alleles discovered using genome-wide association studies produce phenotypic effects with potential clinical utility. We provide the first link between a low penetrance polymorphism for prostate cancer and a potential test in human tissue and bodily fluids.

O52 PROGESTERONE RECEPTOR STATUS IN BREAST CANCER PATIENTS: ASSOCIATION WITH DISEASE CHARACTERISTICS AND PATIENT SURVIVAL

Coll J, Healy NA, Coyne J, Malone C, McLaughlin R, Sweeney K, Kerin MJ

Department of Surgery, National University of Ireland, Galway

Introduction

NICE Guidelines published in February 2009 state that the progesterone receptor (PR) status of invasive breast cancer should not be routinely assessed. As a result the significance of the progesterone receptor has been widely debated. The objective of this study was to compare tumour-specific features and survival rates of breast cancer tumours depending on their oestrogen and progesterone receptor status.

Methods

Patients diagnosed with breast cancer between 1995 and 2005 were selected from a prospectively maintained database. ER and HER2/neu status, age, grade, stage of disease were recorded. During this period hormone receptor status was determined using immunohistochemistry. Disease free and overall survival was determined for each of the patients. Statistical analysis was performed using SPSS.

Results

1190 patients were diagnosed with breast cancer between 1995 and 2005. Of these 851 had both ER and PR assessed. 468 (55%) patients were designated ER+/PR+, 119 (14%) ER+/PR-, 77(9%) ER-/PR+ and 187(22%) ER-/PR-. Those patients in the ER+/PR- group were older than patients in the other groups with a mean age of 63.75 ($p < 0.001$). Patients designated ER- were more likely to have a higher grade of disease ($p < 0.001$). ER+/PR+ tumours had a higher proportion of HER2/neu negative tumours than the other 3 groups ($p < 0.001$). Patients in the ER-/PR+ group had a distinct survival advantage at 5 years follow-up.

Conclusion

This study highlights the importance of the PR in predicting response to therapy and association with aggressive phenotype and suggests a role for individualised treatment depending on hormone receptor status.

Take-home message

This study illustrates that the PR is an important indicator in predicting response to therapy in breast cancer and should be routinely assessed.

053 THE INHIBITION OF GLYCOLYSIS USING A PYRUVATE DEHYDROGENASE KINASE II INHIBITOR INDUCES APOPTOSIS AND SENSITISES MELANOMA CELLS TO TEMOZOLOMIDE

O'Leary DP, Hallihan P, Wang JH, Redmond HP
Cork University Hospital

Introduction

Metastatic melanoma has a poor prognosis and remains a therapeutic challenge. This has been partly attributed to the high mitochondrial membrane potential of melanoma cancer cells which renders them resistant to apoptosis.

Aims

(i) to investigate the effect of the pyruvate dehydrogenase kinase inhibitor, sodium dichloroacetate (DCA), which normalises mitochondrial membrane potential, on melanoma cell survival (ii) to investigate if DCA sensitises melanoma cell lines to temozolomide (iii) to study the mechanisms by which DCA induced apoptosis

Methods

The melanoma cell lines B164A5 & MeWo were used. Cellular glycolysis and oxidative phosphorylation were measured with luminescent oxygen and pH-sensitive probes. Cell viability and apoptosis were examined using the resazurin assay and FACScan analysis. Caspase 3, 7 and 9 activity and mitochondrial membrane potential were determined by the Caspase-Glo Assay and flow cytometry. Cytochrome c activation was assessed using confocal microscopy. Bax and bcl-2 expression was examined using western blot.

Results

DCA treatment resulted in a decrease in cell viability and increased apoptosis that was both dose/time-dependent. DCA also normalised the mitochondrial membrane potential, induced cytochrome c release and activated caspase 3, 7, and 9 which occurs in a mitochondrial permeability transitional pore independent manner. DCA also sensitised the melanoma cells to the alkylating agent Temozolomide and induced cell death.

Conclusion

DCA inhibits glycolysis in melanoma cells and causes activation of the mitochondrial-induced apoptotic pathway. It also sensitises melanoma cell lines to Temozolomide. Thus manipulation of glycolysis in metastatic melanoma cells may be a potential therapeutic target

Take-home message

Manipulation of glycolysis in metastatic melanoma cells may be a potential therapeutic target

054 IMMUNOHISTOCHEMISTRY CONFIRMS DOWNREGULATION OF PROTEIN MARKERS ASSOCIATED WITH RESISTANCE TO RADIOTHERAPY

Dalia ELFadl^{1,2}, Victoria Hodgkinson², Ervine Long³, Andrew W Beavis^{2,4}, Philip J Drew^{2,5}, Michael J Lind^{2,4,5} and Lynn Cawkwell^{2,5}

1. Academic Surgical Unit, University of Hull, UK. 2. Cancer Biology Proteomics Group, Post Graduate Medical Institute, University of Hull, UK. 3. Histopathology Department, Hull Royal Infirmary, Hull, UK. 4. Queens Centre for Oncology and Haematology, Castle Hill Hospital, Hull, UK. 5. Hull York Medical School, UK

Introduction

Adjuvant radiotherapy is integral in treating early stage breast cancer. Resistance to radiotherapy may contribute to locoregional recurrence. We previously created 5 radioresistant cell sublines (breast and oral cancer) and applied proteomic antibody microarray technology and western blot to identify potential markers of resistance. Here, we aimed to confirm differential expression using immunohistochemistry in a retrospective series of clinical samples.

Methods

Ethics approval was obtained. A retrospective series was selected using clinical and pathology records. Patients who had locoregional recurrence within four years of breast conserving therapy constituted a radioresistant (test) group. Those with known risk factors of recurrence were excluded. A radiosensitive (control) group included patients who were disease free at 10 years. The two groups were matched with regards to age, tumour type, size, grade, DCIS and ER status. Potential markers were selected for clinical validation. Standard immunohistochemistry was performed on archival tissue. Slides were scored by two independent investigators.

Results

31 samples were included (15 test group, 16 control group). Four potential markers were tested. Two; DR4 and 26S proteasome, showed down-regulation of expression in the radioresistant group. This was statistically significant ($p=0.0187$ and 0.0032 respectively - Fisher's exact), and confirmed proteomic results. Importin- α and PIASx were downregulated in 66% and 70% of samples respectively, and there was no difference between the two groups.

Conclusion

Immunohistochemistry has successfully confirmed DR4 and 26S proteasome as markers of resistance. Further studies utilising larger sample numbers are needed. These proteins could have important roles as predictive biomarkers.

Take-home message

Downregulation of biomarkers has been confirmed using immunohistochemistry. Their involvement in the radioresistance pathways could be beneficial in prognostication and treatment planning in cancer patients.

055 PRE-OPERATIVE NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC INDICATOR IN URINARY BLADDER CANCER

J. S. Rai, P. Ravindra, S.A.Thomas, H. L. Ratan

Royal Derby Hospital, Derby, UK

Introduction

Elevated pre-operative neutrophil to lymphocyte ratio (NLR) has been identified as a predictor of survival in patients with hepatocellular and colorectal cancer. The aim of this study was to examine the prognostic value of an elevated preoperative NLR following radical surgery for urinary bladder cancer.

Methods

Patients who underwent resection for urinary bladder carcinoma from October 1999 to December 2008 were identified from a local cancer database. Data on demographics, conventional prognostic markers, laboratory analyses including blood count results, and histopathology were collected and analysed using SPSS software.

Results

A total of 106 patients were identified undergoing radical cystectomy for bladder cancer with a median age at diagnosis of 66 (IQR 61-72) years. The mean pre-operative time of blood sample collection was 6 days (IQR 1-8). The average neutrophil count was 5.52×10^9 /litre, average lymphocyte count 1.85×10^9 /litre, whilst the average NLR was 2.21 (IQR 1.38-2.61). NLR was demonstrated to be a significant predictor of lymph node involvement ($p < 0.001$), disease recurrence ($p < 0.001$) and death ($p < 0.001$).

Conclusion

Preoperative NLR appears to offer useful predictive ability for lymph node involvement, disease-free and overall survival following resection in urinary bladder cancer. This study demonstrates the possibilities of further work into use of NLR as a simple and very cost effective prognostic tool.

Take-home message

The pre-operative neutrophil to lymphocyte ratio in patients with urinary bladder cancer is an important predictor of lymph node involvement, disease recurrence and death. It is potentially a simple and very cost effective prognostic tool.

O56 A POTENTIAL ROLE FOR IRON AND HAEM IN BREAST CANCER

Thomas Roe, Fiona Hoar, Chris Tselepis

Birmingham University Institute for Cancer Sciences

Introduction

Overwhelming evidence implicates iron in gastrointestinal carcinogenesis. It is unclear is whether this association is confined to gastrointestinal malignancies or whether iron represents a generic carcinogen in all cancers.

Methods

Expression of iron import (TfR1, HCP-1, LRP1, DMT-1 and Dcytb), export (FPN, BCRP, and FLVCR) and storage (ferritin) proteins was determined by immunohistochemistry on normal breast, ductal carcinoma in situ (DCIS) and breast cancer sections. Breast cell lines were cultured with iron and haem to assess effects on intracellular iron levels and cell phenotype (viability, proliferation, migration and anchorage independent growth).

Results

Immunolocalisation studies showed significant over expression in iron importers (Dcytb, DMT-1, and TfR1) and exporters (FPN, BCRP) in cancer compared to normal breast tissue. Culture studies demonstrated that culturing breast cancer lines with iron or haem resulted in increased cellular iron accumulation associated with significant increases in viability, proliferation, migration and anchorage independent growth. These responses were not observed in the benign HB2 cell line.

Conclusions

Breast cancer development is associated with modulation in expression of iron transport proteins, likely reflecting the increased demand of cancer cells for iron. This increased iron load is likely drives the tumourigenic phenotype, suggesting iron chelators as a potential treatment for breast cancer.

Take-home message

Initial laboratory studies suggest there may be an important role for deranged transcellular iron transport in breast catcinogenesis, as has been shown in GI cancers. Further work will elucidate whether there is any therapeutic potential for treatments such as iron chelators

ORAL PRESENTATIONS 2A VASCULAR

057 PERSISTENT ELEVATION OF CYSTATIN C FOLLOWING ENDOVASCULAR ANEURYSM REPAIR (EVAR)

MF Abdelhamid^{1,2}, RSM Davies², RK Vohra², AW Bradbury¹, DJ Adam¹

1. University Department of Vascular Surgery, Birmingham Heartland Hospital. 2. University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham.

Introduction

Cystatin C (Cyst C) is a sensitive marker of reduced glomerular filtration. Serum creatinine (sCr) and creatinine clearance (CrC) may under-estimate the extent of renal damage following EVAR. The aim of this study is to describe changes in renal function following standard and fenestrated EVAR using Cyst C, sCr and estimated glomerular filtration rate (eGFR).

Patients and Methods

29 patients of mean (range) age 76.9 (55-89) years underwent measurement of Cyst C and sCr before; one day; and one, six and twelve months after EVAR (10 fenestrated and 19 standard). eGFR was calculated, for the same time points, using the Modification of Diet in Renal Disease (MDRD) formula.

Results

At 24 hours, there was significant increase in Cyst C (1.35 vs 1.25 mg/l, $p < 0.005$) and sCr (118 vs 106 $\mu\text{mol/l}$, $p = 0.028$) and a significant drop in eGFR (54 vs 62 ml/min/1.73m², $p = 0.04$). Cyst C continued to increase and was significantly higher at 1 (1.35 [1.17-1.67] mg/l, $p < 0.002$), 6 (1.42 [1.24-1.67] mg/l, $p < 0.005$) and 12 (1.45 [1.25-1.7] mg/l, $p < 0.005$) months. By contrast, sCr and eGFR did not show any significant change at 1, 6 and 12 months.

Conclusion

EVAR is associated with a significant increase in Cyst C which started 24 hours after the procedure and continued for 12 months. sCr and eGFR, which only showed significant change at 24 hours, may under-estimate long term renal damage following EVAR. This may support the evidence that Cyst C is more sensitive than sCr in detecting minor renal damage.

Take-home message

Persistent impairment of renal function following EVAR.

058 NEGOTIATING TORTUOUS ILIAC ARTERIES IN ENDOVASCULAR ANEURYSM REPAIR

Gokani VJ, Choke E, Dennis MJ, McCarthy MJ, Nasim A, London NJ, Naylor AR, Sayers RD, Bown MJ

Leicester Royal Infirmary

Introduction

Tortuous iliac arteries prevent endovascular aneurysm repair (EVAR). Our unit performs a 'trial of Lunderquist' (ToL) prior to surgery to assess suitability of EVAR on all patients whose iliac arteries are deemed too tortuous appear to allow uncomplicated stent insertion. The aim of this study was to determine the outcomes of EVAR in patients who successfully pass ToL.

Methods

A retrospective case notes review of all patients undergoing ToL in a single centre between December 2005 and June 2010 was performed.

Results

In a 55 month period, 33 of 336 patients considered for EVAR underwent ToL (10%; mean 8/year; median age 75 years). The mean time from ToL to definitive procedure was 48 days. Of the 33 patients requiring the trial, 30 patients passed (91%) and 23 (70%) of these went on to EVAR. Of those patients who passed ToL, 4 patients (13%) had no further procedure due to medical co-morbidities unrelated to ToL. Three patients (9%) passed the trial and are currently awaiting EVAR. All patients who underwent EVAR had grafts successfully deployed with no intra-operative complications. During follow-up, 2 patients were found to have asymptomatic type 2 endoleaks. Of those 3 patients who failed ToL, 2 underwent successful open surgery and 1 is awaiting open AAA repair.

Conclusion

Our data indicates that in patients with grossly tortuous iliac anatomy ToL is a useful method for determining likely successful stent deployment. This enables us to provide improved pre-operative counseling and bespoke stents are not bought unnecessarily.

Take-home message

Trial of Ludnerquist is a useful method for determining likely successful stent deployment in patients with tortuous iliac arteries during endovascular aneurysm repair.

O59 IDENTIFYING NOVEL CANDIDATE GENES IN UNSTABLE CAROTID ATHEROSCLEROTIC PLAQUES

MK Salem, HZ Butt, E Choke, RD Sayers, AR Naylor, MJ Bown

Vascular Surgery Group, Department of Cardiovascular Sciences, University of Leicester

Objectives

The objective of this study was to use Human Whole-Genome microarray analysis to compare the gene expression signature of unstable carotid atherosclerotic plaques. Instability was independently defined using the criteria of; (1) patient symptomatology (symptoms within 2 weeks) (2) evidence of spontaneous embolisation during pre-operative Transcranial Doppler (TCD) monitoring and (3) histological grade 3 & 4 plaques.

Methods

24 patients undergoing Carotid Endarterectomy (CEA) were recruited; Asymptomatic n=9, symptomatic n=15 (9 patients had symptoms within 2 weeks). Seven patients had TCD evidence of spontaneous embolisation. Seven plaques were graded as unstable by an independent histopathologist blinded to clinical details. RNA extracted from plaques harvested during CEA were hybridised onto the array. Analysis was performed using GenomeStudio (v1.0).

Results

Three independent analyses were performed, and differentially expressed genes (>1.5 fold, p<0.05) were sought for; (1) recency of symptoms - 367 genes, (2) evidence of embolisation - 2353 genes and (3) histological grading - 216 genes. A total of 29 novel genes not previously associated with carotid plaque instability were identified in 2 of the 3 analyses stated. Genes of interest include motif-chemokine 19 (CCL19), Ephrin Type-B Receptor (EPHB1), Mitogen activated protein kinase 4 (MAPK4), Transcription Factor E2F5 (E2F5) and Ubiquitin-Conjugating enzyme E2 (UBE2T).

Conclusions

The differential expression of 29 genes not previously associated with carotid atherosclerotic plaque instability has been demonstrated in plaques that have been independently shown to be histologically and phenotypically unstable. These genes related to apoptosis, cell signalling and inflammation, could represent novel markers i.e. making them targets for pharmacotherapeutic interventions.

Take-home message

Novel genes have been identified in unstable carotid plaques, that could represent targets for pharmacotherapeutic interventions.

O60 VO2 PEAKS BUT ANAEROBIC THRESHOLD IS EXHAUSTED IN THE PREOPERATIVE ASSESSMENT OF PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

Kordowicz AGR¹, Sohrabi S^{1,2}, Foster K², Howell SJ³, Scott DJA^{1,2}

(1) Leeds Vascular Institute, The General Infirmary at Leeds (2) Division of CardioVascular and Diabetes Research, University of Leeds (3) Academic Unit of Anaesthesia, The General Infirmary at Leeds

Objective

We examined whether performance on cardiopulmonary exercise (CPX) testing could predict long term outcome in patients undergoing AAA repair.

Methods

Between 02/07 and 09/09, 134 patients (115 men) undergoing open or endovascular (EVAR) AAA repair underwent preoperative CPX testing. Anaerobic threshold (AT) and peak oxygen consumption (VO₂peak) (in ml kg⁻¹ min⁻¹), were recorded. 30-day and 12-month mortality were determined from our database. Data are expressed as median (interquartile range).

Results

70 open AAA repairs and 64 EVARs were performed. 30-day mortality was 3.7% and 12-month mortality was 7.5%. The data were analysed in two groups, (a) survivors and (b) non-survivors; both groups were well matched for age and cardiovascular risk factors. VO₂peak was significantly higher in survivors; 15.3 (13.2 - 17.8) in group (a) and 12.4 (9.3 - 16.5) in group (b) (p=0.031). AT did not differ significantly between groups; 10.7 (9.2 - 12.8) in group (a) and 10.6 (8.4 - 12.5) in group (b) (p=0.621).

Conclusion

Median VO₂peak was significantly higher in one year survivors following AAA repair and may provide a means of identifying patients who will benefit from surgery. Conversely, AT is not an independent predictor of one-year mortality. This may reflect inter-observer variability in its derivation.

Take-home message

The results of cardiopulmonary exercise tests should be interpreted with caution; peak oxygen consumption provides a means of predicting long-term (one year) mortality following abdominal aortic aneurysm repair but anaerobic threshold is not an independent predictor of mortality.

O61 DISCOVERY OF PLAUSIBLE “CANDIDATE BIOMARKERS OF AAA” AT PROTEIN LEVEL: A PILOT STUDY.

S Ehsan¹, SE Slade², G Balls, DJL Jones, HZ Butt, NJM London, RD Sayers, MJ Bown

¹ University of Leicester ²The University of Warwick

Introduction

AAA causes significant mortality and morbidity despite screening and recent advances in surgical repair. There is a clinical need for biomarkers and pharmacological targets which could improve clinical care.

Methods

A prospective case-control study was performed. Plasma from ten patients with AAA and ten healthy age and gender matched controls was obtained. Pooled plasma samples were depleted of the highly abundant plasma proteins (Seppro IgY-14 LC-2 column), digested using Rapigest methodology and analyzed in triplicate by quantitative label-free collisionally switched mass spectrometry (Q-ToF Synapt HDMS, Waters Inc). The data analysis was undertaken on two levels. For the exact mass and retention time signatures (EMRT) multiple regression analysis was carried out. Protein level identification utilised the IdentityE algorithm whilst the differential expression was analyzed by the ExpressionE algorithm within Protein Lynx Global Server™ (Waters Inc) software.

Results

Differential expression was observed for 1580 ions by the EMRT level analysis. On the protein level we confidently detected low abundance proteins present in femtomole quantities in the sample which are usually invisible to other proteomics methodologies. In total for both samples 304 proteins were identified. We observed significant differences in expression across 82 proteins. Unique expression was noted for 14 proteins in patients with AAA and similarly 23 proteins were only observed in controls. Comparing the two groups another 45 proteins exhibited significant differential expression (p value ≤ 0.05).

Conclusion

This work has uncovered putative AAA biomarkers for further validation. The work will also help discover novel mechanistic pathways associated with AAA.

Take-home message

Patients with AAA exhibit a plasma protein profile that is significantly different to that of controls.

O62 PREDICTING INDIVIDUAL PATIENT MORTALITY RISK IN ELECTIVE AAA SURGERY

Grant SW¹, Grayson AD², Purkayastha D¹, Wilson S¹, McCollum CN¹ on behalf of the VGNW participants

(1) Academic Surgery Unit, University Hospital of South Manchester, (2) Southport & Ormskirk NHS Hospitals

Introduction

A reliable preoperative prediction of risk for elective AAA repair would be valuable to surgeons and patients. A multivariate risk prediction model for 30-day mortality following elective open and endovascular abdominal aortic aneurysm (AAA) repair has been developed using a large surgical database.

Methods

Prospective data on 2,765 consecutive patients from 22 hospitals who underwent elective open or endovascular AAA repair from Sept 1999 - Oct 2009 was randomly split into development ($n=1,936$) and validation datasets ($n=829$). Logistic regression analysis was undertaken using a forward-stepwise technique to identify risk factors for 30-day mortality.

Results

Variables associated with 30-day mortality (n=98, 5.1%) in the development dataset included; anti-platelet medication (p<0.001), female gender (p=0.002), open surgery (p=0.002), age (p=0.005), creatinine (p=0.006), diabetes (p=0.029) and respiratory disease (p=0.031). The receiver operating characteristic (ROC) curves for predicted probability of 30-day mortality in the development and validation datasets were 0.73 and 0.70 respectively. The model showed good calibration in both datasets. Observed versus expected 30-day mortality in the validation dataset (50(6%) deaths) for low, medium and high risk groups was 3.2% v 2.0%, (p=0.27), 6.1% v 5.1%, (p=0.67) and 11.1% v 10.7%, (p=0.88) respectively with no significant difference between observed and expected.

Conclusions

This multivariate model predicted 30-day mortality following elective AAA repair across all risk groups particularly when the mortality risk is high. Surgeons may find it useful to calculate patient-specific risk for case mix adjustment of their results and in the consent process. Validation against the National Vascular Database is now planned.

Take-home message

We have developed a multivariate risk prediction model for 30-day mortality following elective open and endovascular abdominal aortic aneurysm (AAA) repair using a large surgical database. This model predicts 30-day mortality following elective AAA repair across all risk groups particularly when the mortality risk is high.

O63 RATES OF SPONTANEOUS EMBOLISATION IN ACUTELY SYMPTOMATIC PATIENTS WITH CAROTID ARTERY DISEASE

MK Salem, APWW Watts, RD Sayers, MJ Bown, AR Naylor

Vascular Surgery Group, Department of Cardiovascular Sciences, University of Leicester

Objectives

Transcranial Doppler (TCD) detected Spontaneous Embolisation (SE) after a TIA/Minor stroke is an independent predictor of recurrent stroke. There is, however limited data on the prevalence of SE in the acute period after onset of symptoms.

Method

156 consecutive patients underwent CEA during an 18 month period and had an accessible window permitting 30 minutes of pre-operative TCD monitoring. A prospective study was conducted with assessors blinded to clinical status.

Results

Spontaneous embolisation was detected in 1/1 (100%), 14/35 (40%), 8/37 (22%) and in 8/50 (16%) of patients presenting within 48 hours, 3-7 days, 8-14 days and greater than 14 days respectively from index clinical event. SE was detected in 8/19 (42%), 12/39 (31%), 6/33 (18%) and in 5/32 (16%) of patients presenting within 48 hours, 3-7 days and greater than 14 days since the most recent clinical event. SE occurred in 6% of asymptomatic patients. Out of 31 patients found to be spontaneously embolising, seven (22.6%) suffered recurrent cerebrovascular events as opposed to 11/92 patients (11.9%) who had no evidence of spontaneous embolisation (OR 2.15 (95% CI 0.75-6.1))

Conclusion

Patients presenting for CEA in the hyperacute period after onset of TIA/Minor stroke have a high incidence of SE and a 23% risk of recurrent cerebrovascular events. These data support natural history studies promoting expedited CEA in recently symptomatic patients.

Take-home message

Patients in the acute period after a TIA/Minor stroke are at high risk of spontaneous embolisation and a recurrent cerebrovascular ischaemic event

O64 IDENTIFYING THE RISK OF RENAL FAILURE FOLLOWING ELECTIVE AAA REPAIR

Grant SW¹, Grayson AD², Sekhar H¹, Purkayastha D¹, Wilson S¹, McCollum CN¹ on behalf of the VGNW participants

(1) Academic Surgery Unit, University Hospital of South Manchester, (2) Southport & Ormskirk NHS Hospitals

Introduction

Renal failure is a recognised complication of AAA repair associated with prolonged hospital stay, lifelong dialysis and increased mortality. We have analysed a large surgical database to identify risk factors for developing acute renal failure following elective AAA repair.

Methods

Peri-operative data was collected on 3,049 consecutive patients from 22 hospitals who underwent elective AAA repair from Sept 1999 - July 2010. 39 patients with significant renal impairment (preoperative serum creatinine > 200 $\mu\text{mol/L}$) were excluded. Logistic regression analysis was undertaken using a forward-stepwise technique to identify risk factors for post-operative renal failure. Renal failure was defined as the requirement for post-operative renal-replacement therapy.

Results

Of the 3010 patients included, 711 had EVAR and 2299 had open AAA repair. Renal failure occurred in 148 (4.9%) patients post-operatively. Post-operative renal failure was associated with age >75 (OR=1.68, 95%CI 1.18-2.39), pre-operative creatinine >150 (OR=3.47, 2.18-5.53), anti-hypertensive medical therapy (OR=1.96, 1.34-2.86), a history of respiratory disease (OR=2.13, 1.49-3.04), supra/juxta renal AAA repair (OR=2.04, 1.24-3.36) open AAA repair (OR=6.94, 2.79-17.24) and return to theatre within 30 days (OR=5.53, 3.56-8.59). The 30-day mortality in patients who developed post-operative renal failure was 39.2% compared with 3.5% in those who did not ($p<0.001$).

Conclusion

Renal failure following elective AAA repair was associated with more than a ten-fold increase in 30-day mortality. Seven risk factors were identified as being associated with post-operative renal failure allowing the potential implementation of prevention strategies for high risk patients.

Take-home message

Renal failure following elective AAA repair is associated with more than a ten-fold increase in 30-day mortality. We have identified from a large surgical database seven risk factors associated with the development of renal failure following elective AAA repair.

ORAL PRESENTATIONS 2B HEPATOBIILIARY/PANCREATIC

O65 TRANSLATION OF SIMULATION TRAINING TO THE OPERATING THEATRE

Kennedy AM, Al-Akash M, Hill AD, Traynor O

National Surgical Training Centre, Royal College of Surgeons in Ireland, Dublin 2

Summary

The surgical community is currently facing a crisis in training requirements. The use of surgical skills laboratories, which incorporate sophisticated virtual reality surgical simulators, will become increasingly important. The current evidence suggests that surgeons trained on simulators have a superior intra-operative performance than an untrained group. We aimed to conclusively demonstrate the value of simulator training to real life operative performance in an Irish setting. Eleven surgical trainees were enrolled in the trial. Six trainees were randomised to a training programme on the LapSim™ surgical simulator. These trainees had to reach objectively set goals on the simulator. The remaining trainees were assigned to the control group. Trainees in both groups were then required to perform supervised video-recorded laparoscopic cholecystectomies at their training hospitals. A total of 39 video-recorded procedures were included in the study. Standard trained participants were twice as likely to transiently fail to make progress ($p < 0.027$). In addition, mean errors were over twice as likely to occur in the standard-trained group ($p < 0.002$). There was no difference time between the two groups but it is important to note that time alone is not the most important metric (as a procedure could be performed quickly but poorly). We have conclusively demonstrated that training on a simulator results in a more polished, smooth and steady performance. In addition, we have shown that VR training results in fewer errors in the first stage of the cholecystectomy procedure. This study should firmly and definitively establish the role of simulation training for surgical trainees.

Take-home message

The use of surgical simulators will play an increasingly important role in surgical training.

O66 IDENTIFICATION OF DIFFERENTIALLY EXPRESSED PROTEINS IN HILAR CHOLANGIOCARCINOMA USING A LABEL FREE SHOTGUN PROTEOMIC APPROACH

SG Farid^{1,2}, RA Craven¹, A Zougman¹, DA Cairns¹, PJ Selby¹, RE Banks¹, KR Prasad²

(1) Cancer Research UK Clinical Centre, St James University Hospital, Leeds UK (2) Department of HPB Surgery, St James University Hospital, Leeds UK

Introduction

Hilar cholangiocarcinoma (HCCA) continues to be associated with poor prognosis due to late presentation and diagnostic inaccuracy. Bile is in close contact to the tumour environment and offers an enriched source of potential biomarkers. We present the first study of its kind to compare the protein profiles of bile in benign and malignant biliary disease to identify candidate biomarkers.

Methods

Bile samples from 5 age and sex matched patients with cholelithiasis and histopathologically confirmed HCCA respectively were obtained at ERCP. Bile was subjected to albumin/immunoglobulin depletion, in solution tryptic digestion and nanoLC/MS/MS using LTQ XL* Linear Ion Trap Mass Spectrometer. Differentially expressed proteins were identified by label free quantification using MaxQuant v1.1.1.14 and the Wilcoxon-Mann-Whitney statistical test ($p < 0.05$). Validation studies were carried out using Western blotting.

Results

In total 1276 unique proteins were described, which is the largest catalogue of bile proteins published to date. Of these, 41 were differentially expressed between benign and malignant disease; in addition to proteins whose expression was previously shown to be altered in CCA (such as downregulation of apolipoprotein AI), several novel proteins were identified. Western blotting confirmed overexpression of a number of these proteins in bile from HCCA patients.

Conclusion

This study represents the most comprehensive bile protein catalogue and identified a number of proteins not previously reported as differentially expressed in HCCA. Preliminary validation has confirmed over expression of selected proteins in bile and these are the subject of further studies to assess their potential as biomarkers.

Take-home message

There is a pressing need for diagnostic markers in cholangiocarcinoma (CCA) to facilitate early diagnosis and eligibility for surgery. Our study provides the largest bile protein catalogue in CCA and presents quantifiable differences in biologically relevant proteins when compared to benign biliary disease.

067 THE ROLE OF MULTISLICE COMPUTERISED TOMOGRAPHIC ARTERIAL PORTOGRAPHY IN THE DETECTION OF COLORECTAL LIVER METASTASES, AND THE FACTORS INFLUENCING PERFUSION DEFECTS

C Jones¹, SA Badger¹, BE Kelly², M Love², PT Kennedy²

Department of Hepatobiliary Surgery, Mater Hospital, Belfast(1), Department of Radiology, Royal Victoria Hospital, Belfast (2)

Introduction

Accurate imaging of colorectal liver metastases is essential. Computerised Tomographic Arterial Portography(CTAP), a method of liver imaging, has not been extensively used in clinical practice. This study therefore aimed to assess CTAP accuracy, and determine factors influencing the uptake of arterial contrast.

Methods

Consecutive metastatic colorectal cancer patients underwent CTAP. Two blinded individuals reported the scans. Contrast density in Hounsfield units was recorded at portal vein, hepatic vein, inferior and superior liver parenchyma. Correlations between perfusion defects, number of metastases, and contrast density were calculated. For surgical patients, CTAP was compared with histology. Ethical approval and written consent were obtained.

Results

55 patients from September 2002 to May 2004 were included. For surgical patients (n=19), CTAP had an accuracy of 86.0%, sensitivity of 89.2% and specificity of 84.4%. There was a positive correlation ($r=0.53$; $p=0.03$) between the difference between superior and inferior contrast, and number of perfusion defects. For the non-surgical group (n=35), CTAP reported 184 lesions, 115 were considered metastatic, with 47 perfusion abnormalities. A negative correlation ($r=-0.41$; $p=0.01$) between perfusion defects and ratio of contrast in hepatic:portal vein was noted. No correlation with the number of metastases was noted.

Conclusion

CTAP can distinguish between metastatic lesions and perfusion defects, while mapping arterial vascular anatomy. In homogenous liver parenchyma there are fewer perfusion defects, while the smaller the hepatic:portal vein ratio more perfusion defects were detected. Further work is justified regarding the timing of contrast and the use of bolus tracking technology to control the scan initiation time to optimise liver perfusion.

Take-home message

CTAP has a role in the imaging of colorectal liver metastases, however further research is required.

068 UPREGULATED MICRO-RNA 21 TARGETS PDCD4 INHIBITING PANCREATIC CANCER PROLIFERATION

I Bhatti¹, A Lee¹, C Tufarelli¹, JN Lund¹, RI Hall², DN Lobo³, M Larvin¹

(1) Division of Surgery, University of Nottingham School of Graduate Entry Medicine, Royal Derby Hospital, Derby DE22 2DN; (2) Surgical Directorate, Royal Derby Hospital, Derby DE22 2DN; (3) Division of Gastrointestinal Surgery, Nottingham Digestive Diseases Centre NIHR Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH.

Background

Pancreatic cancer (PaCa) is an aggressive, late presenting malignancy. Improved survival requires earlier diagnosis, staging and new therapies. MicroRNAs (miRNA) are short non-coding RNA sequences that regulate gene expression and are dysregulated in many cancers including PaCa. Over-expression of miRNAs may inhibit tumour suppressor genes, promoting carcinogenesis. The aim was to investigate candidate miRNA expression in cell lines and tumours, followed by functional studies.

Methods

Samples were yielded from tumour and adjacent tissue in 24 PaCa patients after LREC approval. Expression levels of candidate miRNAs (miR-21, -148a, -375, -181b & -151) were measured in MIA-Pa-Ca-2, HUP-T3 & PSN-1 pancreatic cancer cell lines, in matched normal and tumour samples, and control pancreatic RNA. Relative expression was quantified using real-time quantitative PCR (RT-QPCR) following reverse transcription of target and control miRNAs. Initial results prompted studies of miR-21 inhibition in MIA-Pa-Ca-2 cells by oligonucleotide inhibitor transfection. Effects were assessed 48 and 72h afterwards, measuring expression of the target tumour suppressor gene PDCD4 at RNA (RT-PCR) and protein (western blotting) levels, cell proliferation and cell death.

Results

miR-21 expression was significantly upregulated ($p < 0.0001$), but miR-148a ($p < 0.0001$) and miR-375 ($p < 0.0001$) were downregulated in cell lines and tumours. miR-21 levels correlated significantly with stage/resectability ($p < 0.001$). There was significant PDCD4 message and protein upregulation ($p < 0.001$ & $p < 0.02$) after 48h inhibition, paralleled by reduced rates of proliferation and cell death.

Conclusions

This study strengthens the view that miRNAs may form useful new diagnostic and prognostic biomarkers for pancreatic cancer, as well as potential new therapeutic targets.

Take-home message

MicroRNA expression was shown to be significantly dysregulated in pancreatic cancer cell lines and human tumours, with miR-21 levels being correlated significantly with stage/resectability suggesting a role in diagnosis and prognosis in pancreatic cancer. Significant PDCD4 message and protein upregulation after miR-21 inhibition with reduced rates of proliferation and cell death may provide potential new therapeutic targets.

069 PATHOGENESIS OF CHEMOTHERAPY ASSOCIATED LIVER INJURY PRIOR TO MAJOR HEPATIC RESECTION

Robinson SM^{1,2}, Mann J¹, Burt AD¹, Manas DM², Mann DA¹, White SA^{1,2}

(1) Liver Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; (2) Department of HPB Surgery, Freeman Hospital, Newcastle upon Tyne, UK

Aims

Chemotherapy (FOLFOX) is used to downstage inoperable colorectal liver metastasis. However this is at the expense of causing chemotherapy associated liver injury (CALI) increasing the risk of post-operative morbidity. The aim of this study was to develop a model to investigate the pathogenesis of CALI.

Methods

: C57Bl/6 mice were randomised to FOLFOX chemotherapy or vehicle alone ($n=6$) weekly for four weeks. 7 days after the final dose mice were culled and tissue harvested. In parallel the MCA38 Colorectal cancer cell line was treated with FOLFOX at IC50 doses for 24 hours before isolation of RNA. Cell culture supernatants were harvested for ELISA and chemotaxis assays.

Results

FOLFOX therapy resulted in reduced weight gain and anorexia (1.18g vs 2.94g $p < 0.01$) in treated animals suggesting systemic toxicity. FOLFOX treated animals developed splenomegaly as determined by a 60% increase in spleen/body weight ratio ($p < 0.01$) and histological splenic injury. There was no histologically detectable liver injury despite biochemical evidence of DNA damage. MCA38 cells treated with FOLFOX do not undergo immunologically silent apoptosis but rather produce chemokines and cytokines e.g. CXCL1&5, CCL2 and IL-6 capable of driving an inflammatory response through the recruitment of innate immune cells.

Conclusion

Our model suggests that FOLFOX causes DNA damage within the liver but alone is not sufficient to produce the histological features of CALI. These changes are likely to be mediated by the pro-inflammatory response generated by FOLFOX treatment of liver metastases. Targeting the inflammatory response to tumour death may help to reduce the incidence of CALI.

Take-home message

Chemotherapy associated liver injury most likely occurs, at least in part, as a result of the inflammatory response to tumour death. Targeting this may prove to be a useful therapeutic target.

070 THE ROLE OF A NOVEL SEMI-SYNTHETIC FLAVONOID (MONOHER) IN PREVENTING MONOCROTALINE INDUCED SINUSOIDAL OBSTRUCTION SYNDROME IN RATS

Tarek M Ezzat, Dipok Dhar, Massimo Malago, Steven WM Olde Damink

HPB and Liver transplantation surgery, Royal Free Hospital, University College London

Background

Sinusoidal Obstruction Syndrome (SOS) is a dire complication after neo-adjuvant oxaliplatin treatment for hepatic colorectal metastasis leading to severe hepatic failure and death. An additional risk of liver failure is documented following hepatic resection in patients with SOS. In this study, we sought to determine the protective effect of monoHer in a rat model of SOS induced by monocrotaline (MCT).

Methods

Male Sprague Dawley rats received a single gavage of MCT (160mg/kg) to induce SOS. Pretreatment with monoHer (500mg/kg, i.p./day) started 24-hr before MCT and continued once daily for 72 hrs. Additionally, in vitro studies were performed to test the beneficial effect of monoHer on oxaliplatin and MCT on proliferation of two colorectal cancer cell lines.

Results

Serum ALT was significantly lower in MonoHer-treated rats when compared with controls at 24h ($p = 0.004$) and 72h ($p = 0.029$). Also there was a significant difference in portal pressure between the monoHer and control group at 72h (7.8 ± 0.58 vs. 11.16 ± 1.65 , $p = 0.007$, respectively). In in vitro study, MonoHer at 1mM concentration antagonized the effect of toxic doses of both oxaliplatin and MCT (8ug/ml and 4mM concentration, respectively). In contrast, only oxaliplatin had dose dependent growth inhibitory effect in colorectal cancer cells and MCT had no effect. MonoHer had no effect on cell proliferation.

Conclusion

MonoHer significantly prevented MCT induced hepatic injury and may serve as a novel therapeutic strategy for SOS treatment. MonoHer could be used safely along with oxaliplatin without any interfering effect.

Take-home message

Oxaliplatin induced Sinusoidal obstruction syndrome is a cause of liver failure after hepatic resections. Prevention of this condition using a novel semisynthetic flavonoid (MonoHer) would improve prognosis of such patients.

071 THE ROLE OF THE BONE MARROW AND NOTCH SIGNALLING IN THE STROMAL MICROENVIRONMENT IN CHOLANGIOCARCINOMA

AJ Robson^{1,2}, K Samuel¹, A Pellicoro¹, OJ Garden², SJ Wigmore^{1,2}, JP Iredale¹, SJ Forbes¹

Centre for Inflammation Research⁽¹⁾ and Department of Surgery², University of Edinburgh

Introduction

Treatment options for cholangiocarcinoma (CC) are limited. Lesions are characterised by a pronounced microenvironment of tumour-associated myofibroblasts, macrophages, immune cells and modified extracellular matrix. Understanding the source and functional role of tumour-associated cells in CC will inform future therapy.

Methods

With ethical and Home Office approval, tumour composition was studied in humans and the thioacetamide rat model of CC over 14 months. Wild type rat recipients of transplanted GFP bone marrow (BM) and sex-mismatched BM were administered thioacetamide. Extra-hepatic derivation of cells was identified using dual immunofluorescence for GFP or Y-Chromosome and cell-lineage specific markers. PCR microarray of human tissue and immunohistochemistry for the Notch pathway was performed. In vitro co-culture of primary stromal cells with CC lines together with Notch inhibition and chemotherapy was undertaken.

Results

In CC, stromal myofibroblasts were of intrahepatic origin, unlike tumour-associated macrophages and immune cells that were actively recruited from the BM, as determined by GFP expression. Unlike other tumours, we found no evidence of BM-derived stem cell contribution to the epithelial component of CC: malignant bile ducts did not express GFP. The Notch pathway was over-expressed in CC, with receptors distributed on bile ducts and ligands on myofibroblasts. Stromal co-culture promoted CC growth. Notch inhibition significantly reduced CC growth and potentiated chemotherapy ($p < 0.05$).

Conclusion

Haematopoietic but not mesenchymal or epithelial components of the CC tumour microenvironment were BM-derived. Locally derived myofibroblasts may play a role in Notch pathway activation. In CC, stromal modification and Notch pathway manipulation are potential therapeutic tools.

Take-home message

In cholangiocarcinoma, haematopoietic cells are actively recruited from the bone marrow to the tumour microenvironment, whereas fibroblasts are locally derived. Notch pathway upregulation in cholangiocarcinoma may be mediated by stromal cells and represent a potential therapeutic target.

072 MOLECULAR MECHANISMS OF L-ARGININE INDUCED EXPERIMENTAL ACUTE PANCREATITIS**O.Masood^{1,2}, A.K Siriwardena¹, J.Bruce¹**

(1) Hepatobiliary Unit, Manchester Royal Infirmary. (2) Faculty of Life Sciences, University Of Manchester.

Introduction

Impairment of cytosolic Ca^{2+} ($[Ca^{2+}]_i$) signaling and acinar cell $[Ca^{2+}]_i$ overload has emerged as a possible mechanism precipitating acute pancreatitis (AP). In the L-arginine (Larg) model of AP, nitric oxide (NO) has been implicated however L-arg-induced AP is largely unaffected by nitric oxide synthase (NOS) inhibitors. Additionally, L-ornithine (Lorn), an NOS-independent metabolite of Larg, also induces AP. Both Larg and Lorn are known to activate calcium-sensing like receptors such as the GPRC6A which may be responsible for initiating $[Ca^{2+}]_i$ overload.

Methods

Pancreatic acinar cells were isolated by collagenase digestion. $[Ca^{2+}]_i$ was measured using fura-2 imaging, oxidative stress by dichlorofluorescein (DCF) and cell death using trypan blue exclusion.

Results

Larg and Lorn (100mM) induced spike-like, reversible increases in $[Ca^{2+}]_i$ in 46% and 74% of cells and Ca^{2+} overload in 11% and 26% respectively. At 500 mM both induced Ca^{2+} overload in all cells however this was also seen with the osmotic control, mannitol. Isosmotic Larg and Lorn (100mM) induced only reversible increases in $[Ca^{2+}]_i$. Neither Larg nor Lorn had significant effects on CCK-evoked $[Ca^{2+}]_i$ oscillations. Both Larg and Lorn induced significant oxidative stress responses (22% +/-3 and 37% +/-5 of a maximum response seen with 3mM H₂O₂, respectively.) Both Larg and Lorn caused cell death in 76% +/- 4 and 89% +/- 7 at 3hours respectively, compared to 35% +/- 4 and 40% +/- 3 with controls (Hepes, Glycine).

Conclusion

The data suggests that the Larg and Lorn causes significant increase in oxidative stress and cell death, although the induced Ca^{2+} overload is probably attributed to non-specific hyper-osmotic effects.

Take-home message

The mechanism of L-arginine induced experimental pancreatitis is multi-factorial and unlikely to be solely attributed to nitric oxide as the current dogma suggests.

ORAL PRESENTATIONS 3A WOUNDS AND TISSUES

073 TISSUE ENGINEERED TRACHEA DEVELOPMENT USING A NOVEL NANOCOMPOSITE MATERIAL

Claire Crowley^{1,2}, Martin Birchall², Alexander Seifalian¹

(1) UCL Division of Surgery & Interventional Science, (2) The Royal National Throat, Nose and Ear Hospital and UCL Ear Institute

Introduction

We have developed a novel nanocomposite polymer for surgical implant applications. It has been successfully implanted in a large animal model for three years proving its biocompatibility, non toxicity and low inflammatory response. It recently underwent its first transplantation into human, as a lacrimal duct, which was a success.

Method

The nanocomposite polymer was extruded with similar mechanical properties to a human trachea and the tracheal construct was designed using numerical modelling. The tensile stress and strain of the polymer were measured using an Instron 5565 tensile tester. The polymer's potential to support chondrocyte, mesenchymal stem cell and epithelial cell attachment and proliferation was examined by seeding the cells onto two different fabrications of the polymer and subsequently analysing the degree of cell growth with a cell viability assay and SEM imaging.

Results

The synthetic trachea has similar viscoelastic properties to a native trachea and the polymer supports tracheal-specific cell attachment and proliferation.

Conclusion

Our synthetic tracheal implant could form the foundation in developing the much anticipated 'off the shelf' tissue engineered technology, contributing extensively to the advancement in treatment and rehabilitation of patients afflicted with tracheal pathology.

Take-home message

Our novel nanocomposite polymer demonstrates great potential for use as a tissue engineered tracheal replacement.

074 THE EFFICACY OF ANTIMICROBIAL WOUND DRESSINGS USED IN THE MANAGEMENT OF MILITARY COMPLEX EXTREMITY INJURY: A PRE-CLINICAL RANDOMIZED CONTROLLED TRIAL

WGP. Eardley^{1,2}, KR. Martin¹, E. Kirkman¹, JC. Clasper², SA. Watts¹

(1) Department of Biomedical Sciences, Defence Science and Technology Laboratory, Porton Down, Salisbury, Wiltshire, United Kingdom. (2) Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine, Vincent Drive, Edgbaston, Birmingham, United Kingdom

Introduction

Extremity injury and complications such as wound infection remain a significant problem for the military. This study investigated the anti-microbial efficacy of four dressings in militarily relevant complex extremity injury.

Methods

Under general anaesthesia, the flexor carpi ulnaris of 24 New Zealand White rabbits was exposed to a high energy impact and then inoculated with 10⁶ colony forming units of *Staphylococcus aureus*. Dressings: gauze soaked in saline, Chlorhexidine or Betadine or Acticoat[®], were randomised and applied 3 hours post injury, to replicate casualty evacuation. Once recovered, animals were checked at least twice daily and body temperature recorded. Analgesia was administered once a day. At 48hrs animals were culled, the muscle harvested and analyzed by a blinded investigator. Group sizes of 6 were required to detect a statistically significant effect of a mean one log reduction in bacterial counts at 48 hours.

Results

No dressing gave a significant reduction in bacterial counts at 48 hours. A paired t-test of contamination versus recovered dose gave p values of 0.903, 0.648, 0.396 and 0.336 for saline, Acticoat[®], chlorhexidine and iodine respectively. Contamination dose between groups compared using ANOVA showed no significant difference (p=0.566). Recovered bacterial loads between groups revealed no significant difference (p=0.280).

Conclusion

This study indicates that over a 48 hour period, dressings with reported anti-bacterial properties offer no advantage over saline soaked gauze in reducing the bacterial burden in a contaminated soft tissue injury. Future work will extend the study temporally and introduce multiple contaminants.

Take-home message

Extremity wounding is a common feature of contemporary combat injury with significant infective complications. Factors affecting wound infection are multiple, but our results would suggest that application of antimicrobial dressings has minimal impact on wound contamination up to 48hrs following injury.

075 EVALUATION OF THE BIOCOMPATIBILITY OF HUMAN GRADE CHITOSAN DERIVATIVE, HUMAN SKIN ALLOGRAFT AND INTEGRA IMPLANT IN RATS.

SJ Mohd. Yussof, AS Halim, SN Saifuddin, WR Wan Mokhtar, WS Wan Kasim, H Jaafar

Reconstructive Sciences Unit, Universiti Sains Malaysia Health Campus, Kubang Kerian, Kelantan, Malaysia

Introduction

Many skin substitutes have been introduced onto the market. Integra is a two-layer skin regeneration system, with an inner layer constructed of a complex matrix of cross-linked fibers that act as a scaffold for regenerating dermal skin cells. Chitosan is linear polysaccharide obtained from chitin by N-deacetylation using strong alkali. Human skin allografts (HSA) is currently the 'gold standard' for temporary coverage of clean, open burn wounds. Objectives: The objective of this study was to conduct in-vivo, preclinical biocompatibility evaluations of Integra, HSA and Chitosan.

Methods

Paravertebral subcutaneous pockets were created for the implantation of test materials. Implants were retrieved after 4, 7, 14, 21 and 28 days. Slides of sections through the implants were examined microscopically to determine tissue reactivity and biocompatibility.

Results

Chitosan and Integra showed similar inflammatory patterns ($p=0.308-1.000$). HSA showed a higher inflammatory reaction ($p<0.001$ at day 4 compared to chitosan) which peaked at days 7 and 14. This reduced to levels similar to Integra and Chitosan at day 28. Chitosan and Integra also shared a similar angiogenesis reaction ($p=0.069-1.000$), initially high at days 4 and 7 and gradually tapering down. HSA showed high angiogenesis throughout the implantation period. Tissue invagination into Chitosan and Integra can be seen by day 4, while HSA started at day 7. All three test materials did not show any prolonged or exaggerated tissue reactions.

Conclusion

Integra, Chitosan and HSA have been shown to be biocompatible. Integra and Chitosan seem to illicit similar tissue responses.

Take-home message

Chitosan is shown to have similar inflammatory, angiogenesis and tissue ingrowth responses to Integra. Based on this study, chitosan could serve as an alternative to Integra and HSA as a skin substitute.

076 TRAUMA: CHARACTERISING THE CYTOKINE RESPONSE TO TISSUE DAMAGE

J. Manson, R. Davenport, A. Coates, H. De'Ath, C. Spoons, S. Khan, I. Raza, C. Rourke, P. Vulliamy, K Brohi

Trauma Clinical Academic Unit, Royal London Hospital and QMUL

Background

Tissue damage following injury generates an acute inflammatory response that has not been characterized in humans. We undertook a prospective, observational cohort study of trauma patients to describe the pattern and time-course of cytokine activation associated with tissue damage and to demonstrate the influence of shock on this response.

Methods

Blood was sampled immediately on arrival, at 24 and 72 hours and analyzed for 7 cytokines (TNF- α , IL-1, IL-6, IL-8, IL-10, IL-12, IFN γ). Data were collected on demographics, mechanism and injury severity score (ISS), base deficit at admission (BD), mortality, the incidence of sepsis and organ dysfunction.

Results

235 patients were recruited within 3 hours of injury, including 39 'controls' that had minimal injury (ISS ≤ 4). The 196 injured, had a median ISS of 22 (IQR 5-59). 77 were not shocked (BD ≤ 2 mEq/l), 119 were shocked (BD > 2 mEq/l). In the injured group, concentration of all cytokines except IL-12 were significantly elevated on admission ($p<0.05$) and showed a dose-

response to injury severity. Shock had a synergistic effect for all cytokines, increasing the damage response between 2 and 22-fold. Admission concentration of IL-6, IL-8 and IL-10 correlated with mortality, development of sepsis and organ failure.

Conclusion

Tissue damage leads to a measurable cytokine response immediately after injury that is associated with worse outcomes. This response is modulated and cannot be separated from the inflammatory effects of shock. Further exploration of a broader panel of cytokines is needed to fully characterize the damage response.

Take-home message

1. Tissue damage alone generates an inflammatory response in trauma. 2. When combined with shock, the effect is amplified. 3. Supports the need for further study and mechanistic work

077 TORSION OF MONOFILAMENT AND POLYFILAMENT SUTURES UNDER TENSION DECREASES SUTURE STRENGTH AND INCREASES RISK OF SUTURE FRACTURE

Hennessey DB¹, Carey E², Simms CK³, Hanly A¹, Winter DC¹

(1) Department of General and Colorectal Surgery, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland (2) School of Chemical and Bioprocess Engineering, University College Dublin, Belfield, Dublin 4, Ireland (3) Trinity Centre for Bioengineering and Department of Mechanical Engineering, Trinity College Dublin, Dublin 2, Ireland

Background

A continuous running suture is the preferential method for abdominal closure. In this technique the suture is secured with an initial knot and successive tissue bites are taken. At each tissue bite, the needle is rotated through the tissue; in doing so, the suture can twist around the knot which acts as an anchor.

Objective

To determine the effect of axial torsional forces on sutures used in abdominal closure. Methods: The effect of axial twisting on polydioxanone (PDS[®]II), polyglactin (Vicryl), polypropylene (Prolene) and nylon (Ethilion) sutures was investigated using a uniaxial testing device.

Results

The maximum tensile force withstood for untwisted sutures was determined: polydioxanone failed at a tensile force of 116.4±0.84 N, polyglactin failed at 113.9±2.4 N, polypropylene failed at 71.1±1.5 N and nylon failed at 61.8±0.5 N. Twisting decreased the maximum tensile force of all sutures; one complete twist per 10mm (i.e. 15 twists) decreased the tensile strength of polydioxanone by 21%, polyglactin by 23%, polypropylene by 16% and nylon by 13%, $p < 0.001$. Excessive twisting caused a non linear decrease in suture strength, with one twist per 75mm (i.e. 20 twists) of polydioxanone decreasing strength by 39%, $P < 0.001$.

Conclusion

The effect of excessive twisting on the mechanical properties of sutures is a previously unrecognised phenomenon. Surgeons should be aware that this can result in a decrease in suture strength and reduce the elasticity of the material, and therefore need to adapt their practice to reduce the torsional force placed on sutures.

Take-home message

Allowing a suture to twist decreases the suture strength and risks suture failure.

078 ENHANCED HAEMOCOMPATIBILITY OF POSS NANOCOMPOSITE: A MATERIAL OF CHOICE FOR CARDIOVASCULAR APPLICATION

Hossein Ghanbari^{1,2}, Maqsood Ahmed¹, Brian G. Cousins¹, George Hamilton³, Alexander M. Seifalian^{1,3}

(1) Centre for Nanotechnology & Regenerative Medicine, Division of Surgery & Interventional Sciences, University College London, London, United Kingdom; (2) Nanotechnology Research Centre, Tehran University of Medical Sciences, Tehran, Iran; (3) Royal Free Hampstead NHS Trust Hospital, London, United Kingdom.

Introduction

Haemocompatibility of cardiovascular implants depends mainly on the induced thrombotic response. Platelet activation, inflammatory response and leukocyte activation induced by biomaterials play central role in haemocompatibility of cardiovascular implants. An advanced nanocomposite has been developed based on polyhedral oligomeric silsesquioxane (POSS) nanoparticle and poly(carbonate-urea)urethane (PCU), with improved properties for cardiovascular application. In this study, haemocompatibility of POSS-PCU was investigated in an in vitro setting.

Methods

Thromboelastograph (TEG) coagulation analyzer was used to analyze whole blood coagulation on the polymer. TEG cups were coated with a thin layer of POSS-PCU and PCU as a control via dip-coating method. Platelet rich plasma and peripheral blood mononuclear cells were extracted from healthy volunteers and exposed to the thin films of POSS-PCU and PCU. Direct ELISA and FACS analysis were used to determine platelet and leukocyte activation and inflammatory cytokine release.

Results

The results showed that incorporation of POSS nanoparticles confers anti-thrombogenic properties to the polymer by a prolonged clotting time and reduced clot propagation and strength. Platelet also adhered less to the POSS-PCU and showed lower activation rate and metabolism. Inflammatory response and leukocyte activation was also significantly less on POSS-PCU samples. The results of flowcytometry showed lower expression of leukocyte activation markers on POSS-PCU and were confirmed by quantitative ELISA results of cytokine release.

Conclusion

These results confirmed that POSS-PCU nanocomposite possesses improved haemocompatibility and anti-inflammation efficacy. This makes POSS-PCU to be considered a material of choice for development of blood contacting devices such as heart valves and bypass graft prostheses.

Take-home message

Application of advanced nanocomposite materials for development of next generation cardiovascular devices with superior features such as improved haemocompatibility could potentially overcome current limitations of cardiovascular implants.

079 HUR AND ITS ROLE IN WOUND HEALING

Bosanquet DC, Harding KG, Jiang WG

Departments of Wound Healing and Surgery, Cardiff University School of Medicine, Cardiff

Introduction

HuR (Human Antigen R) is a ubiquitously expressed member of the Hu family. It is known to have a variety of biological functions which are based on its ability to stabilize mRNA bearing AU- and U- rich elements, thereby affecting their expression. It has been shown to have a central role in carcinogenesis and tumour progression by binding to mRNA that encode proteins involved in cell division, angiogenesis and metastasis. Its role in wound healing is currently unknown.

Methods

We utilised fresh frozen tissue from chronic non-healing (51) and chronic healed (20) venous ulcers, and analysed the level of HuR transcripts using Q-RT-PCR (recorded as: HuR/GAPDH ratio). We developed a subline HaCaT-HuRrib using a HuR transgene to transfect a human keratinocyte cell line, displaying stably reduced HuR expression. We used the ECIS9600 (Electric Cell-substrate Impedance Sensing) model and tested cell adherence and cell migration using an electric wounding methods (results in ohms).

Results

There was a non significant increased trend in HuR expression in healed wounds (median (IQR):0.044(0-0.16)) compared to non-healing wounds (0(0-1.0), $p > 0.05$ by Mann Whitney U test). The HaCaT-HuRrib cell-line demonstrated a slower rate of adhesion (230.7 ± 2.8 ohms) compared to control (247.9 ± 4.1 ohms, $p < 0.001$, by 2-tailed t test). It also showed a slower rate of migration (450.7 ± 27.8 ohms) compared to control (292.6 ± 27.5 ohms, $p < 0.001$).

Conclusion

The HuR protein appears to have an effect on increasing keratinocyte migration, and thus promote wound healing. As such, HuR may play an important role in determining which wounds are at risk of not healing.

Take-home message

HuR, a protein known to play an important role in carcinogenesis and tumour progression, may also promote wound healing through increasing keratinocyte migration.

080 THE ROLE OF EHM2 IN WOUND HEALING

Bosanquet DC, Ye L, Harding KG, Jiang WG

Departments of Wound Healing and Surgery, Cardiff University School of Medicine, Cardiff

Introduction

Ehm2 (for expressed in high-metastatic cells) is a member of the NF2/ERM/4.1 superfamily and is involved in membrane-cytoskeletal interactions via the FERM domain. It is associated with an increased malignant potential in malignant melanoma, prostate carcinoma and breast carcinoma. Its role in wound healing, specifically with regards to keratinocyte motility and migration, has yet to be investigated.

Methods

Using fresh frozen samples from acute surgical and chronic venous ulcer wounds and normal tissue (n=35), we analysed the level of the EHM2 transcripts using Q-RTPCR (recorded as:EHM2/GAPDH ratio). We generated an anti-EHM2 transgene to transfect a human keratinocyte cell line (HaCaT, positive for EHM2 in the wild type) and subsequently developed a subline HaCaTehm2rib with reduced EHM2 expression. The impact of EHM2 knockdown on cell adhesion and migration was determined using an ECIS (Electric cell-substrate impedance sensing) assay.

Results

Ehm2 expression was significantly higher in acute wounds (median (IQR):7.1(4.4-169.8)) when compared to chronic wounds (median (IQR):2.7(0.77-4.8), p=0.038). There was no significant difference between normal tissue (median (IQR):3.3(0.29-19.4)) and both acute (p=0.26) and chronic wound tissue (p=0.58). Wound healing ECIS demonstrated HaCaTehm2rib had a significantly slower rate of cell adhesion to matrix, and cell migration speed, when compared with control cells.

Conclusion

We propose that Ehm2 plays an important role in wound healing by its effect on cell motility and migration, particularly in keratinocytes. Furthermore it may be a useful marker in detecting wounds prone to chronicity and non-healing.

Take-home message

The protein Ehm2 appears to play an important role in wound healing due to its effect on keratinocyte motility and migration.

ORAL PRESENTATIONS 3B UPPER GI

081 MICRORNA-31 MODULATES TUMOUR SENSITIVITY TO RADIATION IN OESOPHAGEAL CANCER

Niamh Lynam-Lennon¹, John V. Reynolds^{1,2}, Graham P. Pidgeon¹, Stephen G. Maher¹

(1) Trinity College Dublin (2) St James Hospital

Introduction

Radiation therapy is fundamental to the treatment of oesophageal cancer. However, radioresistance is a significant clinical problem, with only ~25% of patients achieving a major pathological response following neoadjuvant-CRT. The elucidation of biomarkers/molecular mechanisms underlying radioresistance is of substantial clinical benefit.

Methods

An isogenic model of radioresistance in oesophageal adenocarcinoma was developed. Global microRNA expression was analysed using human microRNA arrays. Overexpression of microRNA-31 was performed using a synthetic pre-miR and Lipofectamine 2000. Radiosensitivity was measured by clonogenic assay. microRNA-31-regulated gene targets were investigated using qPCR-based gene arrays. Diagnostic tumour biopsies were collected from 37 oesophageal cancer patients prior to neoadjuvant-CRT and microRNA-31 and SMUG1 expression was measured by qPCR.

Results

microRNA profiling of a novel isogenic radioresistant oesophageal adenocarcinoma model revealed downregulation of microRNA-31 in radioresistant cells. Overexpression of microRNA-31 re-sensitised radioresistant oesophageal cancer cells to radiation, and altered the expression of 13 DNA repair genes. Increased microRNA-31 expression and microRNA-31-mediated downregulation of the DNA repair gene SMUG1 in pre-treatment tumour tissue biopsies was significantly associated with a good response to neoadjuvant-CRT, and was indicative of increased overall survival and absence of lymph node metastasis.

Conclusion

We demonstrate for the first time the functional role of microRNA-31 in modulating the cellular response to radiation. Reduced microRNA-31 expression in tumour tissue of non-responders suggests a mechanism for resistance to neoadjuvant-CRT, possibly via abrogation of microRNA-31-mediated regulation of SMUG1 and enhanced DNA repair. This strongly implies a role for microRNA-31 as a biomarker of response to neoadjuvant-CRT in oesophageal cancer.

Take-home message

The identification of biomarkers predicting the response to neoadjuvant treatment in oesophageal cancer is of substantial clinical benefit. For the first time, we demonstrate a functional role for microRNA-31 in modulating the cellular response to radiation, and highlight a potential role for microRNA-31 as a biomarker of response to neoadjuvant-CRT in oesophageal cancer.

082 A POTENTIAL PATHOLOGICAL ROLE FOR OMENTAL CD8+ T CELLS IN OESOPHAGEAL ADENOCARCINOMA.

Joanne Lysaght, Emma Allott, Claire Donohoe, Julia Howard, Narayamasamy Ravi, Graham P Pidgeon, John V Reynolds

Institute of Molecular Medicine, Trinity College Dublin

Introduction

Visceral adipose tissue is believed to be fuelling a state of chronic inflammation in obese patients, establishing an environment favourable for tumour growth. However, the exact immunological mechanisms remain unclear. Recent animal studies have pointed to an important role for visceral adipose tissue CD8+ T cells in driving inflammation. This novel study aimed to phenotypically characterise CD8+ T cells in the omentum of oesophageal adenocarcinoma patients (OAC).

Methods

Peripheral blood and omentum were taken from 35 OAC patients and 12 non-cancer patients. T cell activation status and cytokine production were assessed by flow cytometry. IFN- γ concentrations were determined by ELISA.

Results

The omentum is a rich source of CD8+ T cells which display an activated inflammatory phenotype, expressing significantly higher ($p < 0.0001$) CD69, CD107a, CD45RO and IFN- γ than CD8+ T cells in the blood. Omental CD8+ T cells also expressed significantly higher ($p < 0.0001$) IFN- γ than CD4+ T cells, suggesting that CD8+ T cells are an important source of this inflammatory cytokine within visceral fat. Interestingly, significantly higher ($p < 0.05$) IFN- γ expression was observed by both omental CD8+ T cells and conditioned media from omental fat fragments, isolated from cancer patients compared with non-cancer controls. The highest circulating levels of IFN- γ were detected in viscerally obese cancer patients compared with non-obese or non-cancer patients.

Conclusion

This novel study demonstrates that omental CD8+ T cells may be key players in fuelling adipose tissue inflammation, potentially mediated by IFN- γ , and may provide an immunotherapeutic target to attenuate chronic inflammation associated with visceral obesity.

Take-home message

CD8+ T cells within the human omentum are a major source of IFN- γ , which may be responsible for activating other immune cells and driving adipose tissue inflammation. The inflammatory profile of CD8+ T cells is exacerbated in oesophageal cancer patients compared with non-cancer controls, suggesting that this inflammatory milieu may be supporting an environment favourable for tumour progression.

083 PRO-INFLAMMATORY AND PRO METASTATIC PATHWAYS ARE ACTIVATED BY OBESITY IN BARRETT'S METAPLASIA

R Casey, N Ravi, JV Reynolds, G Pidgeon

Trinity College Dublin

Introduction

Barrett's oesophagus, a squamous to columnar cell metaplastic condition in the oesophagus, is the only known clinical precursor of oesophageal adenocarcinoma. Excess adiposity is understood to be a causal factor in Barrett's oesophagus and oesophageal adenocarcinoma, though the exact molecular mechanisms remain elusive.

Methods

Adipose conditioned media (ACM) was prepared from omental adipose tissue from viscerally obese male oesophageal adenocarcinoma patients. Non-neoplastic Barrett's epithelial cells, were cultured in the presence of this ACM over a 24hr period and variations in gene expression was analysed using Human cancer pathway profilers. Genes that showed significant up/down regulation were validated via q-PCR. Gene targets identified in vitro were subsequently analysed in Barrett's metaplasia biopsies from both obese and non obese patients.

Results

After culture in ACM, non-neoplastic Barrett's epithelial cells showed altered expression of a range of genes associated with tumorigenesis. MMP1, IL-8 and VEGFA mRNA levels, increased after ACM treatment while TIMP-3, RB1 and MCAM, mRNA levels decreased. Expression of these targets were then analysed in Barrett's metaplasia biopsies from obese and non obese patients. IL8 expression was significantly up-regulated ($P=0.0395$), in Barrett's metaplasia from obese patients compared to non obese patients.

Conclusion

Growth of non-neoplastic Barrett's epithelial cells in ACM, altered the expression of several well established oncogenes. In Barrett's metaplasia from obese patients, IL8 expression was significantly up-regulated ($P=0.0395$) compared to non obese patients. This adipose tissue derived IL-8 may contribute to the inflammatory microenvironment arising from excess adiposity, potentially contributing to the carcinogenic progression of Barrett's oesophagus.

Take-home message

Obesity can activate certain pro-carcinogenic pathways and these may be responsible for the neo-plastic progression of Barrett's oesophagus to Oesophageal adenocarcinoma

084 PRE-TREATMENT COMPLEMENT SYSTEM SERUM PROTEIN LEVELS PREDICT RESPONSE TO NEOADJUVANT CHEMORADIATION FOR OESOPHAGEAL CANCER

Stephen G. Maher¹, Dermot T. McDowell¹, Sinead A. Murphy¹, Ben C. Collins², Cian Muldoon³, William M. Gallagher², John V. Reynolds¹

Departments of (1) Surgery and (3) Histopathology, Institute of Molecular Medicine, Trinity Centre for Health Science, Trinity College Dublin, St. James's Hospital, Dublin 8; (2) Proteome Research Core, Conway Institute for Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin 4.

Introduction

Only ~30% of oesophageal cancer patients have a major pathological response to neoadjuvant-CRT. The aim of this study was to analyse the serum proteome early into neoadjuvant-CRT to reveal biomarkers indicative of response to therapy.

Methods

31 oesophageal cancer patients received a standard neo-CRT regimen. Pathological response to therapy was assessed using the Mandard Tumour Regression Grade system. Serum was collected at pre-treatment, 24h and 48h timepoints into treatment. Albumin/IgG-depleted serum samples were analysed using SELDI-TOF-MS. Protein/peptide expression difference mapping was performed and the data applied to the EPO-KB database. High-scoring candidates were assayed by ELISA. A Leave-One-Out Cross Validation (LOOCV) prediction algorithm was employed to assess the ability of candidate biomarkers to correctly predict therapeutic outcome.

Results

16 patients had a poor response to therapy, while 15 had a good response. On CM10 chips, 9 protein peaks were significantly different between the two treatment response groups, some at baseline, others at 24h and 48h into neo-CRT. Spectral peaks m/z _8617.685 and m/z _8928.422 were identified as C4a and C3a, respectively, via the EPO-KB. ELISA revealed significantly higher pre-treatment levels of C4a and C3a in poor versus good responders. Subdivision of the response groups by TRG indicated an inverse correlation between levels of C4a and C3a and pathological response to neo-CRT. LOOCV revealed that these two serum proteins predict response to therapy with a sensitivity and specificity of 78.6% and 83.3%, respectively.

Conclusion

This study has identified C4a and C3a as potential pre-treatment biomarkers predicting response to neoadjuvant-CRT for oesophageal cancer.

Take-home message

In a pre-treatment setting, the complement system proteins C3a and C4a can be used to predict oesophageal cancer patient response to therapy.

O85 OMENTAL ADIPOSE TISSUE INCREASES OESOPHAGEAL AND COLORECTAL TUMOUR GROWTH THROUGH A VEGF-MEDIATED MECHANISM

Eric P. van der Stok^{1,2}, Emma Allot¹, Julia Howard¹, Claire L. Donohoe¹, Joanne Lysaght¹, Rob Cummins³, Elaine Kay³, John V. Reynolds¹, Graham P. Pidgeon¹

(1) Dept. Surgery, Institute of Molecular Medicine, Trinity Centre for Health Sciences, St. James's Hospital Dublin. (2) Dept. Surgery, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands. (3) Dept. Pathology, Beaumont Hospital, Royal College of Surgeons Ireland, Dublin

Introduction

Obesity is an independent risk-factor for oesophageal/colorectal adenocarcinoma. Adipose tissue is an endocrine organ secreting numerous factors, including Vascular Endothelial Growth Factor (VEGF). In previous studies, VEGF was identified to be upregulated in an oesophageal cell line following co-culture with omental adipose tissue (OAT) by affymetrix-array. We aimed to investigate the effect of OAT-derived VEGF on tumour survival.

Methods

OAT and serum were harvested from oesophageal/colorectal adenocarcinoma patients and adipose tissue explants cultured to produce adipose conditioned media (ACM). VEGF was quantified in ACM and serum by ELISA. Proliferation of oesophageal (OE33, JH-ESO) and colorectal (HCT15) adenocarcinoma cells following culture with ACM and neutralising-VEGF antibody was determined by BrdU. VEGF levels in tumour tissue was assessed by qPCR. In a 200-patient tissue microarray, VEGF expression was related to clinico-pathological parameters and obesity status.

Results

Omental ACM increased the proliferation of oesophageal and colorectal cancer cells (142% and 180% respectively), and neutralising VEGF significantly ($p < 0.05$) reduced tumour cell proliferation in all lines examined. VEGF levels in the serum were significantly elevated in centrally obese (determined by CT) relative to normal weight patients. VEGF expression was higher in oesophageal tumours from centrally obese patients, and expression in TMAs (Tissue Micro-Arrays) is currently being assessed with respect to overall survival and nodal involvement.

Conclusion

VEGF from OAT increased proliferation in oesophageal/colorectal cancer cells. VEGF expression in oesophageal cancer was higher in centrally obese patients. These findings suggest anti-VEGF strategies are warranted in obesity-associated malignancies, alone or in combination with conventional chemotherapies.

Take-home message

Adipose tissue upregulates tumour cell proliferation through secretion of VEGF. Therapeutically targeting the VEGF-pathway in obese cancer patients warrants further investigation.

O86 PROGNOSTIC IMPACT OF P53 EXPRESSION IN OESOPHAGEAL ADENOCARCINOMACoats MV^{1,2}, Walsh SV¹, Baker L², Jordan L¹, Thompson AM^{1,2}, Exon DJ²

(1) NHS Tayside, Ninewells Hospital, Dundee

(2) University of Dundee, Ninewells Hospital, Dundee

Introduction

Despite advances in multimodality treatment, the outcome for oesophageal adenocarcinoma (AdC) remains poor. Improved understanding of oesophageal tumour biology and the incorporation of predictive molecular biomarkers into clinical practice may help individualise treatment pathways and impact survival. P53, a tumour suppressor gene is frequently inactivated (mutated) in solid tumours, resulting in abnormal accumulation of p53 protein. This study aimed to determine the prognostic significance of p53 expression (tumour & lymph node) in patients who underwent surgical resection for AdC.

Method

One hundred and sixty three patients with oesophageal AdC underwent potentially curative oesophageal surgery between 1997 & 2009. A tissue microarray was constructed using tumour (T) & lymph node (LN) cores from 40 consecutive patients and immunostained using anti-p53 (DO-1) antibody. P53 expression was quick-scored using automated image analysis (Aperio) and correlated with clinico-pathological parameters, overall (OS) and progression-free survival (PFS).

Results

The 5-year OS was 29.7% with a median survival of 20 months. Significant independent prognostic indicators for OS and PFS included male sex ($p < 0.01$), smoking status, T-stage, lympho-vascular invasion, LN and margin positivity ($p < 0.001$). P53 expression was identified in 31/40 patients. Although tumour-p53 protein expression was not predictive of OS or PFS, absent LN-p53 was prognostic ($p < 0.001$ HR 3.13) and independent (β 0.06) using a Cox regression model.

Conclusion

Assessment of lymph node p53 protein expression has the potential to predict survival in patients with oesophageal adenocarcinoma.

Take-home message

P53 protein expression in lymph node tissue has the potential to predict survival in patients with oesophageal adenocarcinoma.

O87 INCREASED BMI DOES NOT ADVERSELY AFFECT VASCULAR FUNCTION MEASURED IN VITRO IN OBESE PATIENTSHye-Chung Kwak¹, Mike Larvin^{1,2}, Saoirse O'Sullivan¹

(1) School of Graduate Entry Medicine, university of nottingham;

(2) Trent Regional Bariatric Surgical Service, Derby Hospitals

Introduction

Literature suggests that increasing adiposity is associated with vascular dysfunction (measured non-invasively). It has not yet been established what the contribution of co-morbidities (such as diabetes and hypertension) is on vascular function in obesity. Therefore, the aim of this study was to establish which patient characteristics correlate with vascular function measured in vitro in obese human subjects.

Methods

The study was approved by Derbyshire Research Ethics Committee. Omental arteries were dissected from specimens removed atraumatically from consenting bariatric and laparoscopic cholecystectomy patients. Vessel rings were mounted on a myograph (Danish Myo Technology, Aarhus) and recorded using Labchart (AD Instruments Ltd, Oxford). Cumulative concentration-response curves were obtained to endothelin, noradrenaline and U46619 (vasoconstrictors); acetylcholine, bradykinin (endothelium-dependent vasodilators), sodium nitroprusside and prostacyclin (endothelium-independent vasodilators) and correlated to various patient characteristics (skin fold thickness, BP, fasting glucose, insulin, HOMA-IR, high density lipoprotein (HDL), cholesterol:HDL, HbA1c).

Results

Insulin and increasing insulin resistance were positively correlated with enhanced relaxation to acetylcholine ($p = 0.01$, $p = 0.01$ respectively), bradykinin ($p < 0.01$, $p < 0.01$) and sodium nitroprusside ($p = 0.01$, $p = 0.01$), but not prostacyclin. Acetylcholine was positively correlated with increasing calculated beta cell function ($p = 0.0126$) and bradykinin was negatively correlated with calculated insulin sensitivity ($p = 0.0006$). HbA1c was positively correlated with contractile responses to vasoconstrictors except to U46619, which was positively correlated with high density lipoprotein levels and increasing body mass index (BMI).

Take-home message

There is no consistent relationship between in vitro vascular function and several markers of metabolic and cardiovascular function, but insulin and HbA1c levels appear to affect some vasoactive agents. Contrary to published literature, we have not found that an increase in BMI or markers of adiposity adversely affect vascular function.

O88 EXCESS VISCERAL ADIPOSITY NEGATIVELY INFLUENCES POST OPERATIVE INFLAMMATORY RESPONSE AND RISK OF COMPLICATIONS IN PATIENTS UNDERGOING GASTROINTESTINAL RESECTION.

Suzanne L. Doyle, Claire L. Donohoe, Julia Howard, Erin McGillycuddy, Graham P. Pidgeon, Joanne Lysaght and John V. Reynolds

Trinity College Dublin

Introduction

Adipose tissue distribution, rather than obesity, is emerging as a key determinant of malignant progression, particularly in gastrointestinal cancer. Visceral adipose tissue is recognised as a metabolically active endocrine organ, fuelling a state of chronic inflammation. The impact of visceral adiposity on standard outcomes in the management of localized gastrointestinal cancer, particularly operative risks, has not been systematically addressed. This study aimed to investigate the association of visceral adiposity with the inflammatory response and incidence of complications postoperatively.

Methods

This retrospective analysis of prospectively collected data included 201 patients who underwent gastrointestinal resection for malignancy with curative intent. Total fat area (TFA), visceral fat area (VFA) and subcutaneous fat area (SFA) were calculated from diagnostic CT scans. Leukocyte counts, C-reactive protein (CRP) and albumin levels preoperatively and at days 1, 3, 7 and 14 postoperatively were obtained from a clinical database. Information on postoperative complications was recorded by a dedicated database manager.

Results

The cohort consisted of 112 upper gastrointestinal and 89 colorectal resections. Following resection, increasing VFA was associated with significantly higher CRP levels. Increasing VFA, but not TFA or SFA, was associated with a higher CRP/albumin ratio on postoperative days 1, 3 and 7 ($p < 0.05$). High VFA was associated with increased risk of infection and minor respiratory complications postoperatively. No association was found between adiposity and mortality.

Conclusion

Excess visceral adiposity is associated with a more pronounced inflammatory response following resective surgery, and is associated with increased risk of infectious and respiratory complications.

Take-home message

Increasing levels of visceral adiposity influence the inflammatory response and risk of complications in patients undergoing gastrointestinal resection for malignancy.

ORAL PRESENTATIONS 4A BREAST

O89 SRC AS A NOVEL THERAPEUTIC TARGET FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER (TNBC)

Walsh S^{1*}, Tryfonopoulos D^{2,3*}, Quinn⁴, Flanagan L⁴, Pierce A¹, McDermott EW¹, Evoy D¹, O'Donovan N², Crown J^{2,3}, Duffy MJ^{1,4}. *Both authors contributed equally this work

1 UCD School of Medicine and Medical Science, University College Dublin, 2 NICB, Dublin City University, 3 Dept of Medical Oncology, 4 Dept of Pathology & Lab Medicine, St Vincent's University Hospital, Dublin, Ireland.

Introduction

TNBC does not express oestrogen or progesterone receptors and lacks amplification of the HER2 gene. Its poor prognosis is attributed to the lack of a specific targeted therapy for its treatment. The aim of this study was therefore to investigate the inhibition of c-src as a potential strategy for the treatment of patients with TNBC.

Methods

Src immunoreactivity was determined using TMAs in 87 TN and 93 non-TN breast cancers. Combinations of dasatinib and cytotoxic drugs were tested in breast cancer cell lines using in vitro proliferation assays. Synergy analysis was performed using the Tchou and Talalay equation on CalcuSyn software.

Results

Expression of cytoplasmic src was observed more frequently in TNBC than non-TNBC (95% compared with 84%, $p=0.012$) Membranous staining for src was found in 74% of TNBCs, versus only 38% of non-TNBCs ($p<0.001$). Using 9 different breast cancer cell lines in culture, dasatinib (an inhibitor of c-src) blocked growth in 3 out of 5 TNBC cell lines with $IC_{50} < 1 \mu M$ (i.e. in MDA-MB-231, HCC-1143, HCC-1937) but in only 1 out of 4 HER2 amplified cell lines. Dasatinib in combination with docetaxel displayed moderate synergy in MDA-MB-231 and HCC-1937 cells ($CI<0.9$). Combined treatment with dasatinib and cisplatin was synergistic in the three dasatinib sensitive cell lines ($CI<0.9$). In MDA-MB-231 and HCC-1143 cells, combined treatment with dasatinib and 5'-DFUR displayed synergy ($CI<0.9$).

Conclusion

We conclude that a combination of dasatinib and cisplatin is a potential new treatment for patients with TNBC.

Take-home message

Increased expression of Src was observed in triple negative breast cancer, compared with non-triple negative breast cancer. In vitro studies suggest that a combination of dasatinib and cisplatin is potentially a new treatment for patients with TNBC.

O90 SILENCING OF TLR4 INCREASES TUMOUR PROGRESSION AND LUNG METASTASIS IN A MURINE MODEL OF BREAST CANCER

A.Ahmed, J.H.Wang, HP Redmond

Department Of Academic Surgery, University College Cork

Introduction

Toll-like receptor 4 is a member of a family of pattern recognition receptors that are involved in host defence against infection. In cancer microenvironment, emerging controversial evidence suggests that TLR4 has a role in maintaining tissue homeostasis by regulating inflammation and tissue repair. Thus far, studies have predominantly focused on the effect TLR4 in cancer cells; however this study focuses on TLR4 in both host immune system and cancer cells.

Methods

3X105 murine mammary adenocarcinoma 4T1 cells and 4T1 cells deficient of TLR4 by lentivirus transduction were inoculated into female wild type (WT) and C3TLR4/BALB/c (TLR4^{-/-}) mice by mammary fat pad injection and divided into a control and a primary tumour resection group. Tumour growth, tumour body weight ratio, lung metastasis and survival of tumour bearing mice were observed.

Results

There was a significant increase in tumour volume on the 2nd, 3rd and 4th week after inoculation of the TLR4^{-/-} mice with 4T1 cells compared to WT ($p<0.001, 0.008$ and 0.006 respectively). The numbers of metastatic lung nodules were significantly higher in the TLR4^{-/-} mice ($p<0.02$). Survival of TLR4^{-/-} mice is dramatically reduced compared to WT ($p<0.02$). The knock down of the TLR4 from 4T1 cells led to a synergistic increased in tumour volume in TLR4^{-/-} mice and compared to normal 4T1 cells ($p<0.001$).

Conclusion

TLR4 has a protective role in the murine metastatic breast tumour model at both host and cancer cells level. Thus, by targeting TLR4 a novel approach in breast cancer treatment can be adopted.

Take-home message

TLR4 has a protective role in the murine breast cancer at both host and cancer cells levels.

091 ASSESSMENT OF AXILLARY LYMPH NODES USING RAMAN SPECTROSCOPY- INTRAOPERATIVE USE IS POSSIBLE

Mr. J Horsnell^{1,2}, Mr P Stonelake³, Mrs. G Shetty³, Dr C Kendall¹, Dr. J Hutchings¹, Prof N Stone¹

(1) Department of Biophotonics Research, Gloucestershire Hospitals NHS Foundation Trust (2) Department of General Surgery, Gloucestershire Hospitals NHS Foundation Trust (3) Department of General Surgery, The Dudley Group of Hospitals NHS Foundation Trust

Introduction

Raman Spectroscopy, a technique based on the inelastic scattering of light, has previously been used to differentiate between normal and metastatic lymph nodes in patients with breast cancer. These studies, however, used a laboratory based spectrometer and took up to 12 hours to assess each node. We aim to replicate these results using a portable spectroscopy system within a time frame that would allow intraoperative use.

Methods

Following ethical approval 38 lymph nodes were collected from 20 patients undergoing axillary surgery. One half of each node was assessed routinely. The other "study half" was assessed by both standard histopathology techniques and Raman spectroscopy. The B&W Tek MiniRamII[®] spectrometer (Newark, USA) was used throughout. 25 spectra requiring a total assessment time of 6min 40secs (16secs per spectra) were collected from each node. Spectral analysis was performed using Matlab[®] software.

Results

25 nodes were defined as negative and 13 as positive for metastases by histopathology assessment. 950 spectra were collected. Principal component analysis (PCA) and PCA fed linear discriminant analysis (LDA) trained by the histopathology result was employed to assess the spectra. PCA fed LDA demonstrated a sensitivity of 97.6% (317/325 spectra) and a specificity of 99.4% (621/625 spectra) at differentiating between positive and negative nodes. Leave one node out cross-validity testing was performed and demonstrated a specificity of 100% and a sensitivity of 92.3% (12/13 nodes).

Conclusion

These results demonstrate that Raman spectroscopy could be used to assess axillary lymph nodes within a time frame that would allow intraoperative use.

Take-home message

Raman spectroscopy is effective at differentiating between positive and negative nodes. The speed at which assessment takes place will allow for intraoperative assessment of sentinel lymph nodes.

092 TRASTUZUMAB TREATMENT OF ENDOCRINE DEPENDENT BREAST CANCER CELLS RESULTS IN UPREGULATION OF ER α

JG Solon, M McIlroy, D Collins, ADK Hill, L Young

Dept of Surgery, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2

Introduction

The mechanism underlying resistance to trastuzumab is unknown, with crosstalk between signalling pathways a potential method. This study aims to elucidate the effect of trastuzumab on the endocrine pathway in breast cancer cells using the ER target gene pS2 to demonstrate activity. Translational studies were performed in a select patient cohort to investigate any clinical implications.

Methods/Results

Estrogen dependent, tamoxifen sensitive MCF-7 (low HER2) and BT-474 (high HER2) and estrogen independent, tamoxifen sensitive LCC-1 (high HER2) breast cancer cells were treated with trastuzumab. Western blotting revealed an increase in ER α protein levels in MCF-7 and BT-474 cells which were not observed in LCC-1 cells. Semi-quantitative RT-PCR was performed on MCF-7 and LCC-1 cells treated with estradiol, tamoxifen and trastuzumab to quantify pS2 mRNA levels. The impact of treatments on pS2 promoter activity was assessed using luciferase assay. Increases in pS2 mRNA were found in MCF-7 cells treated with trastuzumab but not LCC-1 cells, which was also observed at a transcriptional level. Immunohistochemistry revealed increased pS2 staining in a cohort of patients who received trastuzumab prior to surgery, indicating increased activity of the endocrine pathway.

Conclusion

We have shown that at mRNA and transcriptional levels, treatment of estrogen dependent cells with trastuzumab results in upregulation of the endocrine pathway, with corresponding increases in ER α protein levels, a potential mechanism for trastuzumab resistance. This finding was replicated in a small clinical cohort. Treatment of breast cancer needs to consider bidirectional crosstalk between the steroid and growth factor pathways to minimise the development of resistance.

Take-home message

Trastuzumab treatment of estrogen dependent breast cancer cells results in upregulation of the endocrine pathway. Treatment of breast cancer needs to consider bidirectional crosstalk between the steroid and growth factor pathways to minimise the development of resistance.

O93 A DIFFERENTIAL INTRAOPERATIVE TEST FOR THE DETECTION OF SENTINEL LYMPH NODE MICRO- AND MACRO-METASTASES IN BREAST CARCINOMA. RESULTS FROM THE FIRST UK CENTRE ROUTINELY OFFERING THE SERVICE IN CLINICAL PRACTICE.

Madani R¹, Thwaites L², Jafferbhoy S¹, Jackson P², Devalia HL¹, Chakravorty A¹, Irvine TE¹, Layer GT¹ and Kissin MW¹

(1) Breast Unit, (2) Department of Histopathology, Royal Surrey County Hospital NHS Foundation Trust, Guildford, Surrey, GU2 7XX

One-Step Nucleic acid Amplification (OSNA), is a molecular biological assay of cytokeratin-19 (a breast carcinoma epithelial marker) mRNA. It can be employed intraoperatively for detection of lymph node metastases in breast cancer. Patients with positive sentinel nodes may proceed to axillary node dissection (AND) to level 1 or level 3 dependent upon the OSNA quantitative result, during the same surgical procedure avoiding second operation and eliminating technical difficulties possibly associated with delayed AND.

Aims

Our Breast Unit was the first in the UK to implement this novel technique. This study reviews our data following introduction of OSNA "live" on whole sentinel nodes (identified using triple methodology).

Methods

Data presented were collected prospectively from December 2008 for 20 months. All patients eligible for sentinel node biopsy (SNB) were offered OSNA. On detection of micro-metastasis ("OSNA++") a level 1 AND, and for a macro-metastasis ("OSNA+"), a level 3 AND was performed. Results: 377 patients had 798 whole sentinel nodes analysed intraoperatively. 69% had wide local excision, 29% underwent mastectomy and 2% SNB alone. 34% of patients (104/377) had positive OSNA results and proceeded to have a differential AND. Of the 129 patients with positive nodes, 36.4% had micro-metastases and 45.7% had macro-metastases.

Conclusion

In our consecutive series over one-third of patients had positive nodes detected and proceeded directly to appropriate axillary surgery. This technique eliminates the necessity for difficult second surgery due to sentinel node positivity and accelerates the pathway to chemotherapy and/or radiotherapy. This benefits patients, their surgeons and their hospitals.

Take-home message

Differential molecular biological analysis of breast cancer whole sentinel nodes is possible intraoperatively using OSNA allowing for appropriate immediate axillary dissection according to degree of metastasis, speeding up patient journey and avoiding a difficult second axillary operation.

O94 IDENTIFYING NEW TRANSCRIPTIONAL TARGETS FOR SRC-1 IN BREAST CANCER

DP McCartan¹, M McIlroy¹, A Faga², P O'Gaora², ADK Hill¹, LS Young¹

1.Endocrine Oncology Research Group, RCSI, 2.Department of Bioinformatics, Conway Institute, UCD

Introduction

SRC-1 has been implicated as an important mediator of breast cancer metastasis through its actions as a coactivator of non-steroidal transcription factors. The aim of this work was to adopt a genome wide approach to identify new SRC-1 transcriptional targets.

Methods

Tamoxifen resistant breast cancer cells were subject to SRC-1 chromatin immunoprecipitation. Libraries were generated from ChIP output DNA by adaptor ligation, gel purification and PCR. Next generation sequencing was carried out using the Illumina/Solexa Genome Analyzer. Sequence tags were mapped to the human genome. Affymetrix whole genome expression arrays were used to analyse gene expression in cells treated with SRC-1 siRNA in comparison with those treated scrambled siRNA.

Results

A total of 5104 more genes with intervals in the promoter region were identified in the tamoxifen treated ChIP Seq sample. 29% of all identified peaks were present in promoter regions. A total of 186 direct SRC-1 target genes were identified with peaks in the promoter from the ChIP Seq data and with significant down regulation ($p < 0.01$) in the SRC-1 knockout when compared to the wild type cell. We have selected three genes with a potential role in mediating cellular migration and invasion for further molecular validation.

Conclusion

An unbiased, genome wide approach has identified a variety of important, direct SRC-1 target genes. Molecular and translational studies will validate these targets to elucidate their putative role in SRC-1 mediated breast cancer metastasis.

Take-home message

This is the first paper to adopt a genome wide approach to identify new transcriptional targets for the coactivator protein SRC1.

O95 SIGNIFICANT GERMLINE MUTATIONS PREDISPOSING TO BREAST CANCER AMONG THE INDIGENOUS WESTERN IRISH POPULATION

Irwin R¹, Healy NA¹, Cody N³, Ennis R², Kerin MJ¹, Green A³, Sweeney KJ¹

(1) Department of Surgery, National University of Ireland, Galway; (2) Department of Radiology, National University of Ireland, Galway; (3) National Centre for Medical Genetics, Crumlin, Dublin

Introduction

Stratification of familial risk of germline mutations predisposing to breast cancer is essential for effective resource utilisation of breast services. Allocation of these resources should be made according to mutation incidence which is unknown in the Irish context. The NICE guidelines recommend that genetic counselling should be reserved for those with a 20% or higher risk of significant germline mutation. The aim of this study was to determine the appropriateness of referral of individuals to the National Centre for Medical Genetics (NCMG) and the incidence of germline mutations in a genetically homogenous western Irish population.

Methods

A review of the NCMG database was performed identifying indigenous western Irish individuals referred for genetic counselling. Data was available on adequacy of pedigree and counselling outcome. Germline mutation testing results and subsequent management plans were recorded.

Results

Between 1994 and 2010, 380 indigenous western Irish clients were referred to the NCMG for genetic testing, of whom 256 (67.4%) were deemed of adequate pedigree for counselling. Over half the clients offered counselling declined, with the remaining 184 (48.4%) counselled and 127 (33.4%) subsequently tested. Clinically significant germline mutations were identified in 35 clients (BRCA1; n=20, BRCA2; n=15).

Discussion

These results reflect poor understanding of hereditary cancer risk, among the referring doctors, reflected in large number of inappropriate referrals. Furthermore, the low germline mutation rate (13.7%) among those deemed of adequate pedigree for counselling suggests that selection criteria should be re-examined and the threshold for counselling increased.

Take-home message

This study highlights the poor understanding of hereditary breast and ovarian cancer risk among referring doctors. It also illustrates the need for re-examination of selection criteria for genetic testing and the counselling threshold increased.

O96 EVALUATION OF THE CONTRIBUTION OF GENETIC VARIANCE TO CHEMOTHERAPY RESPONSE IN BREAST CANCER

Mrs Helen Ballal¹, Miss Roshan Koron¹, Dr Nitin Khirwadikar², Mr Chris Holcombe², Professor D Ross Sibson¹

1 Institute of Translational Medicine, Cancer Research Centre, University of Liverpool, 2 Royal Liverpool Hospital

Introduction

Molecular markers for underlying cellular pathways may complement clinical classifications leading to a more accurate prediction of chemotherapy response. We are therefore assessing the predictive value of naturally occurring genetic variants selected in a hypothesis driven manner.

Methods

300 samples from a retrospective tissue bank cohort were used under ethics approval. Variants having significance for processes contributing to outcome were considered. These included apoptosis, cell cycle, metabolic drug response, and metastasis related genes. Scoring was by real-time PCR analysis.

Results

T stage is associated with variants in HER2neu ($p=0.008$), the metastasis related gene SPP1 ($p=0.03$) and Bax ($p=0.01$) and was near significance for the apoptotic related gene MDM2 ($p=0.09$). SPP1 genotype was also related to oestrogen receptor status ($p=0.03$). MTHFR variants thought to be a risk factor for breast cancer and early relapse were in this cohort associated with the presence of lymphovascular invasion ($p=0.02$). Variants showing trends associated with overall survival were HER2neu ($p=0.17$), SPP1 ($p=0.13$), apoptotic pathway genes (p53 ($p=0.08$), MDM2 ($p=0.11$)) and metabolic genes GSTP1 ($p=0.08$) and CYP2B6 ($p=0.06$). Overall survival was related to gene variants in HER2 and SPP1 ($p=0.02$ each), and p53 and Bcl2 ($p=0.04$ each) and showed a trend towards Cyclin D1 ($p=0.06$) variants. Disease free survival was related to p53 and HER2 variants ($p=0.009$ and 0.02 , respectively) with a trend towards SPP1 variants ($p=0.06$).

Conclusion

Genetic variants may be attractive biomarkers, stratifying patients for chemotherapy.

Take-home message

Genetic variants may be useful biomarkers in predicting patient's response to chemotherapy and personalising treatment in the future.

097 EXPRESSION OF GENES RELATED TO NEUROTROPHIN SIGNALLING IN BREAST CANCER - IN SEARCH OF NOVEL THERAPEUTIC TECHNIQUES

Helen Earley¹, Healy N¹, Gorman A², Miller N¹, Kerin MJ¹

Department of Surgery (1) and Biochemistry (2) National University of Ireland Galway

Introduction

One of the potential mechanisms underlying the heterogeneity of breast cancer is believed to result from the complex interactions between oestrogen and growth factor signalling pathways. Neurotrophins are a superfamily of polypeptides including Nerve-Growth-Factor (NGF), Brain-Derived-Neurotrophic-Factor (BDNF) and their receptor molecules Neurotrophin Tyrosine Kinase-3 (NTRK3), Receptor-Interacting-Serine-Threonine-Kinase-2 (RIPK2) and Brain-Expressed-X-Linked (BEX1), which stimulate cell survival and differentiation. The aim of this study was to quantitatively examine the expression of these neurotrophin signalling genes in breast cancer patients. Methods A cohort of breast cancer ($n=56$) and normal ($n=17$) tissue samples was compiled from the Department of Surgery BioBank, UCHG. Samples were classified on the basis of clinicopathological parameters. Expression levels of candidate genes were performed using triplicate Taqman assays and a validated endogenous control. Relative quantitation was determined using the comparative CT method ($-2^{-\Delta\Delta CT}$). Statistical analysis was performed using Qbase and SPSS software.

Results

A significant reduction in NGF expression was observed in tumours compared to normal tissues. Conversely, RIPK2 expression was significantly increased in tumour samples ($p<0.001$). Expression levels of targets were then compared based on intrinsic subtype. Significant associations between BEX1 ($p<0.05$) and NTRK3 ($p<0.01$) were observed in HER2/neu negative tumours. NTRK3 also showed significant variation in expression between the Luminal A and Luminal B subtypes.

Conclusion

The significantly higher levels of BEX1 and NTRK3 expression in poor prognosis HER2/neu negative tumours indicates the potential of these genes as novel therapeutic targets. This is the first study to quantify expression of these targets in relation to breast cancer.

Take-home message

The significantly higher levels of BEX1 and NTRK3 expression in poor prognosis HER2/neu negative tumours indicates the potential of these genes as novel therapeutic targets. This is the first study to quantify expression of these targets in relation to breast cancer.

098 TGF- β 1 MEDIATED STIMULATION OF VEGF SECRETION BY BREAST CANCER CELLS

M. Costello, R.M. Dwyer, J. Ryan, M. Hartmann and M.J. Kerin

Division of Surgery, School of Medicine, National University of Ireland, Galway

Introduction

The cytokines TGF- β 1 and CCL5 have been implicated in breast cancer pathogenesis. Previous studies in this laboratory have shown a positive correlation between the two factors in breast cancer patients both at a circulating and gene expression level. The aim of this study was to investigate the effect of CCL5 and TGF- β 1 on breast cancer epithelial cells individually and in combination.

Methods

T47D (hormone receptor positive) and MDA-MB-231 (hormone receptor negative) cell lines were incubated for 72 hours in the presence of CCL5 (25ng/mL or 50ng/mL) +/- TGF- β 1 (2ng/mL). Following incubation, conditioned media was harvested and subjected to ELISA to quantify levels of CCL5, TGF- β 1 and VEGF secreted by the cells. RNA was also extracted and subjected to RQ-PCR to detect changes in expression of CCL5, TGF- β 1 and their principal receptors CCR5 and TGF- β RII.

Results

In T47D cells, when cultured in the presence of CCL5, a dose dependant increase in TGF- β 1 secretion was observed. In the MDA-MB-231 cell line, incubation with TGF- β 1 caused a significant increase in CCL5 secretion. In addition, VEGF levels increased >6-fold in the presence of TGF- β 1 (MDA-MB-231:209.34pg/mL, MDA-MB-231 + 2ng/mL TGF- β 1:1534.9pg/mL). Gene expression analysis of both cell lines showed a change in TGF- β 1 expression across all incubation conditions, with the greatest effect seen in cells incubated in the presence of the ligand.

Conclusion

CCL5 and TGF- β 1 both alone and in combination, have a distinct effect on breast cancer cell lines and may play a role in tumour angiogenesis through stimulation of increased VEGF secretion.

Take-home message

CCL5 and TGF- β 1 may play a role in tumour angiogenesis through increased VEGF secretion. This study suggests a mechanism for TGF- β 1 mediated stimulation of this process and warrants further investigation.

099 DEVELOPMENT OF IMMUNOHISTOCHEMICAL SURROGATES FOR PREDICTION OF BREAST CANCER PATIENT OUTCOME VIA HIGH-THROUGHPUT ANTIBODY GENERATION AND VALIDATION USING TISSUE MICROARRAY TECHNOLOGY

R.T. Dolan^{1,5}, S. Penny¹, C.M. Kelly¹, D.J. Brennan¹, E. Rexhepaj¹, K. Jirstrom², F. Ponten³, M. Uhlen⁴, W.M. Gallagher¹, M.R. Kell⁵

(1) UCD School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Ireland; (2) Lund University, Sweden; (3) University of Uppsala, Sweden; (4) Royal Institute of Technology, Stockholm, Sweden; (5) Department of Breast & Endocrine Surgery, Mater Misericordiae University Hospital, Dublin, Ireland.

Introduction

Omic-based discovery approaches, such as DNA microarray-based gene expression profiling, have provided powerful tools for biomarker identification, however the development of immunohistochemistry (IHC) based surrogates may provide more clinically applicable assays.

Methods

We applied a novel bioinformatic technique to identify a cohort of several hundred candidate progression-associated biomarkers. Of these genes, 137 targets were then selected for antibody production. Antibodies were screened via Western blot analysis and IHC against a range of normal (n=48) and tumour (n=20) types, as well as cultured cells (n=66), represented on tissue microarrays (TMAs). Highly optimised antibodies were screened against a TMA constructed from a cohort of 512 consecutive breast cancer cases to validate the surrogate.

Results

Screening revealed 3 potentially prognostic markers; PBK ($p = 0.002$) and ANLN ($p = 0.001$) were poor prognostic markers, whilst PDZK1 was a good prognostic marker ($p < 0.001$). Validation of the 3 protein signature using IHC in 247 breast cancers confirmed the association with decreased breast cancer-specific survival (BCSS) ($p = 0.002$). This novel signature was associated with tumour grade ($p=0.001$), nodal status ($p=0.021$), ER ($p=0.002$), PR ($p=0.007$), HER2 ($p=0.022$) and Ki67 status ($p<0.001$). Multivariate Cox regression analysis revealed that the panel score was an independent predictor of BCSS (HR - 4.99, 95% CI 1.13 - 22.06, $p = 0.034$).

Conclusion

We have developed a comprehensive biomarker pathway that extends from discovery through to validation on TMA and is yielding clinically relevant biomarker panels.

Take-home message

We developed a comprehensive biomarker pathway extending from discovery through to validation on TMA, that yielded a novel 3 Panel protein signature as an independent prognostic determinant in breast cancer. Such developments represent an important translational gateway into the era of individualised medicine.

O100 EXPRESSION PROFILING OF CIRCULATING MIRNAS IN BREAST CANCER**NA Healy, HM Heneghan, AJ Lowery, Miller N, MJ Kerin**

Department of Surgery, National University of Ireland, Galway

Introduction

MiRNAs are a class of short, single stranded RNA molecules that play key roles in the regulation of gene expression. The recent identification of the presence and dysregulation of systemic miRNAs in association with malignancy illustrates their potential as biomarkers. The aim of this study was to validate the presence of miR-195 and let-7a in the circulation of breast cancer patients and identify additional miRNAs that may lend to the sensitivity and specificity of these miRNAs.

Methods

Whole blood was prospectively collected from 200 pre-operative breast cancer patients and 70 age-matched healthy controls. Following RNA extraction, reverse transcription was performed using primers specific to each miRNA target of interest. Expression levels of the miRNAs were quantified using RQ-PCR. Data was correlated with clinicopathological parameters and analysed using a combination of QBasePlus and SPSS v17.0.

Results

This study confirmed significantly deranged expression levels of systemic miR-195 and Let-7a in breast cancer patients. For both of these miRNAs expression levels were observed to be consistently higher in breast cancer patients ($p < 0.001$) when compared with disease free controls. In addition miR-342 and miR-181c also displayed higher mean expression levels in cancer cases. Let-7a was deemed to have higher expression levels in in situ disease and these expression levels decreased with progressive stages of disease.

Conclusion

This study highlights the presence and dysregulation of cancer-specific miRNAs in the circulation of breast cancer patients and highlights the potential for this systemic miRNAs to aid in both diagnosis and prognostication of this disease.

Take-home message

This study illustrates the potential for circulating miRNAs to act as biomarkers in the diagnosis and detection of recurrence in breast cancer.

ORAL PRESENTATIONS 4B TRANSPLANT

0101 OPTIMISATION OF CARDIAC PRELOAD AND ITS EFFECTS ON EARLY GRAFT FUNCTION FOLLOWING RENAL TRANSPLANTATION USING OESOPHAGEAL DOPPLER MONITORING (ODM)

A Bagul, SL Bell, SA Hosgood, U Mathuram Thiyagarajan, H Pereria, ML Nicholson
University Hospitals of Leicester

Introduction

Optimal volume maintenance is essential to prevent acute renal failure during major surgery and to ensure graft function after renal transplantation. We report the use of ODM to optimize flow related haemodynamic variables during peri-operative management of renal transplantation.

Methods

16 consecutive patients undergoing renal transplantation were analysed with an OD probe in addition to central-venous-pressure (CVP) and blood-pressure (BP). The aim was to maintain a descending aortic corrected flow time (FTc) of ≥ 375 ms

Results

The patient group included the following demographics; age 48 ± 12 , BMI 25 ± 4 , Hb 11.4 ± 1.8 , M:F 11:5, Hypertension 11, while all received Methyl prednisolone 500mg and were from ASA III. The FTc at start (S) of operation was 365 ± 29 , reperfusion (R) 371 ± 33 and end of surgery (E) 412 ± 100 , which is associated with a cardiac-output (CO) [S(5.5 ± 1.6);R(6.17 ± 1.6);E(7.18 ± 1.9)] ($p=0.040$). The CVP[S(9.8 ± 3.2);R(13 ± 1.4);E(13.1 ± 13.3)] and systolic BP [S(97 ± 17);R(110 ± 17);E(124 ± 19)] also significantly improved. The patient median stay was 8 days, while none developed delayed-graft-function(DGF) or pulmonary oedema. The eGFR on day 11 was 59 ± 17 compared to a pre-op of 10 ± 4 and similarly the serum creatinine was 125 ± 54 compared to 602 ± 219 .

Conclusion

Oesophageal Doppler monitoring can be used to non-invasively optimise the cardiac pre-load and thus quantifies a randomised controlled study to assess its effects with just CVP and BP peri-operative monitoring during renal transplantation.

Take-home message

Oesophageal doppler monitoring can be used to optimise the perioperative fluid management in renal transplantation

0102 EXPERIMENTAL TRANSPLANTATION OF DECELLULARISED INTESTINAL SCAFFOLDS

M Somasundaram¹, A Nowocin¹, SM Gabe², PJ Friend³, PD Sibbons¹, TI Ansari¹

1. Northwick Park Institute for Medical Research, Harrow, UK. 2 St Mark's Hospital and Academic Institute, Harrow, UK. 3. Nuffield Department of Surgery, University of Oxford, UK.

Introduction

Morbidity associated with transplantation of autologous tissues has led to the perception of tissue engineered grafts as a viable alternative. Attempted tissue engineering of the small intestine has been undertaken but the colon has received scant attention by comparison. We describe the development of a large intestinal extracellular matrix (ECM) scaffold for transplantation in a large animal model.

Methods

Heart beating retrieval of 15cm distal colon with intact vascular arcade was performed in swine. Decellularisation was performed using a peristaltic pump, supplying intestinal and vascular lumens with a combination of SDS[†], trypsin & EDTA^Ω and DNAase enzyme solutions. Histological analysis by H&E and Picrosirius/ Miller's Elastin staining was used to establish an adequate decellularisation protocol. Vascular transplantation of future specimens was performed using various surgical approaches. Isolation of organoid units (cellular aggregates within a villus core of epithelial cells and mesenchymal tissue) for cell seeding of the ECM was attempted using established cell culture protocols.

Results

Decellularised colon, with maintenance of ECM architecture was demonstrated histologically. The scaffold was implanted in swine, with small vessel thrombosis limiting graft survival. Colonic organoid units were isolated, with further characterisation currently being undertaken.

Conclusion

Large animal colon can be successfully decellularised enzymatically whilst maintaining ECM and small vessel architecture. Overcoming the surgical challenges of transplantation and revascularisation may pave the way for cell seeding with organoid units and form a novel future treatment. [†] Sodium Dodecyl Sulphate, ^Ω ethylenediaminetetraacetic acid.

Take-home message

Successful decellularisation of the colon to create a scaffold for cell seeding may provide a route to creation of a neo-intestine.

0103 NAKED SMALL INTERFERING RNA (SIRNA) OF CASPASE-3 IN PRESERVATION SOLUTION AND AUTOLOGOUS BLOOD PERFUSATE PROTECTS ISOLATED ISCHAEMIC PORCINE KIDNEYS

Bin Yang, Sarah A Hosgood and Michael L Nicholson

Transplant group, Department of Infection, Immunity and Inflammation, University of Leicester, Leicester General Hospital, University Hospitals of Leicester, United Kingdom

Introduction

Ischemia/reperfusion injury (IRI) plays key roles in graft viability and post-transplantation function. Caspase-3 associated with apoptosis and inflammation is up-regulated by IRI. We propose that naked siRNA targeting caspase-3 may prevent IRI and improve kidney quality during preservation.

Methods

Porcine kidneys were retrieved after 10 minutes of warm ischaemia and flushed with 500 ml of hyperosmolar citrate (HOC). Caspase-3 siRNA was administered directly into the renal artery in HOC solution (30 mg/L) with the renal vein clamped, and into autologous blood (1.5 mg/L), both of which were stored for 24 hours on ice. The kidneys were then reperfused with oxygenated autologous blood for 3 hours on an isolated organ perfusion system to assess renal function.

Results

In the siRNA treated group the expression of 32 kD caspase-3 precursor and 17 kD active subunit was down-regulated by 30% and 56% respectively. Consequently, apoptotic cells in the renal cortex were significantly decreased by 47%, whereas inflammatory cells were only marginally reduced by 26%. Caspase-3 siRNA also doubled oxygen consumption and significantly neutralised perfusate pH. Renal blood flow from 5 minutes to 3 hours was gradually increased by caspase-3 siRNA, marginally improved at the end of 3-hour reperfusion by 45%.

Conclusion

The administration of caspase-3 siRNA directly to the kidney and haemoperfusate during cold preservation improved IRI with reduced caspase-3 and apoptosis, and better renal oxygenation and acid-base homeostasis. This proof of principle experiment using a novel siRNA therapy in large animal organs provides valuable data for human kidney transplantation.

Take-home message

The administration of caspase-3 siRNA directly to the artery of the kidney and haemoperfusate during cold preservation improved IRI with reduced caspase-3 protein and apoptosis, better renal oxygenation and acid base homeostasis. This proof of principle experiment using a novel siRNA therapy in large animal organs provides valuable and transferable data for the potential modulation of human kidney donors.

0104 HYPOTHERMIC MACHINE PERFUSION AFTER STATIC COLD STORAGE DOES NOT IMPROVE THE PRESERVATION CONDITION IN AN EXPERIMENTAL PORCINE KIDNEY MODEL

Sarah A Hosgood, Atul Bagul, Ismail H Mohamed, Michael L Nicholson

University Hospitals of Leicester

Background

Hypothermic machine perfusion (HMP) is emerging as an improved method of preservation compared to static cold storage (CS) techniques. However, the effects of combining the techniques as a more practical approach to preservation have not been fully determined.

Methods

Porcine kidneys were retrieved after 10 minutes in situ warm ischaemia, then flushed with Hyperosmolar citrate (HOC) preservation solution and preserved for a total of 18 hours by either CS, HMP or 14 hours CS followed by 4 hours of HMP (4 HMP). Kidneys were reperfused for 3 hours with oxygenated autologous blood on an isolated organ perfusion system to assess renal function and injury parameters.

Results

Intrarenal resistance (IRR) was significantly higher in the 4 HMP group compared to the other groups [Area under the curve (AUC) IRR; 4 HMP 8.48 ± 2.97 , HMP 3.78 ± 1.68 , CS 3.41 ± 1.80 mmHg/min; $P=0.011$] and levels of creatinine clearance (CrCl) lower compared to HMP (AUC CrCl; 4 HMP 2.3 ± 0.6 , HMP 9.8 ± 7.3 , CS 2.2 ± 1.7 ml/min/100g.h; $P=0.022$). Levels of endothelin-1 (ET-1) were higher in the 4 HMP and CS groups (ET-1; 4 HMP 21.6 ± 4.0 , CS 24.2 ± 2.3 HMP 11.4 ± 4.6 pg/ml; $P=0.002$) and cellular damage significantly increased in the 4 HMP group.

Conclusion

This study demonstrated no advantage of the addition of 4 hours HMP after a significant period of static cold storage in porcine kidneys with warm ischaemic injury. Renal and tubular cell function were not improved and there was indication of an additional loss of cellular integrity.

Take-home message

There should be some caution in combining preservation techniques to enhance the preservation condition of ischaemically damaged kidneys.

O105 DONOR TYPE DOES NOT INFLUENCE THE INCIDENCE OF MAJOR UROLOGICAL COMPLICATIONS AFTER KIDNEY TRANSPLANTATION

Kourosh Saeb-Parsy¹, Vasilis Kosmoliaptsis¹, Linda D Sharples², Christopher J Watson¹, Menna R Clatworthy³, Craig J. Taylor⁴, Gavin J Pettigrew¹, J Andrew Bradley¹

(1) Department of Surgery, Cambridge; (2) MRC Biostatistics Unit, Cambridge; (3) Department of Renal Medicine, Cambridge; (4) Tissue Typing Laboratory, Cambridge

Background

There has been a marked recent increase in the proportion of kidneys transplanted from live donors (LD) and donors after cardiac death (DCD) compared to donors after brain death (DBD). The purpose of this study was to compare the incidence of major urological complications (MUCs: urinary leak and ureteric stenosis) in kidney transplants procured from LD, DCD and DBD donors and to identify factors associated with MUCs.

Methods

We studied 901 consecutive renal transplants (LD:181, DCD:198 and DBD:522) performed in the Cambridge Transplant Centre during 1998-2008 by retrieving data from a prospective, cross-audited database and detailed case-note review. A ureteroneocystostomy over a double pigtail ureteric stent was performed in all transplants and ureteric stents were removed after approximately 6 weeks.

Results

3 patients developed urine leak and 21 developed ureteric stenosis (US). There was no significant difference in the incidence of US in kidneys retrieved from LD (2.8%), DBD (1.7%) or DCD (3.5%) donors ($p=0.28$). Ureteric stenoses were treated by surgical reconstruction. Recipients with US had a higher incidence of acute rejection (48% vs 27%; hazard ratio 3.2, $p=0.005$) and urinary tract infections prior to the diagnosis of US (48% vs 19%; hazard ratio 3.0, $p=0.01$). The incidence of delayed graft function (38% vs. 26%), cold ischaemia times (12.9 vs 13.5 h) and graft survival was not significantly associated with US.

Conclusion

The incidence of MUCs is similar in kidneys transplanted from LD, DCD and DBD donors. When complications do occur, they can be treated successfully by surgical reconstruction.

Take-home message

The incidence of urological complications is similar in kidneys transplanted from LD, DCD and DBD donors.

O106 PRE-EMPTIVE IMMUNOSUPPRESSION USING TACROLIMUS FOR LIVING KIDNEY TRANSPLANTATION

Mohamed IH, Hosgood SA, Nakedar S, Bagul A, Horsburgh T, Nicholson ML

Department of Infection, Immunity and Inflammation, Transplant Surgery Group, University of Leicester, Leicester General Hospital

Introduction

Recent clinical practice guidelines advocate the use of pre-emptive immunosuppression in live donor kidney transplantation without a clear evidence base. This analysis compares the efficacy of pre-emptive immunosuppression with Tacrolimus mono therapy versus standard immunosuppression commenced at the time of transplantation.

Methods

Prospectively collected data was used to compare the outcome of a series of live donor kidney transplants in which 99 patients received pre-emptive Tacrolimus mono therapy for two weeks (PE) and 100 patients received standard immunosuppressive therapy beginning on the day of transplantation (control). The main outcome measures were the incidence of biopsy-proven acute rejection (BPAR) at three months, allograft function and allograft survival.

Results

Pre-emptive immunosuppression with Tacrolimus mono therapy did not decrease the incidence of BPAR at three months (PE 13/99 vs. Control 6/100; $P=0.097$). There were no differences in allograft function measured by serum creatinine at one year (PE 130 ± 36 vs. Control $142\pm 69\mu\text{mol/L}$; $P=0.6829$). One-year graft survival was equivalent in the two groups (PE 96.9 vs. Control 97.0%; $P=0.9915$). There were no differences in Tacrolimus levels at one week post-transplantation in the two groups (PE 13.6 ± 3.6 vs. Control 11.1 ± 5.8 ; $P=0.1276$).

Conclusion

This study suggests that pre-emptive immunosuppression with Tacrolimus mono therapy has no effect on the outcomes of live donor kidney transplantation.

Take-home message

Pre-emptive immunosuppression with Tacrolimus mono therapy for a period of two weeks does not confer any advantages to the recipients of live donor kidney transplants.

0107 PRIMARY HUMAN HEPATOCYTE FATE IS MODULATED BY INTRACELLULAR REACTIVE OXYGEN SPECIES GENERATION AND CD154 DURING HYPOXIA-REOXYGENATION INJURY

Ricky H Bhogal, David H Adams, Simon C Afford

University of Birmingham

Background

After liver transplantation, tissue hypoxia is followed by reoxygenation (H-R). Hypoxia and H-R can lead to hepatocyte death. During hypoxia and H-R, hepatocytes are exposed to pro-inflammatory cytokines including the Tumor Necrosis Factor- α (TNF- α) super-family member CD154. This ligand can activate CD40 receptors expressed by hepatocytes resulting in apoptosis. Hypoxia and H-R leads to the generation of reactive oxygen species (ROS), but whether CD154-CD40 can augment ROS accumulation within human hepatocytes is not known. We determined the mechanistic relationship between activation of CD40, ROS generation and human hepatocyte cell death during normoxia, hypoxia and H-R.

Methods

Isolated human hepatocytes were exposed to an in vitro model of hypoxia and H-R. Hepatocyte ROS production, apoptosis and necrosis were determined by labelling cells with 2',7'-dichlorofluorescein, Annexin-V and 7-AAD respectively in a three-colour reporter flow cytometry assay.

Results

Co-incubation of hepatocytes with recombinant CD154 augmented ROS accumulation during normoxia and H-R enhancing apoptosis and necrosis. Pre-treatment of hepatocytes with the NADPH oxidase inhibitor, Diphenyliodonium (DPI) inhibited CD154-mediated ROS production with concomitant decrease in hepatocyte death. The JNK inhibitor SP600125 and p38 inhibitor PD196319 attenuated CD154-mediated apoptosis but not necrosis. CD154 mediated NADPH oxidase-dependent Fas Ligand (FasL) expression during hypoxia and H-R.

Conclusion

CD40 activation induces human hepatocyte apoptosis via two mechanisms; the accumulation of ROS and activation of JNK and p38 during normoxia and H-R and FasL expression during hypoxia. These findings demonstrate that different signalling pathways are initiated by CD40-CD154 during normoxia, hypoxia and H-R to induce human hepatocyte cell death.

Take-home message

Reactive Oxygen Species are able to regulate human hepatocyte cell death during hypoxia and hypoxia-reoxygenation by modulating a number of intracellular signaling pathways.

0108 DONATION AFTER CARDIAC DEATH (DCD) FOR LIVER TRANSPLANTATION: IDENTIFYING THE USABLE GRAFTS

Diego Davila¹, Ruben Ciria¹, Javier Briceño², Wendy A. Littlejohn¹, Parthi Srinivasan¹, Andreas Prachalias¹, Hector Vilca-Melendez¹, Wayel Jassem¹, Mohamed Rela¹, Nigel Heaton¹

(1) King's College Hospital, London, UK (2) Hospital Reina Sofia, Cordoba, Spain

Introduction

Shortage of organs for transplantation has led to the reintroduction of DCD with the hope of increasing the donor pool.

Methods

Retrospective analysis of DCD and Donors-after-Brain-Death (DBD) offers to our Unit from 2001 to 2009. Accepted and declined DCD offers were compared (T-test and chi-square) and divided among Cardiac-arrest and No-Cardiac-arrest.

Donors who arrested were divided into used and unused grafts. Descriptive comparisons and conditional step-forward logistic-binary-regression models to assess predictors of Cardiac-Arrest and usability were performed.

Results

Of 982 DCD offers, 550 were accepted. Of these, 315 patients had Cardiac-Arrest and 155 livers were used for transplantation. Donor age, ITU stay, GGT, AST and ALT were statistically higher in the declined offer group. In the DCD group, donor age >50 years (RR=1.786 [1,078 - 2,958]) and use of inotropes (RR=0.159 [0,091-0,279]) were independent predictors of Cardiac-Arrest and Cardiac-Arrest in the regression model (Prediction capability=71,1%). Donor age>50 years (RR=2,823 [1,429-5,577]), Body-Mass-Index>30 (RR=6,095 [2,242-16,569]), Warm-Ischemia-Time>25 minutes (RR=5,622 [1,721-18,365]), ITU stay>7 days (RR=3,526 [1,165-10,671]) and ALT≥4x normal rates (RR=3,187 [1,019-9,971]) were risk factors for the graft usability. The relative risk of non-usability was 21% (13,3%-28,7%), 42% (28,3%-55,1%), 58,3% (45%-72%), 79% (71,3%-86,7%) and 100% according to the accumulation of 1 to 5 risk factors respectively.

Conclusions

DCD is a significant source of grafts in our programme. We have developed models, which might be used to predict death and graft usability in potential DCDs which may help to avoid unnecessary retrievals and healthcare expenditure.

Take-home message

Donor age>50 years, Body-Mass-Index>30, Warm-Ischemia-Time>25 minutes, ITU stay>7 days and ALT≥4x normal rates are risk factors for the graft usability.

O109 POSITIVE LUMINEX IN CADAVERIC RENAL TRANSPLANTATION AND ITS EARLY PREDICTABILITY OF GRAFT FUNCTION, REJECTION EPISODES.

U Mathuram Thiyagarajan, A Bagul, T Horsburgh, ML Nicholson

University Hospitals of Leicester

Introduction

Until now a positive immunological crossmatch was considered as a contraindication for renal transplantation. The Luminex crossmatch is highly sensitive on detecting human leucocyte antigen (HLA) antibodies. This study aimed to assess the effect of a positive Luminex and its early predictability of graft function and biopsy proven acute rejection (BPAR) in cadaveric transplantation.

Methods

This study was carried out on a retrospectively collected data of all cadaveric renal transplant recipients between 2007-2009 with 1 year follow-up. During the data collection the investigator was blinded for crossmatch results; graft function was assessed by estimated GFR (eGFR) and rejection episodes. All recipients were on standard tacrolimus /rapamycin, MMF and prednisolone immunosuppression.

Results

All recipients (n= 53) were grouped according to the HLA class I and II results. HLA class I positivity noted in 17 and was negative in 36. Similarly, HLA class II antibody was positive, negative in 12, 41 respectively whilst 7 of them were positive for both. The HLA class I and II positive group did not show any difference in e GFR (P =0.75) after transplantation. HLA class I positive group had higher rejection rate (P =0.04) but not in HLA class II (P = 0.19).

Conclusion

From our study we conclude that HLA class I and II antibody does not affect early and intermediate graft function and HLA class I positivity is an independent risk factor for biopsy proven acute rejection.

Take-home message

HLA class I and II antibody does not affect early and intermediate graft function and HLA class I positivity is an independent risk factor for biopsy proven acute rejection in cadaveric renal transplantation.

O110 LONGEVITY OF THE DIRECT AND INDIRECT CD4 T CELL ALLOIMMUNE RESPONSES

J. Ali, K. Elliott, M. Negus, R. Motallebzadeh, T. Conlon, K. Saeb-Parsy, E. M. Bolton, J. A.

Bradley, G. J. Pettigrew

Department of Surgery, University of Cambridge

Introduction

The immune response to an organ transplant is unique because, in addition to self-restricted 'indirect' recognition of processed alloantigen, recipient CD4 T cells recognise intact alloantigen 'directly' on donor antigen presenting cells (APCs). The direct response is particularly strong and thought to dominate the early transplant response, but because donor APCs are short-lived, chronic rejection is thought to be mediated by the indirect pathway. The relative longevity of the two pathways has not, however, been formally examined.

Methods

Fluorescently-labelled monoclonal populations of transgenic CD4 T cells, each of which recognise donor MHC-I, MHC-II or minor alloantigen directly or indirectly, were adoptively transferred to recipients of mouse heart allografts either on the day of transplant or after 5 weeks. Flow cytometric analysis was used to assess the strength of the alloimmune response by quantifying division of the adoptively transferred CD4 T cells.

Results

Directly-alloreactive CD4 T cells divided extensively at day one but minimally after five weeks. The indirect alloresponse to donor MHC-I was equally strong early and late after transplantation, but the indirect allorecognition of MHC-II was short-lived presumably due to eradication of MHC-II-expressing donor APCs. The indirect alloresponse to minor alloantigen persisted but was less marked after five weeks.

Conclusion

Our results confirm the transience of the direct alloimmune response, but unexpectedly highlight that the longevity of the indirect response is also dependent upon alloantigen availability. This raises important questions regarding how CD4 T cell help is provided for production of late anti-MHC class II alloantibody.

Take-home message

Whereas direct allorecognition is a short lived process, the longevity of indirect allorecognition is dependent upon alloantigen availability.

0111 B-CELL RICH NODULAR INFILTRATES IN CHRONIC ALLOGRAFT INJURY

DJ. Clark^{1,2}, Z. Dang¹, M. Clay¹, G. Borthwick¹, J. Hughes¹, L. Marson¹

(1) Centre for Inflammation Research, University of Edinburgh (2) University of St Andrews

Introduction

Highly effective immunosuppressive agents have led to significantly reduced rates of acute rejection following renal transplantation, but this has not led to improved long term graft survival. Chronic allograft dysfunction (CAD), characterised by histological changes of interstitial fibrosis and tubular atrophy (IFTA), leads to the loss of function of 5% renal transplants per annum, requiring patients to return to dialysis.

Methods

We have developed a murine model of chronic allograft injury, characterised by tubular atrophy and interstitial fibrosis. Kidneys from BM12 mice are transplanted into C57bl/6 recipients, which are MHC matched except at a single class II locus. Syngeneic C57bl/6 transplants served as isograft controls. We have undertaken a series of time course experiments (day 5, 2, 4, 8 and 12 weeks; n=5-8 per group) which outline the progressive development of IFTA, and have characterised the associated cellular infiltrates.

Results

There was significant tubular atrophy seen at 4 weeks in allografts compared with isograft controls (p=0.01). Similarly, progressive fibrosis was confirmed in allografts following staining with picosirius red (p=0.01), collagen I (p=0.04) and α -smooth muscle actin (p=0.001) compared with isograft controls. We have demonstrated early macrophage and T cell infiltration by day 14, and the development of B-cell rich nodular infiltrates situated in the perivascular compartment, with associated new lymphatic vessel formation, suggestive of lymphoid neogenesis.

Conclusion

We have developed a clinically relevant model for the study of novel therapeutic strategies in chronic allograft injury, for which there is currently no treatment available.

Take-home message

Chronic allograft injury represents a significant challenge to the transplant community. We describe a clinically relevant and exciting model that can be used to develop novel therapeutic strategies.

0112 THE EFFECTS OF UROKINASE ON EARLY GRAFT FUNCTION IN LIVE DONOR KIDNEY TRANSPLANTATION

Anita Mitra, Jennifer Murphy, Sarah Hosgood, Umasankar Thiyagarajan, Michael Nicholson.

Department of Infection Immunity and Inflammation, Transplant Surgery Group, University of Leicester

Background

Thrombolytic agents have been used to enhance the preservation condition and improve graft outcome in deceased kidney donation. However, there is no evidence for the routine use of such agents in living donor kidney transplantation to improve early graft function.

Methods

A pilot study of 99 live donor kidney transplants was performed. Forty-nine cases with Urokinase added to the preservation solution and fifty without Urokinase representing the control group. Slow graft function (SGF) was defined as a less than 10% fall in serum creatinine within the first 24 hours, and early graft function measured by area under the curve serum creatinine (AUC Cr) over the first 7 days after transplantation.

Results

The incidence of SGF was 24% in the control group compared to 8% with the addition of urokinase ($p=0.054$). However, there was no difference in AUC Cr between the urokinase and control groups (1666 ± 687 vs 1676 ± 692 $\mu\text{mol/L}\cdot\text{day}$ respectively; $p=0.883$). There were no incidences of intravascular thrombi and no adverse events reported from the use of Urokinase.

Conclusion

The addition of Urokinase to the kidney preservation solution reduced the incidence of SGF in a cohort of live donor kidney transplants. SGF has a negative impact on patient and graft survival, and occurs more frequently in live donor kidney transplantation than is often realised. This study shows the use of Urokinase warrants further investigation in this field.

Take-home message

Our pilot study has shown that Urokinase reduced the incidence of slow graft function when added to preservation fluid in live donor kidney transplantation. Slow graft function has a negative effect on graft and patient survival, thus its use warrants further investigation in this field.

ORAL PRESENTATIONS 5A VASCULAR

O113 BLOOD VOLUME DISPLACED FROM AN INCOMPETENT GREAT SAPHENOUS VEIN DURING A STANDARDISED VALSALVA MANOEUVRE.

Lattimer CR^{1,2}, Azzam M¹, Kalodiki E^{1,2}, Geroulakos G^{1,2}

(1) Ealing Hospital and Imperial College, London. (2) Ealing Hospital, Middlesex

Background

A Valsalva manoeuvre (VM) like coughing, getting up or the strain occurring during stocking application may happen following foam sclerotherapy.

Aim

Measure the haemodynamic effects of a standardised VM within an incompetent great saphenous vein (GSV).

Methods

Twenty-three patients (23 legs), median age 45 years (range 23-78), median GSV diameter 7.5mm (IQR 1.9) awaiting endovenous treatment underwent a VM in the supine position. Time averaged mean velocity, peak velocity (PV) and terminal GSV diameter were measured using ultrasound, during a 3 second strain and relax cycle.

Results

Four patients had no reflux with 1 patient unable to perform the VM. In the remaining 18 patients during the strain phase the median (IQR) calculated GSV area, PV and calculated displaced volume was 56.1 mm²(30.1), 34.0 cm/sec(105.0) and 24.9 ml(30.6) respectively. In the recovery phase the corresponding measurements were 43.6 mm²(21.9), -18.4 cm/sec(-18) and -9.2 ml(-9.9). There was significantly more blood displaced during reflux than during recovery (median 24.9 ml vs -9.2 ml, $p < 0.0005$, Wilcoxon).

Conclusion

These results demonstrate that a VM causes significant haemodynamic effects where bolus foam displacement into deep veins and blood-foam mixing may occur. Patients should avoid all activities which may cause a VM. A pre-applied below knee stocking may be of benefit.

Take-home message

A Valsalva manoeuvre may hamper the safety and efficacy of foam sclerotherapy. Patients should remain still and calm during and after foam sclerotherapy.

O114 DURABILITY OF A SUTURELESS ENDOVASCULAR STENT-GRAFT BASED ON NITINOL STENTS BONDED TO A NANOCOMPOSITE POLYMER

M Desai^{1,2}, R Bakhshi², A Darbyshire², M Ahmed², J Eaton-Evans³, Xiang Zhou³, Zhong You³, AM Seifalian², G Hamilton^{1,2}

1. Department of Vascular Surgery, Royal Free Hampstead NHS Trust, London, UK 2. Division of Surgery and Interventional Science, University College London, London, UK 3. Department of Engineering Science, University of Oxford, Oxford, UK

Introduction

All currently used endovascular stent-grafts involve PTFE or PET requiring suturing to metal framework, which is cost-intensive and source of late complications. The aim of this study is to physiologically test 'fatigue life' of stent-graft that incorporates surface-modified Nitinol bonded to nanocomposite polymer(UCL-NanoTM) with improved strength, compliance and haemocompatibility.

Methods

Aortic stent-grafts were tested in 37°Celsius distilled water using in vitro accelerated circumferential pulsatile model to simulate in vivo hydrodynamic loading. After analysis for 400-million cycles equivalent to 10-years in human body according to FDA guidelines, they were analysed by visual inspection, SEM, FTIR, and stress-strain studies. Dynamic compliance was measured using pulsatile flow phantom. Comparison was made with zero-cycled control.

Results

All stent-grafts successfully completed accelerated pulsatile fatigue at pulse pressure 94±14 mm Hg over 12-months. There was no migration and SEM images confirmed uniform surface topography of Nitinol and polymer without any fractures. FTIR showed reduced intensity of polymer OH bonds at wavenumber 3000-3500 cm⁻¹ but there was no difference in bond strength as confirmed by linear elasticity test. Tensile strain of fatigue-tested polymer compared favourably with zero-cycled control at 50% to 500% stress ($P = .69$). At mean pressure range 60-120 mm Hg, overall compliance of fatigue-tested graft was 3.48±1.27 %per 100 mm Hg x 10⁻² with no significant difference compared to control (3.26±0.65%; $P = .47$).

Conclusion

An innovative stent-graft shows durability under simulated physiological conditions. Sutureless technology with new biocompatible material has potential to address some problems associated with present generation devices and reduce reintervention rate. PTFE-Polytetrafluoroethylene PET-Polyethylene terephthalate FDA-Food and drug administration SEM-Scanning electron microscopy FTIR-Fourier transform infrared spectroscopy

Take-home message

We present an endovascular stent-graft based on sutureless technology and a new biocompatible nanocomposite polymer that has the potential to address some limitations of current devices and reduce reintervention rate. This can improve the outcome from endovascular aneurysm repair and could make it the treatment of choice.

0115 IMMUNOHISTOCHEMICAL COMPARISON OF THE NERVE PROFILE OF VASCULAR MALFORMATIONS: IMPLICATIONS FOR CLINICAL MANAGEMENT OF VENOUS MALFORMATION ASSOCIATED PAIN

Gokani VJ, Kangesu L, Harper J, Sebire NJ

Great Ormond Street Hospital for Children

Introduction

More than 90% of venous malformations (VM) are associated with pain, which is presumed related to phlebolith formation and subsequent nociceptive mediator release. Increasing evidence supports a link between angiogenesis and nerve patterning. Since vascular malformations are aberrations of angiogenesis, it was hypothesized VM pain may be due to differences in nerve profiles associated with VM.

Methods

Immunohistochemical staining was performed on retrospective archival paraffin embedded samples of arteriovenous (AVM, n=9), capillary (CM, n=4), lymphatic (LM, n=29) and VM (n=14). Antibodies to three nerve markers, neurofilament, S100 and protein gene product 9.5 were employed. Light microscopy was used to assess the density of interstitial nerves and nervi vasorum. Assessments were validated by a second investigator. Significance testing was performed using Mann-Whitney U and Fisher's exact tests.

Results

There was no significant difference in nerve profile between VM and AVM or CM. LM and normal cutaneous control each exhibited a lower nerve density compared to VM ($p < 0.0075$). No statistical difference was noted in the nervi vasorum score between groups tested.

Conclusion

VM-associated pain is unlikely to be due to anatomical differences in associated nerve structure. As the nerve profile between VM and normal cutaneous control appears to be distinct, further work may elucidate common neurogenic/angiogenic mediators in the pathogenesis of vascular malformations which could prove targets in treating the pain of these conditions. In the meantime, current regimes of compression and non-steroidal anti-inflammatory drugs should be continued. Abbreviations AVM: arterio-venous malformations CM: capillary malformations LM: lymphatic malformations VM: venous malformations

Take-home message

As the nerve profile between VM and normal cutaneous control appears to be distinct, further work may elucidate common neurogenic/angiogenic mediators in the pathogenesis of vascular malformations which could prove targets in treating the pain of these conditions. In the meantime, current regimes of compression and non-steroidal anti-inflammatory drugs should be continued.

0116 IMAGING INTRAPLAQUE INFLAMMATION IN CAROTID ATHEROSCLEROSIS WITH 11C-PK11195 PET/CT

Joseph Shalhoub, Oliver Gaemperli, David RG Owen, Frederic Lamare, Ornella E Rimoldi, Paolo G Camici, Alun H Davies

Imperial College London

Introduction

Intraplaque inflammation plays an important role in the progression and destabilisation of atherosclerotic plaques. Hybrid imaging combines structural and functional (biological) modalities. We sought to determine whether intraplaque inflammation could be measured with PET/CT angiography using 11C-PK11195, a selective ligand of the peripheral benzodiazepine receptor which is highly expressed in activated macrophages.

Methods

and Results: Research Ethics Committee approval was obtained (09/H0707/2). Patients (n=32) with carotid stenosis (9 symptomatic and 23 asymptomatic, mean age 70±9 years) underwent 11C-PK11195 PET/CT imaging. 11C-PK11195 uptake into carotid plaques was measured using standardised uptake values and TBR (normalised to venous blood). On CT images, composition was assessed by measuring carotid plaque CT attenuation. 11C-PK11195 TBR values were higher in symptomatic compared to asymptomatic patients (1.06±0.20 versus 0.86±0.11, p=0.008). 11C-PK11195 TBR correlated with specific binding on 3H-PK11195 autoradiography (r=0.7704, p=0.025). On CT angiography, symptomatic plaques had a lower attenuation than asymptomatic plaques (46±31 versus 86±44 Hounsfield units, p=0.001). Both TBR and CT plaque attenuation had high negative predictive values (91% and 92%, respectively) for detecting symptomatic patients. However, the best positive predictive value (100%) was achieved when combining TBR and CT attenuation.

Conclusion

Imaging intraplaque inflammation in vivo with 11C-PK11195 and PET combined with contrast-enhanced CT angiography is feasible and can help to distinguish between recently symptomatic and asymptomatic plaques. Plaques with low CT attenuation and increased 11C-PK11195 uptake seem to be those at highest risk of thromboembolic events. Abbreviations CT, computed tomography; PET, positron emission tomography; TBR, target-to-background ratio.

Take-home message

Imaging intraplaque inflammation in vivo with 11C-PK11195 and PET combined with contrast-enhanced CT angiography is feasible and can help to distinguish between recently symptomatic and asymptomatic plaques.

O117 HELIX-B PEPTIDE OF EPO DECREASES ISCHAEMIA-INDUCED APOPTOSIS OF SKELETAL MYOTUBES

Dhiraj Joshi¹, Janice Tsui¹, Xu Shiwen², Hemanshu Patel¹, Sadashivam Selvakumar¹, David Lawrence³, David Abraham², Daryll Baker¹

1. Vascular Unit, University Department of Surgery, Royal Free Hospital, London. (2) Centre for Rheumatology & Connective Tissue Disease, University College London, London (UK). (3) Heart Hospital, London.

Background

Pharmacotherapy in management of critical limb ischemia (CLI) is inadequate. Erythropoietin (EPO), acting through its tissue-protective heteroreceptor complex (EPOR-CD131) is protective in many tissues and we have previously demonstrated the expression and upregulation of EPOR-CD131 in ischaemic human skeletal muscle. However, EPO also instigates profound haemopoiesis that increases the risk of thromboembolism. ARA-290, a peptide obtained from helix-B of EPO molecule is tissue-protective but not haemopoietic. This makes it feasible for use in CLI. The aims of this study are to demonstrate the tissue-protective properties of EPO and ARA-290 in an in vitro model of skeletal muscle ischemia and to assess the angiogenic potential of EPO and ARA 290 in vitro.

Methods

An in vitro simulated model of skeletal muscle ischemia was developed using C2C12 skeletal myotubes cultured in hypoxic chambers. The expression of EPOR was demonstrated in myotubes through immunohistochemistry and western blot. Myotubes were exposed to simulated-ischemia after pre-treatment with EPO/ARA 290. Apoptosis was measured by nuclear staining, cleaved caspase-3 assay and LDH-release. Angiogenic potential of EPO and ARA-290 was assessed in HMEC-1 cells by proliferation, migration and tube-formation assays.

Results

ARA-290 and EPO significantly decreased the number of apoptotic nuclei, cleaved caspase-3 and LDH-release in skeletal myotubes exposed to simulated ischemia (p<.01). However, only EPO was found to significantly increase proliferation, migration and tube-formation of endothelial cells (p<.05).

Conclusion

ARA-290 may potentially reduce ischaemia-induced tissue damage in CLI whilst avoiding side effects of EPO. These in vitro results provide support for further in vivo studies

Take-home message

It may be possible to use non-haematopoietic derivatives of EPO for treatment of Critical limb ischaemia

0118 THE USE OF COMPUTER AIDED DIAGNOSIS IN RISK ASSESSMENT FOR ABDOMINAL AORTIC ANEURYSM RUPTURE

Barry Doyle¹, Peter Coyle², Pierce Grace², Eamon Kavanagh², Paul Burke², Stewart Walsh², Tim McGloughlin¹

1 Centre for Applied Biomedical Engineering Research (CABER), University of Limerick, Ireland

2 Mid-Western Regional Hospital Vascular Department, Limerick, Ireland

Introduction

Ruptured Abdominal Aortic Aneurysms (rAAAs) represent a significant cause of morbidity and mortality accounting for approximately 10000 deaths annually in the UK. Traditionally the decision to intervene is based on a maximum diameter exceeding 5.5cm however there are a number of other factors, such as Peak Stress in the aneurysm wall, which influence rupture. This study aims to determine the benefit of computer modelling of individual patients aneurysms using Finite Element Analysis (FEA) on models derived from their CT scans.

Methods

42 stable electively repaired AAAs and 10 symptomatic/ruptured AAAs were examined in order to determine the peak wall stresses, locations, the Finite Element Analysis Rupture Index (FEARI) and multiple geometric parameters. Results were analysed using SPSS v16 to determine significant correlations. Those performing FEA were blinded to the actual rupture locations determined at time of surgery.

Results

Results showed that mean diameter, wall stress and FEARI were all higher in ruptured cases (Diameter: 75.5 v 64.8 mm; Stress: 0.80 v 0.56 MPa; FEARI: 1.01 v 0.66). 3D asymmetry is better correlated to maximum wall stress (repaired: $P=0.002$ v $P=0.033$) than diameter (repaired: $P=0.032$ v ruptured: $P=0.174$). Included was a stable 11.5 cm AAA that exhibited similar peak stress as 5 cm AAAs. Exact correlations between regions of peak stress and subsequent rupture locations were observed.

Conclusion

These results suggest that computational modelling of AAAs could provide an important tool in addition to factors such as maximum diameter in the decision making process for intervention.

Take-home message

Additional data from computational modelling of aneurysms can aid in the decision making process for intervention (repair) by identifying those at high risk of rupture.

0119 MAGNETIC RESONANCE T1 MAPPING PREDICTS SUCCESSFUL VENOUS THROMBOLYSIS

Prakash Saha, Marcelo Andia, Ulrike Blume, Andrea Wiethoff, Tobias Schaeffter, Colin Evans, Anwar Ahmad, Ashish Patel, Bijan Modarai, Alberto Smith, Matthew Waltham

Academic Department of Surgery, Cardiovascular Division & Division of Imaging Sciences, King's College London BHF Centre of Research Excellence and NIHR Biomedical Research Centre at Guy's and St. Thomas' NHS Foundation Trust, London, UK

Introduction

Novel thrombolytic delivery systems are changing the treatment paradigm for deep vein thrombosis (DVT), but older, well-organised thrombi remain unsuitable for intervention. A technique that identifies thrombi that are amenable to lysis would be desirable.

Methods

An MRI 3D T1-mapping protocol was developed for imaging venous thrombi induced in mice. T1-relaxation times were quantified between 4 and 28 days after induction ($n=33$). The thrombus was sectioned along its entire length. Collagen content was measured histologically as a marker of organisation and compared with T1-relaxation times in corresponding MR slices. Results were validated by three blinded observers. Tissue plasminogen activator (Actilyse) was injected (10mg/kg) between 4 and 16 days after thrombus induction ($n=16$). T1-mapping was performed before and 24hrs after Actilyse administration. Successful thrombolysis (vein recanalisation) was measured as an increase in the velocity of flow across the IVC greater than 0.3cm/s (confirmed by histology).

Results

T1-relaxation time increases with thrombus age and organisation (763±22ms, 4d; 617±36ms, 7d; 673±51ms, 10d; 728±58ms, 14d; 945±66ms, 21d; 1194±59ms, 28d). Collagen content is proportional to T1-relaxation time during thrombus resolution ($R^2=0.80$, $p<0.0001$, $n=15$). T1-relaxation times were significantly shorter in the group successfully treated with thrombolysis ($P=0.002$, $n=16$). ROC curve analysis shows an optimal cut-off point of ~700ms. The sensitivity and specificity for predicting successful thrombolysis was 100% and 88%.

Conclusion

This is the first study to show that T1-mapping quantifies organisation of experimental venous thrombi and identifies those suitable for thrombolysis. This technique could identify DVT patients in whom thrombolysis would be successful.

Take-home message

This is the first study to develop a novel imaging method to characterise the organisation of venous thrombosis, and can be used to predict successful thrombolysis.

0120 ANALYSIS OF MICROVESSELS WITHIN CAROTID ARTERY TO DETERMINE PLAQUE STABILITY

Elsbeth J. R. Hill¹, Mohammad Chowdhury², Ferdinand Serracino-Inglott², Mark Slevin³, M. Yvonne Alexander¹

1) Cardiovascular Research Group, School of Medicine, The University of Manchester, Manchester, UK; 2) Department of Vascular Surgery, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; 3). ICC, St Pau University, Barcelona, Spain.

Introduction

A challenge facing surgeons is selection of patients for carotid endarterectomy. While some patients with carotid atherosclerosis develop unstable plaque and subsequent stroke, others form more stable plaque and are asymptomatic. Previous work implicates intimal microvessels as key contributors to plaque instability, and identifies the angiogenic growth factor HGF as a possible biomarker. Identifying differences between mature and leaky microvessels may help to predict risk of plaque rupture and guide surgical intervention to patients who will most benefit.

Methods

Endarterectomy specimens were taken from symptomatic and asymptomatic patients; microvessel morphology was interrogated using immunofluorescence. Post-mortem human carotid artery specimens were stained for mature and leaky microvessels, dissected out with either fine-needle or laser-capture microdissection for RNA extraction. Patient serum was analysed for the concentration of 27 cytokines. Ten patients with carotid disease and ten healthy controls were recruited.

Results

Mature and leaky microvessels were seen to co-exist within carotid artery adventitia displaying stable and unstable morphology respectively. Laser-capture of microvessels was achieved enabling isolation of selected vascular cells from adventitial tissue. Levels of the pro-inflammatory cytokines, interleukin (IL)-6 and IL-15 were significantly elevated in patients compared to controls ($p < 0.05$). The chemotactic cytokines eotaxin and MCP-1 were also elevated ($p < 0.01$), together with the anti-inflammatory interleukin-1 receptor antagonist ($p < 0.05$). Symptomatic patients were found to have significantly reduced circulating levels of platelet-derived growth factor. IL-12 and IL-17 levels were higher in symptomatic compared to asymptomatic patients ($p < 0.05$).

Conclusion

These data support an association between circulating inflammatory cytokines, growth factors and symptomatic carotid disease.

Take-home message

This novel approach to understanding the molecular basis of stroke risk has potential to allow the targeting of surgical intervention to patients who will most benefit.

0121 ANGIOGENIC MONOCYTES MOBILISED IN RESPONSE TO CRITICAL LIMB ISCHAEMIA ARE FUNCTIONALLY IMPAIRED

AS Patel, A Smith, P Saha, K Mattock, J Humphries, R Siow, M Waltham, B Modarai

King's College London BHF Centre of Excellence, Academic Department of Surgery, Cardiovascular Division. The NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

Objective

Monocytes (CD14+ve cells) expressing the angiopoietin receptor, Tie2, are thought to play a critical role in angiogenesis. Our pilot studies have shown that these cells are mobilised in patients with critical limb ischaemia (CLI). We aimed to further investigate this pro-angiogenic response.

Methods

The proportion of Tie2+ve monocytes was measured in blood from 40 patients with CLI, 20 age/sex-matched and 20 young controls by flow cytometry. Tie2+ve and Tie2-ve monocytes from patients and controls were isolated by FACS-sorting for in-vitro angiogenesis assays. A panel of 12 circulating angiogenic/inflammatory factors was measured by multiplex ELISA in CLI patients and controls ($n=10$ /group).

Results

Patients with CLI had 10-fold higher CD14+ve/Tie2+ve cells compared with age/sex-matched and young controls (3.52%±0.28 vs 0.39%±0.09 and 0.23%±0.04, respectively $p<0.0001$). Tie2-expression by monocytes was confirmed by RT-PCR. Overall, Tie2+ve monocytes induced greater microtubule length ($P=0.03$), area ($P=0.004$) and number of nodes ($P=0.04$) compared with Tie2-ve monocytes ($n=18/\text{group}$). However, the angiogenic potential of Tie2+ve monocytes from patients with CLI was significantly lower than monocytes from healthy controls ($p<0.05, n=9/\text{group}$). Circulating levels of angiopoietin-2 (799±128 vs 384±62pg/ml), IL-6 (79±29 vs 17±6pg/ml) and MCSF (39±11 vs 14±1pg/ml) were significantly higher in CLI patients compared with controls respectively ($p<0.05$).

Conclusion

Tie2+ve monocytes are mobilised in response to CLI but these cells have a reduced capacity for angiogenesis. Raised circulating levels of IL-6 and MCSF, both of which are known to impair the angiogenic properties of monocytes, may account for this observation. In-vitro "re-conditioning" of monocytes and other candidate cells may improve the clinical benefits of angiogenic cell therapy using autologous cells.

Take-home message

Angiogenic monocytes are mobilised in patients with critical limb ischaemia, but these cells are functionally impaired. In-vitro "re-conditioning" of these and other candidate cells may improve the modest results seen to date in clinical studies using autologous cell therapy for critical limb ischaemia.

0122 A NOVEL SYNTHETIC ANG-1 MIMETIC LIGAND FOR VASCULAR PROTECTION AND TISSUE ENGINEERING APPLICATIONS.

E Issa, AJM Moss, NJM London, NPJ Brindle

The University of Leicester

Introduction

Angiopoietin-1 (Ang1) is a relatively recently discovered vascular ligand which has been shown to have substantial potential therapeutic applications in treating a range of pathologies. Furthermore, it is essential for the vascularisations for the regenerated tissue in regenerative medicine application. However, this large glycoprotein shows variable solubility and biological activity as a recombinant protein and is difficult to produce. This project aims to develop small, stable Ang1 mimetic proteins for use as potential therapeutic lead molecules.

Methods

A small synthetic ligand was designed and expressed in E.Coli. Cell surface binding was examined by immunofluorescence staining and the ability of the ligand to activate cellular signalling was tested by phospho-specific immunoblotting. Functionally, the influence of the ligand on endothelial cells migration was studied using Boyden chamber chemo tactic assay.

Results

A synthetic ligand was produced of molecular mass 12kDa compared with the 70kDa native ligand. This ligand binds angiopoietin receptor in vitro. In cellular assays the ligand interacts with the endothelial cell surface and activates the angiopoietin receptor. In addition it stimulates downstream signalling pathways including the phosphatidylinositol 3-kinase/Akt and Erk1/2 pathways. The ligand activates endothelial cell migration.

Results

The novel synthetic ligand is easy to produce, can be expressed in E Coli, are highly soluble and stable, activate the angiopoietin receptor. The properties of these synthetic ligands suggest they may be lead molecules for generating potential therapeutic Ang1 mimetics.

Take-home message

The novel Ang-1 mimetic ligand activates protective endothelial responses. The ligand can be incorporated into tissue engineering scaffold while retaining angiogenic activities.

0123 AN IMPACT OF INSTITUTION-WIDE POLICY CHANGES ON TWO WEEKS TARGET FOR CAROTID ENDARTERECTOMY

K Abbas MRCS^{1,2}, RS Vohra PhD, MRCS¹, M Salhab MD, MRCS², MD Sinclair MRCS¹, PJ Kent MD, FRCS¹, MJ Gough MD, FRCS¹

1) York Hospital NHS Foundation Trust, Wigginton Road, York, UK YO31 8HE. 2) The Leeds Vascular Institute, The General Infirmary at Leeds, Great George Street, Leeds, UK LS1 3EX.

Introduction

Maximum benefit is achieved with carotid endarterectomy (CEA) within 2 weeks of index neurological event in symptomatic patients. This study assesses the impact of unit policy changes on 2 weeks targets for CEA performance as per NICE (National Institute for Health and Clinical Excellence) guidelines.

Methods

Daily TIA clinics, emergency admission stroke protocol and next day CEA policies were adopted for study period (group 1= 01/08/08 - 31/07/09). The outcome was compared with study period (group 2= 01/01/07 - 31/12/07) before policy changes.

Results

Both cohorts had similar demographics before (n=65) and after (n=52) the changes (72.6yr v 70.1yr, p=0.178; 70.8% v 65.4% males, p=0.531). Following policy changes, time taken from index neurological event (INE) to CEA reduced significantly from 23 days (IQR10-122) to 6.5 days (IQR 4-12), p<0.001 with 32.2% v 82.7% (Odds Ratio=10.75, Confidence Interval=4.41-26.20, p<0.001) CEA performed within 2 weeks of INE. Policy changes further reduced the time to carotid duplex (10 days v 2 days, p <0.001) and vascular assessment (6 days v 3 days, p=0.012). Peri-operative stroke rate did not differ significantly between group 1 & 2 (1.52% v 3.85%, p=0.433). Uni-variate analysis showed that presentation with stroke (0% v 86.36% in group 2) and TIA (27.66% v 75.0% in group 2) resulted in expedited procedure following implementation of policies. However, amaurosis fugax presentation did not result in expedited procedure (100% v 100 % in group 2).

Conclusion

The study showed significant improvements in meeting two weeks targets for carotid endarterectomy following implementation of policy changes.

Take-home message

Simple steps of unit-policies changes can lead to significantly improved patient care

0124 LAMIN A/C OVER- EXPRESSION AT REGIONS EXPOSED TO HIGH WALL STRESS; A NOVEL, MECHANO-SENSITIVE PATHWAY IN ABDOMINAL AORTIC ANEURYSM (AAA) PATHOGENESIS

Amir H. Malkawi¹, Robert J. Hinchliffe¹, X. Yun Xu², Grisha Pirianov¹, Evelyn Tornsey¹, Ian M. Loftus¹, Gillian Cockerill¹, Matt M. Thompson¹

(1) St George's Vascular Institute, St George's Healthcare NHS Trust, London. (2) Department of Chemical Engineering and Chemical Technology, Imperial College, London

Introduction

Patient specific wall stress analysis demonstrated that not only wall stress was higher in AAA at risk of rupture, but that site of rupture correlated well with regions of high wall stress supporting the biomechanical principles of rupture at areas where wall stress exceeds wall strength. This study investigates changes at the molecular level in regions exposed to high wall stress.

Methods

FEA (ADINA R&D Inc., Watertown, USA) was performed on patients with AAA scheduled for open repair. Full-thickness biopsies were obtained intraoperatively from regions of high and low stress. RNA extraction was performed (RNeasy Fibrous Tissue Mini Kit, Qiagen), Illumina HumanRef-8 v3.0 Expression BeadChips were used for whole genome expression profiling. Protein expression was assessed by western blotting.

Results

FEA was performed on 11 patients with AAA scheduled for elective open repair. Paired samples were obtained from high and low stress regions. There was a significant over-expression of LMNA (Lamin A/C) (p< 0.02) in regions exposed to high wall stress. Protein expression of Lamin A/C and cleaved Lamin A/C was also increased in high stress regions as assessed by western blotting.

Conclusions

This is the first study to identify a role for Lamin A/C in AAA pathogenesis, particularly the over-expression of Lamin A/C in regions of aneurysm wall exposed to high wall stress compared to low stress regions. Lamin A/C has an important role in cytoskeletal and nuclear mechanics, mechanotransduction and apoptotic transcriptional pathways. Our results identify novel pre-rupture changes at the molecular level in AAAs in regions exposed to high stress.

Take-home message

Biomechanical factors and changes at the molecular level in AAA are often investigated separately. Considering both has identified a possible role for Lamin A/C, a mechanosensitive nuclear filament in AAA pathogenesis

ORAL PRESENTATIONS 5B COLORECTAL

0125 ANALYSIS OF PROTEASOMAL SUBUNIT EXPRESSION REVEALS RPT4 EXPRESSION AS A POTENTIAL MARKER IN COLON CANCER.

Niamh McCawley^{1,2}, Susan Conlon³, Elaine W. Kay³, Caoimhín G. Concannon¹, Jochen H.M. Prehn¹, Deborah A. McNamara²

(1) Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland, (2) Department of Colorectal Surgery, Beaumont Hospital, Dublin, Ireland, (3) Department of Pathology, Beaumont Hospital and Royal College of Surgeons in Ireland, Dublin, Ireland.

Summary

Identifying novel molecular markers that can predict which patients with colon cancer will respond to adjuvant chemotherapy, thereby tailoring individual therapies to patients is needed. Research has focused on the ubiquitin-proteasome system (UPS) and its potential as a target in a number of different malignancies. The UPS is the major pathway for the degradation of the intracellular proteins and as such can modulate a variety of cell signaling pathways. Expression levels of proteins involved in the UPS were assessed in a cohort of 18 patients with stage III colonic adenocarcinoma, using fresh frozen colonic tissue and subsequently in a large tissue microarray (TMA) of patients with Stage II and III colonic carcinoma. (n=240) Immunohistochemical and immunoblotting techniques demonstrated upregulation of ubiquitinated proteins in tumour specimens compared with normal colonic specimens. Parallel up-regulation in expression of regulatory subunits of the proteasome were observed. (p<0.001) Caspase dependent apoptosis was detected when colon cancer cells were treated with the proteasome inhibitor, bortezomib and cells were highly sensitive to proteasome inhibition with significantly increased levels of apoptosis (p<0.05) compared to untreated control cells. Utilizing siRNA technology, silencing of Rpt4 induces apoptosis and prevents proliferation of colon cancer cells. (p<0.05) Interestingly, Rpt4 expression predicted reduced disease free survival (p=0.0217, log rank test p=0.007) and death (p=0.0467 log rank p=0.025) in node negative patients. We have demonstrated increased levels of ubiquitinated proteins despite elevated proteasomal levels, supporting an overstressed UPS and have identified a cohort of node negative, stage II patients who may benefit from further adjuvant therapy.

Take-home message

Manipulation of the ubiquitin proteasome system (UPS) may have potential for the development of future chemotherapeutics in colon cancer.

0126 POTENTIAL THERAPEUTIC IMPACT OF ROUTINE PRE-OPERATIVE STAGING WITH FDG-PET/CT IN HIGH AND LOW RISK RECTAL CANCER

Chris Hunter¹, Aurelie Garant², Te Vuong³, Giovanni Artho⁴, Robert Lisbona⁴, Muti Abulafi¹, Gina Brown⁵

1) Mayday University Hospital, Croydon, U.K., 2) Laval University, Canada, 3) Jewish General Hospital, McGill University, Canada, 4) McGill University Health Centre, Canada, 5) The Royal Marsden NHS Foundation Trust, Sutton, U.K.

Introduction

FDG-PET/CT is not currently recommended for routine staging of rectal cancer. We evaluated the diagnostic yield of FDG-PET/CT in MRI staged high and low risk rectal cancers.

Methods

In a multicentre prospective observational trial, 236 patients with rectal cancer were recruited to a study evaluating FDG-PET/CT. All patients underwent MRI staging and were stratified into high and low risk (high risk: extramural venous invasion, extramural spread>5mm or T4, pelvic sidewall lymph nodes, N2 or involved circumferential resection margin). The primary aim was to evaluate detection rates of metastatic disease using FDG-PET/CT. The secondary aim was to determine the diagnostic yield of FDG-PET/CT according to MRI risk features.

Results

Imaging data was available for 230/236 (97.5%) patients. Overall, FDG-PET/CT did not significantly increase detection of metastatic disease compared with computed tomography for the whole group 33/230 (14.4%, 95%CI 10.4-19.5%) versus 22/230 (9.6%, 95%CI 6.4-14.1%). FDG-PET/CT had a significantly higher diagnostic yield for distant metastases in MRI high risk rectal cancers, (28/136, 20.6%, 95%CI 14.7-28.2) versus (5/94, 5.3%, 95%CI 2.3-11.9, OR 6.4, p=0.001) for low risk patients and also identified significantly more metastases not visible on conventional CT (OR 4.6, 95%CI 1.3-16.2, p=0.001). In patients with high risk features on MRI the rate of distant metastases uniquely identified on FDG-PET/CT was 13.2% (95%CI 8.5-20.0).

Conclusion

It is possible to identify a high risk group using routine rectal MRI with a high diagnostic yield on PET/CT. Patients in this group have significantly more metastases identified on PET/CT than CT alone. FDG-PET/CT - [18F]Fluorodeoxyglucose positron emission tomography/computed tomography MRI - Magnetic resonance imaging

Take-home message

The high diagnostic yield and rate of distant metastases detected by FDG-PET/CT alone supports staging by functional imaging in MRI selected high risk patients.

0127 CHARACTERISATION OF ENDOTHELIN-1 BINDING SITES IN COLORECTAL CANCER AND ANTAGONISTIC ACTION OF THE ENDOTHELIN A RECEPTOR ANTAGONIST ZIBOTENTAN(ZD4054)

S Haque¹, M Loizidou¹, X Shiwen², D Abraham², N Farooqui¹, H Welch¹, M Winslet¹, O Ogunbiyi¹, J Growcott³, M Dashwood⁴

Departments of Surgery (1) and Clinical Biochemistry (4) and Centre for Rheumatology and Connective Tissue Disease (2), UCL, London, UK; (3) AstraZeneca, Alderley Park, Macclesfield, UK.

Background

Endothelin-1 (ET-1) acts via two G-protein coupled receptors, ETAR and ETBR. Overexpressed ET-1 and ETAR in colorectal cancer (CRC) promote growth and progression. We investigated the distribution of ETAR and ETBR in patient tissue sections. ET-1 affinity (Kd) and receptor density (Bmax) was determined in whole tissue homogenates and colorectal fibroblasts. In addition the effect of the orally active ETAR specific antagonist zibotentan (ZD4054) on ET-1 receptor binding (IC50) was evaluated against subtype selective laboratory compounds.

Material and Methods

ET-1 receptor distribution and binding characteristics (Kd; Bmax) were determined using in vitro autoradiography on patient sections, tissue homogenates and primary fibroblasts. Immunohistochemistry (IHC) identified stromal structures.

Results

ET-1 binding to cancer and normal colon tissue had similar characteristics. There was greater ETAR than ETBR binding in CRC sections. Both cancer and normal tissues had strongest binding to stromal cells, particularly fibroblasts (IHC). Furthermore, characterising primary fibroblasts revealed high density and affinity ET-1 binding (Bmax 3.03 ng/mg; Kd 213.6). Inhibition studies showed ETAR antagonists (BQ123; zibotentan) more effectively reduced ET-1 binding (IC50 values 0.1µM, 10µM respectively) than ETBR antagonism BQ788 (IC50; 1mM).

Conclusion

ET-1 binds strongly to CRC stromal structures, (fibroblasts; endothelial cells), and is consistent with ET-1 signalling contributing to tumorigenesis. We further demonstrated that the orally active ETAR antagonist zibotentan reduces ET-1 binding to CRC tissues. This study provides further evidence for the potential therapeutic use of the specific ETAR antagonist zibotentan as an adjuvant treatment for CRC. CRC=colorectal cancer; ET-1=Endothelin-1; ICH=Immunohistochemistry

Take-home message

We demonstrate that the orally active ETAR antagonist zibotentan reduces ET-1 binding to CRC tissues. This study provides further evidence for the potential therapeutic use of the specific ETAR antagonist zibotentan as an adjuvant treatment for CRC.

0128 HYPOXIA INHIBITS COLONIC ION TRANSPORT VIA ACTIVATION OF AMP KINASE

D Collins^{1,2}, S Kopic³, J Bachlechner³, JP Geibel³, DC Winter²

(1) University College Dublin, (2) St. Vincent's University Hospital, Dublin, (3) Department of Surgery & Physiology, Yale School of Medicine

Background

Colonic hypoxia is the endpoint in the pathogenesis of many surgical disorders including acute ischemia and large bowel obstruction. Acute hypoxia is known to modulate colonic epithelial ion transport however the underlying mechanisms are poorly understood. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is an ultrasensitive energy sensor, present in enterocytes, that regulates cell processes under conditions of metabolic stress.

Aims

We hypothesised that activation of AMPK is an early event in the response to hypoxia, mediating of the acute effects of hypoxia in this setting.

Methods

Human mucosal epithelium from colectomy specimens was mounted in Ussing chambers. Chloride secretion was quantified as changes in short circuit current (ΔI_{sc}) in $\mu A.cm^2$. Hypoxia was induced by switching to nitrogen perfusion (95% N₂/5% CO₂). Rat colonic crypts were isolated by calcium chelation, and intracellular chloride (Cl_i) was measured by MQAE fluorescence. The contribution of AMPK in this hypoxic response was evaluated by pre-treating tissues with the AMPK inhibitor Compound C. Institutional review board approval was granted for this study. Results: Hypoxia decreased chloride secretion in human colon and isolated crypts (n=8, p<0.03). Pre-treatment of tissues with the AMPK inhibitor compound C significantly reversed these effects (n=8, p<0.04).

Conclusion

This study demonstrates that acute hypoxia inhibits electrogenic chloride secretion in rat and human colon through an AMPK mediated mechanism. AMPK is therefore a key component of the adaptive response to mucosal hypoxia and may represent a potential therapeutic target in ischemic states.

Take-home message

Activation of AMPK occurs during acute colonic ischaemia. Manipulation of this pathway may restore mucosal function during periods of acute ischaemia.

0129 THE PERI-OPERATIVE ROLE OF THE ANTI-NEOPLASTIC AGENT TAUROLIDINE IN COLON CANCER: A PROSPECTIVE MULTICENTER RANDOMISED CLINICAL TRIAL

Neary PM¹, O'Leary P¹, Hallihan P¹, McCourt M¹, O'Riordain MG², Kirwan WO¹, O'Boyle C³, Gough D³, Andrews E¹, Eustace JA¹, Ryan K⁴, Wang JH¹, Redmond HP¹

(1) Department of Academic Surgery, Cork University Hospital, University College Cork, Wilton, Cork (2) Mercy University Hospital, Cork (3) Bon Secours Hospital, Cork (4) Royal College of Surgeons in Ireland, Dublin

Introduction

Residual micro-metastases at the time of tumour resection show an accelerated metastatic growth pattern secondary to the systemic inflammation-stimulatory effects of surgery which significantly augments tumour recurrence. The aim of this study is to examine the effect of the anti-neoplastic agent taurolidine on the processes involved in surgery induced tumourigenesis.

Methods

In the setting of an ongoing multicentre prospective randomised clinical trial, 25 patients undergoing curative colon cancer resection were randomly allocated to receive intravenous peri-operative taurolidine or normal saline, with each adhering to standardised peri-operative care. Serum and plasma were analysed pre-operatively and post-operatively at 3 hours, 6 hours and day 1, 2, 3 and 5, for neutrophil and monocyte receptor expression of TLR4, Cd14, and Cd11b. Pro- and anti-inflammatory cytokine release were also examined at these time points.

Results

TLR4 monocytic receptor expression was significantly attenuated in the taurolidine treated patients (16.3±0.7 vs. 12.5±1.4, p=0.039). Neutrophil and monocyte receptor expression of Cd14 was significantly reduced in the taurolidine treated patients day 5 post-operatively (14.6±1.0 vs. 11.9±0.6, p=0.038 and 680.6±79.1 vs. 496.3±80.8, p=0.018, respectively). Neutrophil and monocyte receptor expression of Cd11b was reduced in the taurolidine group, maximally at day 5 (448.0±90.0 vs. 246.2±33.2, p=0.061 and 594.3±185.7 vs. 277.1±40.0, p=0.130, respectively). Pro-inflammatory cytokines were also reduced in the taurolidine treatment group.

Conclusion

Taurolidine administration to patients undergoing colon cancer resection attenuates the post-operative inflammatory response that is responsible for peri-operative tumourigenesis. Expansion of peri-operative taurolidine anti-cancer therapy to phase three trials is warranted. ISRCTN77829558

Take-home message

Results of this study demonstrates the potential of taurolidine administration during the peri-operative period in improving cancer therapy

O130 WHOLE GENOME METHYLATION ANALYSIS REVEALS A DISTINCT PATTERN OF METHYLATION IN COLORECTAL CANCER

Andrew D Beggs^{1,2,3}, Angela Jones¹, Senthil Ganapathy³, Shiyam Nizar³, Devinder Kumar³, Shirley Hodgson³, Muti Abulafi², Ian Tomlinson³

(1) Wellcome Trust Centre for Human Genetics, University of Oxford (2) Mayday University Hospital, Croydon, UK (3) St Georges, University of London

Introduction

There has been great interest in the potential of DNA promoter methylation both as a diagnostic marker and also to further understanding of the mechanisms of initiation of colorectal cancer. Previous studies have examined few genes, in small numbers and without comparing with matched normal and adenoma tissue to increase power of detection.

Aim

To carry out a whole genome methylation analysis of matched tumour normal pairs and adenomas to identify potential biomarkers and pathways. Methods 12 fresh-frozen tumour-normal pairs and 5 adenomas were bisulphite converted and hybridised onto Illumina Methylation27 arrays. Percentage methylation at each gene was measured, normalised, and analysed using an empirical Bayes model and gene set enrichment analysis (GSEA).

Results

Over 2,000 genes were found to be significantly differentially methylated in the transition between normal mucosa and colorectal cancer. The bulk of the methylation occurred between adenoma to carcinoma, with demethylation of multiple genes seen during adenoma formation. The highest differentially methylated gene in both adenomas and carcinomas was GRASP (p-value 1.68×10^{-6}), which regulates the p14ARF complex which regulates p53 dependent apoptosis. In GSEA, extensive methylation was seen in the DCC/netrin pathway associated genes during carcinoma formation.

Conclusion

The highest differentially methylated gene, GRASP, is a plausible potential biomarker for the detection of colorectal cancer. Its biological function also gives interesting insights into colorectal cancer development, suggesting that dysregulation of p53 mediated apoptosis via inactivation of the p14ARF pathway is necessary for carcinogenesis. Its potential as a biomarker should be investigated further.

Take-home message

Methylation of the GRASP gene may be a novel biomarker for colorectal cancer, and detailed analysis has allowed a greater insight into how methylation modulates colorectal carcinogenesis.

O131 MICRORNAS BASED BLOOD ASSAY FOR EARLY DETECTION OF COLORECTAL CANCER

Mr. Muhammad Imran Aslam^{1,2}, Dr. James Howard Pringle¹, Mr. Baljit Singh², Mr. John Stuart Jameson²

1) Department of Cancer Studies and Molecular Medicine, Robert Kilpatrick Clinical Sciences Building, Level 2, Leicester Royal infirmary, P. O Box 65, Leicester. LE2 7LX 2) Department of Colorectal Surgery, Leicester General Hospital, University Hospitals of Leicester NHS Trust.

Introduction

Colorectal Cancer (CRC) screening with faecal occult blood testing is generally considered to lack the desired convenience, sensitivity and specificity for use as a general screening test. This explains why the search for an improved and non invasive screening test has continued despite a recent commencement of National Bowel Screening Programme in the UK. The aim of this study was to evaluate the potential use of circulating microRNAs in CRC screening.

Methods and Patients

MicroRNA expression profiling with the Applied TaqMan[®] MicroRNA Array v2.0 (quantification of 740 mature microRNAs and endogenous controls) was performed on the plasma RNA from age and gender matched patients with CRC (n=12), adenoma (n=10) and controls (n=12) with normal colonoscopic examination. To identify the CRC related microRNAs in the plasma, the expression profiles from cancerous and adjacent non-cancerous resected tissue from the same five patients with CRCs were also obtained.

Results

Based on the differential expressions ($\Delta\Delta Ct$), a subset of tumour related microRNAs in the plasma (including miR-16, miR-23b, miR-186, miR-431, miR-455-5p, miR-483, miR-487b, miR-519) was found to have a significant ($p < 0.001$) diagnostic value. In this subset, a combination of four miRNAs in the plasma was associated with 100% accuracy of detection for adenomas and carcinomas. Expression profiling also identified the microRNAs correlating with the grade of dysplasia in adenomas.

Conclusion

Detection of circulating microRNAs can serve as sensitive, non invasive screening test for CRC. However, these microRNAs need to be validated on larger cohort for their specificity and sensitivity of detection.

Take-home message

Plasma MicroRNA based detection of colorectal cancer and adenoma offers a potential screening test for early detection of colorectal cancer.

O132 DOES A PREOPERATIVE CARDIOPULMONARY EXERCISE TEST IDENTIFY A SUBGROUP OF PATIENTS WHO BENEFIT FROM INTRAOPERATIVE GOAL DIRECTED THERAPY DURING ELECTIVE COLORECTAL SURGERY?

Mr C Challand, Dr R Struthers, SN N Mellor, Mr K Hosie, Prof JR Sneyd, Dr G Minto

Derriford Hospital, Plymouth

Introduction

Intra-operative Goal Directed fluid Therapy (GDT) has been shown to reduce length of stay and decrease morbidity in elective colorectal resections. Pre-operative Cardiopulmonary Exercise testing (CPET) characterises baseline aerobic fitness. We hypothesised that CPET might identify a subset of unfit patients who benefit more from GDT.

Methods

This single centre, double-blind prospective randomised-controlled trial recruited 179 patients stratified by CPET as high risk (n=56; Anaerobic Threshold, AT 8.0-10.9 mlO₂/kg/min) or standard risk (n=123; AT >11.0 mlO₂/kg/min). Oesophageal Dopplers were placed in all patients: measurements were visible only to an investigator. Control fluid therapy was solely at the discretion of the anaesthetist. Intervention (GDT) patients were given additional algorithm-directed colloid boluses by the investigator.

Results

Patient demographics and surgical details were comparable between the groups. Mean Cardiac Index and Stroke Volume at skin closure were higher in the intervention group (4.2 vs. 3.4 l/min/bsa, 112.0 vs. 95.4 ml; p<0.001). Intraoperative GDT had no impact on median length of hospital stay (8.9 vs. 6.7 days [intervention:control], p=0.221). For standard risk patients, the GDT group had a prolonged length of stay (8.8 vs. 6.0 days; p=0.060), particularly those having colonic resections (8.7 vs. 4.9 days; p=0.007). For high risk patients length of stay was similar between groups (9.9 vs. 9.1 days p=0.636)

Conclusion

Preoperative CPET identified a group of standard risk patients who had a prolonged length of hospital stay following intraoperative GDT. Recent improvements in baseline fluid management may have attenuated the benefits of Oesophageal Doppler-guided GDT seen in earlier studies.

Take-home message

Intraoperative GDT may be deleterious for standard-risk patients having elective colonic resections.

O133 ENDOTHELIN-1 STIMULATED GENE INDUCTION WITHIN COLORECTAL FIBROBLASTS AND THE EFFECT OF ENDOTHELIN RECEPTOR ANTAGONISM ON KEY GENES.

S Haque¹, H Welch¹, M Dashwood², X Shiwen³, D Abraham³, M Heetun¹, N Farooqui¹, I Taylor¹, M Winslet¹, M Loizidou¹

Departments of Surgery (1) and Clinical Biochemistry (2) and Centre for Rheumatology and Connective Tissue Disease³, UCL, London, UK

Background

The vasoactive peptide ET-1 contributes to colorectal tumourigenesis. At the cellular level, ET-1 promotes proliferation in epithelial cancer cells, via one of its two receptors (ETA). Additionally, ET-1 may activate surrounding fibroblasts and promote the creation of supporting tumour stroma. We identified genes that were up/down-regulated within fibroblasts post-ET-1 exposure and evaluated ETA & ETB receptor antagonism on gene expression.

Methods

Illumina micro-arrays determined differential gene expression post-ET-1 stimulation of 4 human colorectal fibroblast strains, isolated from areas adjacent to colorectal cancers. To confirm expression of genes of interest, we examined time point induction mRNA levels (RT-PCR; real-time RT-PCR). ETAR (BQ123) and ETBR (BQ788) antagonistic effects were measured at the mRNA and protein levels (Immunoblotting).

Results

Four-hour ET-1 induction had a significant effect on gene up/down-regulation (>2-fold) in all 4 fibroblast strains (97 genes $p < 0.01$; 14 genes $p < 0.01$ & >2-fold). We determined mRNA/protein levels of 2 up-regulated genes: CTGF (pro-proliferative/migratory/angiogenic); ADM (angiogenic); and one down-regulated gene STC1 (alters proliferation/apoptosis). ET-1 induced (i) maximum expression of CTGF and ADM (1-2hr) which was reversed by ETA&ETB antagonism; (ii) transient up-regulation (1 hour) followed by down-regulation of STC1 (4hr), in-line with array data; again reversed by ETAR&ETBR antagonism.

Conclusion

ET-1 stimulated cancer-associated fibroblasts contribute to signalling that promotes colorectal cancer growth, desmoplasia and neovascularisation. ETA and ETB receptor antagonists block a number of these signals. This study provides further evidence for the potential therapeutic use of Endothelin receptor antagonists as an adjuvant treatment for colorectal cancer. ET-1=endothelin-1; CTGF=connective tissue growth factor; ADM=adrenomedullin; STC1=stanniocalcin-1

Take-home message

ET-1 stimulated cancer-associated fibroblasts contribute to signalling that promotes colorectal cancer growth, desmoplasia and neovascularisation. This study provides further evidence for the potential therapeutic use of Endothelin receptor antagonists as an adjuvant treatment for colorectal cancer.

O134 EFFECT OF PELVIC COMPRESSION ON NERVE AND BLOOD SUPPLY TO THE ANAL CANAL IN AN ANIMAL MODEL

Karen M. Griffin, Colm O'Herlihy, Ronan O'Connell, James F.X. Jones

University College Dublin

CEP: Cortical evoked potential; EAS: External anal sphincter

Introduction

Vaginal childbirth can damage delicate nerve and blood vessels which supply the anal canal and lead to faecal incontinence. The aim of this study was to measure the cortical evoked potential (CEP) to anal canal stimulation, external anal sphincter (EAS) tissue PO₂ and femoral artery blood flow in a rat model which mimics second stage labour.

Methods

15 female Wistar rats were anaesthetised with urethane (1.5g/kg i.p.) and the pelvic pressure raised for one hour with retrouterine balloons as previously described (Healy et al. 2008). The CEP was recorded using an extradural multi-electrode array. EAS tissue PO₂ (oxylite 2000 system) and femoral artery flow (Transonic®) measurements were monitored throughout the experiments. Data was analysed with a 2 way ANOVA with respect to a sham inflation group.

Results

Following balloon inflation the CEP amplitude decreased significantly from $10.7 \pm 1.3 \mu\text{V}$ to $3.2 \pm 1.5 \mu\text{V}$ ($p = 0.0002$). Tissue PO₂ before balloon inflation was $56.8 \pm 5.31 \text{ mmHg}$ and this decreased significantly to $24.2 \pm 2.4 \text{ mmHg}$ following inflation ($p < 0.0001$). Hind limb blood flow also decreased following balloon inflation from $1.30 \pm 0.04 \text{ ml/min}$ to $0.99 \pm 0.08 \text{ ml/min}$ ($p = 0.0008$).

Conclusion

These results show that in our animal model of obstetric injury to the pudendal nerve there is a combined insult of neuropathy and ischemia of the anal canal.

Take-home message

An animal model of obstetric injury causes neuropathy and ischemic insult to the anal canal.

O135 AKT PATHWAY AS A POTENTIAL THERAPEUTIC TARGET FOR TREATING METASTATIC COLORECTAL CANCER

Mr Anur Miah, Dr Shi Yu Yang, Prof Marc Winslet

Division of Surgery and Interventional Science, Royal Free Hospital and University College London Medical School, London

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide and has significant morbidity and mortality. Often disease is advanced at presentation and some 57% of patients have metastasis, accounting for >90% of CRC patient deaths. Cancer cell migration is a key process in developing metastatic disease, and interference in this mechanism could pave the way for new therapeutic options. Akt is a well-known regulator of various cellular functions

including proliferation, apoptosis and glucose metabolism. Emerging evidence suggests Akt may play a vital part in the development of CRC metastases. The aim of this study is to investigate how interference in Akt pathway affects metastatic CRC cell survival and migration.

Method

Metastatic colorectal cancer (SW620) cells were treated with Akt inhibitors at different concentrations. Cell viability was assessed at 24 and 48 hours. Expression of different migration related proteins following Akt inhibition were assessed using western blot. At different treatment concentrations of Akt inhibitor, cellular migration was assessed using an in-vitro cell scratch assay method.

Results

Inhibition of Akt significantly decreased metastatic CRC cancer cell viability ($p < 0.01$) and promoted cell death. It also reduced migration related protein expression. Inhibition of Akt at higher doses showed significant reduction of metastatic CRC cell migration compared to control. Conclusion: Inhibition of Akt pathway caused significant metastatic CRC cell death and reduced migration related proteins supporting its role as a suitable therapeutic target. It also affected metastatic CRC cell migration: this provides a rationale for its use in treating CRC metastatic disease. CRC = Colorectal Cancer

Take-home message

Inhibition of the Akt pathway promotes metastatic colorectal cancer cell death, reduces expression of migration related proteins as well as reducing CRC cellular migration. This supports its notion as a therapeutic target for metastatic colorectal cancer.

O136 THE EFFECT OF PRE-OPERATIVE ADJUVANT THERAPY ON THE BODY COMPOSITION AND CARDIOPULMONARY STATUS OF PATIENTS WITH COLORECTAL CANCER AWAITING RESECTION

S. Rahmani¹, A Fisher¹, S. Turvill², S Howells², and D. Burke¹

The John Goligher Department of Colorectal Surgery 1, and Department of Anaesthesia 2, The General Infirmary at Leeds, Leeds.

Introduction

The modern treatment of colorectal cancer consists of surgery, with or without adjuvant pre-operative radiotherapy, chemotherapy or chemoradiotherapy (APT) in selected cases. In the UK, therapy may be given prior to surgery in an attempt to facilitate surgical excision. However, there is some evidence that APT in other cancers may adversely affect the patient's health and increase the risk of operative morbidity. This study examined the affect of APT on the cardiopulmonary status and body composition, in patients with colorectal cancer.

Methods

Ethical approval was obtained. Patients with colorectal cancer were recruited from the colorectal MDT. Measurements of body fluid composition, using a tetrapolar, single-frequency Holtain BC Bio-impedance analyzer, and cardiopulmonary function, using exercise testing were made before and two weeks after the administration of APT.

Results

Between January and August 2010, 15 patients with colorectal cancer were recruited (median age 64, range 41-80 years, 10 male, 14 rectal cancers). There was a significant decline in VO₂-max (pre therapy (Median, IQR.) (20.9, 12.2 - 29.6) vs post therapy (17.9, 11.8 - 24), $p=0.04$) and an increase in extracellular water (pre therapy (Median, IQR.) (15.7, 10.2 - 21.2) vs post therapy (16.1, 11.3 - 20.9), $p=0.04$) following adjuvant therapy. There were no significant changes in anaerobic threshold or intracellular water.

Conclusion

These preliminary data suggest that APT for colorectal cancer has an effect upon body composition and cardiopulmonary reserve, which may be deleterious. This could affect the morbidity of surgery. *APT= adjuvant preoperative therapy *MDT= Multidisciplinary Team *VO₂-max= Maximum Oxygen consumption

Take-home message

Adjuvant pre-operative chemo and/or radiotherapy does affect the body physiology of patients with colorectal cancer which in turns might increase the post-operative complications. Hence, a period of optimization is needed before undergoing any surgical resection.

POSTER PRESENTATIONS

P1 THE EFFECT OF DRUGS COMMONLY USED FOR PYODERMA GANGRENOSUM ON THE EFFICIENCY OF GENE TRANSFER TO HUMAN KERATINOCYTES

Alexandra Teagle, James Birchall, Rachel Hargest

Cardiff University

Introduction

Pyoderma gangrenosum is a rare neutrophilic dermatosis, characterised by painful, typically pre-tibial, cutaneous ulcers. Treatment is empirical; first-line therapy is corticosteroids and/or cyclosporine, with topical wound management and analgesia. PG is a good target for gene therapy since the skin is easily accessible. Liposomes are non-viral gene transfer vectors that readily penetrate the epidermis' lipid bilayers, and are particularly suited for use in gene therapy applied to the skin, as their effects generally remain localised. However, gene therapy strategies alone are rarely successful clinically, so the use of gene therapy as an adjunct is an interesting area for study. This study aimed to investigate the effect of drugs used to treat pyoderma gangrenosum on the efficiency of in vitro transfection of keratinocytes with the reporter gene β -galactosidase, using the FDA approved vector, Lipofectamine.

Methods

Cells of the HaCaT line were cultured in growth medium containing either no drug, or one of three drugs used to treat pyoderma: hydrocortisone, methotrexate, or infliximab. After 24 hours, the keratinocytes were transfected with the reporter gene. β -gal expression was measured at 4 hours, and on days 1, 3, 5, 7, 9, and 11 post-transfection.

Results

Maximum β -gal expression (8.91%) was demonstrated using culture medium containing hydrocortisone. Expression was greatest on day 1 post-transfection in hydrocortisone-treated cells, and day 3 in other treatment groups.

Conclusion

This study is a step towards developing a topical gene-based treatment for pyoderma gangrenosum, which represents a promising future strategy in the management of this painful and debilitating condition.

Take-home message

This study demonstrated that drugs used in the treatment of pyoderma gangrenosum, a painful and debilitating skin condition, can enhance or impair gene transfer to keratinocytes in vitro, which is also time-dependent. Gene therapy represents a promising future strategy for the treatment of this disease.

P2 THE LIVER-KIDNEY EX-VIVO AUTOLOGUS PERFUSED PORCINE MODEL FOR THE STUDY OF ISLET AUTOTRANSPLANTATION IN LARGE ANIMALS

WY Chung, A Alzaraa, G Gravante, D Al-Leswas, C Pollard, OS Ling, MA Webb, S Illouz, MS Metcalfe, A Dennison

Department of Hepatobiliary and Pancreatic Surgery, University Hospitals of Leicester, UK

Introduction

We have previously described our ex-vivo autologous perfused porcine liver model for the study of hepatic physiology. Unfortunately hyperglycemia and metabolic acidosis require external supplements of insulin and bicarbonate and accurate and stable blood sugar levels and acid base balance are crucial when studying islet autotransplantation especially in the early implantation phase. We have developed a new model incorporating the kidney to clear excess metabolites and improve the environment for the islet transplantation.

Methods

Following sacrifice at the local abbatior and immediate exsanguination into a pre-heparinised container, the porcine liver and kidney were harvested, flushed with cold Soltran solution and transported on ice. The organs were connected to a circuit consisting of a centrifugal pump, oxygenator, heat exchanger and blood reservoir, and perfused with the autologous blood for 6 hours. Blood samples were collected and arterial blood gas analysis performed hourly.

Results

The glucose concentration was normalised in the liver-kidney model and no exogenous insulin was required contrasting sharply with the previous liver alone model. Acid-base balance was also well controlled and no sodium bicarbonate was required to maintain a normal pH.

Conclusion

Hyperglycemia and metabolic acidosis are dramatically improved in the liver-kidney circuit, which is an ideal model for the ex-vivo study of pancreatic islet autotransplantation. In addition this model reproduces the physiological and metabolic responses of the liver sufficiently accurately to obviate the need for the use of live animals.

Take-home message

Hyperglycemia and metabolic acidosis are dramatically improved in the liver-kidney circuit, which is an ideal model for the ex-vivo study of pancreatic islet autotransplantation. In addition this model reproduces the physiological and metabolic responses of the liver sufficiently accurately to obviate the need for the use of live animals.

P3 APPLICATION OF PROTEOMICS TO BILE BIOMARKER DISCOVERY IN CHOLANGIOCARCINOMA

SG Farid^{1,2}, RA Craven¹, J Peng¹, GK Bonney¹, PJ Selby¹, RE Banks¹, KR Prasad²

(1) Cancer Research UK Clinical Centre, St James University Hospital, Leeds UK (2) Department of HPB Surgery, St James University Hospital, Leeds UK

Introduction

We have investigated the utility of bile as a proximal bio-fluid for biomarker discovery compared to serum and characterise the bile proteome in patients with cholangiocarcinoma (CCA) using complimentary proteomic approaches.

Methods

2D DIGE was used to compare the protein profiles of bile and serum in 4 patients with CCA and gels were analysed by Progenesis SameSpots™ (v3.3). In parallel a 'shotgun' Gel-LC-MS/MS approach was utilised to characterise the bile proteome using nano-HPLC/MS/MS and data searched against the IPI database with the Mascot search engine (v2.3).

Results

Principal component analysis of 2D gel profiles detected 205 of 713 protein spots to have a significant difference in abundance between bile and serum. A shotgun approach identified 922 unique proteins in bile of patients with CCA and 180 proteins were common to all patients. Ingenuity Pathway analysis (v8.6, Ingenuity Systems Inc) for protein localization and function applied to these common proteins demonstrated the presence of a number of proteins relevant to diseases such as bile duct cancer and cellular proliferation including vimentin, phosphoglycerate kinase 1 and heat shock protein 70.

Conclusion

Our preliminary results support the hypothesis that bile contains cancer-associated proteins leaking from the tumour microenvironment in higher abundance to the general circulation. Our study is the largest to date and the first to catalogue biliary proteins in multiple patients, considerably extending the knowledge of bile proteome in CCA.

Abbreviations: 2D DIGE: Two-dimensional Difference in Gel Electrophoresis; HPLC/MS/MS: High pressure Liquid Chromatography/Mass Spectrometry

Take-home message

There is a pressing need for diagnostic markers in cholangiocarcinoma (CCA) to facilitate early diagnosis and eligibility for surgery. Our study provides the most comprehensive description of the bile proteome in multiple patients with CCA and includes many previously described putative markers and novel proteins not yet reported in bile.

P4 P-POSSUM SCORE PREDICTION OF MORTALITY IN PATIENTS UNDERGOING LIVER RESECTION FOR COLORECTAL METASTASES.

Thomas RL, Madani R, Lordan JT, Worthington TR, Karanjia ND

Royal Surrey County Hospital, Guildford, Surrey, UK

Introduction

Possum score predicts operative risk, severity and mortality. Variants used in colorectal patients (Cr-possum) and the elderly (E-possum) accurately predict mortality, forming part of colorectal pre-operative assessment. Few reports describe possum enumeration prior to liver resection. There is conflicting evidence regarding its accuracy in predicting mortality following resection of hepatocellular carcinoma and no large studies have been performed in patients undergoing resection of colorectal liver metastases. We prospectively analysed P-possum scores in patients undergoing liver resection for CRLM.

Methods

Data were prospectively gathered between 1996 and 2009 (n=480). Pre-operative assessment, peri-operative, post-operative management and follow-up were standardised according to unit protocol.

Results

P-possum median predicted mortality was 4.92%; actual 60-day mortality was 1.87%. Neither pre-operative physiological score nor p-possum predicted mortality were associated with 60-day mortality (p=0.244 and p=0.567 respectively). Where predicted mortality was less than 3%, there was improved overall survival to last follow-up, p=0.021. Pre-operative possum scores were not linked to post-operative morbidity (p=0.126), operative blood loss (p=0.874) or hospital stay (p=0.163). Metachronous CRLM had higher pre-operative possum scores (p=0.004) although were significantly older than early or synchronous CRLM (p=0.005).

Conclusion

P-possum predicted mortality is overestimated in patients undergoing resection of CRLM, however it may have a role in defining risk in elderly patients undergoing liver surgery. P-possum is not predictive of post-operative mortality and morbidity except in patients with metachronous CRLM. Low p-possum predicted mortality is associated with improved overall survival in these patients. CRLM: colorectal liver metastases.

Take-home message

Possum scoring may have a role in stratifying risk in patients undergoing liver resection for colorectal metastases although the risk of mortality is overestimated by the possum score.

P5 “RECANALISED UMBILICAL VEIN: A METHOD OF MEASURING PORTAL OXYGENATION”

Pollard CA¹, Chung WY¹, Gravante G¹, Webb MA¹, Illouz S¹, Musto P², Al-Leswas D¹, Metcalfe MS¹, Press M³, Dennison AR¹

(1) Department of Hepatobiliary and Pancreatic Surgery, Leicester General Hospital, Leicester, UK. (2) Department of Anesthesia, Leicester General Hospital, Leicester, UK. (3) Royal Free and University College Medical School, University College London, London

Introduction

Following autotransplantation islets rely on oxygen diffusion before a specific newly formed vascular supply is established from the liver. Previous experimental studies have shown that hyperbaric oxygenation during and immediately following transplantation improves islet cell function and survival. A direct measurement of the portal and central venous oxygen concentrations is important to better understand the correlation between survival and the effects of manipulation of the oxygen supply. Direct portal vein measurements are technically difficult in humans but our group routinely infuse islets via a recanalised umbilical vein, which provides access to the portal system postoperatively. Our purpose is to investigate the oxygen consumption during the perioperative period of islet infusion with serial measurements of the portal and central vein oxygenation.

Methods

After removal of the pancreas and restoration of biliary and gastrointestinal continuity the ligamentum teres is transected and the obliterated umbilical vein identified, recanalised and a Vygon® Nutricath S 11 French catheter is inserted and used for the islet infusion. The ligamentum teres is then exteriorised, sutured to the skin and covered. Portal and central venous blood samples were serially collected in the perioperative period and the oxygen concentrations analysed.

Results

The one hour post-islet infusion oxygen consumption is nearly two-fold higher than the pre-islet values. This returns to normal in three hours.

Conclusion

Estimates of portal and systemic oxygen saturations are valuable when following islet oxygen consumption and may help future studies where an increase in the inspired oxygen (FiO₂) might influence the survival of the islets.

Take-home message

Estimates of portal and systemic oxygen saturations are valuable when following islet oxygen consumption and may help future studies where an increase in the inspired oxygen (FiO₂) might influence the survival of the islets.

P6 THE ROLE OF COMPRESSION IN ANKLE FRACTURE

Sultan MJ, Zheng TT, Hodhody G, Kurdy N, McCollum CN

University Hospital of South Manchester

Introduction

Long-term ankle pain, stiffness or swelling is frequent following ankle fracture. We investigated whether engineered compression stocking (ECS) influenced functional outcome and quality of life (QoL).

Methods

Ninety patients, < 72 hours following ankle fractures, (59 conservative and 31 operative fixation) were randomised to i) ECS + air-cast boot or ii) air-cast boot alone. Patients were followed at 2, 4, 8, 12 weeks and 6 months for Olerud Molander Ankle Score (OMAS), American Orthopaedic Foot and Ankle Score (AOFAS) and SF12v2 score with duplex imaging for deep vein thrombosis (DVT) at 4 weeks.

Results

Of 90 patients recruited, 50 have completed 12 weeks follow up to date. The mean (95%CI) circumferences of the injured ankle as a percentage of the normal ankle were 107%, 100%, 100% and 99% at 0, 4, 8 and 12 weeks for ECS + boot

compared with 110%, 107%, 109% and 107% for boot alone ($p < 0.001$). By 12 weeks, the mean OMAS score for ECS + boot was 87, significantly better than 61 for boot alone ($p < 0.001$). AOFAS scores were also significantly improved by ECS ($p < 0.001$). Mean SF12v2 scores were 106 for ECS + boot and 95 for boot alone ($p = 0.016$). Of the 78 completing duplex imaging at 4 week, 5 (13%) of 38 ECS + boot patients had a DVT compared with 10 (25%) of the 40 boot alone patients ($p = 0.30$).

Conclusion

ECS improve functional outcome and quality of life following ankle fractures.

Take-home message

Compression improves recovery following ankle fracture.

P7 BOVINE URETERIC XENOGRAFT FOR DIFFICULT HAEMODIALYSIS VASCULAR ACCESS: SINGLE CENTRE EXPERIENCE OVER 4 YEARS PERIOD

Ismail W, Frost J, Hosgood S, Mohamed IH, Nicholson ML

Transplant Unit - Leicester General Hospital - University Hospitals of Leicester

Introduction

single centre series to assess performance of a depopulated bovine ureter vascular graft for haemodialysis in patients for whom conventional access was not possible over 4 years period.

Methods

the SynerGraft® vascular graft model (SGVG 100) is a bovine ureter modified by a tissue-engineering depopulation technology. SGVG 100 was implanted in patients with a failed fistula or vascular access graft (mainly for Brachio-Axillary and thigh loop graft). Graft patency was the primary outcome; secondary outcomes included adverse events and associated treatments.

Results

71 SGVG 100 were implanted in 70 patients; Primary patency was 37% (+/- 6 % SD) and secondary patency was 45% (+/- 6% SD) at 1 year, while the rate of infection was 3% for the entire series. The mean time to occlusion (33 events) was 374 +/-182 days with patency re-established in 16 of 20 surgical interventions. 5 of 8 stenotic grafts has angioplasty for luminal/anastomosis stenosis, 4 were successful. 7 grafts demonstrated areas of dilatations; however, 4 grafts continued to be usable. Mean age was 57 +/- 13 years.

Take-home message

- This series demonstrate the SGVG 100 is a reasonable alternative in tertiary difficult vascular access patients when autologous vein is not available - Interventional radiology is an essential element for secondary patency success.

P8 THE USE OF NITROBLUE TETRAZOLIUM TO DETECT BACTERIAL VIABILITY AS A METHOD OF ASSESSING THE EFFICACY OF SURGICAL SKIN PREPARATIONS.

Glen L, Bayston R, Scammell B, Ashraf W

Biomaterials and related infections group, School of Clinical Sciences, University of Nottingham

Background

Skin biopsies rather than swabs are a rarely used gold - standard to assess surgical skin preparation efficacy. Gram staining can not determine whether bacteria persisting in the skin are still viable. Live-dead stains are unsuitable due to nonspecific staining. Nitroblue tetrazolium (NBT), which is reduced to crystals in the presence of NADPH oxidase, was tested as an alternative stain.

Methods

A full thickness skin biopsy was taken after surgical skin preparation with alcoholic povidone iodine, using an 8mm x 4 mm elliptical punch. Samples were halved and one half frozen in isopentane, then sectioned. Slides were washed in water. 4% NBT solution was used to flood the slide and left for 1 minute before rinsing with water. Neutral red was used as a counterstain. Slides were mounted with DPX mountant and viewed under a light microscope at x1000 using oil immersion.

Results

Gram staining showed gram positive cocci in all 22 samples and gram positive bacilli in 13 samples. NBT staining showed viable cocci in all 22 samples and viable bacilli in 11 samples.

Discussion

Selwyn and Ellis (1972) used skin biopsies but were unable to state whether bacteria found were viable. This is the first instance of NBT being used to detect bacterial viability to assess the efficacy of surgical skin preparation. 1. Selwyn S, Ellis H. 1972. Br Med J 1:136-140

Take-home message

Surgical skin prep can be evaluated using nitro blue tetrazolium as a viability stain.

P9 HLA POSITIVITY BY LUMINEX CROSSMATCH AND ITS EARLY EFFECTS IN LIVE DONOR RENAL TRANSPLANTATION

U Mathuram Thiyagarajan, A Bagul, W Ismail, T Horsburgh, ML Nicholson

Leicester General Hospital / University Hospital of Leicester

Introduction

The clinical significance of the presence of anti-human leucocyte antigen (HLA) antibodies prior to renal transplantation remains unclear. This study was done to assess the role of a positive crossmatch detected by Luminex and its effects on early graft function.

Methods

The Luminex is a solid phase assay by using micro-spheres and it is more sensitive on detecting HLA antibodies than conventional tests. This retrospective analysis involved 88 consecutive live donor recipients between May 2007-2009 and with a minimum follow-up of one year following transplantation. The parameters assessed were graft function and biopsy proven acute rejection (BPAR).

Results

The demographics between the 2 groups showed no difference age, sex, and immunosuppression. Luminex positive HLA class I were 18 whilst HLA class II were 11. The HLA class I positive group showed no difference in renal function assessed by eGFR ($P = 0.45$) or rejection episodes ($P = 0.11$). Similarly in negative HLA class II group the eGFR ($P=0.95$) and rejection episodes (0.19) are statistically not different compare with HLA class II positive group.

Conclusion

Pre-transplant positive HLA class I, II by Luminex does not have any influence on early graft function and rejection episodes within one year in live donor renal transplantation.

Take-home message

Positive HLA class I, II antibody detected on Luminex does not have any effect on early graft function and acute rejection episodes.

P10 ASSESSMENT OF THE ROLE OF APTITUDE IN THE ACQUISITION OF ADVANCED LAPAROSCOPIC SURGICAL SKILL SETS: RESULTS FROM A VIRTUAL-REALITY BASED LAPAROSCOPIC COLECTOMY TRAINING PROGRAMME

Emmeline Nugent¹, Hazem Hseino¹, Emily Boyle¹, Borislav D Dimitrov², Kieran Ryan¹, Brian Mehigan³, Arthur Tanner¹, Oscar Traynor¹, Paul Neary^{1,4,5}

(1) National Surgical Training Centre, Royal College of Surgeons in Ireland, Dublin 2. (2) Department of General Practice, Royal College of Surgeons in Ireland, Dublin 2. (3) Department of Colorectal Surgery, St. James's Hospital, Dublin 8. (4) Division of Colorectal Surgery, The Adelaide and Meath Hospital Incorporating the National Children's Hospital, Dublin 24. (5) Trinity College Dublin.

Background

The surgeons of the future will need to have advanced laparoscopic skills. The current challenge in surgical education is to teach these skills and to identify factors that may have a positive influence on training curriculums. The primary aim of this study was to determine if aptitude impacts on ability to perform a laparoscopic colectomy.

Methods

A one day practical laparoscopic colectomy course was held by the National Surgical Training Centre at the Royal College of Surgeons in Ireland. The course consisted of a didactic session, a warm up session and the performance of a laparoscopic sigmoid colectomy on the ProMIS HALC simulator. Objective metrics such as time and motion analysis were recorded. Each candidate had their psychomotor and visual spatial aptitude assessed.

Results

Ten trainee surgeons that were novices with respect to advanced laparoscopic procedures attended the course. A significant correlation was found between psychomotor aptitude and performance on both the warm up session and laparoscopic colectomy ($R > 0.7$, $p = 0.04$). There was no significant correlation found between visual spatial aptitude and performance.

Conclusion

Psychomotor aptitude positively influences ability to perform advanced laparoscopic surgery. The results add weight to the evidence that a paradigm shift in education programmes is required in training surgeons advanced laparoscopic techniques.

Take-home message

Trainee aptitude impacts on ability to perform advanced laparoscopic procedures. Incorporating aptitude assessment into training curriculums may aid in outlining the learning pathway for the trainee.

P11 A QUALITATIVE STUDY OF DECISION MAKING (DM) IN CANCER CARE: A GLOBAL PERSPECTIVE.

Srinivasaiah, N¹, Appleton B², Kuriakose M A³, Monson, J. R⁴, Drew P J⁵ Hargest R⁶

1. Specialty trainee in General Surgery, Welsh Deanery, Cardiff, UK. 2. Consultant surgeon, POW hospital, Bridgend, UK. 3. Professor of Surgical Oncology, Mazumdar Shaw Cancer Centre, Bangalore, India. 4. Chief, Division of Colorectal Surgery, University of Rochester, Rochester, NY 5. Prof. & Honorary consultant, Royal Cornwall Hospital, Truro, UK 6. Senior lecturer & consultant surgeon, UHW, Cardiff, UK

Objective

DM in surgery & Cancer care is a complex cognitive task. Patient preferences should play a role. We aim to explore opinions and thoughts among surgical colleagues about DM.

Methods

Focus group discussions were undertaken in England, Wales and India. The discussions were audio-taped and transcribed. Qualitative methodology was adopted for analysis. Thematic analysis using framework approach was done thereby identifying Themes & Outcomes.

Results

A number of Themes and Outcomes were derived. Common convergent themes across all groups were patient-individuality, empowerment, educational, socio-economic & cultural factors. The divergent themes included cost & affordability, patient-choice, trust & beliefs, role of family members in DM, issues of QOL, consent and the role of nurses and other professionals in providing psychosocial support. The derived outcomes included the need to increase the evidence-base, clinician/patient knowledge and provide adequate information. Tailoring information to patient's needs & directing them to reliable sources was identified. Risk-communication, ongoing support and allowing patients to make individual decisions were other outcomes. Indian FGD produced similar outcomes to the above, plus the changing role of the government from being a health-care provider to health-care insurer, increased awareness of HOM, and encouraging patient representation in DM.

Conclusion

DM in cancer-care is a complex physical & cognitive process based on evidence-base, patient-needs, clinician-experience, judgement & importantly patient preference. Patient DM in cancer care is slowly evolving in England, compared to the Welsh population where joint DM seems to be the norm. In India decisions seem to be predominantly clinician led.

Take-home message

Clinicians should bear the multi-factorial nature of decision making and patient preferences should be considered when decision making.

P12 CIRCULATORY CYTOKINES AS PROGNOSTIC MARKERS OF MORTALITY IN SEVERE SEPSIS

J Sarveswaran, NM Orsi, S Homer-Vanniasinkam & D Burke

John Golligher Colorectal Unit, The General Infirmary at Leeds, Great George Street, Leeds.

Introduction

In patients with severe sepsis, previous work has suggested that individual circulatory cytokines may be valuable prognostic markers. Since cytokines operate within complex networks, their predictive value may be improved by the simultaneous measurement of multiple cytokines. This could allow early, aggressive management in patients predicted to fare badly. This study examined established and novel prognostic cytokines in patients with severe sepsis.

Methods

Between January and December 2008, patients admitted to ICU within 24 hours of the onset of severe sepsis were recruited and 28-day mortality rate was recorded. Exclusion criteria included patients on immunosuppressants or chemotherapy and those with a moribund status. Ethical approval (REC W06/Q1107/42) was obtained. Whole blood (1ml) was taken, centrifuged and resultant plasma stored until analysis for 18 separate cytokines by multiplex immunoassay. This included the novel cytokines Interleukin (IL)-13, IL-15 and IL-17. Data were expressed as pg/ml and analysed by Mann-Whitney-U tests.

Results

Sixty patients were included, of whom 27 (45%) died. Levels of all 18 cytokines were higher in non-survivors compared with survivors. Concentrations were significantly higher for IL-1beta, IL-2, Tumour Necrosis Factor- α , IL-10, IL-12(p70), IL-13, IL-15, IL-17, Interferon-gamma and Monocyte Chemoattractant Protein-1 ($p < 0.05$).

Conclusion

These results confirm the value of cytokines as potential prognostic markers of 28-day mortality in severe sepsis. They also highlight a novel prognostic role for cytokines IL-13, IL-15 and IL-17. The simultaneous analysis of multiple cytokines may allow greater accuracy in the prediction of mortality in patients with severe sepsis.

Take-home message

The multiplex immunoassay allows the simultaneous analysis of multiple cytokines in one plasma sample. Hence the measurement of multiple prognostic cytokines may allow a greater accuracy in predicting mortality in patients with severe sepsis.

P13 MUTATIONAL ANALYSIS OF COLORECTAL CANCERS AND DYSPLASIA ARISING IN PATIENTS WITH ULCERATIVE COLITIS AND COMPARISON TO THEIR SPORADIC COUNTERPARTS

Mr. S. Sharma, Mr. C. Knowles and Professor A. Silver

Centre for Digestive Diseases, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry,

Summary

Inflammatory bowel disease (IBD) comprises of predominantly two forms of disease entity; ulcerative colitis (UC) and Crohn's disease. Patients with Ulcerative Colitis are at a significantly increased risk of colorectal cancer (CRC). The molecular and genetic events underlying the progression of CRC in IBD are not well understood. We examined a collection of UC-associated cancers (UC-CRCs) ($n=6$) and matched normal controls as well as UC-associated dysplasia (UC-DALM) ($n=18$) with associated normal tissue and assessed microsatellite instability (MIN) and chromosomal instability (CIN) status of these samples and compared the results to sporadic-colorectal cancer (Sp-CRC) tissue. Our results showed that the mean age was 54.5 (cancer) compared to 52.5 of the dysplastic group, highlighting the rapid progression from dysplasia to cancer. We found that 17% of UC-associated lesions were MSI+. Most mutations were found in the MSI- tumours (83%, 5/6) and only a single PIK3CA mutation located in a MSI+ UC-DYS. In contrast, mutation frequency in Sp-CRC is higher in MSI+ lesions (63.4% 26/41). The three UC-CRC cancers (all MSI negative) did not exhibit reduction of copy number at the chromosomal regions targeted, namely chromosomes 2, 5 and 17. In contrast SNP analysis of sporadic MSI negative CRCs identified extensive copy number loss or gains in these three regions. In conclusion, despite some similarities to sporadic cancer, IBD CRC remains a distinct genotypic and phenotypic entity. Our investigation further proves this but also identifies early changes characteristic of dysplasia formed in the background of chronic inflammation.

Take-home message

Oncogenic mutations can be present early in IBD related dysplasia. This may be useful in identifying high risk patients of developing colorectal cancer.

P14 THE LIVER-KIDNEY EX-VIVO AUTOLOGOUS PERFUSED PORCINE MODEL- A NOVEL SYSTEM FOR STUDYING THE RENIN-ANGIOTENSIN SYSTEM

WY Chung, A Alzarraa, G Gravante, D Al-Leswas, C Pollard, MA Webb, S Illouz, MS Metcalfe, A Dennison

Department of Hepatobiliary and Pancreatic Surgery, University Hospitals of Leicester, UK

Introduction

Although the renin-angiotensin system (RAS) has been extensively investigated in-vivo, it has never been studied in an ex-vivo model. The liver-kidney autologous perfused porcine model excludes both organs from the influence of hormones, the autonomic nervous system and endogenous regulatory substances facilitating a clearer interpretation and understanding of the results. In addition the response of the RAS to manipulation of the portal, systemic venous or arterial blood pressures can be studied and may reveal the mediators responsible for these changes.

Methods

Following sacrifice at the local abattoir and immediate exsanguination into a pre-heparinised container, the porcine liver and kidney were harvested, flushed with cold Soltran solution and transported on ice. The organs were connected to the circuit consisting of a centrifugal pump, an oxygenator, a heat exchanger and a blood reservoir, and perfused with the autologous blood for 6 hours. Blood samples were collected and arterial blood gas estimated hourly.

Results

There was a clear oscillation (60-90 mmHg) when the hepatic artery pressure was lower than 70 mmHg which was also observed with incremental adjustments of renal artery flow rates. These phenomena demonstrate RAS system activity within the isolated perfused system.

Conclusion

The ex-vivo liver-kidney perfusion model is an alternative method to study the RAS system that provides a disconnection from numerous systemic influences and allows specific and accurate adjustments of arterial and venous pressures and flow.

Take-home message

The ex-vivo liver-kidney perfusion model is an alternative method to study the RAS system that provides a disconnection from numerous systemic influences and allows specific and accurate adjustments of arterial and venous pressures and flow.

P15 RECTAL IRRIGATION: AN EFFECTIVE OPTION IN THE MANAGEMENT OF FUNCTIONAL BOWEL DISORDERS

David S.Y. Chan, Avanish Saklani, Maria Lewis, Puthucode Haray

Prince Charles Hospital

Introduction

The management of patients with functional bowel disorders range from simple dietary advice to complex surgery or offering patients the option of a stoma. We offer rectal irrigation as an option after simple conservative measures have failed. Current evidence regarding the benefits of rectal irrigation in functional bowel disorders is scanty. This study aimed to assess the efficacy of rectal irrigation in patients with functional bowel disorders.

Methods

Retrospective analysis of patients presenting to our functional bowel clinic from 2005 to 2009. The Cleveland Clinic constipation and incontinence scores were used to assess outcomes.

Results

Ninety-one patients (80 female, median age 51 yrs; range 17-78) had undergone rectal irrigation for the following indications: chronic constipation (n=32), slow transit constipation (n=18), obstructed defaecation (n=10), faecal incontinence (n=31). Mean constipation scores improved from 18.72 to 11.45 following rectal irrigation (p=0.001). Twenty-one (42%) patients are still using irrigation with mean duration of irrigation 10.7 months (1-36) and 90% patients would recommend it to others. Seven (14%) patients with constipation required surgical intervention. In patients presenting with incontinence, the mean incontinence scores improved from 16.2 to 10.8 (p=0.005). Surgery was required in 7 patients.

Conclusion

Rectal irrigation can be a useful tool in the management of functional bowel disorders and should be tried prior to the consideration of any surgical remedy.

Take-home message

Rectal irrigation is a useful option in the management of functional bowel disorders.

P16 ASSESSMENT OF RECTAL AFFERENT NEURONAL FUNCTION USING EVOKED POTENTIALS IN PATIENTS WITH CONSTIPATION AND RECTAL HYPOSENSATION - A PILOT STUDY

EV Carrington¹, R Burgell¹, D Lelic², S Surguy³, A Drewes², Q Aziz³, CH Knowles¹, SM Scott¹

(1) Academic Surgical Unit (GI Physiology Unit), Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, United Kingdom. (2) Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark. (3) Neurogastroenterology Group, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, United Kingdom.

Introduction

Impaired rectal sensation (rectal hyposensitivity) is present in one quarter of patients with chronic intractable constipation. The mechanisms contributing to its development are not fully understood, but may result from a functional deficiency of rectal afferent nerves. This study aimed to demonstrate feasibility of rectal evoked potentials (EPs) as a tool to evaluate the integrity of sensory innervation in patients with constipation and rectal hyposensitivity in comparison to healthy controls.

Methods

Rectal EPs (recording electrode over Cz) were recorded in 5 patients and 5 healthy controls in response to electrical stimulation of the rectum at 10 cm from the anal verge using a specialized bipolar stimulating electrode (4 sets of 50 stimulations, 0.2 Hz frequency, 0.2 mS pulse width). Stimuli were delivered at reported pain threshold. EP peak latencies were analysed.

Results

Sensory threshold to electrical stimulation was higher in patients than controls (median 25 [range 5-30] mA vs. 8 [3-23] mA). However pain intensity was similar between the two groups (36 mA vs. 31 mA). Latency to the first negative peak was 69 [19-76] mS in control subjects. In patients with rectal hyposensitivity 4/5 subjects had a latency >76 mS (median 99 [39-156] mS), suggesting prolonged neuronal conduction velocities either peripherally or centrally.

Conclusion

Rectal EPs are a feasible tool to assess integrity of the rectal afferent pathway. Prolonged latencies in constipated hyposensate patients suggest a primary defect in sensory neuronal function. Further investigation is required to confirm these findings. Abbreviation. EP = Evoked Potential

Take-home message

Rectal EPs are a feasible tool to assess integrity of the rectal afferent pathway. Prolonged latencies in constipated hyposensate patients suggest a primary defect in sensory neuronal function.

P17 CORRELATION ANALYSIS OF INITIAL AORTIC DIAMETER, ANEURYSM VOLUME AND PEAK WALL STRESS IN ABDOMINAL AORTIC ANEURYSM (AAA) EXPANSION.

JA.Khan, FAK. Mazari, MNA. AbdulRahman, IC. Chetter, PT. McCollum

Academic Vascular Surgical Unit, University of Hull, Hull, United Kingdom.

Introduction

Ultrasound surveillance is routinely performed in abdominal aortic aneurysms (AAA) with maximum antero-posterior(AP) diameter <5.5cm. Scanning intervals vary according to aneurysm size and expansion rate. In general, larger aneurysms expand at greater rate than smaller aneurysms; however, this expansion is highly variable and difficult to predict. This study was designed to investigate the relationship of peak wall stresses (PWS), initial aneurysm volume and maximum AP diameter with the AAA expansion rate.

Methods

54 patients (44men, mean age 77.2±6.8years) were recruited to AAA surveillance and followed up prospectively. Abdominal CT scan was performed in all patients to define the aneurysm type, morphology, extent and to measure PWS through finite element analysis. Initial AAA volumes were calculated from 3D CT reconstructions. Expansion rates were derived from sequential ultrasound performed at regular intervals according to clinical need. Correlations between PWS, initial volume & initial maximum AP diameter and expansion rate were analysed using Spearman Rank Correlation, SPSSv16.0.

Results

Median initial maximum AP aortic diameter was 5.0cm (IQR4.5-5.4cm). PWS was 0.43mPa(IQR0.32-0.51mPa) and initial AAA volume was 270cm³(IQR 156-349cm³). Median expansion rate was 0.24mm/month(IQR0.17-0.45mm/month). Correlation analysis: PWS and initial AAA volume did not show any significant correlation with expansion rate [PWS($r=0.22p=0.11$); Volume($r=0.24p=0.09$)]. Initial maximum AP aortic diameter showed a weak correlation ($r=0.28$) with AAA expansion rate which was statistically significant ($p=0.04$).

Conclusion

AAA expansion rate is independent of PWS and initial AAA volume and correlates weakly with AP diameter. Identification and modification of factors affecting AAA expansion rate remains an area for further study for prevention of rupture.

Take-home message

AAA expansion rate is independent of PWS and initial AAA volume and correlates weakly with AP diameter. Identification and modification of factors affecting AAA expansion rate remains an area for further study for prevention of rupture.

P18 THE EFFECTIVENESS OF WARD BASED HIGH DEPENDENCY BAY (HDB) IN THE EARLY POST-OPERATIVE MANAGEMENT OF OESOPHAGECTOMIES AND GASTRECTOMIES.

A.A. Warsi*, A. Wilkins, N. Patel, R.G. Berrisford, G. Sanders, J. Rahamim, T. Wheatley.
Derriford Hospital, Plymouth.

Introduction

Early post-operative management of oesophagectomies in ITU is well recognised. We have made effective use of high dependency bay on surgical ward, with appropriate nursing and medical staff, in the early post-operative management of oesophagectomies. This has obviated the need for treating these patients in a more expensive ITU setting.

Methods

All patients who underwent oesophagectomy between January 2008 and November 2009 were included in the study. Data were collected retrospectively from case notes and prospectively from computerised cancer database. Pre-operative comorbidities, investigations, type of resection, morbidity and in-hospital mortality, duration of stay and final pathological stage were analysed. An estimate of cost saving was made by taking account of non-ITU post-operative care.

Results

There were 33 oesophagectomies, 25 male and 8 females. The median age at resection was 62 years (range 44 to 85). 27 (81%) patients were managed on the dedicated Upper GI surgery ward. There was 1 planned and 5 unplanned admission to ITU- 4 was early (within 7 days) and 1 was late. The average estimated cost saving for the patients not routinely admitted to ITU was £20,000/- Early complication comprised of 2 anastomotic leaks, 2 chyle leaks, 1 stroke, 1 DVT, 2 hospital acquired pneumonia. late complication included 1 dumping, 2 reflux. 6 patients had late dysphagia requiring endoscopic dilatation. There was 1 in hospital mortality at 12 days.

Conclusion

Major operations such as oesophagectomies can be effectively and efficiently managed on a dedicated surgical ward without routine post-operative ITU admission with good outcome.

Take-home message

Complex major operations such as oesophagectomies can be effectively and efficiently managed on a dedicated surgical ward without routine post-operative ITU admission with good outcome.

P19 ROLE OF NF-KAPPA B SIGNALLING IN NEUROBLASTOMA

D Mullasery, V See, D Spiller, B L Pizer, C Dominici, HP McDowell, ECJesudason, MR White, PD Losty

Department of Academic Paediatric Surgery and Oncology, University of Liverpool, Alder Hey Children's Hospital

Background

Neuroblastoma (NBL) is a common solid tumour in childhood with <40 % survival despite advances in chemo-radiotherapy and aggressive surgical resection. We hypothesised that activation of the transcription factor NF- κ B may be one of the potential leading mechanisms underlying chemoresistance in neuroblastoma.

Methods

NF- κ B activity was measured using reporter gene assay (luminometry with NF-Luc) and real time and A20). Sensitivity of NBL cell lines and (RT-PCR (target genes I κ B α , I κ B primary cell cultures to cytotoxics (etoposide and doxorubicin) and NF- κ B inhibitors were measured using MTT assay. Cell death was confirmed by caspase 3/7 assay and annexin V-propidium iodide binding (confocal microscopy). Data were analysed using ANOVA and Bonferroni methods.

Results

All NBL cell lines showed relative drug resistance to cytotoxics. Luminometry and real-time RT-PCR confirmed the NF- κ B pathway was activated by cytotoxics in NBL cell lines. NF- κ B inhibition using chemical (Bay11-7082 and BMS-345541) and biological agents (I κ B α and mutant I κ B α) resulted in significant cell death in NBL cell lines and primary cultures. Cell death was a result of apoptotic mechanisms. Synergistic cell death was not observed with combination chemotherapy and BMS ($p < 0.05$). BMS notably induced inhibition of the p53 pathway.

Conclusion

NF- κ B inhibition may have potential therapeutic application in NBL. The pivotal role of NF- κ B and p53 in cell fate decisions suggests that therapeutic agents will need careful screening for effects on both pathways to develop agents which would simultaneously inhibit NF- κ B and activate p53.

Take-home message

NF- κ B inhibition may have potential therapeutic application in NBL. The pivotal role of NF- κ B and p53 in cell fate decisions suggests that therapeutic agents will need careful screening for effects on both pathways to develop agents which would simultaneously inhibit NF- κ B and activate p53.

P20 LASER HAEMORRHOIDECTOMY: AN EFFECTIVE AND AMBULATORY HAEMORRHOIDECTOMY

M Khandelwal^{1,2}, M Hemadri^{1,2}, E Ewart¹, PJ Moore^{1,2}

1)Scunthorpe General Hospital 2)Yorkshire Laser Centre

Introduction

Laser Haemorrhoidectomy is performed as a day case procedure under local anaesthetic and sedation for symptomatic grade 3 and 4 haemorrhoids. The conventional operation, Milligan-Morgan haemorrhoidectomy which consists of excision of haemorrhoids is done under general anaesthetic with a diathermy or sharp dissection. Laser Seal is obtained by Diomed 810 nm or CO2 10600nm at 20 watts.

Methods

Retrospective analysis of 102 consecutive patients who have undergone the laser haemorrhoidectomy from 2006 to 2009. They had regular clinic follow up at 2 and 6 weeks post-operatively.

Results

102 patients in 3 years. Male: Female ratio was 48:54, Age range: 32 to 81 years. One patient was converted to general anaesthetic (1%). All patients (except two, ie. 2%) were discharged within 2 hours. One due to administration of general anaesthetic who was discharged as day-case; other due to post operative bleeding and was admitted for 3 days of conservative management. Four readmissions (4%) (2 patients due to post-operative oedema, 2 patients due to oedema and pain). All of them were discharged after observation. Four patients developed post operative chronic Anal Fissures (4%). They healed with 6 weeks of 0.2% Glyceryl trinitrate cream.

Conclusion

Laser seal haemorrhoidectomy in our hands is showing good results. It enhances patient experience. It also has cost benefits due to very short stay as most patients go home within two hours of procedure. It also avoids the risks of a General Anaesthetic in most of the cases.

Take-home message

Laser Haemorrhoidectomy is cost-effective, day case procedure and avoids a General Anaesthetic to patients. It might be the next step forward in Haemorrhoid surgery.

P21 THE EFFECTS OF PSYCHOLOGICAL DISTURBANCES ON PAIN AND SURGICAL OUTCOME IN PATIENTS REQUIRING ARTHROSCOPIC SUBACROMIAL DECOMPRESSION

Thomas Yeoman, Carlos Wigderowitz

University of Dundee Medical School, Ninewells Hospital, Dundee

Introduction

Preoperative depression and anxiety have been linked to poorer postoperative outcomes; increased pain and longer recovery. Few previous studies have investigated these relationships in patients requiring upper limb orthopaedic surgery. This study explored the relationship between preoperative depression and anxiety and postoperative shoulder pain and function in patients requiring ASAD for impingement syndrome.

Methods

This prospective study investigated a consecutive series of patients undergoing ASAD in 2009/10. Mental state, shoulder function and shoulder pain were assessed using the Hospital Anxiety and Depression Scale, the Oxford Shoulder Score and the Pain Visual Analogue Scale. Questionnaires were completed 2 weeks preoperatively and 3 and 6 weeks postoperatively. The local research ethics committee approved the study.

Results

21 patients (7 male; mean age 55 years) participated. Preoperatively, 5 (24%) patients were anxious, 5 were depressed and 2 were both. Spearman's rank order correlation demonstrated no significant correlation between preoperative depression and anxiety and postoperative shoulder function or pain. Preoperative anxiety correlated significantly with preoperative shoulder pain ($p < 0.05$) but only moderately with pain postoperatively. Preoperative depression predicted postoperative anxiety. Wilcoxon signed ranks test demonstrated significant improvements in patient shoulder function, pain and mental state at 6 weeks postoperatively ($p < 0.05$).

Conclusion

Weak associations were found between anxiety and shoulder function, and between depression and shoulder pain and function. These associations would remain insignificant even if the sample size was trebled. However correlations were seen between anxiety and pain. Furthermore a significant improvement in mental state was seen 6 weeks postoperatively. ASAD arthroscopic subacromial decompression

Take-home message

Preoperative depression does not predict shoulder pain or function after ASAD. However there are stronger links between preoperative pain and anxiety that may warrant further investigation.

P22 THERE IS NO ROLE FOR INTRA-ABDOMINAL PRESSURE MONITORING FOLLOWING MAJOR ELECTIVE COLORECTAL SURGERY

Aitken E, Gough V, Prentice J. & Macdonald A.

Monklands District General Hospital, Airdrie

Background

Intra-abdominal pressure (IAP) monitoring within ITU is now well established. However its role in following elective general surgery remains unclear.

Methods

All patients undergoing major elective colorectal resection between August 2009 - August 2010 were enrolled. Four hourly post-operative transvesical IAP measurements were made until the patient was discharged from HDU. These were correlated with physiological parameters (heart rate, blood pressure, urine output), patient demographic data (age, ASA, BMI) and standardised scores of mortality/ organ failure (SOFA, APACHE-II, P-POSSUM). Uni- and multi-variate analysis was performed.

Results

115 patients (60 males: 55 females) were enrolled (mean age 55.8y.o. (range 25-87)). 59 patients had laparoscopic surgery (6 converted). 89.6% had primary anastomoses. 12 patients developed significant post-operative complications, including 6 clinical anastomotic leaks requiring re-operation. Two patients died. Mean duration of HDU and hospital stay was 4 and 10.5 days respectively. Mean SOFA score was 3.3+/-1.6; mean APACHE-II score was 10.4+/-4.7. Mean IAP was 7mmHg (days 1-5). There was no significant difference in IAP between patients who developed complications and those who did not (p=0.72). Only two patients had an IAP of >12mmHg at any point. Both these patients had a BMI >35. All patients developed anastomotic leaks after discharge from HDU, therefore IAP monitoring had been discontinued prior to the leak. Four of the six had IAP measurements prior to re-laparotomy (9-11mmHg).

Conclusion

Routine IAP monitoring within surgical HDU has no role following elective colorectal surgery. It is labour intensive and is not predictive of either complications or mortality.

Take-home message

Routine intra-abdominal pressure monitoring has no role following major elective colorectal surgery. It is not predictive of either complications or mortality

P23 RISK FACTORS FOR COMPLICATIONS FOLLOWING BREAST REDUCTION.

Srinivasaiah N¹, Iwuagwu OC¹, Stanley PW², Hart NB², Platt AJ², Drew PJ¹

1 Breast Unit, Castle Hill Hospital, Cottingham, UK. 2 Department of Plastic Surgery, Castle Hill Hospital, Cottingham, UK.

Introduction

Reduction-mammoplasty (RM) has been shown to benefit physical, physiological and psycho-social health. However, there are some recognised complications. It would be beneficial to identify those patients at higher risk and to modify risk factors when possible. We aimed to determine the effects of resection weight, BMI, age & smoking on complication rates following Reduction mammoplasty

Methods

Data was gathered as a part of RCT examining psycho-social & QOL benefits of Reduction mammoplasty. 67 consecutive female patients undergoing inferior pedicle Reduction mammoplasty were recruited. Complications were recorded prospectively. Data gathered included resection-weight, BMI, age and smoking status. SPSS was used for statistical analysis.

Results

Of the 67 patients, 16 (23.9%) had complications. Higher resection-weight, increased BMI and older age were associated with a higher rate of complications with p values of $p < 0.001$, $p = 0.034$ and $p = 0.004$ respectively. In the complications group the mean resect weight, BMI & age were 1,813 (SD 763.7) grams, 30.5 (SD 3.3) kg/m² & 47.1 (SD 12.7) years respectively. The uncomplicated group had mean scores of 1,253 (SD 469.5) grams, 27.9 (SD 4.4) kg/m² & 36.9 (SD 11.5) years respectively for resect weight, BMI & age. 9 (13.4%) were current smokers, 20 (29.9%) were ex-smokers and 38 (56.7%) ever smoked. The incidence of complications was highest amongst current-smokers and lowest amongst those who had never smoked. There was a 37% increase in complications in current smokers ($p < 0.01$).

Conclusion

Higher resection weight, increased BMI, older age and smoking are significant risk factors for complications after breast reduction surgery.

Take-home message

Patients undergoing reduction mammoplasty should be advised to reduce weight & stop smoking prior to the procedure, to prevent complications.

P24 LONG TERM OUTCOME OF UVULOPALATOPHARYNGOPLASTY (UVPPP) - A 10 YEAR STUDY

Chan, J., Rashid, M., Mahalingappa, Y., and Karagama, Y.

Tameside General Hospital NHS Foundation Trust

Introduction

Snoring is an important cause of sleep disturbance. To our knowledge, our survey has the longest patient-centred follow up in the literature of patients who underwent UVPPP for primary snoring. Our survey explores its effectiveness, the variables which could influence its effectiveness and its side effects.

Methods

Retrospective survey of 136 adults who underwent UVPPP between 1980- 2001. 96 (72%) returned postal questionnaires were analysed using Microsoft Excel™ and SPSS™ (Statistical Package for the Social Sciences).

Results

71.9% still snore 10 years post-UVPPP, 50.7% of whom snore less. Despite only 28% became snore-free after UVPPP, 72% thought the operation had improved their symptoms from snoring. However 47% said they would not have the operation again and the most common reason was that the procedure was too painful and snoring persisted (25%). There is a significant association between smoking and gender and snoring post-UVPPP ($\chi^2(1) = 21.80$; $\chi^2(1) = 4.38$, $p < 0.05$ respectively).

Conclusion

In our 10 year follow up of patients who underwent UVPPP for snoring, 71.9% still snore and 72% of patients attributed their improved symptoms from snoring to the operation. Smoking and gender may have contributed to the persistence of snoring after UVPPP indicating that these factors would have to be addressed before committing to this procedure. UVPPP is not demonstrated here to be a reliable cure for primary snoring. However, despite the length of the survey it is an observational study at best. There remains a need for a well conducted experimental trial to answer the questions posed in this survey.

Take-home message

In our 10 year follow up of patients who underwent UVPPP for snoring, 71.9% still snore. UVPPP is not demonstrated here to be a reliable cure for primary snoring.

P25 TEMPORARY GASTRIC NEUROMODULATION FOR INTRACTABLE NAUSEA AND VOMITING

S Ullah, R Arsalai-Zadeh, P Sedman, G Avery, J MacFie

Academic surgical unit-Castle Hill Hospital-Cottingham.

Background

Gastric neuromodulation (GN) has been advocated for the treatment of drug refractory gastroparesis or persistent nausea and vomiting in the absence of a mechanical obstruction. There is, however, little objective data to support its use particularly with regards to effects on gastric emptying.

Methods

Six patients, (M:F=4:2, mean age 49, range 44-57 years) underwent the procedure. Three patients had confirmed slow GI transit. Aetiology included previous gastric surgery in 2, diabetes in 1 and idiopathic nausea and vomiting in 3 patients. GN pacing-wires were placed endoscopically and left in situ for 7 days. Patients underwent gastric scintigraphy before and 24-hr after the commencement of GN. Total gastroparesis symptom score(TSS), vomiting frequency score/week (VFS) health-related quality of life(QOL), physical composite score (PCS) and mental composite score (MCS) using SF12 questionnaire, gastric emptying(GE), nutritional status and weight were compared before and after GN.

Results

TSS improved after GN in comparison with baseline (4 ± 4 vs. 14 ± 4). VFS improved in 5 patients (14 vs. 2). PCS improved in 4 patients (mean 31 ± 4 vs. 43 ± 1); MCS improved in 5 patients (mean 33 ± 13 vs. 40 ± 15). All patients reported an improvement in oral-intake. Significant weight gain (mean 1 kg, range 0.3-2.4) was observed over 7 days. Gastric half emptying time improved in 4 patients.

Conclusion

GN improved upper GI symptoms, QOL and nutritional status in patients with intractable nausea and vomiting. GN does effect gastric emptying in this chronically debilitated group of patients.

Take-home message

Gastric neuromodulation improves intractable nausea, vomiting and gastric emptying.

BBA SECTION

BP1 MICRODIALYSIS TO MONITOR BURN WOUND METABOLISM IN THE EARLY POST-BURN PERIOD: CORRELATION WITH LASER DOPPLER IMAGING

EE Breuning, D Richards, P Gosling, NS Moiemem

Introduction

Microdialysis is a minimally invasive method of monitoring live tissue fluid for biochemical analysis. It has great potential for monitoring the progression of the burn wound. This study aimed to correlate biochemical changes within the burn wound with Laser Doppler Image (LDI) evidence of burn wound progression.

Methods

Ten adult patients with full thickness (FT) burn <15%TBSA, were recruited. Three microdialysis probes were inserted intradermally into the centre of the burn, the periphery of the burn and unburned skin. Microdialysate was collected half hourly until 36 hours post burn and analysed for glucose, lactate, pyruvate and glycerol. Lactate: pyruvate ratio (LPR), a measure of anaerobic metabolism, was calculated. Laser Doppler Images were taken on admission and after 36 hours post-burn.

Results

Three patients showed clear evidence of wound progression on LDI. Each of these patients showed biochemical evidence of local ischaemia (LPR>25) within the burn and/or within the normal skin. A further 2 patients had borderline evidence of wound progression on LDI with signs of ischaemia on microdialysis. 1 patient had no evidence of wound progression on LDI with no evidence of ischaemia on microdialysis. Four patients had incomplete data for either microdialysis or LDI.

Conclusion

For those patients with complete data, there was good correlation between microdialysis evidence of dermal ischaemia and LDI evidence of burn wound progression. This pilot study shows promising results for the use of microdialysis to monitor the progress of the burn wound through the early post-burn hours.

BP2 GRAM NEGATIVE BURN WOUND INFECTION: PROTAGONISTS, TRENDS AND STRATEGIES

Ernest A. Azzopardi, MRCSEd MSc Surg MD^{1,2} Dean E Boyce, FRCS (Plast) FRCS(Eng)²; William A Dickson, MBE, FRCS(Glas) FRCS²

* Ernest Azzopardi is a PhD student at Cardiff University;

(1) Wound Biology Group, Cardiff University, 5th Floor, 5F03 Dental Building, Academic Ave. Heath Park, Cardiff, CF144XY (2) Welsh Centre for Burns & Plastic Surgery, Swansea, UK

Abstract

Gram-negative infection remains a major contributor to morbidity mortality and cost of care but no multinational epidemiological studies specific to burn patients exist. Mapping these trends would identify pathogens of actual and imminent concern to burn physicians, develop prognostic patient profiles and facilitate the identification of novel targeting mechanisms. We sought to define a contemporary gram-negative burn wound profile and identify trends in emerging Gram-negative burn wound infections (BWI) within the last 60 years.

Methodology

Phase 1: A multiplatform and multidatabase search over 60 years; Phase 2: Evidence-based critical appraisal (140/240 studies selected). Phase 3: Retrieval of missing data from index institutions.

Results

A common BWI profile was identified across 4 continents (*Pseudomonas* $\mu=97.6$, *Klebsiella* $\mu=30.2$, *Acinetobacter* $\mu=17.4$, *Enterobacter* $\mu=18.2$, *E.coli* $\mu=5$; *Proteus* $\mu=4$ new infections/1000patient years). Furthermore, *Aeromonas* infection, although presently a minority of Gram-negative bacterial infections at present, was identified an emerging pathogen of note (76 % of identified publications, *Aeromonas hydrophila* =96% of isolates; mortality=10.7%). The following patient profile indicated predisposition to *Aeromonas* infection: mean age ($\mu=33.7$ years, range $17 \leq R \leq 80$, SD=15.6), TBSA ($\mu=41.1\%$, range $8\% \leq R \leq 80\%$, SD=15.2); FTSB ($\mu=27.7\%$, range $3\% \leq R \leq 60\%$, SD=16.6) and a male predominance (81.3 %). Multidrug resistance in this group was higher in burn patients than the general patient population. *Stenotrophomonas maltophilia*, *Vibrio* spp., *Chryseobacterium* spp. *Alcaligenes xylosoxidans* and *Cedecia lapigei* were also reported. Arresting the thermal injury by untreated water was the common predisposing factor.

Discussion

Identification of a common bacterial profile allows for pre-emptive surveillance. These pathogens' propensity to rapidly acquire multidrug resistance strongly argues for further studies to identify common molecular mechanisms across this bacterial spectrum that may be used to safely and effectively engineer antimicrobial therapy.

BP3 POLYMER THERAPEUTICS FOR EFFECTIVE ANTIMICROBIAL TARGETING IN BURN INJURY

Azzopardi EA, Ferguson EL, Thomas DW

Polymer therapeutics group, Cardiff University, 5th Floor, 5F03 Dental Building, Academic Avenue Heath Park, Cardiff, CF14 4XY

Abstract

Gram-negative infection is a leading cause of mortality. Antimicrobial development has been outpaced by Gram-negative multi-drug resistance. While older antibiotics such as colistin remain effective, their use is extremely limited by their inherent nephro/neurotoxicity. Novel methods for safe and effective delivery would, therefore, radically improve patient treatment. Polymer therapeutics are nanomedicines allowing custom-engineered targeted optimal drug delivery through conjugation with a water-soluble polymer. The new macromolecule would benefit from passive targeting through the Enhanced Permeability and Retention effect. Conjugation would mask in-transit toxicity. Degradation of dextrin by μ -amylase at the infected site would unmask colistin reinstating its antimicrobial activity. This study aims to develop the first fully customisable library of bioresponsive dextrin-colistin conjugates for safe and effective antimicrobial delivery in infection.

A range of native dextrans (6,700-51,000 g/mol) were functionalised by succinylation (2-40 mol%). The resulting polymers showed correspondingly incremental molecular weight, but little change in polydispersity (PDI 1.52-1.82). Degradation of functionalised dextrin by α -amylase was characterised as exponential decay, and predictably determined by the degree of succinylation (dextrin 2>5>10>15mol%, $R^2=0.807-0.980$) and molecular weight. Subsequently, a library of dextrin-colistin conjugates was synthesized using low-molecular weight dextrin (6,700 g/mol; 2-15 mol% succinylation). GPC and FPLC confirmed the presence of a high molecular weight conjugate, (typically 14,000-19,000 g/mol; colistin content of 9-21% w/w). Conjugates contained 0.7-1.7 dextrans per colistin molecule, attached via 2-4 binding sites. Preliminary results suggest that polymer modification predictably increases its degradation time. Dextrin-colistin conjugation is feasible and optimal conjugation conditions have been identified, resulting in predictable macromolecular constructs. Significant unmasking of colistin activity in the presence of α -amylase suggests that restoration of antimicrobial activity is feasible in vivo. Further experiments will investigate antimicrobial release rates, antimicrobial activity and toxicity in-vitro and ex-vivo.

BP4 GASTRIC PERFUSION: AN OUTCOME MEASURE IN BURNS RESUSCITATION

E. Vlachou, R. Papini, N. Moimen

University Hospital Birmingham Burns Centre, Birmingham, UK.

Introduction

Gastric perfusion in the acute clinical setting has been a source of great controversy. The aim of this study was to assess the predictive value of gastric perfusion monitoring during the acute phase of thermal injury.

Method

Twenty adult patients with burns greater than 15% Total Body Surface Area, admitted to a single burns unit over a period of two years were recruited following informed consent. The mean TBSA was 32% (range 16-51%) and the mean age 40 (range 18-79). Gastric mucosal pH and PCO₂ data was collected hourly over 36 hours from admission by air tonometry. The patients' urine output and vital signs were closely monitored throughout the study period and all interventions documented.

Results

Deterioration in gastric perfusion is defined as a rise in pCO₂ > 6.5 kPa. Episodes of relative gastric ischaemia during the acute post-burn phase correlated well with systemic hypoperfusion. In burns greater than 27% TBSA the deterioration in gastric perfusion reliably preceded a fall in urine output and Mean Arterial Pressure by one to three hours.

Conclusion

Gastric mucosal pCO₂ is an earlier predictor of hypovolaemia than urine output or blood pressure in acute thermal injury. This non-invasive and sensitive outcome measure could therefore become a valuable adjunct to burns resuscitation.

BP5 MONOCYTE RECRUITMENT VIA THE CX3CR1 RECEPTOR INFLUENCES BURN WOUND HEALING**AJP Clover^{1,2}, AHS Kumar², NM Caplice²**

1 Department of Plastic Surgery, University College Cork, Cork, Ireland

2 Centre for Research in Vascular Biology, University College Cork, Cork, Ireland

Introduction

Current research focusing on cell based therapies using bone marrow or dermal progenitor cells is a new paradigm aimed at improving wound healing biologically. Recent studies have highlighted the potential benefit of bone marrow cells, reducing the time to cutaneous healing, contributing to the dermal fibroblast population, and secreting angiogenic factors. A network of cytokines regulates the delivery of these cells into wounds. CX3CL1, also known as fractalkine is one such cytokine expressed on activated endothelial cells, which triggers the recruitment of CX3CR1 positive bone marrow progenitor cells. Its role in burn wound healing has not been previously established.

Method

A scald burn was induced on the dorsum of CX3CR1 transgenic mice heterozygous for GFP knock in or CX3CR1 dysfunctional mice homozygous for GFP knock in at the CX3CR1 locus respectively. The rate of wound healing was assessed over 12 days. Tissue was obtained for analysis by immunohistochemistry.

Results

The rate of wound healing was delayed if the receptor CX3CR1 was not functioning when compared with animals with the receptor functioning (n=12). The number of CX3CR1 expressing monocytes was doubled in the healing wound when the receptor was functioning (p<0.001), the numbers of macrophages recruited into the healing wound was doubled (p<0.005) and the amount of the ligand fractalkine was also doubled (p<0.005).

Conclusion

This study identifies a role for the cytokine, Fractalkine and its receptor, CX3 CR1 in burn wound healing. This will be an attractive target to recruit cells into burns that could improve healing.

BP6 ANALYSIS OF PUBLIC ATTITUDES TOWARDS THE USE OF AUTOLOGOUS AND ALLOGENIC CELLS IN TISSUE ENGINEERED PRODUCTS FOR BURNS**AJP Clover^{1,2}, B Lane O'Neill³, AHS Kumar²**

1 Department of Plastic Surgery, University College Cork, Cork, Ireland

2 Centre for Research in Vascular Biology, University College Cork, Cork, Ireland

3 The Medical School, University College Cork, Cork, Ireland

Introduction

The first trials using stem cells to improve burn wound healing are now beginning. However there is no data on whether the public view cell therapy using autologous or allogenic cells as acceptable either as a treatment for acute burns or for burns scar treatments. Data does exist on opinions towards the use of these cell types for diabetes and Parkinson's disease.

Methods

A survey was carried out of patients attending plastic/ burns outpatients and medical outpatients to assess opinions towards using autologous and allogenic cells as treatments for acute burns and burns scarring. This was compared to similar opinions for use in diabetes and Parkinson's disease.

Results

279/ 280 surveys were completed. Most patients were comfortable using their own cells to improve acute burns healing (97%) or burns scar treatment (97%), whereas less were happy to use cells from another unrelated human for burns healing (67%, p<0.001) or for the effects of scarring (70%,p<0.001). Patients are more likely to accept allogenic cells for the treatment of burns as opposed to cosmetic reasons (67% v 54%, p<0.01). There was no difference observed between plastic surgical patients and medical patients in acceptance of allogenic cells for burns, Parkinson's disease or diabetes.

Conclusion

There is good acceptance for the use of both autologous and allogenic cells for use in the treatment of burns and scarring. Levels of acceptance are similar for use of these cells in other diseases where stem cell therapy is being proposed as a treatment.

BP7 TOPICAL NEGATIVE PRESSURE THERAPY: DOES IT ACCELERATE NEOVASCULARISATION WITHIN THE DERMAL REGENERATION TEMPLATE, INTEGRA? A PROSPECTIVE HISTOLOGICAL IN-VIVO STUDY

Jeremy Yarrow, Dia Kamal, Daniel Kearns, Derek Mendonca, Naiem S Moiemem

Background

The use of topical negative pressure (TNP) dressings with dermal regeneration template (DRT), Integra, has improved outcomes and simplified aftercare. Previous clinical studies have suggested accelerated vascularisation; with a reduction in the duration of the 1st stage after the application of Integra, from 2 to 4 weeks to as little as 4 days, but with no histological evidence. However, histological studies, without TNP, have shown that vascularisation occurs between the second and the fourth week. This study set out to examine histologically the rate of DRT neovascularisation when combined with TNP.

Methods

Eight patients with nine reconstruction sites were enlisted. Unmeshed Integra and fibrin sealant to promote adherence were used. TNP was applied for the duration between the 1st and the 2nd stages. Patients underwent serial biopsies on days 7, 14, 21 and 28 post-application. The biopsies were stained with H&E and endothelial markers CD31 and CD34. Template vascularisation was assessed as a percentage of the template depth in which patent, canalised vascular channels could be demonstrated.

Results

The median percentage of the template depth which demonstrated canalised channels was 0%, 20%, 61% and 80% for days, 7, 14, 21 and 28, respectively.

Conclusion

The application of TNP dressings to dermal templates can reduce shearing forces, restrict seroma and haematoma formation, simplify wound care and improve patient tolerance. However, this study could not demonstrate that TNP accelerates neovascularisation as verified by the presence of histologically patent vascular channels.

BP8 THE DESIGN AND DEVELOPMENT OF A NEW BURNS DRESSING

Vivienne M Kershaw, Dave Pritchard and Mike Walker

Introduction

Partial thickness burns are typically very painful and their treatment traumatising, especially during dressing changes. The benefits of using carboxymethyl cellulose (CMC) dressings on burns for exudate management, minimising dressing changes, and managing pain have been demonstrated¹. However, there are some aspects of the dressings which can be improved: ease of removal, comfort and flexibility during wear. These needs have been identified as supplementary benefits for the patient and carer, in addition to the existing benefits of CMC dressings.

Method

A new patent-pending technology has been developed which involves a thin hydroentangled, silvered or non-silvered web of CMC, to which parallel rows of Nylon stitching are added to create a stronger, more textured material. The combination of the Nylon, the textured effect and the optimised CMC web leads to the improvements identified above. The new technology was assessed in vitro and compared with a current CMC dressing.

Results

Compared with a current CMC dressing, the new textured technology had the following benefits:

- Less shrinkage upon hydration and after drying out
- More flexibility during use
- Faster and easier removal of dried dressings when re-hydrated with saline
- Improved wet and dry integrity of the dressing

The new dressing retains benefits of gelling CMC dressings such as intimate contact, low bioadhesion, and sequestration. In a clinical setting, the dressing was shown to perform well².

Conclusion

Based on in vitro data, the new Nylon-reinforced textured design provides a number of improvements over current CMC dressings for burns treatment, while still providing the benefits of these dressings.

References

- 1 Caruso DM, Foster KN, Hermans MHE, Rick C, "AQUACEL® Ag in the management of partial thickness burns: results of a clinical trial", *J Burn Care and Rehabil.* 2004 25: 89-97
- 2 Caruso DM, et al, "A Phase II Comparative Study of a Carboxymethyl Cellulose Silver Dressing Reinforced with Nylon for Partial Thickness Burns", accepted for presentation at ABA 2009, San Antonio TX

BP9 THE PHYSICO-CHEMICAL PROPERTIES OF SILVER CONTAINING BURN DRESSINGS

Vivienne M Kershaw, Dave Pritchard and Mike Walker

Introduction

Silver-containing dressings are widely used to assist in the management of infected wounds and those at risk of infection. Individual dressings may vary in their clinical performance due to differences in the physico-chemical properties of the dressing. When a wound surface is exposed to silver-containing antimicrobial dressings, it is important that:

- There is intimate contact across the wound surface so that the bacterial populations at the wound interface are exposed to the antimicrobial agent.
- Silver is available to counter increased bioburden,
- Dressing retains wound fluid and does not spread infection laterally across the wound surface.

Methods

An in vitro study designed to assess the overall physico-chemical characteristics of eight silver containing burn dressings was carried out. The dressings were tested for percentage fluid retained under compression load, intimate contact with simulated wound tissue, lateral fluid spread, silver content and dissolution availability of silver into physiological saline.

Results

The results indicated marked differences in all of the above in vitro tests

Conclusion

An understanding of the overall physico-chemical properties of a wound dressing is an important aspect of choosing the appropriate dressing to ensure a successful outcome in the management of wounds which are infected or at risk of infection. These results indicate that the new silver-containing carboxymethylcellulose burn dressing has shown good overall exudate management properties, as well as providing excellent contouring to uneven wound surfaces. These characteristics are likely to decrease the opportunity for bacterial proliferation in the wound environment and therefore should help to reduce the risk of clinical infection.

BP10 IL-12 EXPRESSION BY GENETICALLY MODIFIED MICROVASCULAR FREE FLAPS RESULTS IN TUMOUR REGRESSION WITHOUT SYSTEMIC TOXICITY

MP Dempsey, JM Michaels, C Hamou, S Ghali, DM Jones, GC Gurtner

Dept of Plastic Surgery, Stanford University, California, USA

Introduction

The widespread clinical use of cancer gene therapy has been prevented by the inability to deliver high levels of local transgene expression while limiting systemic host response. Our lab has developed an ex vivo technique to transfect microvascular free flaps with a recombinant adenoviral vector which expresses the anti-tumour cytokine IL-12. Using this approach, we are able to target treatment specifically to the required area without eliciting the known toxic effects associated with systemic administration of IL-12.

Methods

Superficial inferior epigastric flaps were dissected in male Fischer rats and perfused with Ad.IL-12 following division of the pedicle. After a one hour incubation period, the flap was flushed with saline to remove unincorporated virions and a microvascular re-anastomosis performed. 1×10^6 beta-hCG secreting MADB-106 tumour cells were injected into the underlying muscle. Tumour growth was monitored directly with calipers and by beta-hCG levels. Serum levels of pro-inflammatory cytokines (IL-6/TNF- α) and liver enzymes (AST/ALT) were measured to assess systemic inflammation and toxicity.

Results

IL-12 expression from the flap and peri-flap tissue was confirmed by ELISA. The rate of tumour growth in the IL-12 treated group was markedly suppressed compared to the control group and the difference in tumour volume became statistically significant after day 15 ($p < 0.05$).

Liver enzymes and pro-inflammatory cytokines were not significantly elevated in treated vs control groups. Histological evaluation of liver, lung and spleen revealed no evidence of inflammation.

Conclusion

Using genetically modified microvascular free flaps we were able to deliver the therapeutic protein IL-12 directly into the local environment of a tumour and suppress its growth without eliciting the toxic systemic effects associated with this cytokine. This technique could provide valuable adjuvant treatment after oncologic surgery for soft tissue cancers. The ex vivo transduced flap would serve not only to correct the resulting defect but also to supply a therapeutic agent to the resected tumour bed.

BP11 FACIAL REANIMATION UTILISING THE IPSILATERAL MASSETER NERVE TO INNERVATE A FREE GRACILIS TRANSFER; OUR EXPERIENCE

J Mennie and P Addison

St John's Hospital at Howden, Livingston West Lothian

Introduction

Inability to produce a spontaneous, symmetrical smile is the most distressing subjective aspect of facial paralysis however it remains one of the most challenging problems to correct surgically. The gold standard is free muscle transfer to the face with co-aptation to a donor nerve. Cross facial nerve graft using a gracilis muscle transfer is a widely accepted technique that achieves this. Here we present our units results of an alternative single stage procedure that utilises the ipsilateral masseter nerve to innervate the muscle transfer.

Methods

Five patients were identified who had undergone facial reanimation with a free gracilis muscle and masseter nerve. Interviews were conducted to provide an insight into the psychosocial effect of the paralysis and response to surgery. Pre- and post-operative photographs were assessed by medical students and patients using an established scoring system. Review of the literature allowed our units outcome to be compared to results from other techniques.

Results

All patients were satisfied with their smile at rest, expressing an improvement in their quality of life and confidence. Three patients achieved a spontaneous smile within a year of surgery. Patients and students graded the aesthetic and functional outcome higher overall after surgery. Our unit's results were above average when compared objectively to other cross-facial nerve studies.

Conclusion

This study provides an insight into the psychosocial subjective aims and benefits of facial reanimation surgery. It also provides evidence that the masseter nerve has a place in reanimation surgery and is capable of allowing spontaneous smile.

BP12 OBJECTIVE EVIDENCE FOR THE USE OF COLEMAN FAT TRANSFER IN SCLERODERMA ASSOCIATED FACIAL LIPOATROPHY

L Bavan, L Owens, PE Butler

Dept of Plastic and Reconstructive Surgery, Royal Free Hospital, London, UK

Introduction

Scleroderma is a chronic systemic autoimmune disease characterised by fibrosis and microvascular alterations in the skin, heart, lungs, kidneys and gastrointestinal tract. The clinical presentations vary greatly depending on the severity of the condition. One particular cutaneous manifestation is lipoatrophy, which many patients report to cause psychological distress and functional impairment.

Although there is no cure for the condition, previous reports suggest surgical intervention, in the form of autologous fat grafting, can provide a solution to scleroderma associated lipoatrophy. In this study we investigate the use of Coleman fat transfer (CFT) to correct the facial disfigurement.

Methods

Patients who received a course of CFT to the face were assessed clinically, completed psychological questionnaires and had 3D images taken, which were analysed using the 3DMD Vultus software to quantify the volume of fat that had successfully taken to the defective area.

Results

The 3D image analysis of 21 patients demonstrated an average volume gain of 2.95cc over the treated areas. This represented a 20.6% graft survival over a mean period of 2.33 months.

Conclusion

This study provides objective evidence for the physical benefit of CFT in scleroderma associated lipoatrophy. However, long term follow up is still required to determine the longevity of grafted fat.

BP13 A ROBUST APPROACH TO FACIAL EYE TRACKING EXPERIMENTS AND THEIR APPLICATION TO PLASTIC SURGERY

R Modi, L Owens, M.Tsakiris, A Clarke, PE Butler

Dept of Plastic and Reconstructive Surgery, Royal Free Hospital, London, UK

Summary

The increasing application of novel technologies to plastic surgery research and practice, and the realisation of the importance of subjective measures of success have opened avenues of exploration. The archetype is the recent use of facial eye tracking (FET) experiments for facial plastic surgery.

Recently, a variety of disciplines have increased their use of FET. However, methodological issues need to be addressed before we can validate and apply FET with certainty. Different approaches to the control of variables, such as the participants, pictures, areas of interest, instructions, procedures and data analyses, reduce the potential for systematic review. Insufficient use of evidence in the design stages exposes results to confounding factors. Additionally, due to the task-dependent nature of FET, the plastic surgeon should consider how best to adapt the design to give useful data.

This review aims to disentangle the literature to suggest a rational, robust and evidence-based approach to FET to help its application in plastic surgery research and potential clinical use. This rational design approach may also be a useful template for other disciplines planning to use FET.

BP14 DEVELOPMENT OF SCAFFOLD FOR AURICULAR TISSUE ENGINEERING USING A NOVEL NANOCOMPOSITE POLYMER

Radoslaw A. Rippel¹, Leila Nayyer¹, Shiyu Y. Yang¹, Martin Birchall^{1,2}, Peter Butler^{1,3}, Alexander M. Seifalian^{1,3}

1 Centre for Nanotechnology and Regenerative Medicine, Division of Surgery & Interventional Science, 2 ENT Institute, University College London, London, UK 3 Dept of Plastic and reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London, UK

Auricular cartilage engineering has emerged as a promising alternative to autologous cartilage grafts for reconstructing ear with cosmetic and functional deformities. Inflexibility, fragility and inappropriate resorption of current cartilaginous constructs to support cartilage regeneration have sparked huge interest amongst research to seek alternatives. The purpose of this study was to evaluate the suitability of a novel nanocomposite (NC) as a biomaterial for the next generation of auricular cartilage.

A non-biodegradable nano structured ear-shaped scaffold was made by incorporating polyhedral oligomeric silsesquioxane (POSS) nanocomposite into poly(carbonate-urea)urethane (PCU) through solvent casting and salt-leaching techniques. Mechanical strength, morphological structure and pore content of the scaffold were studied by Instron tensile tester, scanning electron (SEM) and an atomic force microscopy (AFM). In-vitro effects on biocompatibility, and cell viability were assessed by using adipose-derived adult stem cells (ASCs).

Casted NC showed higher tensile strength (62.91 ± 2.277 MPa) than salt-leached NC (0.89 ± 0.147 MPa) ($p < 0.05$) and used as internal part of the ear construct to enhance its stability. This NC had more flexibility and tensile strength compare with sheep auricle cartilage (7.97 ± 3.307 MPa). SEM revealed interconnectivity and homogeneously surface with average pore sizes (40-100 μm) throughout the salt-leached scaffold, which employed as external surface of the construct. Additionally, AFM showed highly roughness topography on this scaffold which increased the cell-material interaction area. Cell viability assay confirmed this nanostructure had a good biocompatibility for proliferation and differentiation of ASC. This study demonstrates that the merger of "state-of-the-art" NC scaffold and ASC could herald the first step towards auricular surgical reconstruction.

BP15 TUMOUR FORMATION FOLLOWING MURINE NEURAL PRECURSOR CELL TRANSPLANTATION IN A RAT PERIPHERAL NERVE INJURY MODEL

Anne C. O'Neill, T. Shane Johnson, Pejman M. Motarjem, Jamal Nazzal, Mark A. Randolph, Evan Y. Snyder, Jonathan M. Winograd.

Plastic Surgery Research Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston MA. The Burnham Institute, La Jolla, California.

Background

The C17.2 cell line is an immortalized line of neural stem cell-like cells isolated from the murine postnatal cerebellum, which have shown a remarkable aptitude for integration and appropriate differentiation at sites of cellular injury in CNS disease models. In this study we sought to determine if the C17.2 cell line would respond to cues in the microenvironment of the injured peripheral nerve and enhance neuronal regeneration in rodent sciatic nerve injury models.

Methods

C17.2 cells were transplanted into a number of sciatic nerve injury models in 45 nude rats, including nerve transection, nerve crush and nerve gap models. Sciatic nerves and gastrocnemius muscles were harvested for histological analysis at 3 months postoperatively.

Results

12 of the animals in this study developed large tumours at the site of cell transplants. Histologically the tumours resembled neuroblastomas. Tumours were confirmed to be of transplanted cell origin by positive beta-galactosidase staining. Tumors occurred only in models where the nerve remained intact or where continuity of the nerve was restored. Cell transplantation did not result in any improvement in neural regeneration or muscle mass preservation.

Conclusion

The high rate of tumour formation demonstrates that the success of neural precursor transplants in the CNS cannot necessarily be extrapolated to the peripheral nervous system.

BP16 THE ROLE OF DISGUST EMOTIONS IN PREDICTING POST-OPERATIVE WOUND CARE

Gaïnd S. Clarke A. Butler PEM

Royal Free Hospital, Hampstead, London

Introduction

Disgust is a universal negative emotion that has been demonstrated to play a role in the observer response to facial disfigurements¹, but has not yet been investigated in relation to wound care. The aims of this study are to determine if the emotion of disgust influences how patients perceive and care for their wound following surgery and to establish whether the disgust response to wounds is universal, or related to individual differences in disgust sensitivity.

Methods

Fifty patients were recruited at Royal Free Hospital on a voluntary basis. In addition to the Haidt disgust sensitivity questionnaire, all participants completed a wound management questionnaire that was developed for the study. Participants were observed to assess parameters including site and severity of the wound, facial expression and vocalisation of disgust.

Results

Patients who were observed to be avoidant of care were found to have higher disgust sensitivity scores than those who were engaged in care, and experienced greater difficulty in managing their wound. Disgust sensitivity was found to be greater in participants less able to look at their wound and those who described feeling nauseous when looking at their wound. Our results show wound site does influence participation in care; 80% of patients with a visible wound on the face, neck or scalp were engaged in care and none were avoidant, compared with those with chest wounds, of whom 33% were avoidant. Surprisingly, 17% of patients were avoidant of care following breast surgery, despite this being an elective procedure in the majority of patients.

Conclusion

We have shown that those patients with higher disgust sensitivity are less engaged in care and experience greater difficulty in self-managing their wound. Therefore screening for disgust sensitivity prior to surgery may allow identification of patients who will need additional support post-operatively. We would encourage all members of the multi-professional team to acknowledge disgust sensitivity as an indicator for vulnerability. The findings have implications beyond the field of plastic and reconstructive surgery, as poor wound healing is a common problem in many areas of medicine and surgery.

BP17 ASSESSING THE CHONDROGENIC POTENTIAL OF A NOVEL BIOMETIC NANOCOMPOSITE POLYMER FOR TISSUE ENGINEERING A NOSE: THE CHONDROCYTE RESPONSE TO NANOSCALE GEOMETRY

Adelola O Oseni, Alexander M. Seifalian, Peter E. Butler

Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London NW3 2QG, UK.

Centre for Nanotechnology and Regenerative Medicine, Division of Surgery & Interventional Science, University College London, London, UK.

Introduction

There is no gold standard scaffold available for tissue engineering nasal cartilage. However the emergence of nanotechnology has created a plethora of opportunities for nanoscale characteristics to be incorporated into scaffolds to enhance cell growth. It is well documented that the natural ECM of most tissues have nano and micro sized architecture

on a level which cells interact. It is for this reason that our lab has developed a nanocomposite polymer based on incorporating polyhedral oligomeric silsesquioxane nanocages (POSS) into poly (carbonate-urea) urethane (PCU), known as UCL-Nano™, in the hope that these nanocages would confer an increased biostability and biocompatibility. We have manufactured morphologically faithful nasal constructs using this polymer and various in vitro studies have demonstrated its superior mechanical, anti-thrombogenic, anti-inflammatory and cytocompatible properties.

Method

To investigate this the chondrogenic ability of the polymer, POSS-PCU sheets with varied concentrations of POSS, 2%, 4%, 6% and 8% were characterised according to their surface nanotopography and matrix arrangement, and compared with PCU using Atomic Force Microscopy, Transmission Electron Microscopy, Environmental Scanning Electron microscopy and Contact angle hysteresis. Sheep nasospetal chondrocytes were then seeded onto these polymers and cell viability and function assessed using in comparison with a PEG-hydrogel, on which chondrocyte growth has been demonstrated, over a 14 day period.

Results

POSS PCU can be used to engineer a morphologically faithful nose. The POSS modified polymer supported chondrocytic growth and attachment over 14 days in vitro ($p < 0.05$). Modifications to surface nanotopography using various concentrations of POSS nanocages can enhance chondrocyte growth depending on length of incubation.

BP18 DEVELOPMENT OF A BIOCOMPATIBLE FLUORESCENT NANOPARTICLE “QUANTUM DOT” FOR APPLICATION IN PLASTIC AND RECONSTRUCTIVE SURGERY AND AN INVESTIGATION INTO ITS CYTOTOXICITY

Lara Yildirim¹, Sarwat B. Rizvi¹, Bala Ramesh¹, Peter Butler^{1,2}, Alexander M Seifalian^{1,2}

¹Centre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional Science, University College London, London, United Kingdom, ²Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London, United Kingdom

Summary

Adequate microcirculation is crucial for tissue viability in reconstructive applications utilising skin-flaps as is post-operative monitoring of blood supply to such tissues. Fluorescent nanoparticles “quantum dots” (QD) have emerged as a new technology for imaging and monitoring microcirculations due to their superior fluorescent qualities compared to conventional dyes. A number of studies focusing on cadmium-based QDs have revealed that residual toxicity is caused by the dissociation and liberation of divalent cadmium from the core. This is one of the major obstacles precluding translational use in clinical settings. Thus, research focuses on developing coating materials which render the toxic core biocompatible and stable. Here, we have synthesised, characterised and assessed the toxicity of cadmium/tellurium (CdTe)-cored QDs coated with the novel nanoparticle polyhedral oligomeric silsesquioxane (POSS). Characterisation was performed using Transmission Electron Microscopy, Fourier Transform Infrared Spectroscopy and fluorescence spectroscopy. Biocompatibility and stability of POSS-coated QDs were tested on hepatocellular carcinoma cell lines and compared to uncoated and mercaptosuccinic acid-coated QDs. Results showed significant advantages of POSS-coated QDs in terms of biocompatibility ($p < 0.001$), stability and dispersion. Coated and uncoated QDs showed a concentration-dependent rise in toxicity ($\geq 10 \mu\text{g/ml}$ and $\geq 5 \mu\text{g/ml}$ critical concentrations of POSS-coated and uncoated quantum dots, respectively). Here, we have demonstrated that nanoparticle coating confers (1) increased biocompatibility ($p < 0.001$), (2) reduced cytotoxicity ($p < 0.001$), (3) a higher degree of dispersion in aqueous solution and (4) and superior stability to CdTe QDs compared to uncoated ones ($p < 0.001$). Therefore, we conclude that QDs coated with the novel nanomaterial POSS show a potential for safe applications in imaging and monitoring microcirculations for reconstructive purposes.

BP19 PHOTOTHERMAL EFFECT OF HEATING CARBON NANOTUBES USING NEAR INFRARED RADIATION: APPLICATIONS IN PLASTIC SURGERY

Aaron Tan¹, Yazdan Madani¹, Sana Khan¹, Peter Butler^{1,2}, Alexander M. Seifalian^{1,2}

¹ Centre for Nanotechnology & Regenerative Medicine, Division of Surgery & Interventional Sciences, University College London, London, UK

² Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, London, UK

Summary

The advent of nanotechnology heralds a new chapter in the realm of regenerative medicine, and it bears particular relevance in plastic surgery. Carbon nanotubes have recently emerged as attractive candidates for thermally ablating subcutaneous tumours. This is due to their unique radiation-absorbing properties, which allows them to function as photothermal agents. The 2010 Nobel Prize in Physics was awarded to scientists for their discovery of graphene. Carbon

nanotubes (CNTs) are allotropes of carbon, and they can be visually conceptualized by “rolling-up” a sheet of graphene into a cylindrical tube. Current literature suggests that the application of near infrared (nIR) radiation to CNTs produces intense heat energy of up to 70°C. Two main classes of CNTs are often deployed: multi-walled carbon nanotubes (MWNTs) and single-walled carbon nanotubes (SWNTs). nIR of differing wavelengths are then used to excite these nanotubes. However, to date, there has been no systemic consensus regarding the ideal CNT type (i.e. MWNT or SWNT) or optimal nIR wavelength to be used for maximizing therapeutic effect while simultaneously minimising “collateral” cell damage. Here, we demonstrate that MWNTs have a higher rate of temperature increase compared to SWNTs, and a wavelength of 808 nm enables CNTs to achieve a higher rate of temperature increase compared to 975 nm. Therefore, we postulate that the application of nIR (of 808 nm wavelength) to CNTs (of MWNT class) can serve as effective photothermal therapy in plastic surgery for thermally ablating subcutaneous tumours.

BP20 DIFFERENTIATION OF ADIPOSE DERIVED STEM CELLS TO SCHWANN CELLS ON A NOVEL NANOCOMPOSITE POLYMER

Tina Sedaghati¹, Amit Pabari^{1,2}, Shi Yu Yang¹, Peter Butler², Ash Mosahebi², Alexander M. Seifalian¹

1 Centre for Nanotechnology and Regenerative Medicine, Division of Surgery & Interventional Sciences, University College London, London, UK, 2 Department of Plastic Surgery, Royal Free Hampstead NHS Trust Hospital, London, UK

Background

Schwann cell transplantation into nerve conduits can enhance peripheral nerve repair. Clinically their application has been limited due to donor site morbidity. Interest in the potential application of adipose-derived stem cells (ADSC) in cell mediated tissue engineering of nerve is growing. We have developed a multichannel, biodegradable nerve conduit from a novel nano-composite polymer. The current study demonstrated that adipose derived stem cells could efficiently differentiate into Schwann cells on our novel biomaterial in vitro based on the expression of SC.

Methods

Human ADSC were differentiated for 21-days on nano-composite polymer, control polymer and tissue culture plates using either SC differentiation media or culture media alone. Morphology of cells was studied by scanning electron microscope (SEM) and differentiation of cells was evaluated by immunocytochemistry and Western blot analysis.

Results

SC media successfully differentiated the ADSCs into SCs. The presence of nanoparticles significantly augmented this differentiation as confirmed morphologically by SEM and immunocytochemistry. Western blot analysis also revealed denser bands of S100, GFAP and P75 in the differentiated cells on the nano-composite polymer.

Conclusion

The current study demonstrates the ability to differentiate ADSCs into SCs. The presence of nano-composite significantly augments this differentiation. Future studies will examine integration of ADSCs in our synthetic multichannel nerve conduit and evaluate it in vivo.

BP21 BASIC BURNS MANAGEMENT E-LEARNING TUTORIAL: A NEW TEACHING TOOL

Dr Francesco Maria Egro

Department of Plastic Surgery, Frenchay Hospital, Bristol

Summary

A background questionnaire proved that structured burns teaching is organised only in few medical schools and medical settings in the United Kingdom. Lack of knowledge on how to correctly diagnose and initially manage burns predisposes healthcare professionals to mismanage burn injuries.

An e-learning tutorial was developed with the objective of providing sufficient knowledge to medical personnel on how to acutely manage burns.

A website with twenty-five web pages were created by using a variety of web programmes and scripts. The content takes into account complete inexperience of the field and comprehensively covers topics such as local and general response to burns, assessment of burns, first-aid, primary and secondary surveys, and referral guidelines. The focus was to create a captivating, fun and interactive website, where the user can be constantly challenged and tested on their newly acquired knowledge. Positive feedback was obtained by consultants, junior doctors, nurses and medical students, confirming the importance and value of this learning tool.

The "Basic Burns Management" e-learning tutorial is a unique and useful tool. Through a joint collaboration with the BBA, the tutorial will be made available to the public on the BBA website by the end of the year.

BAUS SECTION OF ACADEMIC UROLOGY

ORAL PRESENTATIONS

U1 CHARACTERISING POTENTIAL FOR PLURIPOTENCY INDUCTION IN HUMAN PROSTATE TISSUE

D. Pal, S.C. Williamson, C.N. Robson, A.C. Rigas, R. Heer
Northern Institute for Cancer Research, Newcastle University

Introduction

Availability of prostate stem cells will facilitate our understanding of prostate development and its progression to cancer. Stem-cell research has been transformed by Yamanaka group's discovery in that adult skin cells can now be reprogrammed by specific stem-cell genes to acquire stem-cell properties. Problems that remain to be addressed include establishing if reprogramming efficiency is dependent on the primary cell type used and determining the extent of differentiation of iPS (induced pluripotent stem) cells into specific cell types.

Methods

We have established primary cultures of prostate stroma and epithelia from benign prostate samples for induction into iPS cells. Samples have been sourced from patients undergoing TURP or cystoprostatectomy. Epithelial cells have been further enriched for CD326+ (epithelial cell adhesion molecules) fractions. Gene-expression profiling on these cells have been performed to determine their inherent plasticity and differentiation status.

Results

We analysed iPS gene expression profiles of epithelia and stroma in order to characterise known stem cell enriching signatures of each cell type. We demonstrated that stromal and epithelial cells expressed a number of stem cell genes (including SOX2, OCT-4, NANOG, LIN28, CD133) suggesting distinct "stemness" attributes of each cell type as well as demonstrating their inherent pliability to the pluripotent stem cell reprogramming mechanism.

Conclusions

Describing the inherent "stemness" of prostate cells highlights the potential pliability of each of these cell types to the pluripotent stem-cell reprogramming mechanism. Prostate-specific iPS cells may be better committed towards demonstrating prostate-specific differentiation and this will allow a novel insight into the mechanism of oncogenesis in prostate cancer.

Take home message

Establishing a prostate iPS model will allow an exciting opportunity to explore novel studies into prostate-specific differentiation. We have established primary cultures in the prostate, demonstrating endogenous expression of pluripotency factors that may facilitate induction into prostate-specific iPS cells.

U2 STEM-CELL REGULATORY PROTEIN PIWIL2 ENRICHES FOR KNOWN STEM-CELL AND CANCER STEM-CELL MARKERS IN PROSTATE CANCER CELLS.

D. Pal, C.N. Robson, S.C. Williamson, K. Nayernia, H.R. Soleimanpour-Lichaei, R. Heer
Northern Institute for Cancer Research, Newcastle University

Introduction

Cancer stem cells are a subpopulation of cancer cells that drive production of the rest of the tumour. In particular, aberrant stem-cell renewal has been implicated in carcinogenesis. The genes of the piwi family are involved in stem-cell maintenance, and are being implicated in an increasing number of cancers. In this study we explored the effects of Piwil2 gene over-expression in LNCaP human prostate cancer cells.

Methods

Real-time PCR was employed to study the effect of this gene on the transcription of known stem cell and prostate specific differentiation markers that have also been implicated in carcinogenesis. Immunohistochemistry for Piwil2 expression was also performed of human cancer prostate material.

Results

LNCaP cells over-expressing Piwil2, compared with wild-type LNCaP, demonstrated higher levels of stem cell-specific markers (Oct-4, SOX-2, LIN28, NANOG) and expression of prostate specific stem cell markers (CD133, CD117, CD44, Nkx3.1). Furthermore, Piwil2 expression was seen to potentiate androgen receptor function. In addition, immunohistochemistry confirmed piwi expression in human prostate cancer material and we are currently investigating its correlation with grade, stage and prognosis.

Conclusions

In summary, we demonstrated induction of a stem-cell phenotype in LNCaP with Pivwil2 over expression. Understanding the importance of this gene in regulating prostate cancer stem cells requires additional investigation and our data for now highlights an attractive potential role for piwil2 as a candidate for use in prostate cancer therapeutics and as a prognostic marker.

Take home message

Pivwil2 expression selects for known stem-cell and cancer stem-cell markers in prostate cancer cell line therefore highlighting a novel therapeutic target.

U3 HER2 OVERCOMES PTEN-LOSS INDUCED CELLULAR SENESENCE TO CAUSE AGGRESSIVE PROSTATE CANCER

I Ahmad, R Patel, J Edwards, OJ Sansom, HY Leung

The Beatson Institute for Cancer Research, Glasgow

Summary

Prostate cancer (CaP) is the commonest cancer amongst adult men in the western world. In this study we demonstrate the role cooperation between PTEN loss and HER2 activation in accelerating prostate carcinogenesis, both in the human and mouse. Either mutation in isolation does not lead to a change in survival in human CaP, but on a PTEN null background HER2 or HER3 overexpression results in a statistically significant reduction in patient survival. Similarly in the mouse, presence of both mutations synergises to lead to rapidly proliferating tumours with an aggressive phenotype, overcoming the well-documented PTEN loss-induced cell senescence phenotype (PICS)¹. Treatment with a MEK inhibitor appeared to negate the effects of activated HER2, returning the tumours to their PICS phenotype. Our data suggests that in patients that have lost PTEN, inhibition of activated MAPK signalling pathways may be a sensible approach for returning these advanced tumours to their senescent state. We have also highlighted the crucial role that transgenic mice will play as preclinical platforms to validate these regimes.

1. Alimonti A, et al. J Clin Invest 2010; 120; 681-693.

Take home message

We demonstrate that in patients that have lost PTEN, inhibition of an activated MAPK signalling pathways may be a sensible approach for returning these advanced tumours to their senescent state.

U4 SYNERGISTIC EFFECTS OF ONCOLYTIC REOVIRUS AND DOCETAXEL CHEMOTHERAPY IN PROSTATE CANCER

S Pandha, L Heinemann, G R Simpson, A Boxall, K Relph, R Morgan

University of Surrey, Guildford

Introduction

The true potential of oncolytic viruses such as Reovirus type 3 Dearing (T3D) may only be realized fully in combination with other modalities such as chemotherapy. We examined the oncolytic activity of reovirusT3D and chemotherapeutic agents, with particular focus on the highly metastatic cell line PC3 and the chemotherapeutic agent docetaxel.

Materials and Methods

The effects of reovirus and chemotherapy on in vitro cytotoxicity were investigated in PC3 and Du 145 cells using combination index analysis and a fluorescence-activated cell sorting-based assay used to determine mode of cell death. The effects of reovirus and docetaxel administered as single agent or combination therapy were tested in vivo in a murine model. The effects of docetaxel and reovirus microtubule stabilisation were investigated by Western blot analysis.

Results

Variable degrees of synergistic cytotoxicity were observed in PC3 and Du 145 cells exposed to reovirus and chemotherapy agents. Combination of reovirus infection with docetaxel exposure led to increased late apoptotic/necrotic cell populations. Reovirus/docetaxel combined therapy reduced tumour growth and increased survival in a PC3 tumour bearing mouse model. Microtubule stabilization was enhanced in PC3 cells treated with reovirus/docetaxel combined therapy compared to other reovirus/ chemotherapy combinations.

Conclusions

Co-administration of a variety of chemotherapeutic agents with live reovirus was able to enhance cytotoxicity synergistically in vitro. The combination of docetaxel with reovirus also delayed tumour growth and improved survival in vivo. Enhanced microtubule stabilisation following combination treatment may explain the mechanism of synergy. These results support the ongoing clinical trials using these agents.

Take home message

Co-administration of a variety of chemotherapeutic agents with live reovirus was able to enhance cytotoxicity synergistically in vitro. The combination of docetaxel with reovirus also delayed tumour growth and improved survival in vivo. These results support the ongoing clinical trials using these agents.

U5 THE TIMING OF PROSTATE CANCER DIAGNOSIS: DEPRIVATION AND PSYCHOSOCIAL VARIABLES AND THEIR LINK WITH HIGH RISK DISEASE**K Boyd, M Place, H Leung, F Winslow, G Hubbard, L Forbat**

Gartnavel General Hospital, Glasgow

Introduction

Early diagnosis is critical in reducing mortality through prostate cancer. The extant literature identifies a range of variables which impact on when men present in primary care. For example, recent evidence suggests that men of a low socioeconomic status / high deprivation are significantly more likely to present with advanced disease and have lower survival rates. Psychosocial theories provide a framework for understanding patterns in the timing of diagnoses, e.g. the role of social context and knowledge/interpretation of symptoms.

Recent audit data in Glasgow indicates that men are diagnosed more often with advanced disease. This study sought to identify (i) the demographic and pre-diagnosis symptom profiles of men presenting with higher grade prostate cancer in Glasgow, (ii) how men describe and account for the timing of their presentation and subsequent diagnosis with advanced disease.

Patients/methods

The study adopted an embedded mixed-method design. A postal survey was conducted of all men diagnosed with prostate cancer in one Scottish Health Board over a two year period (N=477). A purposive sub-sample of men and their partners (N=30) were then invited to participate in qualitative interviews.

Results

Early survey results (response rate of >65%) illuminate links between deprivation, clinical risk (PSA/Gleason/TNM and reported pre-diagnosis symptomatology) and psychosocial delay. Full analysis will be presented at the conference.

Conclusion

Findings indicate the need for health promotion messages, and primary care, to attend to the psychosocial context in which men are identifying and interpreting their symptoms to expedite access to urologists.

Take home message

Understanding 'delayed' presentation to urology with prostate cancer must take account of both clinical risk factors and psychosocial variables. Such an understanding will help improve early detection rates.

U6 PREDOMINANCE OF CD8 T CELL INFILTRATION COINCIDES WITH RECIPROCAL REDUCTION IN REGULATORY T CELLS FOLLOWING PROSTATE CRYOTHERAPY**MI Ismail, S Bokae, N Annels, J Davies, H Pandha**

University of Surrey, Guildford

Introduction

In this study we examine the relationship between CD4+, CD8+ and regulatory T cell populations within primary and locally recurrent prostate cancer postcryotherapy.

Materials and Methods

Prostate cancer specimens from 15 patients treated with salvage cryotherapy and 16 patients diagnosed with primary prostate cancer and received no treatment were analysed using Immunohistochemical staining. For determination of lymphocyte subsets, prostate tumour tissues were stained with anti-CD3, anti-CD4, Anti CD8 and anti-FOXP3 antibodies and immunofluorescence was detected using confocal microscope.

Results

Total numbers of CD3+ CD4+ cell population are similar in the control and precryotherapy groups and significantly lower in the postcryotherapy group (P=0.0414). CD3+ CD8+ T cells are significantly prevalent in the postcryotherapy group compared to the control (P=0.049). Cryotherapy resulted in a significant reduction in the numbers of CD4+ FOXP3+ cell population compared to control and precryotherapy groups (3.265 ± 0.8251 , 13.37 ± 1.343 and 7.318 ± 0.8084 respectively P <0.0001).

Conclusions

Cyotherapy resulted not only in a rise in infiltrating cytotoxic CD8+ T cells but also a reciprocal fall in the numbers of infiltrating regulatory T cells and subsequently may enhance immunity to tumours, resulting in delayed tumour growth and improvement of antitumor immunity

Take home message

Cryotherapy may effectively prime antigen-specific immunity and there may be ways of enhancing this effect with the co-injection of cytokines or professional antigen presenting cells to increase the efficacy of the treatment.

U7 THE IDENTIFICATION, INTERNAL AND EXTERNAL VALIDATION OF A BIOMARKER PANEL TO DISTINGUISH BETWEEN GLEASON 3+4 AND 4+3 PROSTATE CANCER

SF Oon, Y Fan, JM Fitzpatrick, H Klocker, RWG Watson

UCD School of Medicine and Medical Science, Dublin

Introduction

The preoperative Gleason score (GS) is critical in evaluating prostate cancer aggressiveness, significance, prognosis and treatment response. In GS7 disease, 3+4 demonstrates a better prognosis than 4+3. However, biopsy GS is poorly concordant with specimen GS and most scoring inaccuracies occur in this category. Our previous 2D-DIGE and ELISA based biomarker discovery strategies identified Insulin-like Growth Factor Binding Protein-3 (IGFBP3), Vascular Endothelium Growth Factor-D (VEGFD), Pigment Epithelium Derived Factor (PEDF) and Zinc-Alpha-2-Glycoprotein (ZAG) as preoperative serum biomarkers to distinguish between GS5 and GS7.

Aim

To identify a panel of biomarkers to distinguish between 3+4 and 4+3 prostate cancer and validate the panel in independent patient cohorts.

Methods

We developed a multiplex approach to simultaneously measure IGFBP3, VEGFD, PEDF and ZAG in the preoperative serum of 19 Irish and 37 Austrian prostate cancer patients. The panel prediction performance was assessed using 500 times bootstrapping with logistic regression. Receiver operating characteristics curves and area under the curve (AUC) values were generated as an indication of prediction accuracy. The biomarker panel prediction model built upon Irish samples was then validated using the independent international samples.

Results

The optimum panel identified was PSA, IGFBP3, PEDF and VEGFD, with an AUC of 0.678. Internal and external validation of this panel yielded AUCs of 0.68 and 0.85, respectively, for distinguishing between GS 3+4 and 4+3.

Conclusion

This is the first panel to distinguish between GS 3+4 and 4+3 prostate cancer and may help to improve the management and prognostication strategies in these patients.

Take home message

An internally and externally validated biomarker panel comprising of PSA, IGFBP3, PEDF and VEGFD can distinguish between Gleason 3+4 and 4+3 prostate cancer and may have significant applications in prostate cancer diagnosis, management and prognosis.

U8 PROSTATE SPECIFIC ANTIGEN ENHANCES THE ANTI-MICROBIAL ACTIVITY OF SLPI AND WFDC2

L Townes, A Ali, CN Robson, J Hall, RS Pickard

Newcastle University

Introduction

Chronic prostatitis is common, characterised by pelvic and ejaculatory pain and may result from continued sub-clinical infection following an initial episode of mild cystitis. During UTI levels of Prostate Specific Antigen (PSA) rise 10-fold, but the reason for this is unclear. PSA is a serine protease and, interestingly, semen contains several proteins containing antimicrobial domains released by serine protease cleavage. We hypothesise that increased levels of PSA during UTI digest these proteins in the tubes of the prostate gland, releasing antimicrobial domains and thus enhancing the prostates antimicrobial response.

Material and Methods

WFDC gene expression in male uro-genital tract (MUT) tissues was determined by RT-PCR. The prostate cell lines Du145 (PSA-) and LnCAP (PSA+) were challenged with uropathogenic Escherichia coli and analysed by Realtime PCR, PSA ELISA and invasion assays. Proteolysis studies were performed with recombinant PSA, WFDC2 and SLPI. Time-kill assays determined anti-microbial activity.

Results

Gene expression of WFDC1, WFDC2, WFDC8, Eppin and SLPI was identified in tissues of the MUT with SLPI and WFDC2 in prostate. Bacterial challenge of prostate cells LnCAP and Du145 with Escherichia coli led to significant increases in WFDC2 and SLPI expression ($p < 0.001$), as well as PSA synthesis ($p < 0.01$). Du145 cells (PSA-) were more susceptible to bacterial invasion than LnCAP cells (PSA+). A 24 hour incubation of $2\mu\text{M}$ PSA with $10\mu\text{M}$ recombinant WFDC2 and SLPI resulted in complete proteolysis of the full-length protein and significantly increased antimicrobial activity.

Conclusion

These results support a protective role for PSA against bacterial infection of the prostate.

Take home message

Prostate specific antigen functions as a serine protease cleaving WFDC proteins present in semen, releasing antimicrobial domains which enhance the antimicrobial response of the prostate.

U9 LOOSE VERSUS STRANDED SEEDS FOR PROSTATE BRACHYTHERAPY - A SYSTEMATIC REVIEW AND META-ANALYSIS

Al Ibrahim, KA Ahmed, PA Acher, ANB Bahsoun, PD Dasgupta, Kahn MS, Popert R
Imperial College NHS trust, London

Introduction

This systematic review analyzes and compares the post procedural outcomes associated with loose versus stranded Iodine seeds in prostate brachytherapy. For each seed implantation type, outcome measures for successful implantation entail several implant specific and dosimetric parameters.

Methods

Comparative studies evaluating outcomes from loose versus stranded seeds were included (Medline/Embase). PRISMA were used for meta-analysis.

Results

Sixteen-studies were identified. One pre-procedural (seed activity) and four post-procedural outcomes (V150, V100, D90 and seed-migration) were suitable for meta-analysis. V100 and D90 were higher in stranded-seeds ($p = 0.007$ and $p = 0.04$). V150 ($p = 0.12$) did not show any significant difference between loose and stranded groups. Seed activity was not significantly different between both groups ($p = 0.61$), however seed migration was significantly increased in the loose seed group ($p < 0.0001$).

Conclusion

D90 (Gy) which is associated with better oncological outcomes favours stranded seed group. V100 was significantly higher in stranded seeds. V150 did not show any significant difference between loose and stranded groups. Seed activity was not significantly different between both groups however seed migration (associated with toxicity, dose asymmetry and embolization to distal organs) was significantly increased in the loose seed group. However, one of the largest studies found that loose seeds were associated better biochemical evidence of no disease (bNED) and thus reduced risk of recurrence. As studies used were low powered, further multicentre RCT are needed to establish long-term effectiveness of loose versus stranded seeds.

Take home message

Post procedural outcomes associated with loose versus stranded seeds in prostate brachytherapy have been reported to be variable by different authors. Our study favours stranded seed type. In the absence of multicentre RCTs a definitive conclusion cannot be made in favour of any seed type.

U10 AN UPDATE ON THE PROSTATE CANCER STEM CELL MODEL - CD133+VE STEM CELL ENRICHED HUMAN PROSTATE CELLS EXPRESS ACTIVE ANDROGEN RECEPTOR

SC Williamson, AC Rigas, CN Robson, R Heer
Northern Institute for Cancer Research, Newcastle University

Introduction

The cancer stem cell model has been established in a number of organs, with such a hierarchy based on CD133 expression existing in prostate cancer. However, the conventional description of a lack of androgen receptor expression

in prostate stem cells and prostate cancer stem cells is controversial. It is well characterised that the androgen receptor is active throughout prostate cancer progression. How is there a preferential selection for gain of androgen receptor function if the cancer is derived from a stem cell lacking the expression of the androgen receptor?

Materials and Methods

We developed a highly sensitive detection method for monitoring the androgen receptor using flow cytometry to screen CD133+VE stem cell enriched progenitor cells in primary benign prostate samples (n=4) and LNCaP cancer cells (n=3). We assessed the activity of the androgen receptor by the expression of androgen receptor regulated transcripts using qRT-PCR in cell-sorted primary benign samples (n=10).

Results

For the first time, we show that the androgen receptor is expressed in CD133+VE stem cell enriched progenitor cells of the prostate, albeit at a low level. Activity of the AR was confirmed by the expression of PSA, KLK2 and TMPRSS2.

Conclusion

Confirming androgen receptor expression in prostate progenitor cells consolidates the prostate cancer stem cell theory; allowing agreement with the established importance of active androgen receptor. This revision of the model can now pave the way for studies of androgen receptor behaviour in stem cells to highlight novel therapeutic options to supplement current strategies.

Take home message

Detection of androgen receptor in prostate stem cells and cancer stem cells is a key step in the consolidation of the cancer stem cell theory with the large body of evidence demonstrating the importance of the androgen receptor in prostate cancer progression.

U11 COMPARATIVE META-ANALYSIS OF THE HUMAN PROSTATE STEM CELL TRANSCRIPTOME DEMONSTRATES THAT PROGENITOR CELLS ARE THE SITE OF MALIGNANT TRANSFORMATION

SC Williamson, R Mitter, AC Rigas, CN Robson, R Heer

Northern Institute for Cancer Research, Newcastle University

Introduction

Although normal stem cells are thought to be favourable targets for transformation, this has not been established in prostate cancer. Here we investigate the relationship between human prostate stem cell molecular signatures with those of prostate cancer and prostate cancer stem cells to identify the cell of transformation and critical genes involved in tumour initiation and tumour progression.

Materials and Methods

Gene expression microarray studies (n=12) were carried out on prostate stem cell enriched cells ($\alpha 2\beta 1\text{HI}$ CD133+VE), transiently amplifying cells ($\alpha 2\beta 1\text{HI}$ CD133-VE) and terminally differentiated cells ($\alpha 2\beta 1\text{LOW}$ CD133-VE), before carrying out meta-analysis with published prostate studies (Varambally et al 2005, Birnie et al 2008)

Results

We confirm that the transcriptome of prostate stem cells maps closely to that of prostate cancer stem cells. Additionally, we identified a novel deficiency in testosterone catabolism present in stem cells and cancer stem cells of the prostate. Furthermore, transcript patterns of prostate progenitors were increasingly apparent with progression to hormone escape and metastatic disease.

Conclusions

The stem cell gene expression signatures support the prostate stem cell as being the site of tumourigenesis. Re-emergence of progenitor gene expression identities in progressing disease highlights enrichment for undifferentiated cells in advanced cancers, or alternatively an adoption of pathways shared with progenitors that promote adaption to treatment resistance. To this effect we identify an enzymatic down-regulation of testosterone catabolism in stem and cancer stem cells, highlighting a novel survival pathway during androgen ablation.

Take home message

Meta-analysis studies support the prostate stem cell as the site of tumourigenesis, with an increasing importance of progenitor signatures with prostate cancer progression, offering new options for targetted therapies.

U12 THE SUN STUDY-A BIOBANK OF SEQUENTIAL BLOOD SAMPLES FROM PATIENTS WITH PROSTATE CANCER**A. Michael, J. Zylstra, H. Pandha**

University of Surrey, Guildford

Introduction

Prostate cancer is the most common cancer in men accounting for around 24% of all male cancers in UK. It is an intractable disease where diagnosis and clinical prediction of the disease course and response to treatment is compromised by the lack of objective and robust biomarker assays, indicative of patient status and outcome. Early stage disease is difficult to diagnose with PSA based tests having limited sensitivity and specificity. Biomarker discovery is constantly one of the primary goals of basic research into prostate cancer.

Methods

We have set out to establish a bio-repository of sequential serum samples from a racially homogenous population of patients with prostate cancer prior to any treatment and then every six months through treatment, follow up and relapse. We also store DNA samples. All samples are collected and stored according to very strict protocols to ensure high quality. This will allow biomarker discovery and their profiling at different stages of disease.

Results

So far we have consented 322 patients of whom 291 have a positive diagnosis of prostate cancer, 15 have HGPIN and 26 nonspecific inflammation or prostatitis. 225 patients have Gleason 6-7 and the median PSA at presentation 8. We aim to collect an equal number of samples from healthy (PSA screened) volunteers to serve as controls. To date we have collected 76 samples.

Conclusion

The biobank samples are available to researchers from other institutions. This is the first biobank of sequential blood samples in patients with prostate cancer.

Take home message

The need for new biomarkers to diagnose and adequately treat prostate cancer is a top priority. This can only be achieved through access to high quality sequential blood samples that reflect different stages of disease process. Such biobank is already set up and available to researchers.

U13 REVERSAL OF CHEMOTHERAPY RESISTANCE IN RENAL CELL CARCINOMA SIDE POPULATION USING TARGETED AGENTS AS NOVEL MDR MODULATORS**M.P.C Liew, C Hart, T Tawadros, C Dive, M Brown, N Clarke**

Paterson Institute of Cancer Research, Manchester

Introduction

Renal cell carcinoma (RCC) is the commonest malignant renal tumour accounting for 40,000 deaths in Europe annually. Metastatic disease is highly chemo-resistant with low response rates (<6%). A key mechanism in chemo-resistance is the ability to efflux chemotherapeutic agents via multidrug resistant pumps (MDR). RCC specimens contain a verapamil sensitive side population (SP), as defined by their ability to efflux the fluorescent dye Hoechst 33342. Moreover, recent reports have suggested that the 'targeted' agents used in metastatic RCC may also affect MDR function.

Methods

RCC SP and Non-SP populations were treated with various chemotherapeutic agents. IC50 values were determined by SRB assay and drug efflux by FACS/microscopy. Combination studies were also conducted using verapamil, temsirolimus, sunitinib and sorafenib as potential MDR inhibitors.

Results

The SP cells displayed great chemoresistance to docetaxel, paclitaxel, adriamycin and etoposide as compared with Non-SP cells (5.4 vs 3.3, 42 vs 13, 90 vs 48nM & 11.6 vs 8.8 μ M respectively). There was no difference seen between cell sub-populations treated with cisplatin or 5-fluorouracil. FACS and microscopy confirmed the efflux of adriamycin from the SP cells. Sunitinib, sorafenib and temsirolimus were able to block the SP at μ M concentrations with a similar efficiency to verapamil, resulting in the sensitisation of the SP cells to docetaxel, paclitaxel, adriamycin and etoposide.

Conclusion

We have identified and characterised a sub-population of RCC cells resistant to several chemotherapy agents via active drug efflux pump mechanisms and that the SP can be sensitised using specific 'targeted' agents as novel MDR modulators

Take home message

We have identified and characterised a sub-population of RCC cells resistant to several chemotherapy agents via active drug efflux pump mechanisms. We have also shown that the resistant 'side' population can be sensitised to chemotherapy agents using 'targeted' agents as novel MDR modulators.

U14 THE ROLE OF SRC IN RENAL CANCER

TQ Qayyum, PA McArdle, M Seywright, DC McMillan, MA Aitchison, JE Edwards
Department of Surgery, University of Glasgow

Introduction

The aim of the study was to assess the expression levels of c-Src, phosphorylated Src, dephosphorylated c-Src at 530 and the downstream marker Fak 861 in renal cancer.

Patients & Methods

In all, 60 patients undergoing potentially curative nephrectomy for localised renal cancer were included. Immunohistochemical staining was utilised to assess expression of c-Src, dephosphorylated c-Src at 530, phosphorylated Src at the Y416 site, and Fak 861. Expression was assessed using the weighted histoscore method.

Results

High membrane c-Src was associated with increased cancer specific survival ($p=0.032$). When assessed individually, membrane, cytoplasm and nuclear expression of phosphorylated Src was not significantly associated with cancer specific survival. However when membrane and cytoplasm expression was combined, high expression was associated with decreased cancer specific survival ($p=0.001$).

Low cytoplasm Fak expression was associated with increased cancer specific survival ($p=0.029$). When expression of Fak was combined with phosphorylated Src, high expression was associated with decreased cancer specific survival ($p=0.003$).

When taking together high membrane c-Src and phosphorylated Src expression, this was associated with increased cancer specific survival ($p=0.029$).

On multivariate analysis, combined expression of membrane c-Src and phosphorylated Src (HR 0.49, 95% CI 0.24-0.99, $p=0.047$) and combined Fak and phosphorylated Src expression (HR 1.88, 95% CI 1.06-3.34, $p=0.030$) were significant independent predictors of cancer specific survival.

Conclusion

The results suggest that activated c-Src is associated with improved survival and activated Src family members are associated with decreased survival. This would imply that another member of the Src family maybe associated with decreased survival.

Take home message

Further work is required to identify which of the Src family members are expressed in renal cancer. This would potentially allow specific inhibitors for these Src family members to be developed.

U15 THE ROLE OF HYPOXIA-INDUCIBLE MIR-210 IN THE BIOLOGY AND PROGNOSIS OF CLEAR CELL KIDNEY CANCER

I McCormick, J Ragoussis, F Hamdy, A Harris
Churchill Hospital, Oxford

Introduction

Hypoxia results in the up-regulation of the transcription factor, HIF and one of its target genes, miR-210. We have previously shown this microRNA to be associated with control of mitochondrial metabolism through targeting of the iron sulphur cluster protein, ISCU. The majority of clear cell renal cancers (CCRCC) harbour VHL mutations, resulting in increased expression of HIF and its target genes.

Methods

RNA and DNA were extracted from 40 CCRCC samples, and 40 matched normal tissue controls. The tumours were sequenced for VHL mutations, and expression of miR-210 was measured by qRT-PCR. A TMA was constructed and stained for proteins including ISCU miR-210 expression was correlated with clinico-pathological data.

Results

miR-210 was found to be over-expressed 15-fold in VHL-mutant tumours, and 8-fold in the VHL non-mutant tumours. Tissue microarrays of the tumours were stained for ISCU. Tumours with high miR-210 expression stained significantly less for ISCU than those with low miR-210. High expression of miR-210 correlates with improved survival, and lower stage and grade. This is in contrast to studies in breast cancer.

In conclusion, we have demonstrated miR-210 over-expression in clinical samples in a VHL-mutation dependent fashion, and evidence that it down-regulates its target ISCU *in vivo*.

Take home message

A hypoxia-regulated microRNA is highly up-regulated in clear cell renal cancer compared to normal tissue. Its expression correlates inversely with expression of its target protein ISCU, and may be associated with prognosis.

U16 RESULTS OF KIDNEY LESION EXPERIMENTS WITH HAPTIC PROBE

J Li, H Liu, P Dasgupta, B Challacombe, L.D. Seneviratne, K Althoefer
Kings College London

Introduction

Mechanical Imaging based on Rolling Indentation (MIRI) is a novel approach for the localization of tissue abnormalities during minimally invasive surgery (MIS). This technique employs a wheeled haptic probe to roll over a soft tissue and visualizes the stiffness distribution of soft tissue into a colour-coded image. This may be of particular value during robotic surgery where haptic feedback is lacking. Our approach concentrates on urological tumours, but it has the potential to benefit other extirpative oncological procedures.

Materials and Methods

The MIRI approach carries out continuous rolling indentation following programmed trajectories along the tissue sample's surface and is capable of covering a large area of tissue surface rapidly. By fusing the information regarding the mechanical tissue dynamics, a colour-coded MIRI is generated to visualize the stiffness distribution within the tissue. To investigate the effectiveness of the MIRI method for biological soft tissue, an experimental study was carried out using kidney samples embedded with simulated tumors made of silicone gel.

Result

Following the reported ex-vivo tests, it can be concluded that tissue abnormality localization using the technique is effective and repeatable, although a sensitivity threshold does exist.

Conclusion

The study shows that the proposed MIRI technique is a suitable substitute for manual palpation. If applied as part of MIS, it has the potential to aid surgeons considerably in extirpative oncological procedures.

Take home message

Results of kidney lesion experiments with haptic probe show that Mechanical Imaging based on Rolling Indentation (MIRI) has the potential to aid surgeons considerably in extirpative oncological procedures in MIS.

U17 FACE, CONTENT AND CONSTRUCT VALIDITY OF A VIRTUAL REALITY SIMULATOR FOR ROBOTIC SURGERY

A. Gavazzi, A. Bahsoun, W. Van Haute, MS. Khan, P. Dasgupta
Guys Hospital, London

Introduction

Simulation as a part of surgical training is gaining popularity. This study aims to establish face, content and construct validity of a virtual reality simulator, the SEP Robot (SimSurgery, Oslo, Norway), in order to determine its usefulness for training.

Methods

Thirty participants (18 novices and 12 experts) received a demonstration of the simulator. All completed the following tasks: arrow manipulation and performing a surgeon's knot. All the participants rated parameters of face and content validity on a structured questionnaire. Ratings were scored on a five-point Likert-scale. Furthermore, task time was compared between experts and novices.

Results

There were no significant differences between the mean values of the scores given by the experts and surgical trainees (mean Likert scores 3.6 and 3.8). 90% of participants rated the trainer realistic and easy to use, 87% considered it generally useful for training and 90% agreed that the simulator was useful for hand-eye coordination and suturing. The experienced group scored significantly higher on the global rating scale and required less time to complete the tasks, thus establishing construct validity.

Conclusions

This study has established face, content and construct validity of the SEP Robot. With increase in adoption of robotic surgery worldwide, this simulator may prove to be a valuable adjunct to clinical mentorship.

Take home message

The SEP robotic simulator has demonstrated face, content and construct validity as a VR simulator for robotic surgery. With steady increase in adoption of robotic surgery worldwide, this simulator may prove to be a valuable adjunct to clinical mentorship.

U18 EVALUATION OF ECONOMIC IMPACT OF ROBOTICS IN UROLOGICAL SURGERY - A SYSTEMATIC REVIEW

K Ahmed, A Ibrahim, TT Wang, MS Khan*, P Dasgupta*

Imperial College London, St Mary's Hospital Campus, *MRC Centre for Transplantation, King's College & Dept of Urology, Guy's Hospital

Introduction

Urology has embraced robotic surgery with 10% of radical prostatectomies being performed using a robot assisted approach. However, cost is still one of the barriers limiting wider dissemination of this new technology. This review analysed studies comparing the use of robotic with laparoscopic and open urological surgery with respect to clinical outcomes as well as cost-efficiency.

Methods

Two reviewers identified abstracts using online databases and independently reviewed full length papers suitable for inclusion in the study.

Results

Laparoscopic and robot assisted prostatectomy are superior with respect to reduced hospital stay, length of surgery, blood loss, sexual potency and urinary continence when compared with open surgery. However, robot assisted prostatectomy remains more expensive than laparoscopic and open surgery. This is due to the costs of robot purchase, maintenance and instruments. The reduced length of stay in hospital and duration of surgery are unable to compensate for these excess costs. Robotic surgery however requires a smaller learning curve (20-40 cases).

Conclusion

Robotic surgery provides a superior alternative to open surgery with the similar postoperative outcomes to laparoscopic surgery but a much lower learning curve. Although costs are high at present, increased competition from manufacturers and wider dissemination of the technology could drive down costs. Further trials are needed to evaluate long term outcomes in order to fully evaluate the value of robots in urological surgery.

Take home message

Robotic surgery provides a superior alternative to open and laparoscopic surgery with a much lower learning curve. Although costs are high at present, increased competition from manufacturers and wider dissemination of the technology could drive down costs. More studies are needed to evaluate overall impact of the cost to the healthcare system.

U19 FEASIBILITY STUDY FOR THE DEVELOPMENT AND IMPLEMENTATION OF CENTRALISED SIMULATION TRAINING

KA Ahmed, P Jaye, M S Khan, P Dasgupta

Guy's Hospital, London

Introduction

With restricted working-hours and increasing concerns regarding patient safety, simulation is establishing its role in urological training. Two areas are relevant to urologists:(1)use of part-task-trainers to develop procedural skills, and (2)use of high-fidelity training environments to develop decision-making and team-working skills. This study aims to establish feasibility and acceptability of a centralised-simulation based training-programme.

Materials and methods

For this London Deanery supported pilot STeLi (Simulation and Technology enhanced Learning Initiative) project, we developed a structured simulation training programme for South Thames trainees. It incorporates: (1) virtual-reality simulators, mechanical bench-top models and a European wet-lab training sessions; (2) Crisis Resource Management (CRM), using SimMan to teach team-working and communication-skills.

Thirty-three specialist-registrars and 5 nurses participated. Feasibility and acceptability were evaluated using questionnaire. Performance-metrics were assessed by OSATS, and qualitative-assessments of CRMs.

Results

Ninety-percent trainees rated the training models as realistic and easy to use. 90% thought that they serve as a good training format. 95% recommended its use during training programs. 90% rated that sessions were well organized. 95% approved the format of the faculty teaching. 60% stated that they would like to have more time in future specifically dedicated to simulation based training.

Conclusion

Centralised-simulation programme that provides training in both technical and non-technical skills is feasible and acceptable. It can be used as an adjunct to workplace-based training. It is anticipated that this STeLi project will improve patient safety despite restricted hours for hands-on surgical training. Studies are needed to evaluate transfer of skills from simulation to real-settings

Take home message

Centralised simulation based training programme is feasible and acceptable to both trainees and trainers. Simulation can be used as an adjunct to the workplace based training.

U20 URINARY MICRO RNA AS A DIAGNOSTIC BIOMARKER IN BLADDER CANCER

S.M Miah, E Dudzic, D Rosario, F Hamdy, J Catto

Royal Hallamshire Hospital, Sheffield

Introduction

MicroRNAs (miRs) are single stranded non-coding RNA molecules 19-25nt in length that post-transcriptionally modulate protein expression. To date our group have already identified differential miR expression in normal and malignant urothelium in addition to the utilisation of miRs to discriminate between low and high-grade bladder cancer (Catto et al. Cancer Res 2009 Nov 1;69(21):8472-81)

The development of a robust urinary biomarker to detect UCC would considerably improve the care of affected patients and reduce the cost of managing bladder cancer patients.

Materials and Methods

One hundred and twenty-one urine samples were utilised – 68 UCC from a wide spectrum of disease and 53 benign controls. MicroRNA was extracted using the MirVana extraction kit. We selected 16 miRs deemed of high interest and determined their presence in our urine samples. MiR expression was determined using real-time semi-quantitative PCR and measured with a Aiglent 2100 bioanalyser. The reference gene RNU-48 was selected as a marker for standardisation.

Results

Nine miRs were shown to be differentially expressed – miRs 15a/15b/27b/100/135b/203/212/328/1224-3p (p-value < 0.01) between UCC and benign urine samples. Down regulation of miR-100 and upregulation of miR-135b were most cancer-specific (Concordance-index >0.74). The combination of miR-100/135b detected bladder cancer with a high sensitivity (0.85) and sufficient specificity (0.66)(Concordance-index 0.81). The addition of miR-15b to this panel increased the sensitivity for UCC to 0.91.

Conclusion

The combination of miR-100/135b has a high sensitivity for bladder cancer. A microRNA panel could be created to detect most bladder cancers and is likely to include miRs-100/135b.

Take home message

Urinary microRNA has the potential to be developed into a diagnostic biomarker for low- and high-grade bladder cancer.

U21 URINARY VOLATILE ORGANIC COMPOUNDS: POTENTIAL BIOMARKERS IN BLADDER CANCER DETECTION

EU Johnson, CSJ Probert, R Persad, N Ratcliffe, S Smith, Ahmed I

Bristol Urological Institute, Bristol

Introduction

Bladder cancer is an important disease with about 350,000 new cases diagnosed annually worldwide. The gold standard for diagnosis is cystoscopy and biopsy; both are invasive and require highly trained personnel. Treated patients have to be followed up by frequent cystoscopies lasting several years in most cases. The discovery of potential markers indicating which individuals should proceed to cystoscopy would be an important addition to bladder cancer management. The odour of urine is produced by volatile organic compounds (VOCs) which can be detected by gas chromatography and mass spectrometry. We analyzed the VOCs in urine of healthy individuals and patients with bladder cancer in search of possible differences which could be harnessed in future as a potential screening tool.

Methods

First void urine was obtained from 64 patients with new non-muscle invasive bladder cancer (41 men, 23 women; mean age 74.6yrs, max 94yrs, min 28yrs) and 71 cancer free patients with haematuria (31 men, 40 women; mean age 62.4yrs, max 88yrs, min 22yrs). The head space above these pH adjusted urine samples was extracted for 20minutes, after equilibration, using a carboxen / polydimethylsiloxane solid phase micro-extraction fibre. This was followed by desorption and VOC identification by gas chromatography / mass spectrometry.

Results

Volatile organic compounds emitted into the head space under acidic conditions were found to be discriminating. The identified compounds were analyzed using forward stepwise discriminant analysis: 9 VOCs when used together ($p < 0.001$), gave 84.7 % correct classification of samples. No reduction was obtained on cross validation of results. This gives sensitivity = 76.6%, specificity = 91.2%.with PPV = 91% and NPV = 81%

Conclusion

Volatile organic compounds in urinary head space change with the development of bladder cancer. Urinary VOCs are exciting novel potential biomarkers in the detection of bladder cancer.

U22 SIDE POPULATION IN HUMAN BLADDER CANCER ENRICHES FOR CANCER STEM CELLS THAT CAN BE TARGETED BY MAPK INHIBITION

AC Rigas, N Jaiswal, SC Williamson, R Pickard, CN Robson, R Heer

Northern Institute for Cancer Research, Newcastle University

Introduction

Side population (SP) cells and ABC transporter expression enrich for stem cells in a number of tissues. We looked to explore this phenotype in characterising urothelial cancer stem cells (CSCs). Putative CSC-specific pathways were explored to identify targets for new treatments.

Materials and Methods

Fluorescence activated cell sorting, based on Hoechst 33342 efflux, was applied to isolate SP cells from a panel of human bladder cancer cell lines. Expression of ABC transporters was investigated by qRT-PCR and immunostaining on flow cytometry. Selected SP cells underwent in vitro and in vivo characterisation of CSC behaviour. Expression of the MAPK pathway, a known promoter of bladder tumourigenesis, was explored as a suitable target.

Results

We report the existence of SP cells in superficial and invasive bladder cancer cell lines. Specifically the cell line RT112 displayed CSC properties including expression of ABC transporters (ABCG2, P-glycoprotein) and stem cell markers (Nanog, Notch-1, SOX2), enrichment of self renewal (3-4 fold, $p < 0.05$) and higher in vivo tumourigenicity (tumour volume, $p < 0.05$). In addition, SP was shown to regenerate both SP and non-SP cells, where non-SP showed serial dilution of their ability to regenerate cultures. Furthermore, we show in vitro that the ERK signalling pathway is a key regulator of SP and its inhibition is a suitable target for therapy, having confirmed the expression of ABCG2 in human bladder cancer specimens ($n=12$).

Conclusion

We confirm that SP enriches for CSCs in human bladder cancer and highlight the ERK pathway as a suitable therapeutic target for bladder cancer.

Take home message

We show the side population phenotype may enrich for cancer stem cells in human bladder cancer and highlight the ERK signalling pathway as a suitable therapeutic target for bladder cancer.

U23 COMBINATION OF A FUSOGENIC GLYCOPROTEIN, PRO-DRUG ACTIVATION AND ONCOLYTIC HSV AS AN INTRAVESICAL THERAPY FOR SUPERFICIAL BLADDER CANCER (VISUALISED BY MICRO CT).

S Pandha, G R Simpson, A Horvath, R S Coffin, T Pencavel, K Harrington

University of Surrey, Guildford, United Kingdom

Introduction

There are still no treatments for superficial bladder cancer (SBC) which alter its natural progression, where 20% of patients develop metastatic disease. SBC is often multifocal, has high recurrences after surgical resection and recurs after intravesical live BCG. OncoVexGALV/CD, an oncolytic HSV-1, has shown enhanced local tumour control by combining oncolysis with the expression of a highly potent pro-drug activating gene and the fusogenic glycoprotein. A version of this virus expressing GM-CSF has shown promising results and is about to enter Phase III clinical trials. The present study aims to test OncoVexGALV/CD as an intravesical therapy for superficial bladder cancer.

Materials and methods

In vitro fusion/prodrug/apoptotic MTS cell base assay. In vivo orthotopic bladder tumour model observed by CT scanning.

Results

Treatment of seven human bladder carcinoma cell lines with the virus, resulted in higher tumour cell killing through oncolysis, pro-drug activation and glycoprotein fusion. To further test OncoVexGALV/CD we have developed a rat orthotopic bladder tumour model, visualised by micro CT, to assess intravesical tumour control. In vivo results showed that intravesical treatment with OncoVexGALV/CD + prodrug (5-FC) reduced the average tumour volume by over 95% compared to controls.

Discussion

Our in vitro and in vivo results indicate that OncoVexGALV/CD can improve local tumour control within the bladder, and potentially alter its natural history.

Take home message

We have shown that a combination of a fusogenic glycoprotein, pro-drug activation and oncolytic HSV can act as an intravesical therapy for superficial bladder cancer. We also demonstrate that treatment of a model for superficial bladder cancer can be visualised by micro CT scanning.

U24 GENOME-WIDE COPY NUMBER, FGFR3 AND PIK3CA MUTATION ANALYSIS OF MULTIFOCAL NON-MUSCLE INVASIVE BLADDER CANCER

R Turo, F M Platt, P Harnden, W R Cross, C D Hurst, M A Knowles

St. James's University Hospital, Leeds

Introduction

Bladder cancer is commonly multifocal and evidence suggests that most have a monoclonal origin and share some but not all identifiable molecular events. The molecular changes that confer selective advantage during tumour evolution represent potential therapeutic targets and biomarkers for disease monitoring. Therefore it is important to assess molecular uniformity. We have combined array comparative genomic hybridization (aCGH) and SNaPshot analysis for the simultaneous detection of copy number aberrations, FGFR3 and PIK3CA mutations in synchronous multifocal tumours.

Materials & Methods

DNAs were extracted from frozen sections of 20 tumours collected from 8 patients. aCGH used 1Mb resolution BAC arrays. SNaPshot analysis scanned for 11 hotspot mutations in FGFR3 and 4 in PIK3CA.

Results

Identical mutations were frequently seen in all tumours from the same patient (3 cases for FGFR3 and 1 for PIK3CA). Copy number alterations were identified in some tumours from all patients. In 2 cases both tumours had identical changes. In 1 case, 2 tumours shared mutations in FGFR3 (S249C) and PIK3CA (E545Q) but all copy number alterations differed. All tumours from 3 patients shared some alterations indicating a monoclonal origin but were otherwise highly divergent. In two patients 1 of 2 tumours exhibited no alterations whereas the second tumour had multiple changes.

Conclusion

Our data suggest that the majority of multifocal tumours are monoclonal in origin but revealed extensive sub-clonal divergence. Thus they may not share relevant therapeutic targets or biomarkers for disease monitoring.

Take home message

The majority of multifocal tumours are monoclonal in origin but reveal extensive sub-clonal divergence. Thus they may not share relevant therapeutic targets or biomarkers for disease monitoring.

U25 THE OPTICAL PROPERTIES OF HEALTHY VERSUS CANCEROUS UROLOGICAL TISSUE

D Nehikhare, I Amygdalos, P Tomplins, M Walker, J Vale, G Hanna

Imperial College London

Introduction

The aim of this study was to determine if it is possible to distinguish between healthy and cancerous urological tissue, by extracting and modelling their optical properties from Optical Coherence Tomography (OCT) images.

OCT imaging provides high-resolution cross-sectional images. Optical properties such as the attenuation coefficient are scientific values which describe how light interacts with tissue. Such measurements have been shown to differentiate between healthy and cancerous tissue in various organs. By combining these two techniques there is potential to add an extra domain to OCT imaging as a potential diagnostic and investigative tool for urological cancers.

Materials & Methods

This study has so far been carried out on 12 patients undergoing elective urological operations. OCT images were obtained from prostate, kidney, and bladder tissue of various pathologies and gradient analysis software was then used to extract the attenuation coefficient from the OCT images. We were then able to model the mean attenuation coefficients of our OCT images and obtain colour-maps. The technique was applied to ex-vivo tissue samples and our results were then compared against the histological reports.

Results

Initial results have shown that there is distinct variation in optical properties between healthy and diseased urological tissue and suggest that OCT and optical property modelling could provide a useful investigative tool.

Conclusions

Our results show that there is a need for further research into extracting optical properties from OCT images. Such work could significantly enhance the benefit of OCT as a potential imaging and diagnostic tool.

Take home message

To the best of our knowledge, this is the first time that the attenuation coefficient has been extracted from OCT images of urological tissue. The major clinical benefit of OCT is to be able to target potential cancers both accurately and time efficiently which will allow the surgeon to choose the optimal biopsy site for diagnosis and assessment of tumour grade and stage and therefore give valuable prognostic information.

U26 ESTROGEN INCREASES EXPRESSION AND SECRETION OF THE INNATE ANTI-MICROBIAL BETA-DEFENSIN-2 IN VAGINAL EPITHELIUM

ASM Ali, CL Townes, M Lanz, J Hall, RS Pickard
Newcastle University, Institute of Cellular Medicine

Introduction

Recurrent urinary tract infection (rUTI) is a troublesome consequence of post-menopausal vaginal atrophy. Infection typically begins with vaginal colonisation by *Escherichia coli* which precedes ascending infection. In healthy women, colonisation is prevented by host innate immunity including synthesis of cationic antimicrobial peptides (AMPs). Localised estrogen treatment reduces rUTI in postmenopausal women and interestingly also in premenopausal women. However, systemic adverse-effects and concerns regarding cancer risk limit usage. Some AMPs are known to be hormone responsive. We hypothesise that estrogen reduces rUTI risk by increased vaginal AMP expression.

Materials and Methods

The VK2-E6/E7 vaginal epithelial cell-line was used as an in vitro model to examine previously identified urogenital AMPs: beta-defensin-1, beta-defensin-2, human alpha-defensin-5 and cathelicidin. Cells were cultured in serum-free growth medium with or without physiological concentrations (4nM) of 17-beta-estradiol and challenged with 100,000 CFU of NU14 *E.coli* and 0.5-1?g/ml *E.coli* lipopolysaccharide (LPS) for 48 hours.

Results

Of the AMPs analysed, only beta-defensin-2 expression levels were significantly up-regulated in cells grown in estrogen with an enhanced response to LPS seen in both mRNA measured by qRT-PCR ($n=6, p<0.05$) and peptide levels measured by ELISA ($n=3, p<0.05$) at 48-hours. Furthermore enhanced beta-defensin-2 expression was linked to increasing estrogen dose. No response was seen with bacterial or LPS challenge in the absence of estrogen.

Conclusions

These data suggest up-regulation of beta-defensin-2 AMP by vaginal epithelium may be one mechanism by which local estrogen enhances immunity against rUTI. Improved understanding of this mechanism may facilitate discovery of novel therapies for rUTI without hormonal side effects.

Take home message

In vitro, estrogen up-regulates the innate antimicrobial peptide Beta-Defensin-2 in vaginal epithelial cells - this may be the key underlying mechanism by which clinical application of topical estrogen helps prevent recurrent urinary tract infection. Understanding this mechanism may allow development of novel treatments which up-regulate innate immunity without use of hormones.

U27 DEVELOPMENT OF ASEPTICALLY PRODUCED SCAFFOLDS FOR SUBSTITUTION URETHROPLASTY.

AJ Bullock, A Mangera, S MacNeil, CR Chapple

University of Sheffield

Introduction

We are developing tissue engineered buccal mucosa (TEBM) for substitution urethroplasty using electrospun polylactide (PLA) as a dermal replacement scaffold. All of the sterilisation methodologies we previously explored had adverse effects on scaffold mechanical properties hence our aim in this study was to explore producing PLA scaffolds under aseptic cleanroom conditions to see if this would be less damaging to scaffolds.

Methods

Poly lactide scaffolds were electrospun aseptically in cleanroom conditions from chemical grade (Sigma) or medical grade (Purac) PLA. The effect of heat annealing was also explored on the mechanical properties of scaffolds. Oral keratinocytes and fibroblasts were isolated, cultured and seeded onto scaffolds and cultured for 14 days. Cell attachment and proliferation were assessed by DAPI nuclear staining and fluorescence microscopy, collagen production was assessed by Sirius red staining, and biomechanical properties were assessed using a BOSE electroforce instrument. Scaffold contraction was calculated from serial photography,

Results

The PLA material produced under clean room conditions was shown to be sterile.

Both chemical and medical grade PLA scaffolds had similar mechanical strength and elasticity to native BM. Cells attached and grew well on all scaffolds, depositing collagen I and exhibiting some degree of post culture contraction. Heat annealing of scaffolds increased their mechanical strength but reduced their elasticity. It also reduced contraction of the scaffolds.

Conclusion

Aseptically produced electrospun PLA scaffolds show promise as a tissue engineered scaffold in terms of biocompatibility and biomechanical properties similar to that of buccal mucosa.

Take home message

The biomechanical properties of a tissue engineered graft are affected by each of the individual processing steps in their creation. Aseptic production rather than post production sterilisation can produce a scaffold with increased strength, and reduced contraction post culture.



SARS

Society of Academic and Research Surgery

Society of Academic and Research Surgery
The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields
London WC2A 3PE

Tel: 020 7869 6640
Fax: 020 7869 6644
Email: sars@rcseng.ac.uk

www.surgicalresearch.org.uk