

Research DAY

Department of Medicine 2018

Thursday, May 24, 2018

ORAL PRESENTATIONS

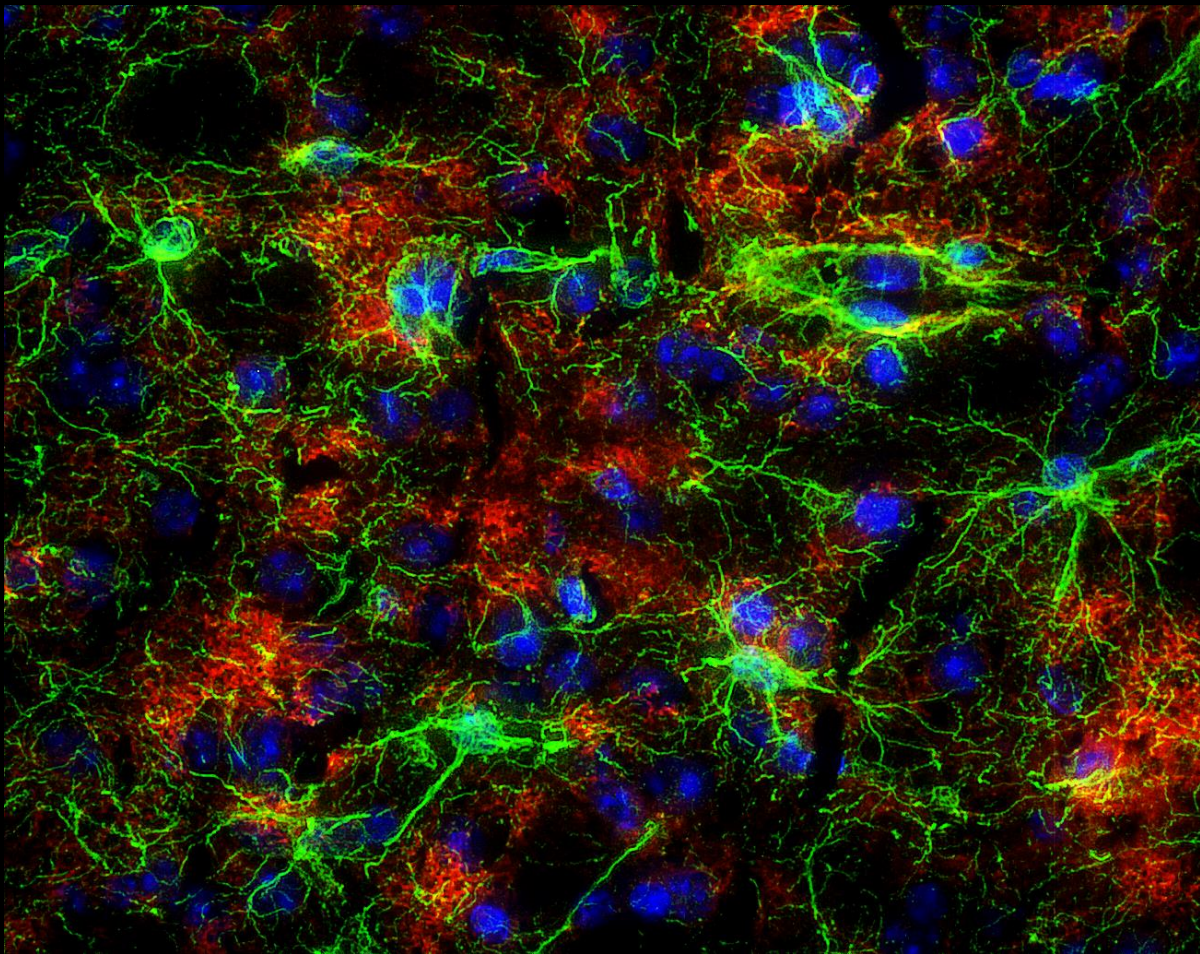
Classroom D, WMC 2F1.04

8:00 a.m. – 5:00 p.m.

POSTER PRESENTATIONS

Lower Level John W. Scott Health Sciences Library

All Day Viewing



Graduate Students | Residents | Postdoctoral Fellows



Research DAY 2018

Department of Medicine

Research has been the life-blood of the Healing Arts in all cultures and throughout history. We continue this tradition in the Department of Medicine, always with the goal of better clinical care. In 2017 members of this Department contributed over 700 research papers to the literature. The work spans the spectrum from molecule to patient and from patient to health systems. Research is central to what we do – it is the life-blood of medicine.

With some help from their supervisors, most of the Department's research work is actually done by residents, graduate students and postdoctoral fellows – and this work is showcased today. The Department of Medicine graduate program is one of the largest at this University with 96 graduate students and 28 postdoctoral fellows, and 300 residents in our core and subspecialty programs. Nearly all trainees are involved in research at some level.

The trainees who are presenting the work today have put a lot of effort into their presentations, and many of them will take their findings to national and international conferences. You can help them by showing how much you value their effort, you can get a preview of what will be published by this Department in the near future, and by chatting with the presenters, you can add your ideas to this ongoing research.

As is the case every year, the oral abstracts will be presented in Classroom D, and posters will be shown in the lower level of the John W. Scott Health Sciences Library (lunch is served). This year, I would like to welcome two guest adjudicators for the oral presentations:

Richard Leigh, MBChB, MSc, PhD, Professor and Head, Department of Medicine Cumming School of Medicine, University of Calgary.

Jessica Yue, MSc, PhD, Assistant Professor, Department of Physiology, University of Alberta

Barbara J. Ballermann, MD

This Day is Dedicated to One of Our Best!

Dr. Sumit (Me2) Majumdar



January 11, 1966 - January 19, 2018

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Research Day Guest Oral Adjudicator

Richard Leigh, MBChB, MSc, PhD, FCP (SA), FRCPC



Richard Leigh is a physician-scientist and the Chair of the Department of Medicine in the Cumming School of Medicine at the University of Calgary.

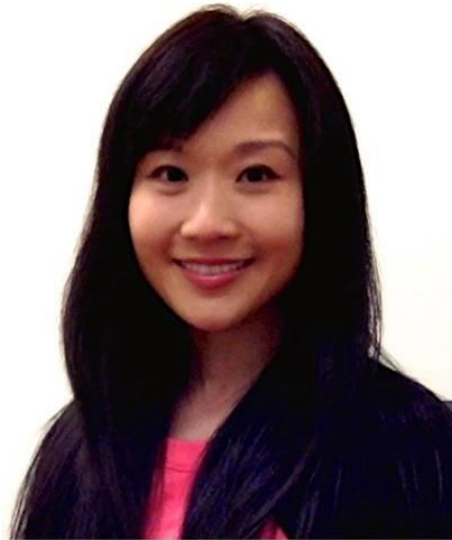
He obtained his medical degree from the University of Cape Town, and subsequently undertook specialist and sub-specialist training in Internal Medicine and Pulmonology at the University of Cape Town, South Africa. This was followed by further research training in the areas of airway inflammation, asthma and COPD at McMaster University in Canada, where he obtained a Masters degree in Health Research Methodology and a PhD in Medical Sciences.

Dr. Leigh's areas of interest include understanding the basic mechanisms underlying airway remodeling in asthma, the assessment of airway inflammation and early phase clinical trials in asthma and COPD. His clinical practice focuses on severe asthma and other airways diseases, and he previously served as the Division Chief of Respiratory Medicine prior to being appointed as the Chair of the Department of Medicine in 2016.

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Research Day Guest Oral Adjudicator

Jessica Yue, MSc, PhD



Dr. Jessica Yue is an assistant professor in the Department of Physiology and a member of the Group on Molecular and Cell Biology Lipids Group, ADI, and the Neuroscience and Mental Health Institute. She completed her graduate studies at the University of Toronto in area of stress physiology and hypoglycemia in relation to type 1 diabetes. Dr. Yue then completed her post-doctoral training at the Toronto General Hospital. There, she studied brain nutrient and hormone sensing mechanisms in the regulation of metabolism. Her work has been published in journals that include Nature Medicine, Nature Communications, Cell Metabolism, Circulation Research, and Diabetes. The current focus of Dr. Yue's laboratory is the in vivo control of glucose, lipid, and energy homeostasis by stress-related hormone actions in the brain. Her research program is supported by CIHR, NSERC, Diabetes Canada, and CFI. She is a Diabetes Canada Scholar and recipient of a Canadian Lipoprotein Conference-Amgen Stewart Whitman Young Investigator Award. Dr. Yue is a member of the College of Reviewers and peer reviewer for national granting agencies such as CIHR (Project Scheme) and Diabetes Canada (operating grants and postdoctoral awards). She is also a reviewer for numerous journals, including: Nature Communications, Cell Reports, Scientific Reports, Diabetes, Diabetologia, Diabetes Care, and American Journal of Physiology Endocrinology & Metabolism.

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Meeting at a Glance

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|---------------|------------------------------------------------------------------------------------------------------------------------------|
| 8:00 – 8:10 | Welcome Address <i>Dr. Evangelos Michelakis, Associate Chair, Research</i> <i>Dr. Barbara Ballermann, Chair</i> |
| 8:10 – 8:10 | Keynote Speaker <i>Dr. Richard Leigh</i> |
| 8:30 – 9:45 | Oral Presentations |
| 9:45 – 10:00 | Break |
| 10:00 – 11:15 | Oral Presentations |
| 11:00 – 1:00 | Poster Presentations and Lunch |
| 1:10 – 1:15 | Announcement of the Translational Research Fellowship Award Winner |
| 1:15 – 1:30 | Translational Research Fellowship Award Presentation |
| 1:30 – 2:30 | Oral Presentations |
| 2:30 – 2:45 | Break |
| 2:45 – 4:00 | Oral Presentations |
| 4:00 | Award Ceremony |

Scoring Criteria

Oral & Poster Presentations (1=Poor, 5= Excellent)

| | |
|------------------------------------------------------------------------|-----------------|
| Clarity and Justification of the Research Questions/Hypothesis | 1 2 3 4 5 |
| Appropriateness of the Methods Used to Answer the Questions/Hypothesis | 1 2 3 4 5 |
| Validity and Relevance of the Results to the Questions/Hypothesis | 1 2 3 4 5 |
| Quality of the Discussion and Conclusion | 1 2 3 4 5 |
| Visual Layout and Visual Impact | 1 2 3 4 5 |
| Oral Response to Adjudicator's Question | 1 2 3 4 5 |
| TOTAL SCORE | <hr/> 35 |

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Morning Oral Presentations

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| 8:45 | Aristeidis Boukouris Supervisor: Evangelos Michelakis | GS | CRMP2A protects cancer cells from autophagy-induced cell death in response to chronic severe metabolic and genotoxic stress | 25 |
| 9:00 | Ammar Hassanzadeh Keshteli Supervisor: Karen Madsen | GS | An anti-inflammatory diet prevents subclinical inflammation and associated changes in gut microbiota and metabolomic profiles in ulcerative colitis patients | 27 |
| 9:15 | Xueyi Chen Supervisor: Dr. Gavin Oudit | GS | Cardiac Endothelial p110 α Regulates Ventricular Remodeling Following Myocardial Infarction | 29 |
| 9:30 | Kasia Zubkow Supervisor: Douglas Zochodne | GS | Novel non-viral RNA interference strategies targeting retinoblastoma protein for rescue and regeneration of peripheral axons | 30 |
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| 10:15 | Nariman Sepehrvand Supervisor: Dr. Justin A. Ezekowitz | GS | A meta-analysis of the randomized clinical trials on the effects of supplemental oxygen therapy in patients with suspected acute myocardial infarction | 32 |
| 10:30 | Kerolous Messeha Supervisor: Andrew L. Mason | GS | The effect of GSK-3B Inhibitor on Primary Biliary Cholangitis in NOD.c3c4 Mouse Model | 34 |
| 10:45 | Bruno Saleme Supervisor: Evangelos Michelakis | GS | Methyl tags on selected mRNAs are needed for the acute translation of stress responsive proteins under major cellular stress | 36 |
| 11:00 | Syed Hussain Supervisor: Sara Davison | GS | Evaluating the Conservative Kidney Management Pathway through the characterization of patient experiences using in-depth interviews - a qualitative study | 37 |

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Afternoon Oral Presentations

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| 1:15 | Translational Research Fellowship Award Winner Presentation | | |
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| 1:45 | Mohammed S. Osman Supervisor: Evangelos Michelakis | PDF Mitochondrial regulation of PD-L1 in Pulmonary Arterial Hypertension - a novel mechanism | 40 |
| 2:00 | Arul Duraikannu Supervisor: Douglas Zochodne | PDF A role for the p21 and p27 tumor suppressors in CNS axon regeneration | 41 |
| 2:15 | Sola Mansour Supervisor: Michael Sean McMurtry | CIM Bleeding risk in cancer patients with venous thromboembolism | 42 |
| 2:30 | Break | | |

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| 3:00 | Robinder Sidhu Supervisor: Robert Welsh | SSR ATRIAL FIBRILLATION IN PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION: ONE YEAR OUTCOMES FROM A CANADIAN REGISTRY | 45 |
| 3:15 | Anas Alrohim Supervisor: Kenneth Butcher | SSR EARLY DABIGATRAN TREATMENT AFTER ISCHEMIC STROKE DOES NOT RESULT IN HEMORRHAGIC TRANSFORMATION | 46 |
| 3:30 | Daniel Sawler Supervisor: Lalit Saini | SSR Two Cycles of Consolidation Chemotherapy are Associated with Similar Clinical Outcomes to Three Cycles in AML Patients with Favorable Risk Cytogenetics | 47 |
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| 11 | Andrew Masoud Supervisor: Allan Murray | GS | Characterization of the role of Apelin in injury repair of the Chronic Allograft Vasculopathy in Mouse heart allografts | 59 |
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| 13 | Anish Nikhanj Supervisor: Gavin Oudit | GS | A Prospective Cohort Study of Heart Disease in Patients with Muscular Dystrophy: Impact of a Multidisciplinary Care Approach | 62 |
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| 81 | Yongneng Zhang Supervisor: Evangelos Michelakis | GS | Cardiac fibroblasts can induce a paracrine mitochondrial suppression of cardiomyocytes in hypoxia | 157 |

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THE MOLECULAR LANDSCAPE IN ULCERATIVE COLITIS

Katelynn Madill-Thomsen, Jeffery Venner, Vojislav Jovanovic, Konrad Famulski, Simone Withecomb, Aducio Thiesen, Richard Fedorak, Philip Halloran, Brendan P. Halloran

Supervisor: Dr. Phil Halloran

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the colonic epithelium, with the inflammasome, T cells, complement activation, and microbiome dysbiosis contributing to pathogenesis. We applied a previously established method of molecular analysis to a set of UC biopsies to elucidate the molecular changes associated with active UC, specifically comparing UC to kidney T cell-mediated rejection (TCMR), as a prototype of a sterile, T-cell mediated disease.

METHODS

71 for-cause UC colonic biopsies from 61 patients were collected at the U of A Hospital in Edmonton, AB and Cedars-Sinai Hospital in LA, California. Biopsies were processed using Affymetrix GeneChip microarrays and the data analyzed in R programming language. Transcript expression data was displayed using volcano plots (showing association between the transcripts and endoscopic Mayo score) and heatmaps. We compared overexpression of top transcripts between UC and TCMR using the DAVID tool.

RESULTS

The volcano plot (Figure 1) showed strong associations between endoscopic Mayo score and decay accelerating factor (CD55), moderate associations with calprotectin genes (S100A8/S100A9), and lesser associations for effector T cell transcripts (i.e. CTLA4, IFNG, CXCL13), several IFNG inducible transcripts, inflammasome transcripts (CASP1), and toll-like receptors (TLR5). Expression of top transcripts in a cell panel showed primary expression in monocytes, macrophages, dendritic cells, and epithelial/endothelial cells, and minimal expression in CD4/CD8 T cells or NK cells. Pathway analysis of TCMR and UC showed major differences between pathway terms and individual transcripts.

CONCLUSIONS

While transcripts associated with cognate T cell inflammatory processes (TCMR) are expressed in UC, there are substantial differences between these processes. Top genes associated with the endoscopic Mayo score in UC were not those associated with effector T cells, but instead represent an inflammatory environment with strong associations to CD55. This suggests that cognate T cell recognition is present in UC but supplemented by a second source of inflammation.

Supervisor: Dr. Phil Halloran

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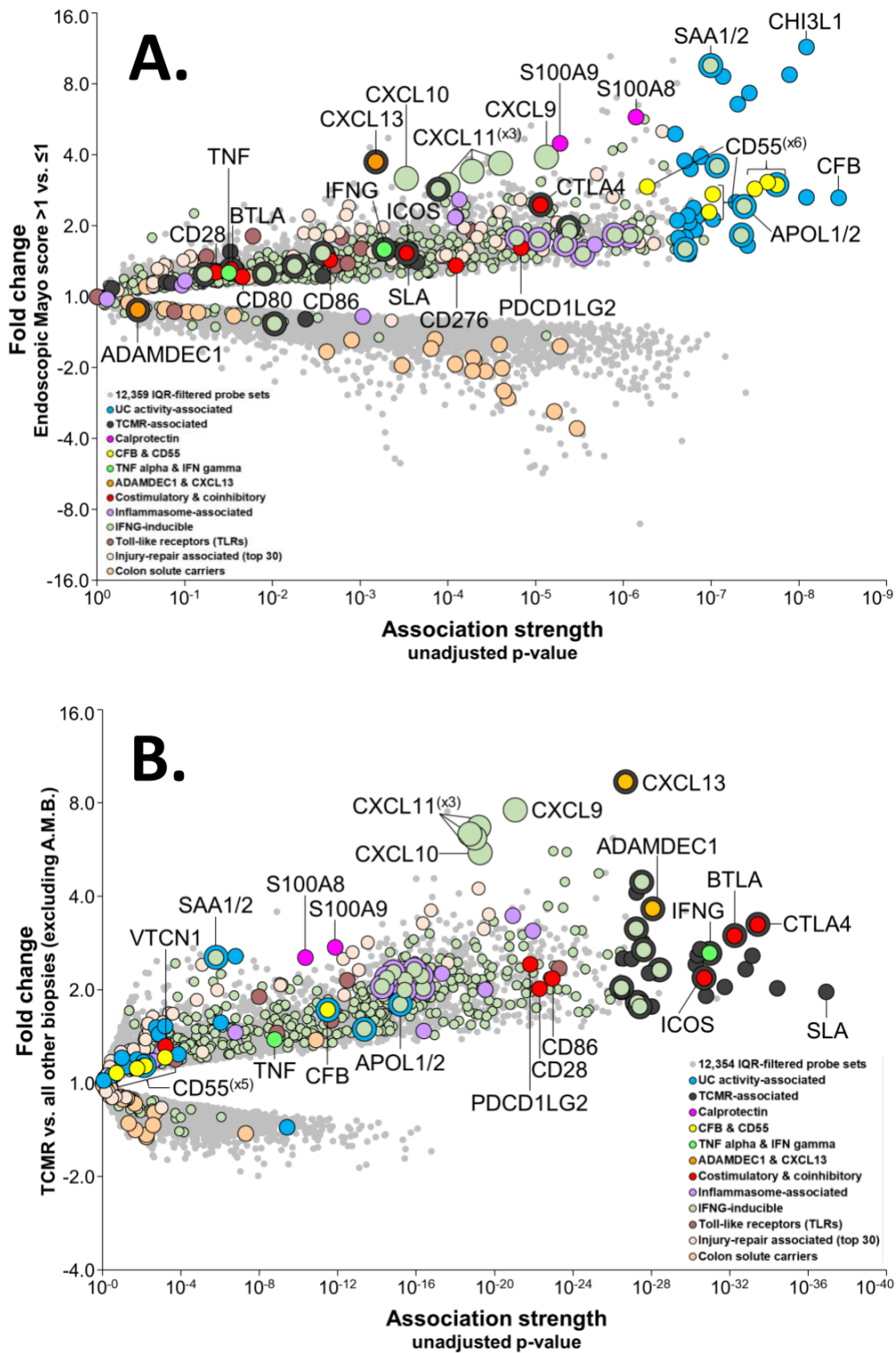


Figure 1. Molecular landscapes of A) UC and B) TCMR by volcano plot. Samples towards upper right have high association and fold change, indicating a significant association with A) Mayo score or B) TCMR, while samples towards the middle left are not strongly associated.

CRMP2A protects cancer cells from autophagy-induced cell death in response to chronic severe metabolic and genotoxic stress

Boukouris AE, Stenson TH, Saleme B, Zervopoulos S, Sutendra G and Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Apoptosis-resistance in response to severe stress is an important mechanism for cellular survival and a hallmark of cancer. Autophagy generally protects against stress-induced apoptosis and death. But if the stress is chronic and severe, the autophagy mediators microtubule-associated protein 1A/1B light chain 3B (LC3B) and p62 complex with and activate caspases and apoptosis (autophagy-induced cell death, ACD). We hypothesized that survival under different conditions of sustained stress may be driven by a common pathway that would promote cell preservation by inhibiting ACD.

METHODS

We performed an unbiased proteomics analysis (2D-gel electrophoresis and mass spectrometry) in cancer cells (A549) exposed to severe metabolic stress [due to ethidium bromide (EtBr) that damages mitochondrial DNA, Sirtuin3-siRNA that globally inhibits mitochondrial function and nutrient starvation (glucose, glutamine)] or DNA damage [due to genotoxic drugs: cisplatin, gemcitabine]]; immunoblots (LC3B, p62, cleaved-Caspases), immunoprecipitation (IP) and mass spectrometry.

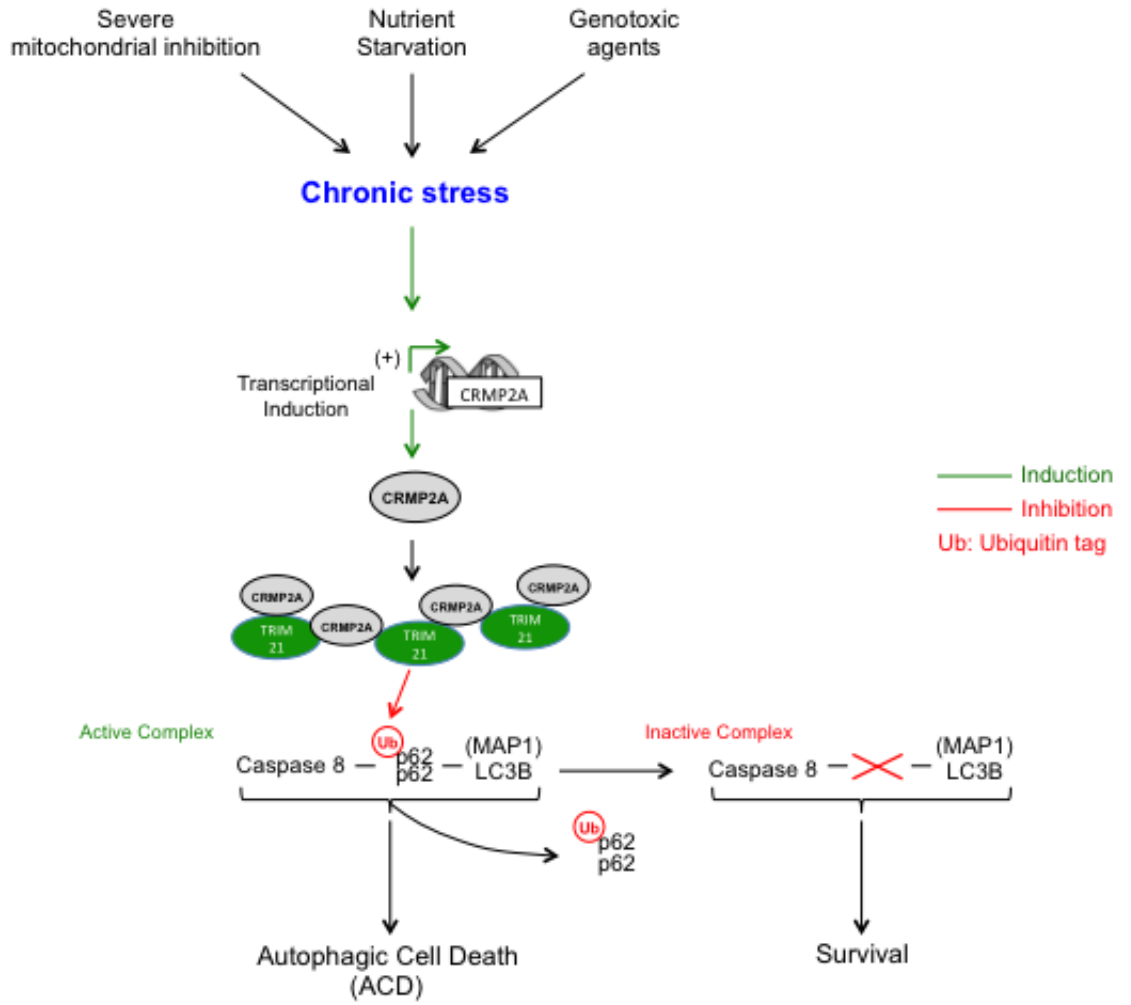
RESULTS

We found a strong induction of Collapsin Response Mediator Protein-2A (CRMP2A) in all metabolic and genotoxic conditions, which also exhibited autophagy. Effective inhibition of CRMP2A with siRNA increased apoptosis significantly in all stressed conditions. Autophagy inhibition (by inhibiting class III PI3K kinase) mitigated the apoptotic effects of CRMP2A loss, suggesting that CRMP2A may be a pro-survival factor and inhibitor of ACD. Indeed, unbiased screening (IP and mass spectrometry) for CRMP2A-binding proteins revealed that CRMP2A binds TRIM21, an E3 ubiquitin ligase that inactivates p62, an inducer of ACD. CRMP2A was present in the cytoplasm of many cancer, but not normal, cell lines.

CONCLUSIONS

CRMP2A is a previously unrecognized pro-survival factor that appears to inhibit ACD through TRIM21, under severe and sustained stress. Induction of CRMP2A may be a previously unrecognized mechanism that cancer uses to survive by preventing ACD. Since cancer cells are often chronically exposed to chemotherapies that have the potential to induce ACD, CRMP2A may be a novel therapeutic target.

Supervisor: Dr. Evangelos Michelakis



An anti-inflammatory diet prevents subclinical inflammation and associated changes in gut microbiota and metabolomic profiles in ulcerative colitis patients

Ammar Hassanzadeh Keshteli, Karen Madsen, Cheryl Nickurak, Karen Kroeker, Heekuk Park, Rosica Valcheva, Rupasri Mandal, David Wishart, Sander van Zanten, Brendan Halloran, Richard Fedorak, Levinus Dieleman
Supervisor: Karen Madsen

INTRODUCTION

Currently there is no RCT on the relationship between ulcerative colitis (UC) and diet. The aim of this study was to investigate the effectiveness of an anti-inflammatory diet (AID) for maintenance of remission in UC patients.

METHODS

In a 6-month RCT, adult UC patients in clinical remission were randomized to either an "AID" or "Canada's Food Guide(CFG)" as control. A dietitian provided dietary recommendations to all patients in monthly face-to-face and telephone sessions. Menu plans in the AID group aimed to increase dietary intake of fiber, prebiotics, probiotics, anti-oxidants and omega-3 fatty acids and to decrease intake of red/processed meat, refined sugar and alcohol. Monthly 24h dietary recalls were used to assess dietary adherence. Stool was collected for fecal calprotectin(FCP) and microbial analysis. Metabolomic analysis was performed on urine, serum, and stool samples collected at baseline and month 6, or at clinical relapse.

RESULTS

Fifty-three patients were randomized (mean age: 41.4 ± 14.7 y, 64.2% females). Five(19.2%) patients in the AID group and 8(29.6%) patients in the CFG group relapsed ($P=0.38$). Patients in the AID group showed an increase in dietary intake of seafoods, yogurt, fiber, zinc, selenium. Over the 6-month intervention, the AID group showed no significant increase in FCP, whereas patients following CFG had a statistically significant increase (Figure 1A). Increased FCP in the CFG group was associated decreased Coriobacteriaceae and Lachnospiraceae and increased Veillonellaceae and Enterobacteriaceae. While metabolomic profiles of the two groups were similar at baseline, there was a clear separation at month 6(Figure 1B). Patients in the AID group had higher glutamic acid (stool), creatinine (stool), and carnosine (urine), but lower hydroxymandelic acid(urine), and acetone (stool).

CONCLUSIONS

Dietary modifications to increase intake of anti-inflammatory foods and decrease inflammatory-type foods was effective in limiting the onset of subclinical inflammation and associated microbial and metabolic changes in UC patients in remission.

Supervisor: Dr. Karen Madsen

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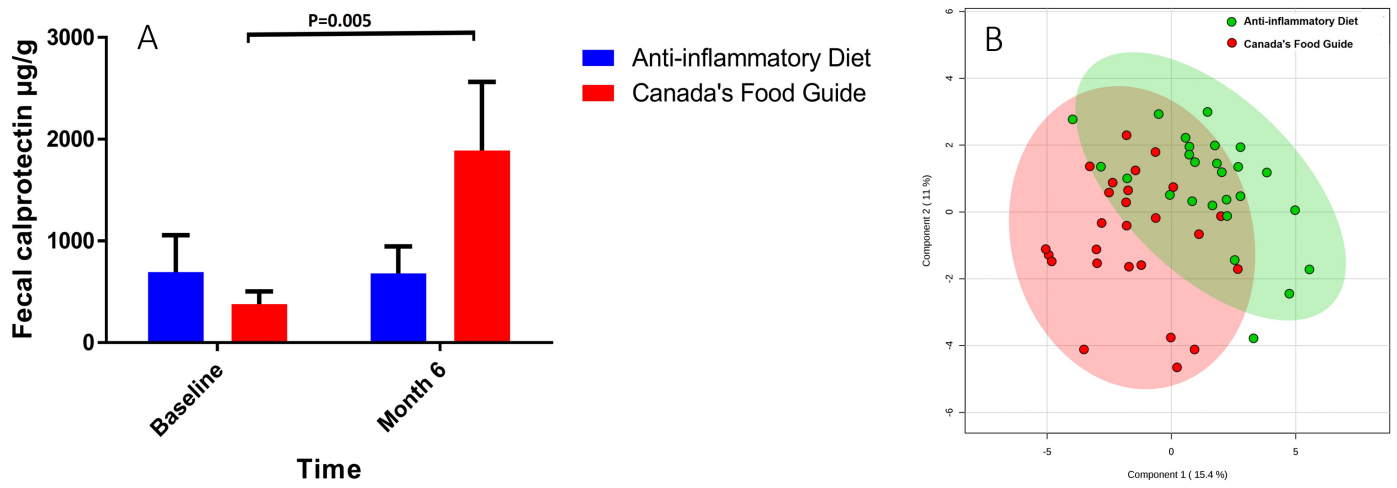


Figure 1. A) Comparison of changes in fecal calprotectin levels from baseline to month 6 or clinical relapse between the Anti-inflammatory Diet and Canada's Food Guide diet groups; **B)** Partial least squares discriminant analysis plot showing a significant difference in the metabolome of patients randomized to the Anti-inflammatory Diet and Canada's Food Guide diet groups at month 6 or clinical relapse as identified by metabolites in urine, serum and fecal samples

Cardiac Endothelial p110 α Regulates Ventricular Remodeling Following Myocardial Infarction

Xueyi Chen, Wang Wang, Jessica DesAulniers, Bart Vanhaesebroeck and Gavin Y. Oudit
Supervisor: Dr. Gavin Oudit

INTRODUCTION

Myocardial infarction (MI) is one of the leading causes of mortality and morbidity in the world. Being the majority of noncardiomyocytes in the heart, endothelial cells (ECs) participate critically in MI-induced cardiac remodeling via manipulating vascular functions. PI3K p110 α is an important downstream effector of vascular endothelial growth factor which critically regulates vascular formation, function, and maintenance. In this study, we aim to elucidate the in vivo implications of endothelial PI3K p110 α inactivation in ischemic hearts.

METHODS

Mice with endothelial p110 α inactivation (p110 α -Tie2) and their control littermate (p110 α Flx) receive tamoxifen (2 mg/mouse for 5 days, intraperitoneal injection) at 9 weeks old to induce kinase-dead p110 α expression in p110 α -Tie2 mice. Mice are randomly subjected to sham- or MI-operation at 12 weeks old. Cardiac function is assessed by echocardiography. Cardiac remodeling, including infarct size, hypertrophy, inflammation, and vascular density, is examined by triphenyltetrazolium chloride staining and immunofluorescence staining. Signaling pathways are assessed by Western blot.

RESULTS

PI3K p110 α and Akt signaling are enhanced in post-MI mouse hearts. Mice with endothelial p110 α inactivation have deteriorated cardiac function examined by echocardiography in comparison to control mice, with an increase of infarct size and myocyte hypertrophy and a decrease of cardioprotective phospho-Akt expression. Importantly, loss of endothelial p110 α enhances MI-triggered inflammatory cell infiltration and lowers myocardial vascular density and the number of proliferating ECs in the infarct and peri-infarct area, indicating the function of p110 α in post-MI inflammatory response and angiogenesis.

CONCLUSIONS

This study indicates that endothelial p110 α is required in post-MI repair to maintain cardiac function by regulating inflammation and angiogenesis.

Supervisor: Dr. Gavin Oudit

Novel non-viral RNA interference strategies targeting retinoblastoma protein for rescue and regeneration of peripheral axons

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¹Neuroscience & Mental Health Institute, University of Alberta

²Division of Neurology, University of Alberta

³Department of Medicine, University of Alberta

INTRODUCTION: Retinoblastoma (Rb1) is a tumor suppressor protein that acts as a cell cycle inhibitor through its interaction with E2F1. In previous work (Christie et al., Nat Commun, 2014), we identified its expression in peripheral sensory neurons and the impact of its knockdown on regeneration. Here we addressed whether two novel strategies for non-viral Rb1 siRNA delivery in two differing models of peripheral nerve damage had the ability to enhance recovery: (i) delayed Rb1 siRNA delivery to the hindpaw using electroporation and analyzing regeneration following a sciatic nerve crush; (ii) Intranasally-administered Rb1 siRNA in a mouse model of chronic type 1 diabetic neuropathy.

METHODS: Mouse models of injury and type 1 diabetes (STZ); Local hindpaw injections/ electroporation of Rb1 or scrambled siRNA over 2 weeks starting on D14 post-crush; Diabetic mice given Rb1 or scrambled siRNA intranasally for 3 weeks; Endpoints: electrophysiology, behaviour, footpad skin biopsies for axon counts; qRT-PCR, immunohistochemistry.

RESULTS: Twenty-eight days following nerve crush, thermal, mechanical, and electrophysiological testing did not reveal significant differences in recovery between the two cohorts, but recovery of thermal sensation between D14 and D28 was greater after Rb1 knockdown. Analysis of footpad biopsies showed that there was a significant increase in the number of axons crossing the dermal-epidermal junction in Rb1 siRNA-treated mice compared to mice receiving scrambled sequences. In diabetic mice with neuropathy, those treated with Rb1 siRNA had higher motor and sensory conduction velocities at endpoint, comparable to values in non-diabetics. Rb1, but not scrambled, siRNA also appeared to restore thermal sensitivity to baseline levels.

CONCLUSIONS. Suppression of Rb1 may enhance axon outgrowth and functional recovery of thermal sensitivity and nerve conduction velocity in models of peripheral nerve damage. These novel forms of siRNA delivery elucidate new avenues for experimental and therapeutic RNA interference. [Supported by CIHR, CDA, and ADI]

Renin-angiotensin system modules renal vascular conductance and resets renal blood flow autoregulation in response to acute renal venous pressure elevation

Xiaohua Huang¹, Shereen M. Hamza^{1,2}, William A. Cupples³, Branko Braam^{1,2}
Supervisor: Dr. Branko Braam

INTRODUCTION

Venous congestion-induced increased renal venous pressure (RVP) decreases renal blood flow (RBF). The renin-angiotensin system (RAS) is likely an important mediator of worsening kidney function at a high RVP. We hypothesized that acute RVP elevation increases vascular tone is due to endogenous angiotensin II (ANG II) and is abolished when ANG II is clamped and that increased RVP leads to reset of RBF autoregulation.

METHODS

Male Lewis rats (350-450g) received a regular sodium diet (n=18) were randomly assigned into groups: time control, increased RVP to 10mmHg or to 20mmHg. Endogenous ANG II was blocked using Enalapril infusion, where desired mean arterial pressure (MAP) was restored by continuous and constant ANG II infusion. To increase RVP, the left renal vein was partial occluded for 120 min following 60 min baseline. A separate group of rats (n=17) was used to access the RBF autoregulation. Renal perfusion pressure was decreased (-10, -20, -30, -40mmHg) by stepwise constriction of the suprarenal aorta every 5 min. The stepwise decrease was repeated with either native or increased RVP.

RESULTS

The hemodynamic impacts of mild RVP increase (from 0.9 ± 0.4 to 9.5 ± 0.7 mmHg) were fully prevented when ANG II was fixed. A major increased RVP (from 0.4 ± 0.3 to 19.5 ± 0.3 mmHg) induced MAP decline at the end of experiments ($\Delta -22.2 \pm 5.0$ mmHg, $P < 0.05$). The renal vascular conductance (RVC) reduction was completely abolished by the ANG II clamp ($\Delta 0.015 \pm 0.004$ ml/min. mmHg). Although ANG II clamped did not prevent the decrease of RBF ($\Delta -1.7 \pm 0.4$ ml/min, $P < 0.05$), it ameliorated the impact on ipsilateral GFR ($\Delta -0.55 \pm 0.19$ ml/min). RBF autoregulation was reset to a lower level of perfusion pressure when RVP was elevated.

CONCLUSIONS

RVP induced modulation of renal hemodynamics was attenuate when ANG II was fixed. This suggests a primary role for the RAS in the vasoconstriction induced by increased RVP. This is also supported by the reset of RBF autoregulation during an increased RVP.

Supervisor: Dr. Branko Braam

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A meta-analysis of the randomized clinical trials on the effects of supplemental oxygen therapy in patients with suspected acute myocardial infarction

Nariman Sepehrvand, Stefan James, Dion Stub, Ardavan Khoshnood, Justin A Ezekowitz, Robin Hofmann

Supervisor: Dr. Justin A. Ezekowitz

INTRODUCTION

Although oxygen therapy has been used for over a century in the management of patients with suspected acute myocardial infarction (AMI), recent studies have raised concerns around the efficacy and safety of supplemental oxygen in normoxemic patients. The aim of this study was to synthesize the evidence from randomized clinical trials (RCT) that investigated the effects of supplemental oxygen therapy as compared to room air in patients with suspected or confirmed AMI.

METHODS

Multiple databases were searched from inception to September 30th 2017. RCTs with any length of follow-up and any outcome measure were included if they studied the use of supplemental O₂ therapy administered by any device at normal pressure as compared to room air. An investigator assessed all the included studies and extracted the data. Outcomes of interests included mortality, troponin levels, infarct size, pain and hypoxemia.

RESULTS

Eight RCTs with a total of 7,998 participants (3,982 and 4,002 patients in O₂ and Air groups, respectively) were identified and pooled. In-hospital and 30-day death occurred in 135 and 149 patients, respectively. Oxygen therapy did not reduce the risk of in-hospital (OR, 1.11 [95%CI, 0.69 to 1.77]) (Figure) or 30-day mortality (OR, 1.09 [95%CI, 0.80 to 1.50]) in patients with suspected AMI and the results remained similar in the subgroup of patients with confirmed AMI. In the pooled analysis (n=5,957), O₂ therapy was not associated with any significant effect on troponin T levels (p=0.64). The infarct size (based on cardiac MRI) in a subgroup of patients was not different between groups with and without O₂ therapy. O₂ therapy reduced the risk of hypoxemia (OR, 0.29 [95%CI, 0.17 to 0.47]).

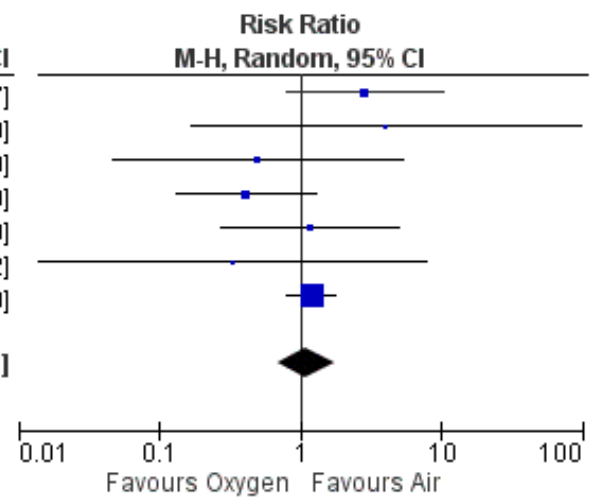
CONCLUSIONS

Although supplemental O₂ therapy is commonly used, it was not associated with important clinical benefits. These findings from 8 RCTs support departing from the usual practice of administering oxygen in normoxemic patients.

Supervisor: Dr. Justin A. Ezekowitz

| Study or Subgroup | Oxygen | | Air | | Weight | Risk Ratio |
|-----------------------|--------|-------------|--------|-------------|---------------|--------------------------|
| | Events | Total | Events | Total | | M-H, Random, 95% CI |
| Rawles 1976 | 9 | 80 | 3 | 77 | 12.0% | 2.89 [0.81, 10.27] |
| Ukholkina 2005 | 1 | 58 | 0 | 79 | 2.1% | 4.07 [0.17, 98.10] |
| Ranchord 2012 | 1 | 68 | 2 | 68 | 3.8% | 0.50 [0.05, 5.39] |
| Stub 2015 | 4 | 218 | 10 | 223 | 14.3% | 0.41 [0.13, 1.29] |
| Khoshnood 2016 | 4 | 85 | 3 | 75 | 9.3% | 1.18 [0.27, 5.09] |
| Heidari 2017 | 0 | 36 | 1 | 36 | 2.2% | 0.33 [0.01, 7.92] |
| Hofmann 2017 | 53 | 3311 | 44 | 3318 | 56.3% | 1.21 [0.81, 1.80] |
| Total (95% CI) | | 3856 | | 3876 | 100.0% | 1.11 [0.69, 1.77] |

Total events 72 63
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 6.88$, $df = 6$ ($P = 0.33$); $I^2 = 13\%$
Test for overall effect: $Z = 0.42$ ($P = 0.68$)



The effect of GSK-3B Inhibitor on Primary Biliary Cholangitis in NOD.c3c4 Mouse Model

Mohammed Sarhan , Kerolous Messeha , Andrew L. Mason
Supervisor: Dr. Andrew L. Mason

INTRODUCTION

Our lab has linked human betaretrovirus (HBRV) infection to primary biliary cholangitis (PBC) and found 98% genetic similarity between HBRV and mouse mammary tumor virus (MMTV) in NOD.c3c4 mice. In vitro studies showed that GSK-3B inhibitor (AR-A014418) has both antiviral & immune modulator effect. To investigate the effect of GSK-3B inhibitor AR-A014418 on autoimmune biliary disease (ABD), we treated NOD.c3c4 mice to assess the cellular immune response to AR-A014418. We hypothesize that GSK-3B inhibitors affect ABD in NOD.c3c4 via immunomodulation and possibly by an antiviral effect.

METHODS

NOD.c3c4 mice were divided into AR-A014418 treated (n=5) and control (n=10) at 8-week age. AR-A014418 was injected intraperitoneally at a dose of 1ml (0.1mg/kg) using phosphate buffered saline as a vehicle. Baseline and monthly alkaline phosphatase (ALP) were assessed by tail bleeds, and biophysical profile with body weight & activity were assessed weekly. At the end of the study, IL-10, IL-12 and other cytokines were assessed in sera by ELISA (Mesoscale).

RESULTS

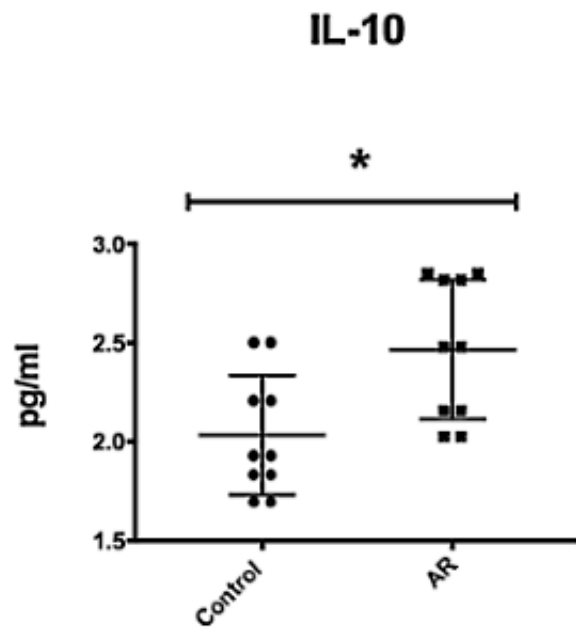
AR-A014418 treated mice showed a significant improvement of biophysical profile; increased body weight, with mean values of increase body weight in treated vs. controls (48.6 vs. 23.2, p 0.017). The mean percentage ALP reduction was significantly improved in treated vs. control NOD.c3c4 mice (-40 vs -54 IU/L, p 0.0005). The treated NOD.c3c4 mice demonstrated increased IL-10 production vs. control with mean values of secreted IL-10 (pg/ml)(2.47 vs. 2.03, p 0.025) and marked reduction of IL-12 vs controls with mean values of secreted IL-12 (pg/ml)(4.1 vs. 18.6, P 0.012).

CONCLUSIONS

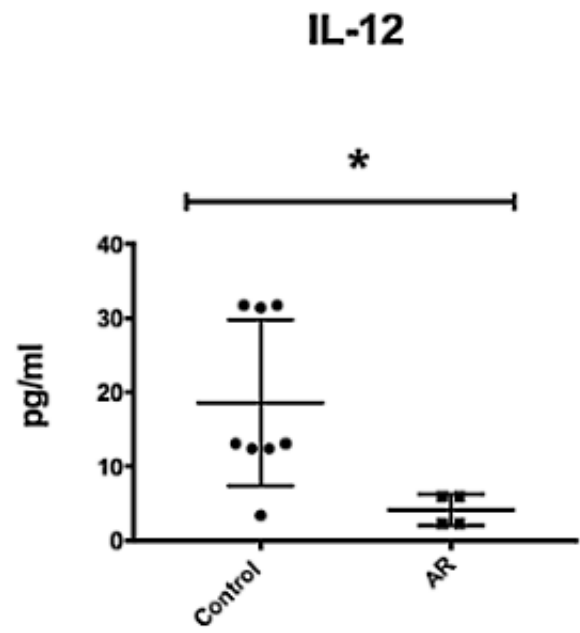
GSK-3B inhibitors demonstrated an improvement in hepatic biochemistry. It significantly reduced ALP and increased IL10 in treated animals, and diminished the proinflammatory cytokines. Our study uncovers a new treatment modality for PBC and may potentially set the stage for further studies on immunomodulatory treatment of PBC.

Supervisor: Dr. Andrew L. Mason

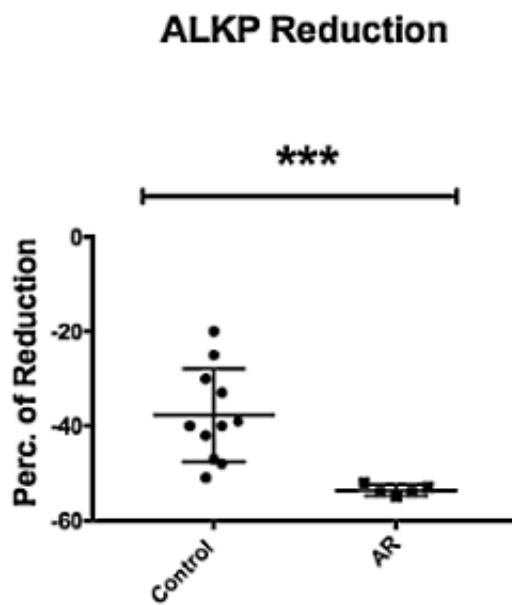
A.



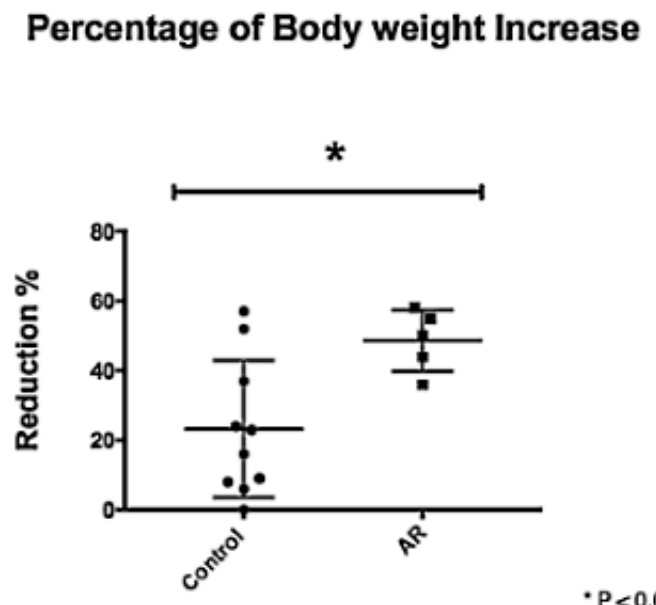
B.



C.



D.



* P < 0.001
** p < 0.0001

Methyl tags on selected mRNAs are needed for the acute translation of stress responsive proteins under major cellular stress

Bruno Saleme, Aristeidis Boukouris, Gopinath Sutendra, and Evangelos Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Methylation of Adenosine 6A is present in <1% of mRNAs, but its role remains elusive. We speculated that translation of proteins critical for acute response to major stress is prioritized and amplified, to optimize a timely response to threat. We hypothesized that methylation on selected mRNAs allows prioritized translation of Stress Response Proteins (SRPs), like chaperones and transcription factors p53 and ATF4, under major stress.

METHODS

RNA Dot blots, immunoblots, qRT PCR, immunofluorescence, S35 labelling, ribosome isolations, cellular fractionation, taxol-mediated microtubule assembly, and S35 labelling of newly synthesized proteins performed in human cell lines (A549, HFF-1).

RESULTS

Cellular stress (via DNA damage (i.e. Doxorubicin or UV) or nutrient deprivation (i.e. Methionine deprivation)) induces translation of transcription factors p53 and ATF4 within minutes (i.e. protein, but not mRNA levels increase). Decreasing mRNA methylation by chemical inhibition or siRNA knockdown of either methyltransferases or methyl-binding proteins, selectively decreases the induction of the SRPs only in stressed conditions, while translation of other proteins remains unaffected. Methylated mRNAs show compartmentalization within the cytoskeletal fraction of the cell, and associate with microtubules. Disruption of the microtubule network, even minutes before a stress, results in significant reduction of SRPs translation efficiency measured by antibodies and qRT-PCR, and S35 labelling. Lastly, methylated mRNAs show a significant shift to a cytoskeletal-associated ribosome pool minutes after a stress, suggesting acute translation of SRPs occurs within a unique pool of ribosomes.

CONCLUSIONS

While the importance of differential methylation of RNAs is yet to be determined, the fact that inhibition of mRNA methylation prevents the translation of SPRs and decreases the ability of cells to handle stress, suggests that this may be a previously unrecognized but fundamental feature of cellular stress response. The implications of this work are wide and include diseases where major stress (like acute ischemia) can be catastrophic within minutes.

Supervisor: Dr. Evangelos Michelakis

Evaluating the Conservative Kidney Management Pathway through the characterization of patient experiences using in-depth interviews - a qualitative study

Hussain, S. Davison, S.N.
Supervisor: Dr. Sara Davison

INTRODUCTION

The literature suggests that for patients with end-stage kidney disease who are frail with multiple comorbidities and poor functional status, dialysis may have limited, if any benefit and high treatment burden. Conservative kidney management (CKM) is a non-dialysis treatment option for elderly patients not wishing to pursue dialysis. Alberta recently launched an online CKM Pathway that standardizes CKM care and focuses on preserving kidney function, mitigating and actively managing disease symptoms and offering holistic psychosocial support to patients and families. This study aimed to characterize patients' and families' experiences with the pathway.

METHODS

A qualitative study was conducted to explore the nature and quality of care received by patients on the CKM Pathway through the kidney clinics in northern and central Alberta. Open-ended, semi-structured interviews were conducted to allow patients and families to give a detailed account of their experiences. Interviews were transcribed verbatim and thematic analysis was done using line-by-line coding and reported under COREQ guidelines.

RESULTS

Ten patient/family interviews were conducted with 16 participants. Three primary themes were identified: 1) CKM decision and values. Patients described their learning journey on choosing CKM and valued quality of life over survival. The education, support and the patient resources provided by the CKM Pathway were central to this process. 2) Impact of patient resources. Education materials were accessible, easily understood, and were particularly effective in symptom management and developing expectations around their care. 3) Community engagement. Patients and families often desired CKM care in their home community but were ambivalent about local providers' ability and willingness to provide CKM care. The CKM Pathway was viewed as a valuable tool to bridge this.

CONCLUSIONS

Patients were highly satisfied with their care using the CKM Pathway in kidney clinic settings. Future evaluations should focus on the CKM Pathway as utilized in community care settings.

Supervisor: Dr. Sara Davison

Monitoring Reperfusion During Endovascular Therapy

Jayne Kosior, Robert Wannamaker, Mahesh Kate, Brian Buck, Jeremy Rempel,
Kenneth Butcher
Supervisor: Dr. Kenneth Butcher

INTRODUCTION

Endovascular therapy (ET) is a highly effective treatment for acute ischemic stroke from large anterior circulation vessel occlusion. In some patients, however, clinical outcomes are poor despite successful recanalization. Little is known about the post-recanalization reperfusion characteristics that may or may not predict outcomes. The ability to monitor perfusion during ET procedures could provide a quantitative method for assessing treatment success in stroke trials, and may help to identify patients at risk of reperfusion injury, e.g., hemorrhagic transformation (HT). We developed a novel methodology, called DSA+, to quantitatively derive perfusion measurements from digital subtraction angiogram (DSA) data and investigated reperfusion following recanalization.

METHODS

DSA+ software compatible with our angiography suite was developed in C++. We retrospectively analyzed data from stroke cases treated with ET at our hospital. The primary outcome was HT on 24h computed tomography (CT). Infarct versus HT bolus arrival time (BAT) and mean transit time (MTT) measurements were compared using unpaired t-tests ($p < 0.05$).

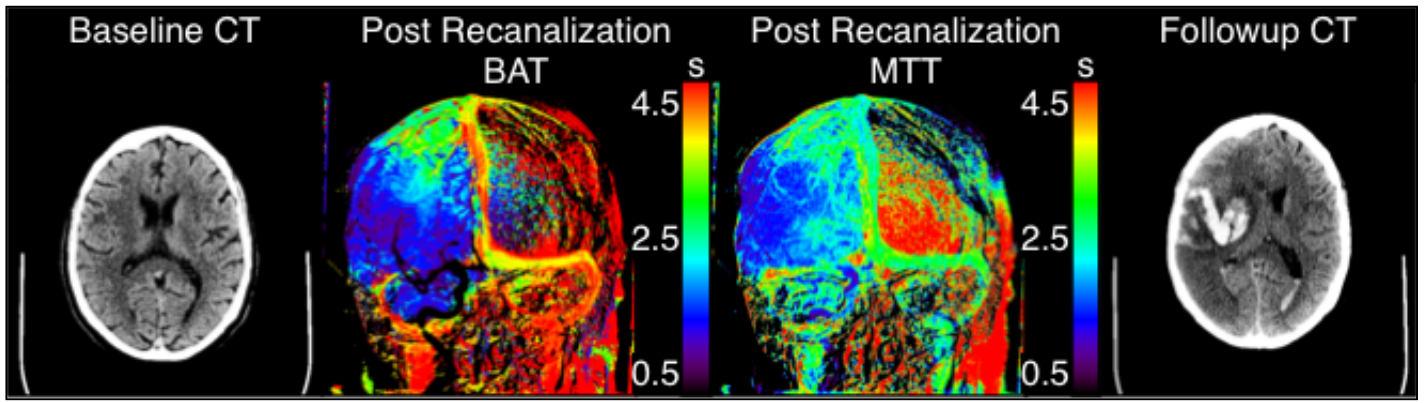
RESULTS

Perfusion maps were generated in 59 patients; 13 had HT. MTT in HT was significantly lower than infarct ($p = 0.01$; $2.1 \pm 1.1s$ vs $2.8 \pm 0.7s$). Eight cases demonstrated elevated MTT, despite successful recanalization. Figure demonstrates measuring reperfusion with DSA+: post-recanalization BAT and MTT maps indicated significant hyperperfusion ($< 2s$) in the region corresponding to the hemorrhage on followup CT.

CONCLUSIONS

Monitoring perfusion during ET procedures could be used to quantify reperfusion success in stroke trials, and to provide insights into reperfusion injury, which may lead to new therapeutic targets (e.g., blood pressure reduction in patients with post-recanalization hyperperfusion to prevent HT). With new guidelines from the Heart and Stroke Foundation of Canada expanding the role of ET, our innovation could see rapid translation into standard practice because it requires minimal changes to current protocols.

Supervisor: Dr. Kenneth Butcher



Mitochondrial regulation of PD-L1 in Pulmonary Arterial Hypertension - a novel mechanism

Mohammed S. Osman, Vikram Gurtu and Evangelos D. Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a deadly disease characterized by vascular remodeling and a cancer-like suppression of mitochondria resulting in resistance to apoptosis. The role of immunity in PAH is recognized but unclear. Patients/animals with PAH have an unexplained increased number of dendritic cells (DCs) perivascularly, and blunted killer cell functions. We hypothesized that suppression of mitochondrial function results in the induction of the inhibitory receptor, program death ligand-1 (PD-L1), a "do not kill/do not eat me" signal, which protects pulmonary artery smooth muscle cells (PASMCs) from recruited killer cells and DCs, respectively.

METHODS

We used human PASMCs derived from patients with PAH, lungs and/or PASMCs from mice lacking Ucp2 (Ucp2KO mice) which have suppressed mitochondrial function and spontaneously develop PAH; and lungs from monocrotaline(MCT)-injected rats (a standard PAH model). We measured PD-L1 expression using immunoblots and qRT-PCR and soluble PD-L1 using ELISA. We also measured PD-L1 in normal PASMCs treated with mitochondrial suppression signals (e.g. rotenone, antimycin A, or hypoxia).

RESULTS

PASMCs from patients with PAH, and rodent PAH lungs/PASMCs had a 2-3 fold induction of PD-L1 protein, but not mRNA levels. Soluble PD-L1 was also induced in the culture medium from both human PASMC (0.045 vs. 0.003 ng/ g protein, $P < 0.0001$) and hypoxic or Ucp2KO PASMCs, compared to controls. Direct mitochondrial inhibition resulted in a large and rapid (< 2 h) increase in PD-L1 levels.

CONCLUSIONS

Mitochondrial suppression, a well-established feature of PAH and cancer, directly increased PDL-1 levels probably by inhibiting its degradation. PD-L1 levels are significantly increased in human and rodent PAH models and may promote resistance to death from immune cells. Our studies may identify novel approaches targeting immune inhibitory receptors like PD-L1 in idiopathic and scleroderma-associated PAH, where standard immunosuppressive therapies have limited roles.

Supervisor: Dr. Evangelos Michelakis

A role for the p21 and p27 tumor suppressors in CNS axon regeneration

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Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.

INTRODUCTION: Retinal ganglion cells (RGCs) that extend optic axons within the CNS have highly limited regenerative capacity when injured. Regenerative failure in the RGCs might be attributed to a gradual decline in their intrinsic growth and the unfavorable extrinsic environment, which includes inhibitory molecules. Recent studies have identified roles for manipulating axon growth inhibitory molecules (PTEN/SOCS3) during optic nerve (ON) regeneration. Similarly, p21 and p27, well-known tumor inhibitory molecules, play a unique role in limiting cell proliferation. p21 and p27 inhibit proliferation by blocking cyclin-dependent kinase/cyclin complexes to mediate growth arrest and induce apoptosis. In this work, we were interested in the role of p21 and p27 in supporting the growth demands of RGCs during ON axon regeneration.

METHODS: Sprague-Dawley rats; ON crushed at 1mm distal to the globe for 10s using a surgical forceps; qRT-PCR and immunohistochemistry; siRNA to p21 or p27 or scrambled sequence siRNA into the vitreous chamber; Regenerating axons labelled with CTB (Cholera toxin B intravitreal).

RESULTS: Within the normal retina, both p21 and p27 had limited constitutive expression in NF200 (neurofilament) labeled RGCs. In control optic nerves, p21 and p27 were expressed largely in axons with limited colabelling in macrophages. Interestingly, both were more prominently expressed in injured distal and proximal ON stumps when compared to the control. Administration of siRNA by intravitreal injection directed to p21 was effective in knocking down its mRNA expression in the optic nerve. Early blinded counts of CTB labelled axons from the ON crush zone suggested enhanced growth in rats treated with p21 siRNA.

CONCLUSIONS: The tumor suppressors p21 and p27 are expressed in RGCs and ON. After crush, knockdown of p21 in the ON appears to enhance axonal regrowth. [Supported by CIHR, DoM, FoMD and UHF].

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Bleeding risk in cancer patients with venous thromboembolism

Sola Mansour, Ghazi Alotaibi, Cynthia Wu, Michael Sean McMurtry
Supervisor: Dr. Michael Sean McMurtry

INTRODUCTION

Cancer-provoked venous thromboembolism (VTE) is associated with significant morbidity and mortality. Cancer patients are at higher risk of both VTE recurrence despite anticoagulation and bleeding complications while on anticoagulation. There are some risk factors of bleeding specific to cancer patients established by some studies. We sought to assess the bleeding rates in cancer patients within one year of acute VTE over a ten-year period in Alberta, Canada and to identify whether cancer site affects these rates.

METHODS

Our population included all adult patients of Alberta diagnosed primarily with acute venous thromboembolism between April 2002 and March 2012. We categorized patients into cancer and non-cancer population and we measured the bleeding rates in both groups then stratify by cancer site within the cancer group. We used purposeful logistic regression to calculate odds ratios and identify some predictors of bleeding.

RESULTS

Of 5,158 cases of cancer-provoked VTE, 127 patients (2.46%) developed bleeding at some point within one year of VTE event compared to 441 of 26,498 cases in the non-cancer group (1.66%). The main site of bleeding was gastrointestinal (91.34%) and the main site of cancer associated with higher bleeding risk was gastrointestinal bleeding (OR 2.60; $p=0.03$). In terms of predictors of bleeding, the following risk factors contributed to the highest risk of bleeding: previous bleeding episode (OR 8.01; $p<0.001$), anemia (OR 5.72; $p<0.001$), liver disease (OR 2.2; $p<0.001$), alcohol use (OR 1.97; $p<0.001$) and hypertension (OR 1.28; $p=0.014$).

CONCLUSIONS

The frequency of bleeding was higher in cancer-provoked VTE and was different across cancer sites. Bleeding is still a big concern in cancer population and more efforts should be made to find the safest anticoagulant modality.

Supervisor: Dr. Michael Sean McMurtry

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Table1: Odds ratios of bleeding in patients with cancer stratified by cancer site along with the mean age and gender distribution

| Site of Cancer | n (%) | Odds ratio (95% CI) | p-value | Mean Age | Sex (females) |
|--------------------------------------------|------------|---------------------|---------|--------------|---------------|
| Colorectal cancer | 15 (11.81) | 1.13 (0.61-2.09) | 0.69 | 65.67 ± 2.66 | 4 (26.67) |
| Cancer of the small intestine | 1 (0.79) | 2.97 (0.37-23.79) | 0.30 | 57 ± 0.0 | 0 (0) |
| Hepatobiliary cancer | 10 (7.87) | 1.46 (0.67-3.18) | 0.35 | 62.1 ± 3.58 | 5 (50) |
| Gastric cancer | 7 (5.51) | 2.60 (1.09-6.19) | 0.03 | 73.29 ± 4.58 | 4 (57.14) |
| Lung cancer | 8 (6.30) | 0.66 (0.30-1.45) | 0.30 | 61 ± 3.79 | 2 (25) |
| Cancer of the kidney, bladder and prostate | 21 (16.53) | 1.46 (0.90-2.39) | 0.13 | 75 ± 2.75 | 2 (9.52) |
| Breast cancer in women | 4 (3.15) | 0.64 (0.23-1.77) | 0.39 | 63.5 ± 9.75 | 4 (100) |
| Endometrial cancer | 3 (2.36) | 1.25 (0.37-4.18) | 0.72 | 69.67 ± 5.78 | 3 (100) |
| Metastases | 36 (28.35) | 2.87 (0.54-15.18) | 0.21 | 62.94 ± 2.48 | 14 (38.89) |

Table 2: Incidence rates of bleeding in cancer compared to non-cancer associated VTE according to the bleeding site.

| Site of bleeding | Cancer-associated VTE | Non-cancer associated VTE | p-value |
|------------------|-----------------------|---------------------------|---------|
| | n (%) | n (%) | |
| GI bleed | 116 (91.34) | 407 (92.29) | 0.046 |
| GU bleed | 0 (0) | 3 (0.68) | 0.811 |
| IC bleed | 3 (2.36) | 19 (4.31) | 0.000 |
| Airways bleeding | 8 (6.30) | 12 (2.72) | 0.063 |
| Hemarthrosis | 0 (0) | 0 (0) | |

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High-cost users of acute care at the University of Alberta Hospital: A deeper dive into predictive patient and system factors

Dr. Arpita Gantayet, Pamela Mathura, Alexis Fong-Leboeuf, Natalie McMurtry, Julie Zhang, Dr. Finlay McAlister, Dr. Narmin Kassam
Supervisor: Dr. Narmin Kassam

INTRODUCTION

The unsustainability of current healthcare costs and challenges of an aging population have made it increasingly important to improve efficiency and efficacy in healthcare delivery. It has been observed in various settings that a small proportion of the population makes up for a large quota of health care utilization. In Alberta, 5% of the population accounts for 66% of healthcare use and costs (CFHI, 2015).

METHODS

The aim of this project is to reduce readmission rates in Internal Medicine patients by using a patient-centered approach. Our objective is to study high-cost users (HCUs) of acute care, identify targetable factors and design quality improvement projects to target modifiable factors. HCUs include patients at UAH with at least three admissions and cumulative length of stay of greater than 30 days. 124 such HCUs underwent chart review to analyze characteristics including social profile, community supports and comorbidities.

RESULTS

GIM accounts for 31% of high-user re-admissions, followed by surgical specialties (26%), GI (16%) and Hematology (15%). The social profile of HCUs emphasized the importance of community supports. 50% were dependent for ADLs, >50% received home care, 10% lived in LTC, 8% in supportive living and 5% had no fixed address. 89% appropriately reported a GP as their primary care contact. Chart reviews identified prominent comorbidities in HCU's and found that 77% of HCUs were prescribed ≥ 7 discharge medications. The LACE score was a good predictor of HCUs.

CONCLUSIONS

A unique interplay of patient and system factors influences re-admissions in high-users. Thus far, we have characterized the medical and social profile of these patients and will use the identified characteristics to develop a tool to predict high-users. We will subsequently design QI projects to target modifiable factors including community resource integration, disposition and medication reconciliation.

Supervisor: Dr. Narmin Kassam

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ATRIAL FIBRILLATION IN PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION: ONE YEAR OUTCOMES FROM A CANADIAN REGISTRY

Robinder S. Sidhu, Jay Shavadia, Erik Youngson, Jeffrey Bakal, Robert C. Welsh
Supervisor: Dr. Robert Welsh

INTRODUCTION

Atrial fibrillation (AF) in patients with acute ST elevation myocardial infarction (STEMI) complicates both acute reperfusion therapy, and long-term medical management. Prior studies have suggested that STEMI patients with prior AF have increased morbidity and mortality compared to those without AF. We aim to provide observations from real world clinical data in this high risk patient population.

METHODS

Data were collected using the Vital Heart Response registry (VHR). The VHR program is an integrated regional program for STEMI patients in Edmonton. Patient data from the VHR registry were linked to other administrative datasets to identify and group patients by those with AF (new or prior) or no AF. Patients with AF were then sub-divided into those discharged with/without oral anticoagulation (OAC). We then calculated risk scores for patients on presentation (including the GRACE, TIMI, CHADS2-VASC). We reported in hospital clinical events, followed by one year outcomes for ischemic (any ischemic event or stroke/TIA/systemic embolism) or bleeding events. Adjusted odds ratio was calculated using logistic regression models with TIMI risk score as continuous variable.

RESULTS

From 2006 - 2011, 3236 patients were hospitalized with STEMI. Ten percent had documented prior AF. These patients were more likely to be older with higher GRACE and TIMI risk scores and were less likely to undergo acute reperfusion therapy and suffered greater in-hospital adverse events, including death. On discharge, AF-STEMI patients were less likely to receive evidence based medications. The risk of stroke/TIA/systemic embolism as well as bleeding event was higher in the AF cohort. Despite a significant CHADS2-VASC score in most AF-STEMI patients, only 42% were discharged on oral anti-coagulation.

CONCLUSIONS

Our study from a real world registry outlines the poor outcomes of AF STEMI patients and the underutilization of evidence based therapies. Further data is needed to help clinicians identify patients at highest risk of ischemic versus bleeding events to guide therapies.

Supervisor: Dr. Robert Welsh

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EARLY DABIGATRAN TREATMENT AFTER ISCHEMIC STROKE DOES NOT RESULT IN HEMORRHAGIC TRANSFORMATION

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Supervisor: Dr. Ken Butcher

INTRODUCTION

Early anticoagulation after stroke in atrial fibrillation (AF) patients remains controversial, due to potential hemorrhagic transformation (HT). The safety of initiating dabigatran within 14 days of stroke is unknown, as these patients were excluded from phase III trials.

METHODS

We enrolled participants with AF and acute ischemic stroke/TIA (<14 days, NIHSS≤3) treated with dabigatran in a prospective, multi-centre open label cohort. CT scans prior to and 7 days after dabigatran initiation were assessed centrally for HT and graded using ECASS criteria (hemorrhagic infarct (HI) 1/2, parenchymal hemorrhage (PH) 1/2). The primary endpoint was symptomatic HT (parenchymal hematoma (PH) type 2 with an NIHSS increase ≥4) within 30 days of dabigatran initiation. Secondary outcomes included any PH at day 7 and recurrent ischemic stroke within 30 days of dabigatran initiation.

RESULTS

We enrolled 100 participants, 65 males, mean age 71.9±13.6 years and infarct volume 7.3±15.1 ml. Median (IQR) time from onset to first dabigatran dose was 2 (1-5) days, median NIHSS 1 (0-2). Pre-treatment HT was present in 4 patients (all HI1). Time to dabigatran initiation was correlated with infarct volume (r=0.61, P<0.0001). No patients developed symptomatic HT. Asymptomatic progression from HI1 to HI2 occurred in 1 patient on the day 7 scan. Asymptomatic HI1 developed in 6 patients. The only predictor of HT was infarct volume (OR=1.075 [1.023-1.130], P<0.004). Six of 7 (86%) patients with new HT/progression were functionally independent (mRS=0-2) at 30 days, which was similar to those without HT (87%, p=0.644). Recurrent ischemic events occurred within 7 days of treatment in 4 patients (3 strokes, 1 systemic embolus), and 50% of these patients were disabled at 30 days.

CONCLUSIONS

Early dabigatran treatment did not precipitate symptomatic HT after minor stroke. Early recurrent ischemic events may be clinically more important.

Supervisor: Dr. Ken Butcher

Two Cycles of Consolidation Chemotherapy are Associated with Similar Clinical Outcomes to Three Cycles in AML Patients with Favorable Risk Cytogenetics

Daniel L. Sawler, David Sanford, Donna Hogge, Joseph Brandwein, Irwindeep Sandhu and Lalit Saini
Supervisor: Dr. Lalit Saini

INTRODUCTION

Patients with core-binding factor acute myeloid leukemia (CBF-AML) when treated with standard anthracycline based induction and repeated cycles of high dose cytarabine (HiDAC) consolidation exhibit high rates of remission and overall survival. Early studies suggested that 3 or 4 cycles of HiDAC consolidation are superior to 1 cycle. The effects of 2 cycles, however, has not been investigated. In this study, we evaluated the impact of 2 cycles of consolidative chemotherapy on the outcomes of patients with CBF-AML.

METHODS

Prior to 2012 patients with CBF-AML in Edmonton were intended to receive 2 cycles of HiDAC consolidation following induction chemotherapy, however patients treated after 2012 were intended to receive 3 cycles of consolidation. Patients treated in Vancouver underwent similar induction and were always intended to receive three consolidative cycles. Pooled data was retrospectively analyzed for all CBF-AML patients treated in these centres between 2003-2017 using an intention to treat approach.

RESULTS

Overall, 108 patients were identified. Seventy-four patients (68.5%) were intended for 3 cycles of consolidation therapy and 34 patients (31.5%) for 2 cycles. There were no differences in baseline characteristics. Rates of hospitalization, bacteremias, ICU requirements, and deaths during consolidation were similar between the groups.

There was no significant difference in overall survival ($p=0.96$; Figure 1, 5-year OS 73% for the 2 cycle consolidation group v 71% for the 3 cycle consolidation group) or relapse-free survival ($p=0.61$; Figure 2, 5-year RFS 63% for the 2 cycle consolidation group v 57% for the 3 cycle consolidation group) within the two groups. Multivariate analysis revealed that patients age, cytogenetics, or transplantation in CR1 did not influence rates of overall survival or relapse-free survival between the two cohorts.

CONCLUSIONS

These data suggest that the use of 2 chemotherapy consolidation cycles compared with 3 does not diminish relapse-free survival or overall survival in patients with CBF-AML.

Supervisor: Dr. Lalit Saini

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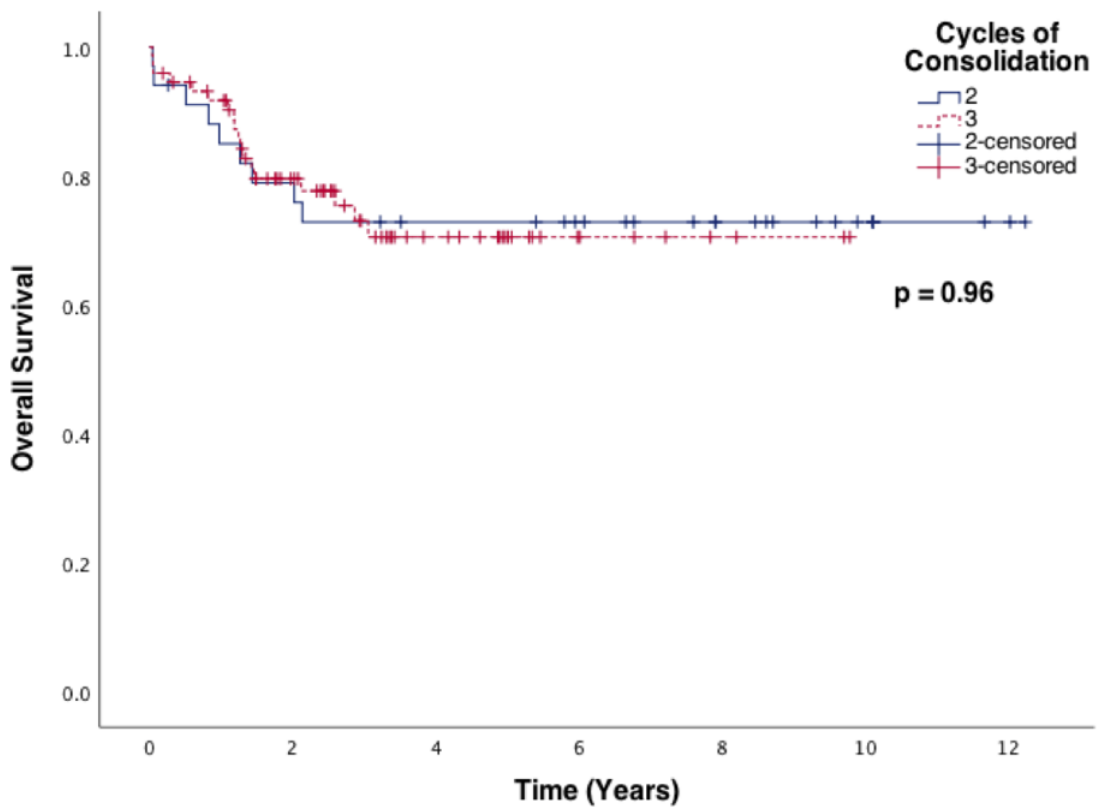


Figure 1. Overall survival of CBF-AML patients based on assignment to treatment with 2 cycles compared with 3 cycles of consolidation chemotherapy.

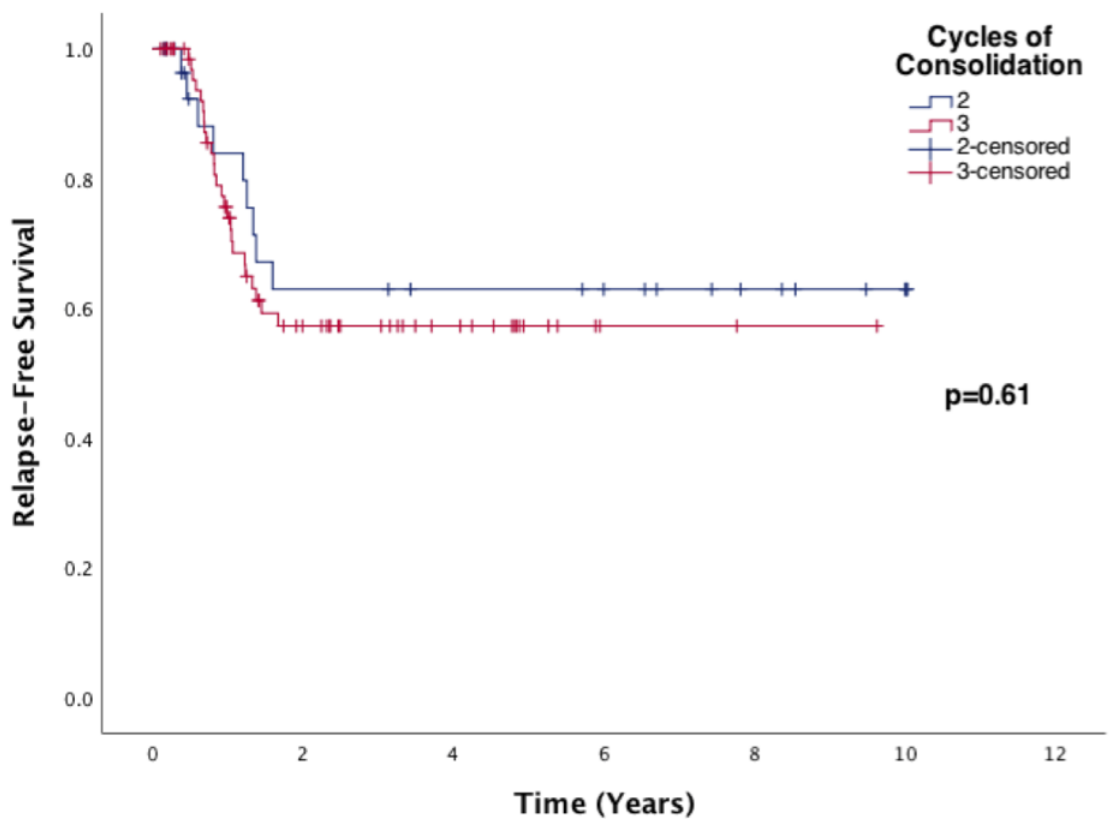


Figure 2. Relapse-free survival of CBF-AML patients based on assignment to treatment with 2 cycles compared with 3 cycles of consolidation chemotherapy.

Investigating the role of endothelial phosphatidylinositol-3-kinase (PI3K) beta in tumor angiogenesis

Abul K Azad, Andrew M Masoud, Pavel Zhabyeyev, Gavin Y Oudit, Ronald B Moore, Allan G Murray.

Supervisor: Dr. Allan Murray

INTRODUCTION

Drugs targeting VEGF-pathway have been approved to treat various cancer types. However, tumor may become resistance to anti-VEGF therapies due to involvement of multiple other signaling pathways. p110 β isoform of PI3 kinases is uniquely coupled to both receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs). Our published data showed that knockdown of p110 β in endothelial cells (EC) attenuates angiogenic sprouting and tip cell marker genes. These data indicate that p110 β is involved in angiogenic pathway. Therefore, we hypothesize that p110 β isoform of PI3K is involved in tumor angiogenesis.

METHODS

B16F10 cells (1×10^6) were implanted subcutaneously in p110 β Tie2/flx/flx or control (flx/flx) mice. Vehicle or sustained sunitinib (40mg/kg) treatment was initiated when tumor reached an average size of 200mm³, and mice were euthanized when tumor reached an average volume of 1000mm³. 2×10^5 B16F10 cells were injected intravenously in p110 β or control mice and were treated with vehicle or 40mg/kg sunitinib for 20 days. 60mg/kg pimonidazole was administered 1 hour before euthanization at day 21. Immunohistochemical analyses were performed for CD31-positive vessels and pimonidazole-positive tumor hypoxic areas.

RESULTS

EC-specific p110 β decreases the growth of B16F10 melanoma line in syngeneic mice after subcutaneous injection compared to the control mice. Similarly, EC p110 β loss decreases tumor metastases in the lung, and the overall tumor area in lung cross-section after tail vein injection. Further, B16F10 metastases had a marked decrease in CD31-positive microvessels in p110 β vs controls tumors. Surprisingly, pimonidazole-positive area in the tumors was normalized in p110 β Tie2/flx/flx vs control mice.

CONCLUSIONS

Our findings here demonstrated that EC-specific inactivation of p110 β decreases primary tumor growth and tumor metastasis accompanied by decreased tumor vasculature, but normalization of the tumor blood flow. Inhibition of endothelial p110 β may be useful as adjuvant therapy and may facilitate delivery and/or response of the tumor to conventional chemotherapy agents.

Supervisor: Dr. Allan Murray

Diabetes knowledge, self-care behaviours in Arabic-speaking adults with type 2 diabetes in Edmonton

Belag A, Alfaituri M, Abuoun H, Alkikhia L, Al Sayah F, Yeung R
Supervisor: Roseanne Yeung

INTRODUCTION

The number of Arabic-speaking immigrants in Canada is growing, as is the prevalence of diabetes in this minority population. Evidence of type 2 diabetes (T2D) knowledge and self-care management in the Arabic-speaking population in Canada is lacking. The objective of the study was to examine diabetes knowledge, self-care behaviours, and health outcomes in Arabic-speaking adults with T2D in Canada

METHODS

We performed a cross-sectional study in Edmonton, AB between July 2017 and January 2018. Data collection involved face-to-face interviews to complete an online survey via Research Electronic Data Capture (REDCap). The interviews were conducted in Arabic. Eligible patients from primary care networks and community centers in Edmonton were recruited. Our survey measured diabetes knowledge level (Michigan Diabetes Knowledge Test), self-care behaviours (Summary of Diabetes Self-Care Activities, SDSCA), medication adherence (Morisky medication adherence scale, MMAS8), and depression screening (Patient Health Questionnaire 2, PHQ-2).

RESULTS

A total of 114 individuals participated in this study. Mean age of participants was 57.6 ± 10.8 years and the majority were male (61.0%). The mean diabetes duration was 11.8 ± 8.6 years. The majority (71.9%) had a family history of diabetes. More than half of respondents reported having hypertension (58.8%) and dyslipidemia (54.4%). More than the half (52.5%) had an average score (7 to 11 points) on their diabetes knowledge, and 25.4 % scored poorly (<7 points). The worst domain for self-care behaviors was exercise (2.1 days/week). For those taking medication (34 %) had high medication adherence. One in five participants (19.3 %) screened positive for depression.

CONCLUSIONS

We found significant gaps in knowledge and self-care behaviours. The findings have implications for the implementation of culturally tailored interventions to enhance diabetes knowledge, self-care behaviors, and clinical outcomes.

Supervisor: Dr. Roseanne Yeung

Identifying intratumor heterogeneity in Mycosis fungoides using high throughput DNA sequencing

Aishwarya Iyer¹, Jordan Petterson², Weiwei Wong², Gane Wong² and Robert Gniadecki¹.

Supervisor: Dr. Robert Gniadecki

INTRODUCTION

Mycosis fungoides (MF) is a common extranodal T-cell lymphoma primarily arising in the skin. In early disease stages, MF presents as skin patches and plaques that in some cases may progress to tumour and disperse to lymph nodes and other internal organs. Early diagnosis is difficult as the histology overlaps with features of inflammatory skin diseases. Even when the diagnosis is established there are no prognostic markers that predict whether the disease will be aggressive or indolent. Lastly, there are no curative treatments and MF will invariably relapse even after aggressive chemotherapy. The disease is a diagnostic, prognostic and therapeutic challenge.

METHODS

The main objective of this study is to address the question of tumour heterogeneity in MF. To date, MF is considered to be monoclonal, derived from a transformed, mature memory T-cell. However, clinical observations and preliminary data suggest that MF comprises multiple subclones, which may be of importance for understanding of disease evolution and resistance to therapy. We plan to address this objective using Whole Exome Sequencing (WES) of MF tissue prepared by laser microdissection (LMD).

RESULTS

Patients with MF usually develop multiple lesions and it is not clear whether advanced lesions (tumours) develop by evolution from plaques or rather emerge from lymphoma precursor cells. Comparison of plaques and tumors based on genetic abnormalities (somatic mutations and copy number variations) revealed that except a single parental clone, tumors and plaques have an independent subclonal population.

CONCLUSIONS

This result provides us the first evidence intratumor heterogeneity at genomic level in MF.

Supervisor: Dr. Robert Gniadecki

The Impact of Advanced Care Planning in Idiopathic Pulmonary Fibrosis

Alia Daoud, Claveria Francisca, Emily Ainsley, Maged Haggag, Richman-Eisenstat
Janice, Meena Kalluri
Supervisor: Dr. Meena Kalluri

INTRODUCTION

We advocate advanced care planning (ACP) as a solution to poor acute end of life care. In 2012, we developed a multidisciplinary collaborative care model with an early integrated palliative approach to better document ACP and facilitate Idiopathic Pulmonary Fibrosis (IPF) patient wishes with respect to their care and death. We reviewed our clinic data to study the impact of ACP in IPF on the preferred location of death and on health resource utilization.

METHODS

We identified 38 deceased IPF patients. Extracted data from the EMR included: demographics, duration of clinic enrollment, ACP documentation including goals of care, preferred place of care and death, dyspnea management, actual place of death and number of hospitalizations.

RESULTS

The ACP-IPF model was implemented in 100% of deceased patients, with a median follow-up period of 17.5 months. Preferred place of death was home in 73.7% and hospice in 13.2%. Actual place of death was home or hospice in 74% with a concordance rate of 84.8%. On average 163 days were spent at home 6 months preceding death. 42% did not use acute care and only 16% needed 2 or more admissions. Opioids were initiated in 81.6%, an average of 150 days preceding death.

CONCLUSIONS

End of life care in IPF is marked by inadequate palliative care and increased acute care. We show that embedded within a multidisciplinary collaborative care model, ACP can be successfully implemented concurrently with routine clinical care to meet patient goals. The care design included early symptom self-management and timely coordination of needed multidisciplinary services to facilitate patient's preferences. This is the first study to show that ACP as part of routine IPF care can improve end of life care by allowing greater adherence to patient choices, early institution of symptom treatments and decreasing acute care utilization in IPF.

Supervisor: Dr. Meena Kalluri

Dual Specific Phosphatases (DUSPs) protect sensory axons

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INTRODUCTION: Polyneuropathy secondary to Diabetes mellitus (DPN) is a neurodegenerative disorder that targets sensory neurons. In some neuropathy models, it has been reported that MAP kinases including DLK promote progression of neuropathies and axonal degeneration. Here we study expression and potential roles, in peripheral neurons, of Dual Specific Phosphatases (DUSPs) that inactivate MAP kinases.

METHODS: DRG (Dorsal root ganglia) array analysis; experimental DPN and nerve injury; immunohistochemistry; adult sensory neuron cell growth analysis; qRT-PCR and Western immunoblots; confocal microscopy.

RESULTS: Two DUSP variants, DUSP1 (MKP1) and DUSP4 (MKP2) were upregulated in the DRGs of chronic diabetic mice as shown by microarray data in a long term chronic DPN model. We confirmed the expression of both DUSP variants in DRG neurons. Interestingly, sciatic nerve axotomy injury was associated with a trend toward the reduction of both DUSP1 and DUSP4 mRNA and protein in rat DRGs. Confocal data showed a decrease in both nuclear and cytoplasmic expression of DUSP. Either DUSP1 or DUSP4 siRNA *in vitro* knockdown decreased neurite outgrowth of adult sensory neurons, indicating an ongoing role for the protein in baseline outgrowth and plasticity. Next, we analysed neurite outgrowth in primary sensory neuron cultures exposed to capsaicin, normally toxic to adult sensory neurons in higher doses, and studied whether DUSP1 knockdown influenced their ability to withstand capsaicin axonopathy. DUSP1 knockdown was associated with greater specific capsaicin axon toxicity, indicating a constitutive protective role of the phosphatase in sensory neurons.

CONCLUSIONS: DUSPs are intrinsic sensory neuron proteins upregulated in chronic diabetes. Data to date suggests that they offer a constitutive role in supporting normal neuron plasticity and protect neurons from axonopathy. Strategies manipulating DUSPs or their partners may be among new molecular approaches to treat neuropathies.

[Supported by CIHR, Diabetes Canada, UofA DoM, UHF]

THE IMPACT OF ENDOSCOPIST CASE VOLUME ON COMPLICATIONS RELATED TO ERCP

Amit Dhillon, Jalisa Kassam, Sergio Zepeda-Gomez, Gurpal Sandha, Vince Bain, Aldo J. Montano-Loza, Richard Sultanian
Supervisor: Dr. Richard Sultanian

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a common interventional procedure used to diagnose and treat a variety of hepatobiliary and pancreatic conditions. ERCP has transitioned from a diagnostic test to a therapeutic intervention. Previous studies have demonstrated that high volume endoscopists (HVE; >75 ERCP /year) have lower complications compared to low volume endoscopists (LVE), despite performing more complex procedures.

The aim of our study was to determine if this strategy resulted in improved ERCP outcomes at our centre.

METHODS

A retrospective chart review of all ERCPs completed between 2014 - 2016, collecting data on cannulation success rate, ERCP complexity score, and any significant post-ERCP complications. These results were compared to ERCP patient outcomes performed between 2010 - 2012.

RESULTS

Successful cannulation was achieved in 92.5% for the HVE group, in comparison to 89.8% for the MVE group, overall success rate was 89.2% in the HVE group versus 86.7% for the MVE group.

Once adjusted for ERCP complexity, the OR for successful cannulation was 1.32, successful completion of the procedure 1.32. Trend toward lower overall complication in the HVE (6.8%) compared to the MVE (8.4%) group. Bleeding rates in the HVE rates were 0.1%, while the mixed group 2.6%. Perforation rates in the HVE rates were 0.2%, while the mixed group 0.6%. Post-ERCP pancreatitis rates was not different for the HVE and MVE groups.

CONCLUSIONS

The overall success and complication rate of ERCP at our centre was significantly improved by limiting ERCP to be performed by select HVE. Adverse events specifically bleeding and perforation rates were lower when completed by HVE. While this data only reflects the experience at a single centre, transitioning complex care of ERCP patients to expert facilities performing HVE may result in improved patients outcomes.

Supervisor: Dr. Richard Sultanian

Lower Blood Pressure is not Associated with Decreased Perfusion in Patients with Intracerebral hemorrhage

Ana C. Klahr, Jayme C. Kosior, Dariush Dowlathshahi, Brian Buck, Laura Gioia, Hayrapet Kalashyan, Alan Wilman, Thomas Jeerakathil, Kenneth Butcher
Supervisor: Dr. Ken Butcher

INTRODUCTION

Acute hypertension management in intracerebral hemorrhage (ICH) remains an area of clinical equipoise. Subacute perfusion seems to be unrelated to systolic blood pressure (SBP). Arterial Spin Labelling (ASL) is a magnetic resonance imaging (MRI) technique that measures cerebral blood flow (CBF) without a contrast agent, making it suitable for serial measurements. We assessed CBF in ICH patients using ASL and tested the hypothesis that subacute and late perfusion is related to SBP.

METHODS

Patients with computed tomography scan confirmed ICH were assessed with ASL at 48 hours, 7 and 30 days post ICH. Regions of interest (ROIs) included the perihematoma, hemisphere, internal and external borderzones, and the perilesion area surrounding diffusion-weighted imaging (DWI) hyperintensities remote from the hematoma. The perihematoma region was defined using co-registered susceptibility weighted images to delineate the hematoma border. Relative CBF (rCBF) was calculated as a ratio of the ipsilateral to contralateral ASL measurements.

RESULTS

Twenty-patients (65% male, mean age \pm SD= 68.50 \pm 12.72) were imaged with ASL at 48 hours (N=12), day 7 (N=6), and day 30 (N=11). Median (IQR) acute hematoma was 13.07 (6.28, 19.28) ml and mean acute SBP was 185.40 \pm 25.53. We did not find that SBP at the time of the scan predicted a decrease in rCBF in any of the ROIs. Higher SBP at 48 hours was related to a slight decrease in hemispheric in rCBF ($p=0.020$). Relative CBF did not differ among timepoints in any of the ROIs region ($p\geq 0.097$). We found both hyper and hypoperfusion surrounding DWI lesions (N=4).

CONCLUSIONS

Perfusion in the regions of interest was not decreased by lowered SBP. This is the first study to show serial measurements of perfusion up to 30 days after ICH using ASL, which is a great tool for CBF assessment, particularly in patients with MRI evidence of ischemia.

Supervisor: Dr. Ken Butcher

Trends in Asthma Epidemiology in Alberta

Ana-Maria Bosonea, Dean Befus, Harissios Vliagoftis, Heather Sharpe, Larry Svenson, the Asthma Working Group, Respiratory Health Strategic Clinical Network, and the Alberta Strategy for Patient Oriented Research Support Unit (SPOR).

Supervisor: Dr. Dean Befus

INTRODUCTION

According to Statistics Canada in 2014, 8.1% of Canadians aged 12 and older reported having asthma diagnosed by a health professional; there were an estimated 274,661 persons with asthma in Alberta. Most epidemiological studies of asthma estimate prevalence and incidence using survey-based data, which has a high rate of differential recall bias and may miss substantial portions of a population. The Ontario Asthma Surveillance Information System (OASIS) group uses provincial health databases and a validated asthma definition: two or more ambulatory care visits and/or one or more hospitalization(s) for asthma in two years. In Alberta, there are studies using provincial databases, but, most of these studies are restricted to ER visits and do not represent the entire asthma population. We used extensive health databases and the same validated definition for asthma as OASIS to investigate and report on province-wide asthma prevalence, incidence and mortality from 1995 to 2015.

METHODS

Data from several administrative databases, provided by Alberta Health, was used for longitudinal data analysis to determine age and sex specific prevalence, incidence and mortality of the asthma population. The population cohort is all individuals residing in the province of Alberta, ages 0 to 99 from 1995-2015.

RESULTS

The age-standardized incidence of asthma in Alberta has decreased from 0.95/100 females and 0.87/100 males in 2000 to 0.69/100 females and 0.65/100 males in 2015. The prevalence increased over the last 15 years for both genders from 8.15/100 females and 7.46/100 males in 2000 to 12.15/100 females and 11.57/100 males in 2015. All-cause mortality is higher in asthmatics versus the non-asthmatic population. For example, in 2015 the all-cause mortality in asthma patients was 1127.86/100,000 compared to the non-asthma population at 790.93/100,000.

CONCLUSIONS

We have shown that the incidence of asthma is decreasing in both females and males and that prevalence continues to increase. All-cause mortality in asthma patients is higher than in non-asthmatics.

Supervisor: Dr. Dean Befus

Intracranial vascular involvement in Takayasu's arteritis: common or not?

Andrea Johnson, Derek Emery, Elaine Yacyshyn, Alison Clifford
Supervisor: Dr Alison Clifford

INTRODUCTION

Takayasu's arteritis (TAK) is large vessel vasculitis of unknown etiology, resulting in arterial stenoses, occlusions, and aneurysms. Although it is well-documented that extra-cranial vascular lesions frequently develop in TAK patients in the absence of clear clinical signs, the development of intracranial lesions is believed to be uncommon.

METHODS

We aimed to review the existing literature regarding intracranial disease in TAK. A PubMed search was performed, to identify papers reporting intracranial vascular involvement in TAK patients.

RESULTS

Forty-one published case reports or case series were identified that described the presence or absence of intracranial vascular lesions in TAK patients. Forty reports relied on the use of imaging modalities, and 1 was an autopsy case report. Imaging methods varied widely, and included transcranial Doppler, computerized tomography angiography (CTA), magnetic resonance angiography (MRA), positron emission tomography (PET), or conventional angiography. Excluding single case reports, of a total of 270 TAK patients, 126 had an evaluation (either radiographic or histopathologic) of the intracranial arteries. Vascular structural changes of the intracranial arteries were identified in 36 patients, or 13.3% overall (range 5-100%.) The majority of papers relying on imaging data were performed retrospectively, with the exception of a single study, which identified lesions in 5 of 21 (24%) consecutively evaluated TAK patients, with or without neurologic symptoms, using MRA or transcranial Doppler. The single autopsy study described a 20 year old TAK patient with widespread histological evidence of vasculitis throughout the intracranial arteries.

CONCLUSIONS

The reported frequency of intracranial vessel involvement in TAK is highly variable, but may be more common than previously suspected. Numbers likely vary due to reporting bias, patient selection, and the type of imaging performed. Gaining an improved understanding of the true frequency of intracranial involvement will be important to aid in appropriately monitoring these young patients.

Supervisor: Dr Alison Clifford

Prion Disease Attenuation by Designed Mobile Genetic Elements

Andrew R. Castle, Serene L. Wohlgemuth, David Westaway
Supervisor: Dr David Westaway

INTRODUCTION

Prion diseases are fatal neurodegenerative disorders that afflict humans, livestock and wild herbivores. Importantly, prion disease susceptibility can be eliminated by knocking out the Prnp gene, which encodes the cellular prion protein (PrPC). Given that loss of PrPC expression is generally well-tolerated, we aim to create a transposable genetic element able to spread a null allele among a population via CRISPR/Cas9 gene editing. Such an approach could confer resistance to affected animal species and would reduce the risk of zoonotic transmission. As a proof-of-principle, we are performing a series of experiments to develop and validate the genetic construct using rodent models.

METHODS

Murine Prnp-targeting guide RNA (gRNA) sequences were selected using a CRISPR design algorithm (crispr.mit.edu) and cloned into the eSpCas9(1.1) vector that can drive cellular expression of both Cas9 and the gRNA. The plasmids were transfected into stable, murine PrPC-expressing RK13 cells and fluorescence-activated cell sorting was used to enrich for cells with reduced PrPC expression. Cas9-induced indels were detected using a T7E1 mismatch cleavage assay. In parallel, Cas9/gRNA complexes were delivered into fertilised mouse oocytes and the pups obtained were screened for Prnp disruptions by sequencing and T7E1 assay.

RESULTS

Preliminary cell experiments suggested some functionality for the chosen gRNAs but the data were inconclusive. However, following the failure of a microinjection approach, an attempt at electroporating a Cas9/gRNA complex into fertilised oocytes resulted in 3 of 5 viable pups carrying heterozygous mutations in Prnp.

CONCLUSIONS

Our results show that we can disrupt the Prnp coding sequence in vivo; therefore we are now starting to assemble the transposable genetic element, which will ultimately encode a fluorescent reporter protein and all the elements of a CRISPR/Cas9 system. The inclusion of a germline-specific promoter for Cas9 will enable transposition of the construct in the germline via homology-directed repair following Cas9-induced cleavage of Prnp.

Supervisor: Dr David Westaway

Characterization of the role of Apelin in injury repair of the Chronic Allograft Vasculopathy in Mouse heart allografts

Andrew Masoud 1, Maikel Farhan 2, Abul K Azad 1, Jiaxin Lin 3, Lin Fu Zhu 3, Gavin Y Oudit 4, Colin Anderson 3 and Allan G Murray 1

Supervisor: Dr. Allan Murray

INTRODUCTION

Heart transplantation is the mainstay treatment for end-stage cardiac patients. Unfortunately, chronic allograft vasculopathy (CAV) limits long-term graft survival, causing mortality beyond the 1st year of transplantation. CAV develops as a maladaptive repair response to the injured endothelial cells (ECs) lining coronary arteries and microvasculature, developing obliterative arterial intimal expansion, micro-vessel injury, decreased blood supply and graft failure.

Apelin (APJ receptor-ligand), a novel peptide (77 amino acids) encoded on the X chromosome, participates in vascular repair from myocardial infarction and kidney glomerular microvascular injury. We hypothesize that Pro-reparative cues (e.g. Apelin) attenuate graft arterial endothelial injury, and subsequent maladaptive repair. Minor antigen-mismatched heart allografts were used to evaluate CAV.

METHODS

CAV was induced via transplanting Apelin-/y (knockout) or Apelin+/y (wild type) hearts into females to elicit a HY-minor histocompatibility antigen-directed, cell-mediated allo-immune response against the male donor hearts. Heart grafts were harvested two or six weeks after transplantation. We characterized intima area, endothelial loss in medium to large-sized arteries, inflammatory cellular infiltration, microvascular density and proliferation.

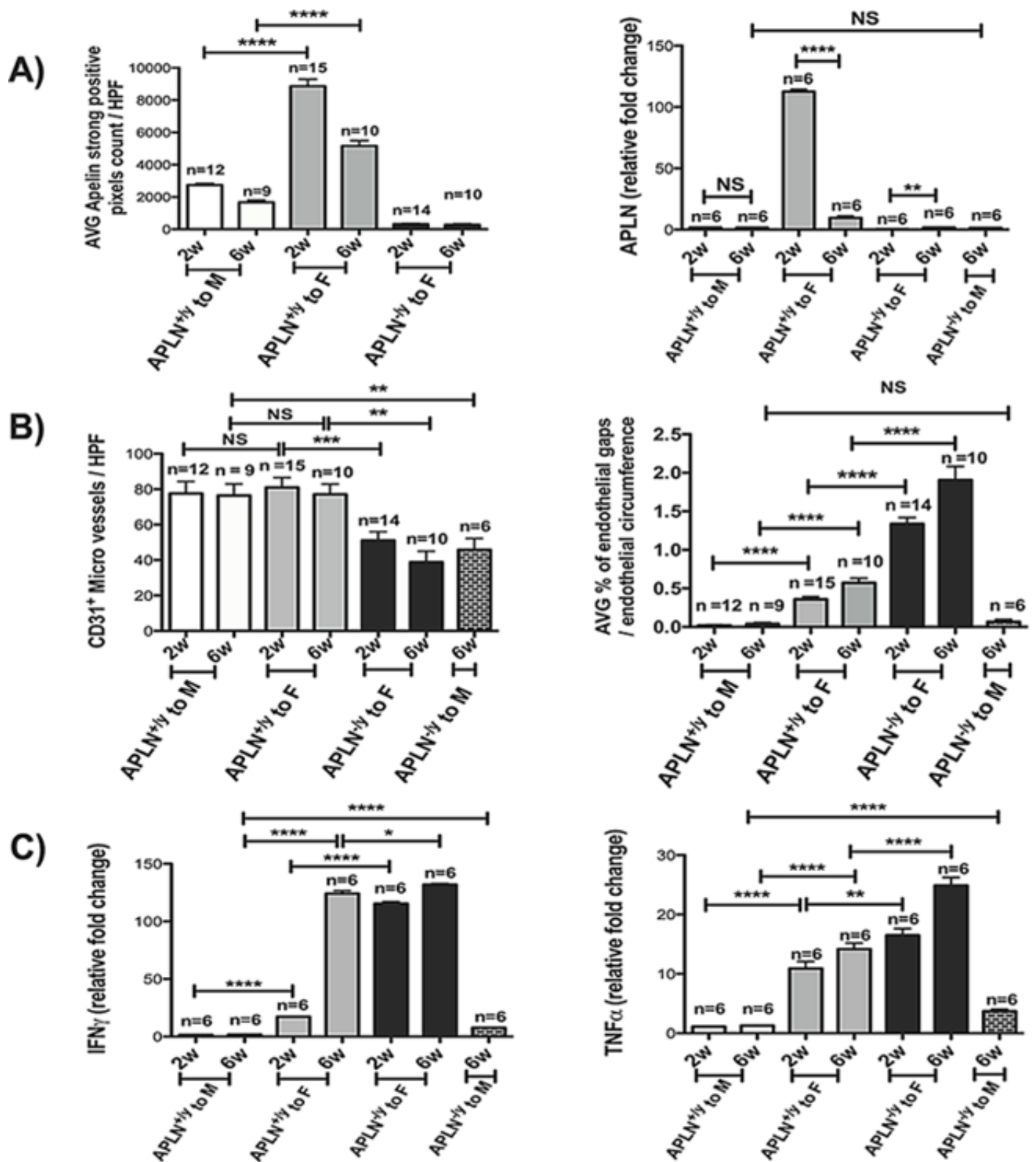
RESULTS

Increased Apelin expression at early time point (2 weeks) following heart transplantation. Apelin-/y hearts showed increased circumference area of endothelial loss (1.337 ± 0.08253 vs 0.3564 ± 0.03327 ; 1.906 ± 0.1767 vs 0.5721 ± 0.05901 ; $P < 0.0001$), intima expansion in conduit arteries (6 weeks), decreased microvessel density (2 and 6 weeks), decreased proliferation and enhanced inflammatory cellular infiltration when compared to controls.

CONCLUSIONS

We conclude that Apelin is induced following heart transplantation; loss of Apelin exacerbates endothelial damage, microvascular rarefaction, an inflammatory cellular infiltrate (2 weeks) and CAV.

Supervisor: Dr. Allan Murray



A) Quantification of the average Apelin staining/HPF & qPCR APLN.
 B) Quantification of endothelial gaps & microvasculature density.
 C) IFN γ & TNF α qPCR. Scale bar = 50 μ m. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001, NS= non significant by Student's t-test.

Effect of kainic acid on APP processing in astrocytes

D. Ourdev (1, 2), A. Schmaus (3, 4), S. Kar (1-4)

Supervisor: Dr. Satyabrata Kar

INTRODUCTION

Kainic acid (KA) is a non-degradable analog of the excitatory neurotransmitter glutamate that, when injected systemically into adult rats, can trigger seizures and progressive neuronal loss in a manner that mirrors the neuropathology of human mesial temporal lobe epilepsy (mTLE). However, biomolecular mechanisms responsible for the consequential neuronal loss remains elusive. We have recently reported that toxicity induced by KA can partly be mediated by astrocyte-derived amyloid β (A β) peptides, which are critical in the development of Alzheimer's disease (AD). Nonetheless, very little is known how KA can influence amyloid precursor protein (APP) levels and processing in astrocytes. Thus, in the present study using human U373 astrocytoma and rat primary astrocytes, we evaluated the role of KA on APP metabolism that can regulate the production/secretion of A β peptides.

METHODS

The U373 human astrocytoma cell line, as well as primary rat hippocampal astrocytes were used. Experiments included Western blotting, immunocytochemistry, MTT cell viability assays, as well as ELISA for A β 1-40 and A β 1-42, and secretase activity assays.

RESULTS

We show that KA treatment increased the levels of the APP holoprotein and its cleaved products (α -/ β -CTFs) in cultured U373 astrocytoma and primary astrocytes, without altering the cell viability. The cellular and secretory levels of A β 1-40/A β 1-42 were found to be markedly increased in KA-treated astrocytes. Steady-state levels of APP-secretases were not altered, but the activity of γ -secretase is significantly enhanced in KA-treated U373 astrocytoma. Furthermore, using selective receptor antagonists, we showed that the effects of KA are mediated by activation of glutamatergic kainate receptor and not NMDA or AMPA receptors.

CONCLUSIONS

These results suggest that KA can activate its own receptor and enhance amyloidogenic processing of APP leading to increased production/secretion of A β -related peptides from activated astrocytes. This may contribute to the development of pathological features associated with temporal lobe epilepsy.

Supervisor: Dr. Satyabrata Kar

A Prospective Cohort Study of Heart Disease in Patients with Muscular Dystrophy: Impact of a Multidisciplinary Care Approach

Anish Nikhanj, Haran Yogasundaram, Bailey Miskew Nichols, Padma Kaul, Ian Paterson, Cecile Phan, Zaeem Siddiqi, Gavin Y. Oudit
Supervisor: Dr. Gavin Oudit

INTRODUCTION

Heart disease is underestimated in patients with muscular dystrophy (MD). Dystrophinopathies, limb-girdle muscular dystrophy (LGMD), type 1 myotonic muscular dystrophy (DM1), and facioscapulohumeral muscular dystrophy (FSHD) are the major types of MD. The purpose of this study was to: 1) Determine the clinical burden of care for patients with MD, focusing on major adverse cardiac events (MACEs); 2) Determine the clinical benefits of a multidisciplinary care approach for the heart disease in these cohorts.

METHODS

Three main clinical aspects of MD patients were tracked: 1) Patient medical examination at the Neuromuscular Multidisciplinary (NMMD) Clinic; 2) Patient cardiac-specific biomarkers, electrocardiogram (ECG), and cardiac diagnostic imaging; 3) Patient clinical outcome data to evaluate disease progression and healthcare burden (outpatient clinic visits and duration of hospitalization).

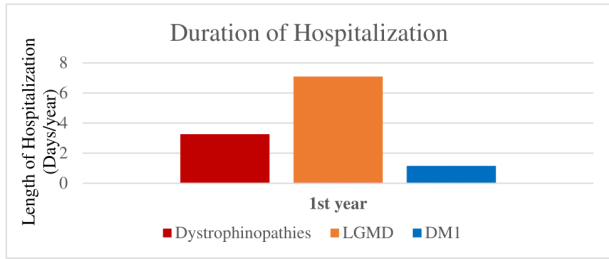
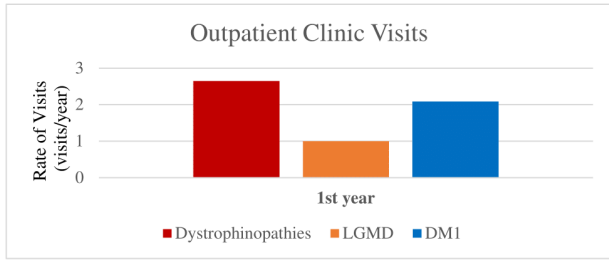
RESULTS

MD patient cohort tracking revealed a high incidence of MACEs, accompanied by a high prevalence of respiratory comorbidities. Cardiac diagnostic imaging allowed for diagnoses of dilated cardiomyopathy (DCM) in 60.6% of the Dystrophinopathies patients (n=33) and 30% of the LGMD patients (n=30). Conduction abnormalities were common in DM1 patients: atrioventricular conduction block in 31.3% of patients; and left bundle branch block (LBBB) in 22.9% of patients (n=48). Enrolment in the NMMD clinic, with associated access to device therapies (CRT pacemakers and ICD) and uptitration of medical therapy, resulted in a decrease in MACEs and partial reversal of adverse cardiac hypertrophy remodeling demonstrated by reduced volumes. A dramatic decrease in outpatient clinic visits was evident in the Dystrophinopathies cohort at: 2.65 to 0.55 visits/year. Days of hospitalization were sharply reduced in the Dystrophinopathies and LGMD cohorts at: 3.26 to 0.47 days/year, and 7.10 to 1.30 days/year, respectively.

CONCLUSIONS

This novel prospective study demonstrates the high prevalence of heart disease in patients with MD, and the benefits of a multidisciplinary approach to improve patient management and dramatically improve clinical outcomes.

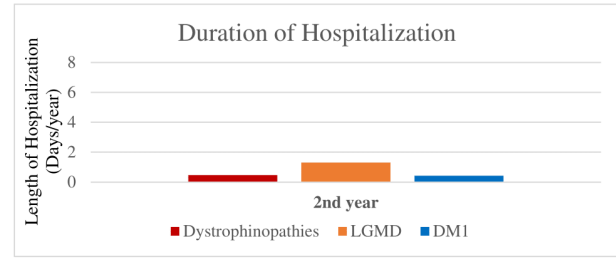
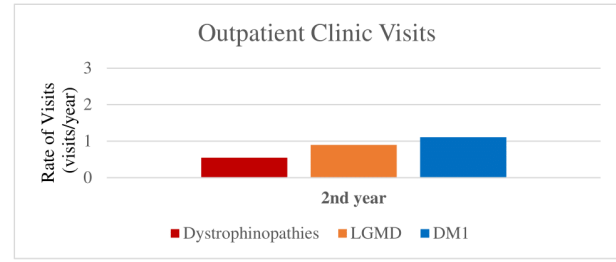
Supervisor: Dr. Gavin Oudit



Multidisciplinary Clinic Visit



Multidisciplinary Care Intervention



Unintended consequences of standardized order sets: An intervention to reduce unnecessary routine testing on a cardiology ward

ANTONIA BARNES, MD, MBA, JENNER LAKUSTA, MSc, MIRIAM SHANKS, MD, FRCPC, SEAN VAN DIEPEN, MD, FRCPC, GLENDA WILLIAMS, BScN, RN and JONATHAN CHOY, MD, MBA, FRCPC

Supervisor: Dr. Jonathan Choy

INTRODUCTION

INTRODUCTION: Excessive laboratory testing is not benign and has been linked to hospital-acquired anemia. Choosing Wisely Canada recommends that physicians should not order repeated basic laboratory tests if these measures are stable, as reduced use of these tests has been shown to be safe and result in significant cost savings. On the cardiology ward at our institution, daily routine laboratory tests and electrocardiograms (ECGs) are routinely ordered via standardized orders without a stop date.

METHODS

METHODS: We designed an intervention to limit extended repetitive use of routine laboratory tests and ECGs. The standardized order set used for patients moving from the coronary care unit (CCU) to the cardiology ward was altered such that the checkbox for a daily ECG was removed and daily routine laboratory tests could only be ordered for 3 days before a repeat order would be required. Charts of patients transferred from the CCU to the ward both before (n = 92) and after (n = 96) the new transfer order forms were put in place were reviewed.

RESULTS

RESULTS: Patients in the “before” group were over 10 times more likely to have a daily routine ECG than those in the “after” group ($p < 0.0001$). Patients with lengths of stay greater than 3 days in the “before” group were 20 times more likely than those in the “after” group to have an order for daily routine laboratory tests extending beyond 3 days ($p < 0.0001$). These effects were over and above those of other variables such as age, gender, and comorbidity score.

CONCLUSIONS

CONCLUSIONS: Assuming similar patient volumes and lengths of stays to those seen during this study, this cardiology ward could achieve cost savings of approximately \$74,000 on routine laboratory testing and \$53,000 on routine ECG by the use of the altered transfer order forms over a 12 month period.

Population-Based Study of Ambulance Use and Health Outcomes for Patients Presenting to the Emergency Department with a Primary Diagnosis of Syncope

Arjun K Gupta, Dat Tran, Robert S Sheldon, Padma Kaul and Roopinder K Sandhu
Supervisor: Dr Roopinder K Sandhu

INTRODUCTION

Emergency Department (ED) visit for syncope is common. However, whether syncope patients are more likely to arrive by ambulance or self-present, and if the mode of arrival modulates patient outcomes is unknown. We examined the rate of ambulance use among syncope patients and compared outcomes between ambulance users and self-presenters.

METHODS

All patients > 18 years presenting to the ED with a primary diagnosis of syncope in Alberta, Canada, between April 2007 to March 2014 were identified for mode of arrival. Outcomes included 30-day mortality, revisits to the ED and re-hospitalization.

RESULTS

Among 48,506 syncope patients presenting to the ED, 50.1% arrived by ambulance. The rate of ambulance use decreased by 3% annually ($p < 0.001$). Compared to patients who self-presented, patients arriving by ambulance were older (61.0 ± 2.17 versus 46.2 ± 21.0 , $p < 0.001$), more likely male (47.7% versus 44.4%, $p < 0.001$) and had a significantly higher comorbidity burden ($p < 0.001$). There was no comorbidity in 67.8% of ambulance users and 80.3% of self-presenters ($p < 0.001$). Ambulance users were more likely to be admitted to hospital (20.2% versus 9.1%, $p < 0.001$) and had significantly higher mortality ($p = < 0.001$) and re-hospitalization rates but fewer re-visits to the ED compared to self-presenters (Figure 1).

CONCLUSIONS

Patients presenting to the ED with syncope were equally likely to arrive by ambulance or self-present. Ambulance users were sicker, which likely accounts for the higher rates of adverse outcomes. However, two-thirds were without comorbidity and future interventions aimed at this group may reduce use.

Supervisor: Dr Roopinder K Sandhu

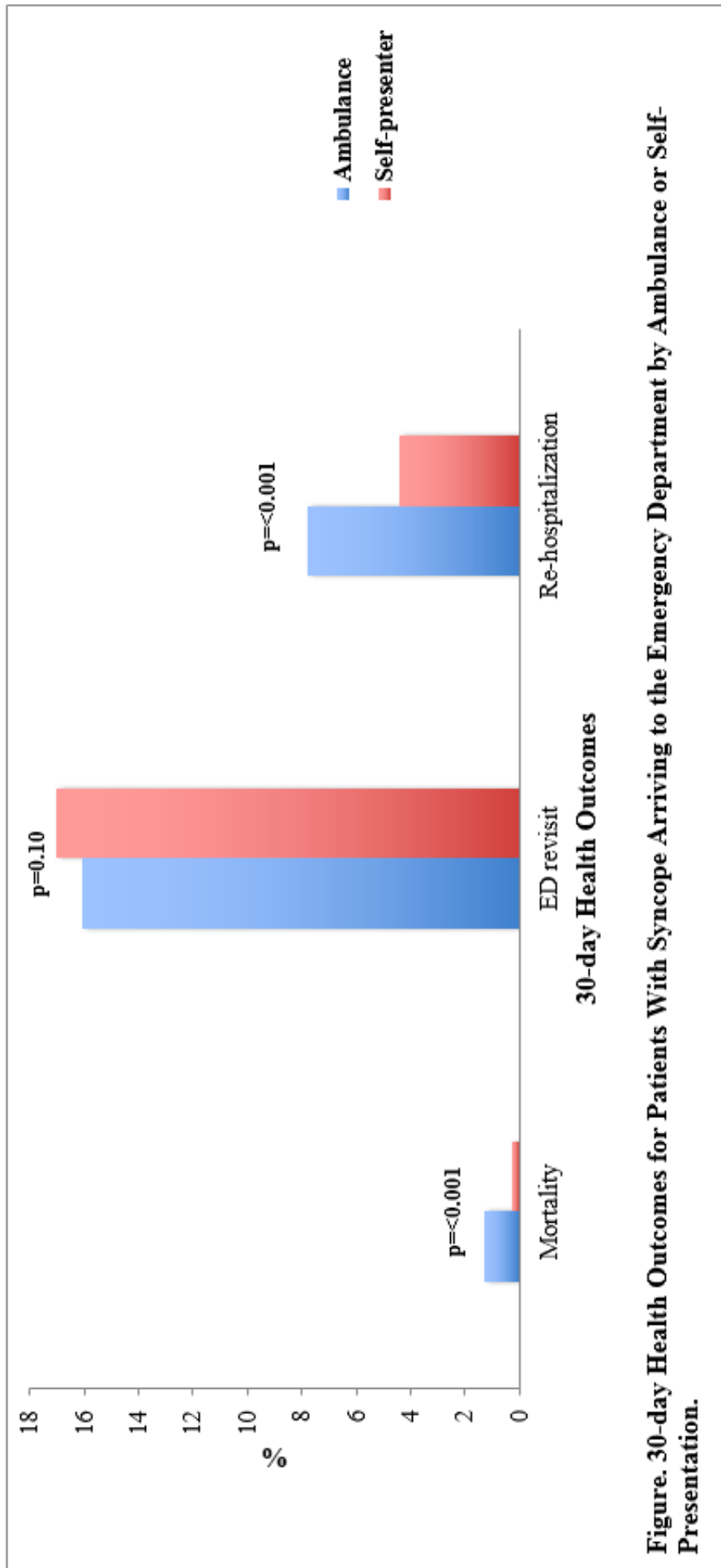


Figure. 30-day Health Outcomes for Patients With Syncope Arriving to the Emergency Department by Ambulance or Self-Presentation.

Temporal and Provincial Variations in Ambulance Use for Patients Presenting to the Emergency Department with a Primary Diagnosis of Syncope in Canada

Arjun K Gupta, Anamaria Savu, Robert S Sheldon, Padma Kaul and Roopinder K Sandhu

Supervisor: Dr. Roopinder K Sandhu

INTRODUCTION

Syncope is a frequent Emergency Department (ED) presentation. However, sparse data exists regarding the proportion of syncope patients who activate medical services compared to self-present. We examined temporal trends and provincial variations in the proportion of patients who arrive by ambulance; and evaluated the association between demographics and clinical characteristics and ambulance use.

METHODS

Hospital data for patients 20 years or older presenting to the ED with a primary diagnosis of syncope were identified in all provinces, except Quebec, between April 2004 to March 2014. Logistic regression models (OR, 95% CI) were used to identify predictors associated with ambulance use.

RESULTS

Among 91,476 syncope patients presenting to the ED with syncope, 60% arrived by ambulance. Activation of ambulance increased from 59.5% in 2004 to 66.5% in 2014 ($p < 0.01$). There were significant variations in ambulance use among provinces. Compared to patients who self-presented, patients arriving by ambulance were older, more likely male and had a significantly higher comorbidity burden. Predictors associated with higher odds of ambulance use were male sex, increasing age, urban residence, presence of comorbidities and the province of British Columbia (Table 1). There was no correlation between higher ambulance use and in-hospital mortality (Pearson correlation coefficient = 0.05; 95% CI, -0.63 to 0.69; $p = 0.89$).

CONCLUSIONS

The use of ambulance services for syncope patients increased significantly over 10 years in Canada, and interprovincial variations remain. Improved education around ambulance activation is needed to prevent unnecessary healthcare costs.

Supervisor: Dr. Roopinder K Sandhu

Table 1. Variables Associated with Ambulance Use

| Variable | OR (95% CI) | p |
|----------------------------------------|--------------------|-------|
| Age (reference <40 years) | | |
| 40-49 years | 1.25 (1.15 , 1.36) | <0.01 |
| 50-59 years | 1.59 (1.48 , 1.71) | <0.01 |
| 60-69 years | 1.83 (1.71 , 1.96) | <0.01 |
| 70-79 years | 2.16 (2.02 , 2.31) | <0.01 |
| ≥80 years | 3.18 (2.97 , 3.40) | <0.01 |
| Male gender | 1.09 (1.05 , 1.12) | <0.01 |
| Urban residence | 1.24 (1.19 , 1.28) | <0.01 |
| 2010 annual income (reference <40,000) | | |
| 40,000-60,000 | 0.88 (0.80 , 0.97) | <0.01 |
| 60,000-80,000 | 0.87 (0.79 , 0.96) | <0.01 |
| 80,000-100,000 | 0.93 (0.84 , 1.03) | 0.18 |
| >100,000 | 0.79 (0.70 , 0.89) | <0.01 |
| Charlson score (reference: 0) | | |
| 1-2 | 1.14 (1.10 , 1.18) | <0.01 |
| 3-4 | 1.21 (1.13 , 1.29) | <0.01 |
| ≥ 5 | 1.15 (1.03 , 1.29) | 0.02 |
| Province (reference: ON) | | |
| NL | 0.83 (0.75 , 0.91) | <0.01 |
| PE | 0.64 (0.54 , 0.76) | <0.01 |
| NS | 0.97 (0.89 , 1.05) | 0.43 |
| NB | 0.84 (0.78 , 0.89) | <0.01 |
| MB | 0.70 (0.63 , 0.77) | <0.01 |
| SK | 0.59 (0.55 , 0.63) | <0.01 |
| AB | 0.93 (0.88 , 0.98) | <0.01 |
| BC | 1.28 (1.22 , 1.33) | <0.01 |

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BCL-2 Inhibitor Venetoclax Enhances Temozolomide Sensitivity in AML

Asmaa Basonbul, MSc and Joseph Brandwein, MD, FRCPC
Supervisor: Dr. Joseph Brandwein

INTRODUCTION

Temozolomide (TMZ) is an alkylating agent, which adds a methyl group to O6 position of guanine, resulting in mismatch pairing with double strand breaks leading to apoptosis. The DNA repair enzyme O6-methylguanine methyltransferase (MGMT) enhances tumor cell resistance to TMZ. BCL-2 is an anti-apoptotic protein preventing cell to death. Venetoclax (Venet) is a small molecule, which promotes cell apoptosis through inhibition of BCL-2 protein. The objective of this study is evaluated the ability of the BCL-2 inhibitor Venet to enhance TMZ sensitivity in acute myeloid leukemia (AML) cells.

METHODS

AML bone marrow blast cells were collected from AML patients. KG1, MV4-11 and MOLM13 AML cell lines were chosen. Western blot was used to measure MGMT and BCL-2 expression. The Cells were incubated with TMZ 5, 10, 15, 20, 50 and 100 μ M in combination with a fixed concentration of Venet. After 2 days, cell viability assay was performed using spectrophotometry and persistence live cells were counted using a TC20 automated cell counter. Synergy was evaluated by the Chou-Talalay method.

RESULTS

Cells expressing high MGMT demonstrated strong resistance to TMZ; however, co-incubation with 1 μ M Venet resulted in a marked enhancement of sensitivity to TMZ. Venet 2.5 nM alone inhibited cell growth by approx. 50% in highly expressed BCL-2, MV4-11 and MOLM13. This dose in combination with TMZ markedly increased the cytotoxicity with nearly 100% inhibition at 100 μ M TMZ, while live cells decreased. A Synergistic effect was demonstrated in all cell lines with combination index (CI) < 1.

CONCLUSIONS

Venetoclax enhances TMZ sensitivity and induces cytotoxicity, in MGMT overexpressing cells. The drug combination design on animal model should be evaluated. Moreover, explore the relationship mechanism between the two inhibitors.

Supervisor: Dr. Joseph Brandwein

Knowledge and Perception towards Fecal Microbiota Transplantation (FMT) and associated Motivators and Deterrents for Stool Donors: a Multicenter Study

Breanna McSweeney, Dr. Jessica Allegretti, Dr. Roxana Chis, Dr. Monika Fischer, Dr. Tanya Monaghan, Dr. Benjamin Mullish, Dr. Elaine Petrof, Dr. Karen Wong, Dr. Dina Kao

Supervisor: Dr. Dina Kao

INTRODUCTION

FMT is a highly effective therapy for recurrent *Clostridium difficile* infection; however, stool donors are essential and difficult to recruit and retain. Our goal was to identify important donor factors that could be used to optimize FMT donor programs and improve donor retention rates.

METHODS

A 32-item questionnaire, scored on a 1-10 Likert scale, was disseminated via several social media platforms as well university listserv in Canada, England and the USA. A logistic regression model was built to predict willingness to donate stool.

RESULTS

802 respondents (387 [48.3%] from 21-30 years old; 573 [71.4%] women) completed the questionnaire between June 22 and September 28, 2017. 334 (41.7%) participants indicated altruism as the main reason for being a stool donor, while 282 (35.2%) indicated economic compensation was an additional motivator. Younger participants, students, and US residents were more likely to be motivated by economic compensation compared with those who are older, non-students and living in the UK and Canada. Based upon the logistic regression model the impact of the examined variables on willingness to donate was the following: being a blood donor: 1.61 (1.12-2.32); positive attitude towards FMT: 1.39 (1.24-1.55); collecting own stool: 0.91 (0.85-0.98); having to see a physician for screening: 0.93 (0.85-0.98); time commitment to donate once a month: 0.84 (0.78-0.91); economic compensation: 1.33 (1.22-1.45); \$20-30 per donation: 1.16 (1.09-1.25); knowing donation is helping others: 1.31 (1.19-1.44); The model predicted the willingness to donate stool with high accuracy (area under ROC= 0.86).

CONCLUSIONS

Altruism was the main reason for becoming a stool donor; however, economic compensation, and positive feedback from their donations were additional motivator. The need for medical examination, high frequency of donations, and the collecting/transporting of stools were potential deterrents. These variables should be taken into consideration when designing FMT stool donor program.

Supervisor: Dr. Dina Kao

Biologic DMARD Prescribing Patterns in Elderly Patients with Rheumatoid Arthritis

Dr. Britney Jones, Imran Hassan, Dr. Walter Maksymowych, Dr. Elaine Yacyshyn
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory process involving progressive destruction of joints. Currently, 30% of rheumatoid arthritis (RA) patients are over the age of 65. As the population ages, shifts in epidemiology and disease patterns will require an appropriate response from the healthcare system. Elderly patients frequently have more active disease; however, inequalities in prescribing patterns tend to favor more aggressive treatment in younger patients. This study identified differences in biologic prescribing patterns between young (<65 years old) and elderly (> 65 years old) patients with RA. Secondary outcomes examined demographic variation and disease activity between patient age groups.

METHODS

A retrospective cohort study of 1581 patients was conducted using information collected from the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics (RAPPORT) Database. This database encompasses an inception cohort of all RA patients in Northern Alberta starting treatment with biologics.

Fisher's exact test was used to determine the age of RA patients at first boDMARD prescription using the cutoff of young (<65 years old) and elderly (> 65 years old). Wilcoxon-Mann-Whitney test was used to stratify disease activity in different age groups using the Health Assessment Questionnaire (HAQ) and Disease Activity Score (DAS28).

RESULTS

A significantly larger proportion of young RA patients were prescribed boDMARDs compared with elderly RA patients (96.8% vs 90.0%; $p = 0.006$). Elderly patients prescribed boDMARDs had significantly higher HAQ (mean 1.69 +/- 0.66; $p = 0.001$) and DAS28 (mean 6.0 +/- 1.68; $p = 0.002$) scores compared to younger patients (mean 1.41 +/- 0.72 and mean 5.29 +/- 1.7, respectively). There was no statistically significant difference in other demographic information including sex, ethnicity, and years of schooling.

CONCLUSIONS

Despite current guidelines recommending early, aggressive disease control including the timely introduction of boDMARDs, this study suggests that a prescribing bias remains. Younger patients with lower levels of disease activity are more likely to receive biologic therapies than their elderly counterparts.

Supervisor: Dr. Elaine Yacyshyn

Effectiveness of a Remote Patient Monitoring Protocol Aiming to Improve Care for Ulcerative Colitis Patients

Beilman, Candace L; Lytvyak, Ellina; Garolera Molas, Marta; Lee, Matt; Peerani, Farhad; Dieleman, Levinus A.; Kroeker, Karen I.; Wong, Karen; Fedorak, Richard N.; Halloran, Brendan P.

Supervisor: Dr. Brendan Halloran

INTRODUCTION

Ulcerative colitis (UC) is a chronic condition characterized by inflammation and ulceration of the colon. Treatment of UC involves long-term maintenance therapy in an attempt to maintain remission and prevent disease flares. However, when patients are not experiencing symptoms, they can be lost to follow-up. This can be problematic because symptoms can have a poor correlation with disease activity. Our center has initiated an outreach protocol in order to remotely monitor the disease activity of UC patients. The aim of our study is to assess the effectiveness of this protocol aiming to improve care for UC patients.

METHODS

UC outpatients at the University of Alberta IBD Clinic who had not been assessed in over six months were asked to participate in the protocol. Patients were excluded if they were taking biologic therapies or had a colectomy. Patients completed a fecal calprotectin stool test and routine blood work. Patients also completed a partial Mayo and a MARS-5 questionnaire to assess disease activity and medication adherence, respectively. A summary of results was reviewed by their gastroenterologist, who completed a survey assessing if the protocol led to a change in disease management.

RESULTS

Demographic characteristics are shown in Table 1. Partial Mayo scores indicated clinical remission in 79% of patients, whereas 17% and 3% of patients were experiencing mild and severe disease, respectively. Four patients (14%) had poor medication adherence according to the MARS-5 questionnaire. Eight patients (28%) had a fecal calprotectin greater than 250 µg/g. Disease management was altered in 61% of patients. Of these patients, 29% had a clinic appointment booked, 53% had an endoscopy appointment booked, and 24% had further investigative tests completed.

CONCLUSIONS

The protocol resulted in a change in management for the majority of UC patients. Approximately 25% of patients who completed the protocol had elevated inflammatory markers despite no symptoms.

Supervisor: Dr. Brendan Halloran

Table 1. Demographic characteristics of participants

| Demographics | n (%) |
|--------------------------|--------------|
| Gender | |
| Female | 16 (55.2) |
| Male | 13 (44.8) |
| Age | |
| 18-34 | 3 (10.3) |
| 35-49 | 8 (27.6) |
| 50-64 | 9 (31.0) |
| 65+ | 9 (31.0) |
| Medications | |
| Mesalamine | 25 (86.2) |
| Azathioprine | 4 (13.8) |
| Topical rectal therapies | 6 (20.7) |

Cost-Effectiveness of Vedolizumab, Infliximab, and Adalimumab as First-Line Therapy for Ulcerative Colitis

Beilman, Candace L.; Fedorak, Richard N.; Halloran, Brendan P.
Supervisor: Dr. Brendan Halloran

INTRODUCTION

Ulcerative colitis (UC) is a chronic condition characterized by inflammation and ulceration in the colon and rectum. Biologic therapies have shown to be effective in inducing and maintaining remission in patients with UC, however there is no general consensus regarding which biologic should be used as first-line therapy. In order to make this decision, the cost of each therapy needs to be taken into consideration. Infliximab, adalimumab, and vedolizumab are commonly used biologics for UC, however it is unknown which biologic is most cost-effective as first-line therapy for patients with moderate-to-severe disease. The aim of our study was to assess the cost-effectiveness of vedolizumab, infliximab, and adalimumab for the management of moderate-to-severe ulcerative colitis.

METHODS

A Markov model was constructed to simulate the clinical disease course of UC patients after initiating vedolizumab, infliximab, or adalimumab using a 1-year time horizon. Drug costs were obtained from the Alberta Health Drug Benefit List, and the remaining costs were determined from the CIHI Patient Cost Estimator. Transition probabilities were attained from a literature review, and loss of response for vedolizumab, infliximab, and adalimumab were obtained from the GEMINI, ACT, and ULTRA trials, respectively. Probabilistic sensitivity analysis was performed to characterize uncertainty related to all input parameters.

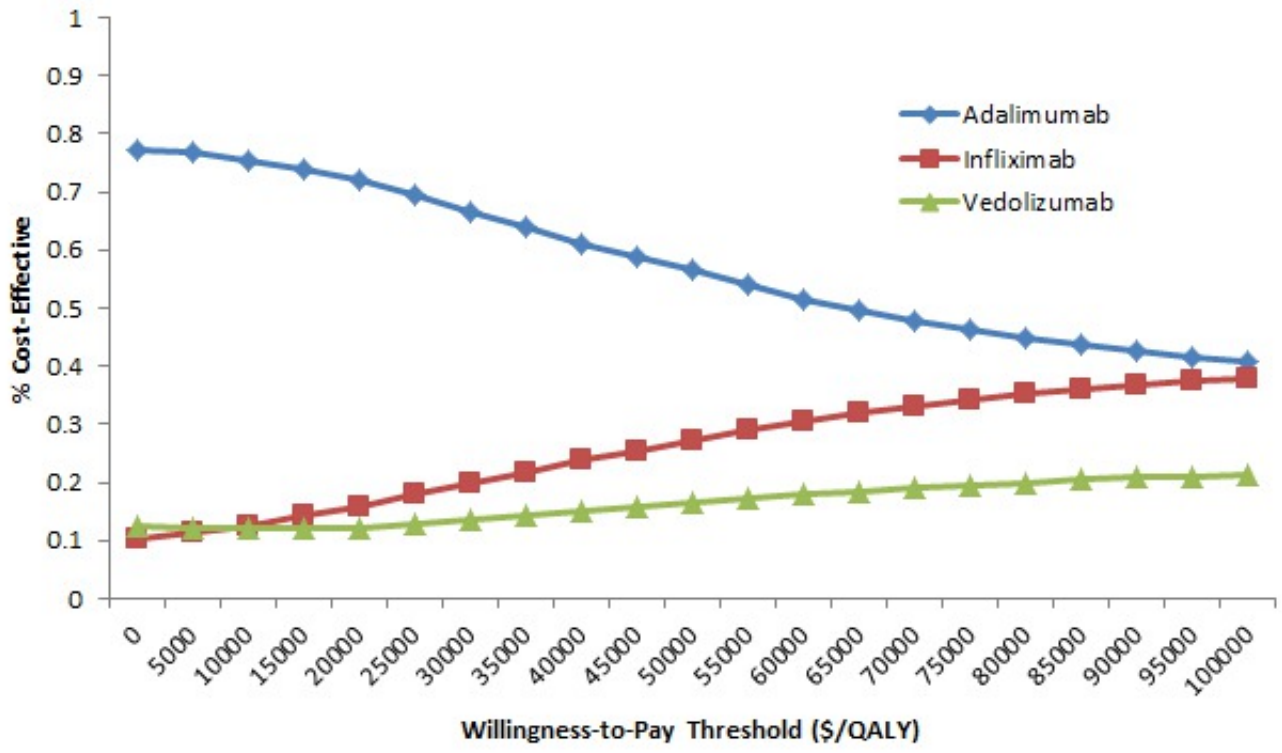
RESULTS

Using a 1-year time horizon, vedolizumab costs \$30,300 per patient and yields 0.47 quality-adjusted life years (QALYs). Infliximab costs \$31,600 per patient and yields 0.54 QALYs. Adalimumab costs \$25,200 per patient and yields 0.50 QALYs. At a willingness-to-pay (WTP) threshold of \$50,000 per QALY, probabilistic sensitivity analysis revealed that vedolizumab, infliximab, and adalimumab had a 16.4%, 27.1%, and 56.5% probability of being cost-effective, respectively.

CONCLUSIONS

All three biologics have similar effectiveness as first-line therapy, however adalimumab's lower cost renders it more cost-effective compared to infliximab and vedolizumab for the management of moderate-to-severe UC.

Supervisor: Dr. Brendan Halloran



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Characterization of immune cell populations of Clinically Isolated Syndrome (CIS) patients and conversion to MS

Chieh-Hsin Lee, Maryam Nakhaei-Nejad, David Barilla, Fabrizio Giuliani
Supervisor: Dr. Fabrizio Giuliani

INTRODUCTION

Clinically isolated syndrome (CIS) is the prodromal phase of multiple sclerosis (MS), with patients having experienced only one neurological episode. Given that up to 70% of CIS patients develop subsequent MS, it is important to differentiate those who will and will not convert to RRMS in the future. This will allow for earlier treatment and also help improve our understanding of the MS disease course.

METHODS

Multi-colour flow cytometry panels were designed to identify up to 50 peripheral blood lymphocyte subpopulations. We compared patients with CIS who do (CIS-C) (n = 7) or do not (CIS-N) (n = 6) convert to RRMS at a later point with relapsing remitting multiple sclerosis (RRMS) patients, which are further divided into early RRMS (RRMS-E) (n = 5) and late RRMS (RRMS-L) (n = 14).

RESULTS

In the B cell compartment, naïve/transitional cells are significantly higher in RRMS-L than RRMS-E, which is similar to CIS-C. In females, RRMS-L have a higher amount than both RRMS-E and CIS-C. Pre-switch cells are significantly higher in RRMS-E than CIS-N. In the T cell compartment, the CD4-to-CD8 ratio is higher in the RRMS group than CIS-N. With both the T_{fh} and Th₂₂ numbers being lower in RRMS than the two CIS groups. CD8⁺CD127⁺CD45RA⁻, a memory population, is higher in RRMS than CIS-N, while CD8⁺CD62L⁻, an effector subpopulation, is lower in RRMS than CIS-N.

CONCLUSIONS

These results show that CIS patients who do or do not convert to RRMS are different in some immune subpopulations, with converters being similar to those already diagnosed with RRMS in some lymphocyte subsets. These results partially support the view that CIS patients who convert are functionally the same as RRMS and suggest that peripheral blood markers may be used to predict future conversion of CIS patients to RRMS and allow for earlier treatment of the disease.

Supervisor: Dr. Fabrizio Giuliani

Restrospective Review of Idiopathic and Isolated Aortitis

Dahye Hong, Elaine Yacyshyn
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

Aortitis is the inflammation of the aorta, and can be diagnosed in patients without a systemic disease, referred to as 'idiopathic aortitis'. A subset of this is 'isolated aortitis', where abnormalities are limited to the aorta. Idiopathic aortitis is poorly defined, and no guidelines exist to direct the workup, treatment, and monitoring of these patients. The objective of this study was to review the charts of aortitis patients to determine demographics, etiology of aortitis, use of systemic treatment, and long-term morbidity and mortality.

METHODS

A retrospective review of medical records was conducted for patients who had surgical intervention for aortitis at Edmonton hospitals in 1998-2008. The patient list was generated from the pathology department, and the records were reviewed. After initial hospital discharge, long-term outcomes were analyzed with outpatient medical records and subsequent inpatient hospital records.

RESULTS

15 patients had pathological aortitis surgically treated in Edmonton. Out of these, 5 had aortitis associated with a systemic condition, and 10 had idiopathic. 8 of the 10 with idiopathic aortitis had isolated aortitis. Only 40% (2/5) of patients with systemic conditions were treated with systemic immunosuppression, while none of the idiopathic aortitis patients were treated systemically. On reviewing subsequent follow-up records, 60% (3/5) of patients with aortitis associated with systemic conditions had developed new vascular lesions on imaging, 20% (1/5) had vascular complications, and 20% (1/5) had death related to the aortitis or surgery. In the idiopathic aortitis group, 10% (1/10) had new lesions on subsequent imaging and 50% (5/10) had complications.

CONCLUSIONS

In patients diagnosed with aortitis in Edmonton, there was a significant portion with idiopathic aortitis. Both groups had inconsistent follow-up, and there was a number of patients who developed subsequent complications post-operatively. There appears to be a need for a systematic approach to aortitis. Further data from Calgary and Ottawa will be combined into a 3-centre study.

Supervisor: Dr. Elaine Yacyshyn

Safety Validation of Microelectrode Insertion in the Lumbar Spinal Cord - Implications Towards Human Spinal Cord Mapping

David S. Hu, Dirk G. Everaert, Amirali Toossi, Ashley Dalrymple, Richard Uwiera, Richard Fox, Hamid M. Shah, Peter E. Konrad, Kevin G. Robinson, and Vivian K. Mushahwar

Supervisor: Dr. Vivian Mushahwar

INTRODUCTION

The overall goal of this project is to provide the translational bench-to-bedside testing evidence for a neural interface developed in our laboratory. The work will focus on investigating the safety of an innovative electrical stimulation paradigm known as intraspinal microstimulation (ISMS) for restoring standing and walking after spinal cord injury (SCI).

METHODS

Yucatan minipigs (45-55 kg & 10-11 month old) will be used in this project. Each animal will undergo a minimum of 3-4 weeks of behavioral training to walk across a 1m X 3.5m rubber mat. During this time, baseline recordings of muscle activity and walking kinematics are recorded using surface EMGs and Vicon Motion capture. They are then subjected to a two-level laminectomy (L4-L5) to expose the lumbar-enlargement region of the spinal cord. A stereotactic frame is then used to guide microelectrode insertions into the spinal cord for a total of 8-12 ipsilateral penetrations. At each penetration, electrical stimuli are delivered through the electrodes (biphasic pulses, up to 150uA amplitude) and the functional outcomes recorded. Over a 4-week period, behavioral and kinematic tests are then performed to assess three neurological components: motor, sensory, and autonomic functions. These will include a qualitative grading scale, PITIBS and Tarlov, and quantitative motion capture for assessing any motor deficits. Examination of the sensory and autonomic components will focus on observations of pain-like behaviors, reflexive responses, and bladder function. Post-mortem histological analyses of the spinal cord tissue with Trichrome Mallory will be used to identify any potential pathological changes.

RESULTS

Preliminary data show that by as early as the 2-week mark, PITIBS scores return to their baseline levels. All reflexes remain present post-operatively, and no signs of spasticity were shown during the course of 4 weeks.

CONCLUSIONS

This provides growing support that microelectrode penetrations in the spinal cord is a safe procedure for spinal cord mapping.

Supervisor: Dr. Vivian Mushahwar

Identifying and prognosticating malignant brain tumors non-invasively using unique metabolomic signatures derived from patient serum and urine samples

Dimas Yusuf, Amitabh D. Singh, Rustem Shaykhutdinov, Jing Wen, Peter Forsyth, Hans J. Vogel, J. Gregory Cairncross, Aalim M. Weljie, Jacob C. Easaw
Supervisor: Dr. Jacob Easaw

INTRODUCTION

BACKGROUND: Metabolomics technology has the potential to revolutionize how we screen, diagnose, and treat cancer, as well as improve upon existing cancer molecular tests that may not sufficiently capture the complexity of most malignancies. In this study, we explore the clinical potential of metabolomics analysis in the diagnosis and risk-stratification of brain tumors.

METHODS

METHODS: To test the hypothesis that brain tumor type and survival could be predicted with metabolomics, we analyzed the pre-operative serum and urine samples of patients with glioblastoma (GBM), oligoastrocytoma (OA2), meningioma (M1) and compared them to healthy controls. (HC). Sera from immune-deficient NOD-SCID mice xenografted with human GBM brain tumor initiating cells were also studied.

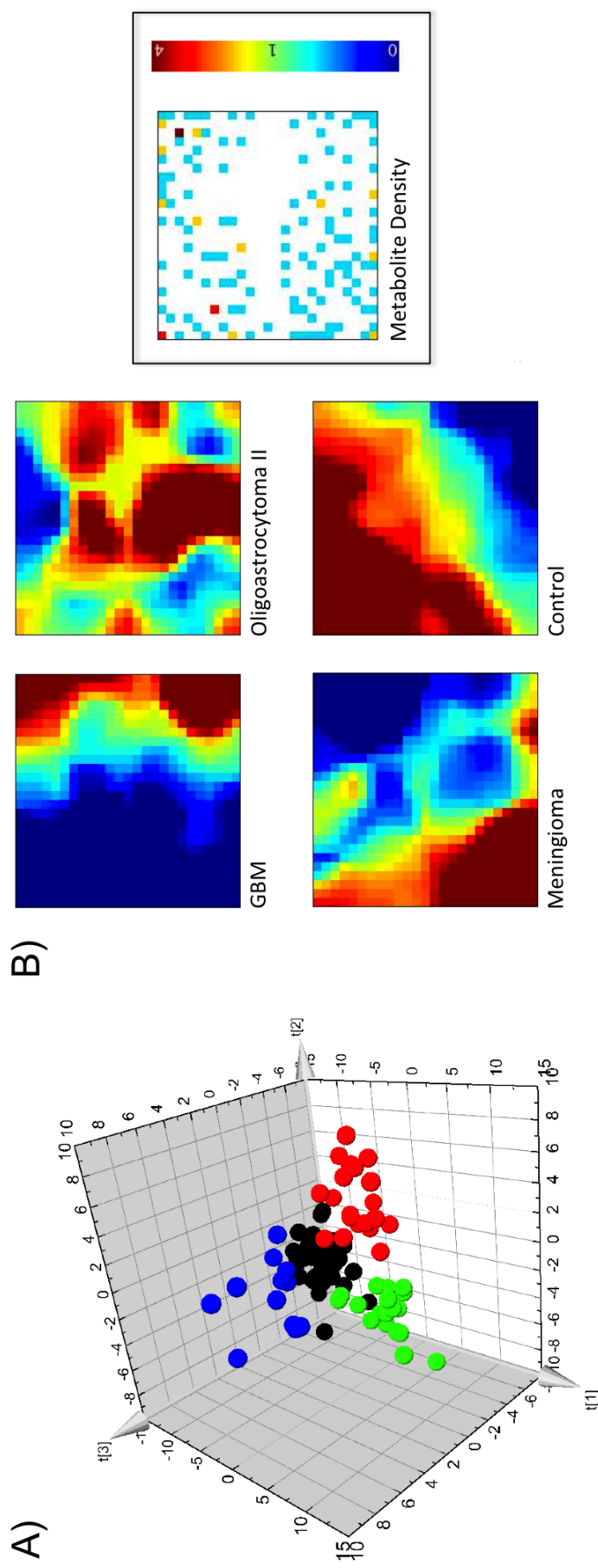
RESULTS

RESULTS: Metabolomics analysis of patient samples was able to accurately differentiate GBM, OA2, M1 and HC ($p = 2.3 \times 10^{-26}$). Subsequently, a prediction model developed and validated internally was able to diagnose GBM with a sensitivity of 86.7% and specificity of 93.8%, and distinguish whether a GBM patient possess O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation ($p = 7.4 \times 10^{-10}$). Within the MGMT methylated group, the model was able to predict longevity ($p = 3.25 \times 10^{-4}$). The model was also able to predict survival irrespective of MGMT methylation status ($p = 2.9 \times 10^{-6}$).

CONCLUSIONS

CONCLUSIONS: In this study, we demonstrate that metabolomic analysis of patient biofluids can identify brain tumors, distinguish brain tumor subtypes, and independently predict MGMT status as well as longevity among GBM patients. Metabolomics analysis can facilitate non-invasive diagnosis of aggressive brain tumors.

Supervisor: Dr. Jacob Easaw



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Factors that are prognostic for survival and recurrence in rare cases of adult medulloblastomas

Dimas Yusuf, Andra V. Krauze, Jacob C. Easaw, Albert D. Murtha, John O. Amanie, Wilson H. Roa, Sunita Ghosh, David D. Eisenstat, Samir I. Patel
Supervisor: Dr. Samir Patel

INTRODUCTION

Adult medulloblastomas account for less than 1% of adult neoplasms. They are challenging to treat due to their rarity and the heterogeneity of treatment options, all of which have limited evidence. In this retrospective review, we examined cases of adult medulloblastoma diagnosed in Alberta during a 70-year period.

METHODS

We reviewed the charts of patients diagnosed with medulloblastoma between 1944 and 2014. We performed Cox and logistic regression analysis to elucidate features that may influence recurrence risk and survival.

RESULTS

We analyzed 78 cases. The median age at diagnosis was 27 (range 16 to 71). Most were male (68%). Most had surgery (92%). By COG risk stratification, 54% were standard risk while 21% were poor risk. RT was administered to 85% of patients, and craniospinal irradiation (CSI) to 81%. Chemotherapy was administered to 48%. Median survival was 4.4 years from diagnosis (range 0 to 20). At last follow-up, 39% were alive and recurrence-free. Patients who had CSI and posterior fossa boost had longer survival ($p = 0.047$ and < 0.01 , respectively) and were less likely to recur ($p = 0.041$ and < 0.01). Chemotherapy was also associated with decreased recurrence ($p = 0.025$).

CONCLUSIONS

Medulloblastomas carry a significant recurrence risk, especially for patients who had subtotal resection. CSI and posterior fossa boost were associated with fewer recurrences and improved survival. COG risk stratification, Chang staging, desmoplastic histology, vermian location, 4th ventricle involvement, tumor enhancement, presence of hydrocephalus and cerebrospinal fluid (CSF) involvement are not significantly prognostic.

Supervisor: Dr. Samir Patel

ONCOPRE: A new chemotherapy benefit prediction algorithm to assist treatment decision making

Dimas Yusuf, Maria Ho, Rekha M. Diocee, Yaling Yin, Caroline Speers, Winson Y. T. Cheung

Supervisor: Dr. Winson Cheung

INTRODUCTION

Oncology is an increasingly complex field of medicine and clinical decision support tools (CDSTs) are needed to help oncologists make optimal treatment decisions. For colon cancer specifically, existing CDSTs such as Adjuvant Online have been used by clinicians for years to estimate the benefit of chemotherapy. Existing CDSTs, however, have not been able to keep abreast of advancements in our understanding of cancer biology, such as the impact of microsatellite instability, BRAF mutations, and newly discovered prognostic markers. Existing CDSTs are also not optimized to run on mobile devices and many rely on outdated underpinnings.

METHODS

We present ONCOPRE, a chemotherapy benefit calculator for colon cancer that addresses the limitations of existing CDSTs. It predicts 5-year colon cancer outcomes based on epidemiological data and the results of landmark trials. To validate ONCOPRE's predictions, we have compared them with the predictions generated by existing CDSTs as well as real-world data from tertiary cancer centers in Canada.

RESULTS

ONCOPRE is able to predict the 5-year disease-free survival (DFS) and overall survival (OS) of colon cancer patients based on age, sex, tumor characteristics and other clinical and cytogenetic prognostic markers. Our predictions compare favorably with the outcomes of landmark trials and historical data. They are precise and are able to handle a wider set of circumstances than existing CDSTs. We believe that these attributes make ONCOPRE the new benchmark in the area of CDSTs for colon cancer outcomes.

CONCLUSIONS

ONCOPRE represents a new CDST that can assist in treatment decision-making and patient counseling. We make the case that the next generation of CDSTs in oncology must take into account contemporary clinical and cytogenetic risk factors as these elements significantly affect outcome. The ONCOPRE platform serves as a potential model on which to develop prediction tools for other forms of cancers. ONCOPRE is freely accessible at <http://www.oncopre.com/>.

Supervisor: Dr. Winson Cheung

Characterization of the stress-associated Calcium-binding protein, spermatid associated 1 (CABS1) in saliva and over expression controls using immunoprobings in Western Blot and Wes®

Eduardo Reyes-Serratos, Marcelo Marcet-Palacios, A. Dean Befus
Supervisor: Dr. A. Dean Befus

INTRODUCTION

Calcium-binding protein, spermatid associated 1 (CABS1) is present in saliva and appears to be a biomarker of stress. We produced four polyclonal CABS1 antibodies (H1.0, H2.0, H2.1, H2.2) and used them in Western Blot (WB) to detect various forms of the molecule. Using H2.0 in WB, saliva samples of individuals subjected to stress showed a 27kDa band whose levels increased after psychological stress exposure. In an exploratory analysis, the presence of bands <27kDa was associated with resilience to stress. Unfortunately, our stock of H2.0 is almost depleted so we have characterized H1.0, H2.1, H2.2 in WB and in another analytical high-throughput technique, Wes®, which uses significantly lower amounts of sample and antibody.

METHODS

Saliva samples and a positive control (CABS1 Over-Expression Lysate (OEL)), as well as a negative control (Control Lysate (CL)), were analyzed in WB and Wes® with H1.0, H2.0, H2.1, H2.2. OEL and CL were separated by electrophoresis and analyzed using Mass Spectrometry (MS) Analysis.

RESULTS

Figure 1 shows a tabulated summary of immunoreactive proteins to all four antibodies in WB and Wes®. When using H2.x series antibodies in WB, corresponding immunoreactive proteins in OEL/CL suggest that these antibodies may be binding to an unknown protein, and also to CABS1. This was confirmed by MS, where presence of CABS1 is positive only in OEL. On the other hand, Wes® shows no immunoreactivity with CL. In saliva, H2.0 is the only antibody in WB that can show bands ≤ 27 kDa. Moreover, saliva tested in Wes® with H2.0 shows a different pattern than the other CABS1 antibodies.

CONCLUSIONS

H2.0 in WB is a suitable analytical platform to assess the presence in saliva of bands ≤ 27 kDa and their association with stress. However, we intend to transition into Wes® and validate other CABS1 antibodies to expand our knowledge of stress and CABS1 across different cohort studies.

Supervisor: Dr. A. Dean Befus

Figure 1. Western Blot (WB) and Wes® patterns of immunoreactive proteins to polyclonal anti-CABS1 antibodies H 1.0, H 2.0, H 2.1, H 2.2 in saliva, a CABS1 Over Expression Lysate (OEL) and its Control Lysate (CL).

| | | Saliva | | | | | | | |
|------------------------|--|--------|-----|-------|-----|-------|-----|-------|-----|
| | | H 1.0 | | H 2.0 | | H 2.1 | | H 2.2 | |
| Molecular weight [kDa] | | WB | Wes | WB | Wes | WB | Wes | WB | Wes |
| 92 | | | | ✓ | | | | | |
| 65 | | | | ✓ | | | | ✓ | |
| 60 | | | ✓ | | | | ✓ | | ✓ |
| 55 | | ✓ | | ✓ | | ✓ | | ✓ | |
| 35 | | | | | ✓ | | | | |
| 28 | | | | ✓ | | | | | |
| 19 | | | | ✓ | | | | | |
| 14 | | | | ✓ | | | | | |
| 11 | | | | ✓ | | | | | |

| | | CABS 1 Over Expression Lysate (OEL) | | | | | | | |
|------------------------|--|-------------------------------------|-----|-------|-----|-------|-----|-------|-----|
| | | H 1.0 | | H 2.0 | | H 2.1 | | H 2.2 | |
| Molecular weight [kDa] | | WB | Wes | WB | Wes | WB | Wes | WB | Wes |
| 97 | | | ✓ | | ✓ | | ✓ | | ✓ |
| 83 | | ✓ | | ✓ | | ✓ | | ✓ | |
| 65 | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 53 | | | | ✓* | | ✓ | | ✓ | |
| 48 | | | | ✓ | | | | ✓ | |
| 31 | | | | ✓ | | | | | |
| 21 | | | | ✓ | | | | | |

| | | Control Lysate (CL) HEK 293T cells | | | | | | | |
|------------------------|--|------------------------------------|-----|-------|-----|-------|-----|-------|-----|
| | | H 1.0 | | H 2.0 | | H 2.1 | | H 2.2 | |
| Molecular weight [kDa] | | WB | Wes | WB | Wes | WB | Wes | WB | Wes |
| 97 | | | | | | | | | |
| 83 | | | | | | | | | |
| 65 | | | | | | | | | |
| 53 | | | | ✓* | | ✓ | | ✓ | |
| 48 | | | | | | | | ✓ | |
| 31 | | | | ✓ | | | | | |
| 21 | | | | ✓ | | | | | |

* Yellow boxes symbolize immunoreactive bands that appear to be the same in both CABS1 OEL and CL

Differences in clinical measures and outcomes in South Asians (SA) vs Caucasians (CA) attending a cardiac rehabilitation program (CRP)

Gami Nanayakkara, Mano Senaratne MD, PhD, Janek Senaratne MD, Karen MacDonald RN, Rhonda Lightfoot RN, Lena Kirincic RN, Wendy Reinhardt RN
Supervisor: Dr. Mano Senaratne

INTRODUCTION

SA have a greater predisposition to cardiac events compared to CA. Although CRP is known to improve outcomes, little data is available regarding benefits acquired by SA considering language barriers, possible lower SES and cultural norms. The study examined issues of a population of patients attending a CRP in Edmonton with a proportionately large SA population.

METHODS

All data was collected and entered into a database formulated within the SPSS data management system. All participated in 4-12 week program including aerobic/isometric exercise, dietary evaluation and other risk factor modifications.

RESULTS

From Jan 1998 -April 2016, 5406 CA and 811 SA attended CRP. Baseline characteristics revealed more nonsmokers (70.6% vs 26.6%, $p < 0.05$), lower BMI (26.8 +/- 0.1 vs 29.4 +/- 0.1, $p < 0.05$) but higher diabetes (27.7% vs 21.5%, $p < 0.05$) in the SA population. Outcome measures revealed that SA spent less time on the program (6.9 wks +/- 0.1 vs 7.3wks +/- 0.1, $p < 0.05$), attended the nutrition class less (36.2% vs 53.4%, $p < 0.05$) and had lower pre CRP 6 min walk results (414.0m +/- 4.0 vs 446.5m +/- 1.6, $p < 0.05$). SA achieved lower 6 min walk improvement from pre-post CRP (63.4m +/- 2.4 vs 70.0m +/- 1.0, $p < 0.05$) as well. Frequency of beta blocker (86.9% vs 86.1%, $p > 0.05$), anti platelet agent (96.3% vs 97.1%, $p > 0.05$), ACEI/ARBS (79.9% vs 80.0%, $p > 0.05$) and cholesterol lowering agent (93.8% vs 91.4%, $p > 0.05$) use was not significantly different.

CONCLUSIONS

While the SA seemed to be prescribed and used proven pharmacologic treatments to the same extent as CA, they appeared to access programs for life style modification less during the CRP. Different socioeconomic circumstances and language issues may play a role in the latter results. Given the higher event rates in SA one may need to consider provision of instruction as well materials in their native language to improve outcomes.

Supervisor: Dr. Mano Senaratne

Differences in Clinical Measures and Outcomes in South Asians Versus Caucasians Attending a Cardiac Rehabilitation Program

Gami Nanayakkara, Mano Senaratne MD, PhD^{1,2}, Janek Senaratne MD^{1,2}, Karen MacDonald RN¹, Rhonda Lightfoot RN¹, Lena Kirincic RN¹, Wendy Reinhardt RN¹

¹ Grey Nuns Community Hospital, Edmonton, Canada, ²Division of Cardiology, University of Alberta, Edmonton, Canada.

Background

- South Asians have a greater predisposition to cardiac events compared to Caucasians
- Subsequent outcomes of South Asians are known to be worse
- Cardiac Rehabilitation is known to improve outcomes in patients with cardiac disease including mortality
- However, little data is available in the literature regarding the relative efficacy of Cardiac Rehabilitation in South Asians compared to Caucasians

Purpose

- To determine the benefits that South Asians derive from a Cardiac Rehabilitation Program and how they compare to Caucasians

Methods

- Cardiac Rehab Program at The Grey Nuns Hospital is a referral program serving patients in Edmonton and Northern Alberta, Canada
- Patients referred to the program between 1998 and 2016 were included, totaling 7390
- Only Caucasians and South Asians were included in the study
- Those with an ethnic origin from the Indian subcontinent were considered as South Asians (India, Pakistan, Bhutan, Sri Lanka, Nepal, and Bangladesh)
- Clinical, investigational, and Cardiac Rehabilitation Program outcomes were prospectively collected and entered into a database
- Statistical analysis was done using the SPSS system

Results

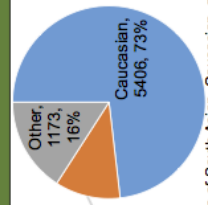


Figure 1. Proportion of South Asian, Caucasian, and other ethnicities that participated in Cardiac Rehabilitation Program from 1998 to 2016

Results

| Baseline characteristics | Caucasian patients | South Asian patients | p-value |
|---------------------------------|--------------------|----------------------|---------|
| Mean age (yrs) | 61.5 | 60.5 | 0.020 |
| Body mass index | 29.4 | 26.8 | <0.001 |
| Rate of diabetes (%) | 21.5 | 27.7 | <0.001 |
| Smokers (%) | 73.4 | 29.4 | <0.001 |
| Beck depression inventory score | 7.2 | 8.0 | 0.040 |
| Hemoglobin A1c | 5.7 | 6.5 | 0.001 |
| Unemployed (%) | 2.5 | 4.5 | <0.001 |
| Homeowners (%) | 4.0 | 12.6 | <0.001 |

Table 1. Baseline characteristics

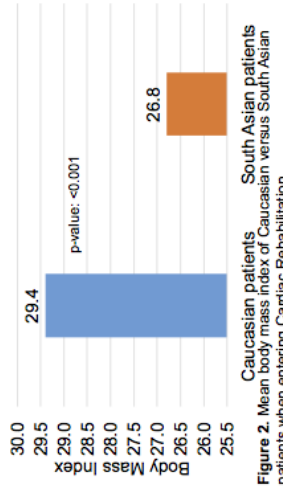


Figure 2. Mean body mass index of Caucasian versus South Asian patients when entering Cardiac Rehabilitation

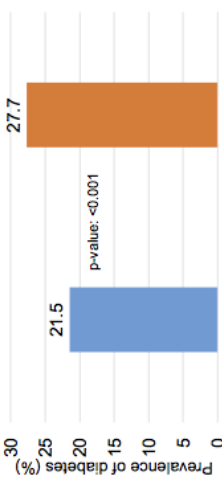


Figure 3. Prevalence of diabetes in Caucasian versus South Asian patients in Cardiac Rehabilitation

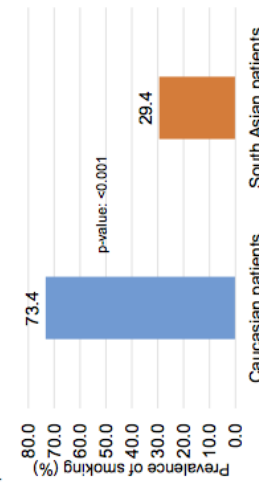


Figure 4. Smoking prevalence in Caucasian versus South Asian patients in Cardiac Rehabilitation

Results

| Outcomes | Caucasian patients | South Asian patients | p-value |
|-------------------------------|--------------------|----------------------|---------|
| Time on Program (wks) | 7.3 | 6.9 | <0.001 |
| Attended Nutrition Class (%) | 53.4 | 36.2 | <0.001 |
| Pre CRP 6min walk (m) | 446.5 | 414.0 | <0.001 |
| Pre CRP 6min walk (m) | 516.5 | 477.4 | <0.001 |
| Post & Pre 6min walk diff (m) | 70.0 | 63.4 | <0.001 |
| Beta Blocker (%) | 86.9 | 86.1 | 0.573 |
| Anti Platelet Agent (%) | 96.3 | 97.1 | 0.217 |
| ACE Inhibitors (%) | 93.8 | 80.0 | 0.641 |
| Statin (%) | 93.8 | 91.4 | 0.152 |

Table 2. Outcomes of Cardiac Rehabilitation Program

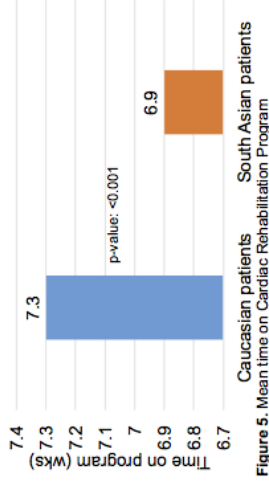


Figure 5. Mean time on Cardiac Rehabilitation Program of Caucasian versus South Asian patients

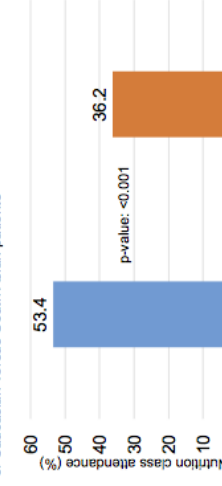


Figure 6. Mean percent of Caucasian versus South Asian patients who attended the nutrition class

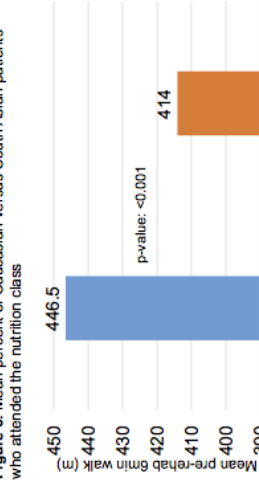


Figure 7. Mean pre-Cardiac Rehabilitation 6 minute walk distance in Caucasian versus South Asian patients

Results

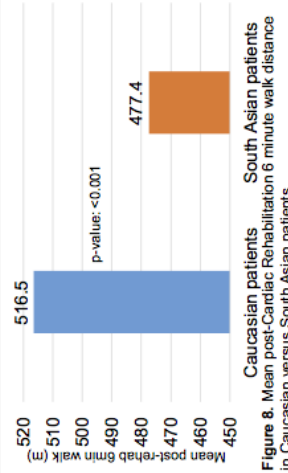


Figure 8. Mean post-Cardiac Rehabilitation 6 minute walk distance in Caucasian versus South Asian patients

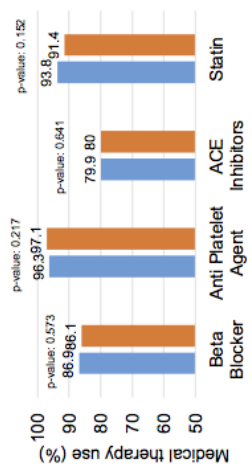


Figure 9. Percentage of patients taking goal-directed medical therapy by class during Cardiac Rehabilitation

Conclusions

- South Asian patients had a lower rate of smoking and average Body Mass Index but higher Beck Depression Inventory scores, and rates of diabetes when compared to the Caucasian patients
- Cardiac Rehabilitation improves 6 minute walk to a lesser extent in South Asians versus Caucasians
- South Asians are prescribed and are using goal-directed medical therapies to the same extent as Caucasians
- However, South Asian patients appeared to access available programs such as the nutrition program less during the Cardiac Rehabilitation Program
- Different socioeconomic circumstances and language issues may play a role in the latter results
- Given the higher event rates in South Asians, one may need to consider provision of instruction as well materials in their native language to improve the benefits gained from Cardiac Rehabilitation Program

Declaration of Interest

None

Contact

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The role of Poly Lactic-co-Glycolic Acid (PLGA) in APP processing and A β -induced toxicity in mouse primary cultured neurons

Geetika Phukan and Satyabrata Kar
Supervisor: Dr. Satyabrata Kar

INTRODUCTION

Impaired lysosomal functioning causes accumulation of material inside lysosomes leading to Lysosomal Storage Disorders (LSD). Studies have linked LSD to neurodegenerative disease pathology along with an impaired autophagy mechanism. In Alzheimer's disease, sequential proteolysis of amyloid precursor protein (APP) leads to accumulation of β -amyloid peptide which subsequently triggers degeneration of neurons and development of disease pathology. Recently, advancement in nanotechnology has led to the application of certain bio-compatible nanoparticles in treatment and diagnosis of neurodegenerative disorders. Previous studies showed that bio-compatible nanoparticles can re-acidify lysosomes, ameliorating lysosomal-related myopathy in genetic model of Parkinson's disease. Here, we propose that bio-compatible nanoparticles can also modulate APP processing and A β -induced toxicity via the lysosomal-autophagic pathway.

METHODS

Neuro2a (N2a) cells expressing amyloid precursor protein (APP-695) harbouring Swedish double mutation (APPSWE calls) and mouse primary cortical neurons were used to investigate the role of biocompatible nanoparticles (100 nm diameter) in APP processing and A β -induced toxicity. MTT assay was performed to check the viability of nanoparticles-treated cells. Western blotting and ELISA were employed to detect changes in cellular levels of various proteins involved in APP processing and lysosomal degradation pathway. Confocal immunostaining was used to investigate cellular localization of biocompatible nanoparticles.

RESULTS

Based on the dose response and time course studies, treating cells to 200 μ g/ml of the nanoparticles for 24h showed optimum cellular responses without inducing toxicity. Nanoparticles altered APP processing in both APPSWE cells and primary neurons in a dose-dependent manner. These particles also altered lysosomal pathway markers in a dose-dependent manner. Immunocytochemical analysis showed endocytosis of nanoparticles into lysosomal compartments inside cells.

CONCLUSIONS

Preliminary data from this study show potential role of biocompatible nanoparticles in ameliorating amyloid-beta induced toxicity in vitro. Further studies are underway to elucidate their mechanism of action and to establish these nanoparticles as potential therapeutic agents for neurodegenerative diseases.

Supervisor: Dr. Satyabrata Kar

Glucocorticoid-induced Osteoporosis Preventative Care in Rheumatology Patients: A Quality Assurance Study

G. Koller, S. Katz, T. L. Charrois, C. Ye
Supervisor: Dr. Carrie Ye

INTRODUCTION

Systemic glucocorticoid therapy is commonly used in the management of rheumatologic diseases, but they come with many side effects. A common, yet manageable, adverse effect is glucocorticoid induced osteoporosis (GIOP) with previous studies reporting fractures in 30 to 50% of patients receiving long-term glucocorticoid therapy. There are several publications that have shown GIOP care is not optimal in the general population; however, little is published on GIOP care amongst patients under the care of rheumatologists.

METHODS

A population-based retrospective quality assurance study of adults seen at the University of Alberta Rheumatology Clinic was performed using Alberta's electronic outpatient medical record "eClinician." Adult patients prescribed prednisone from January 1st to December 31st, 2016 by a rheumatologist were initially included for review. The average prednisone dose within the first 3 months was calculated. Those whose average dose met the American College of Rheumatology (ACR) treatment guidelines for GIOP prevention (≥ 7.5 mg/day for ≥ 3 months) were assessed for concurrent GIOP preventive care including supplementation of calcium and vitamin D, prescription of pharmacotherapy, and requisition and completion of DXA scan within 6 months of starting prednisone.

RESULTS

745 discreet courses of prednisone were prescribed in 433 patients with 113 meeting inclusion criteria. Following the prescription, 83% (94/113) were supplemented with vitamin D and calcium, 50% (56/113) were prescribed osteoporosis pharmacotherapy, and 46% (52/113) were given both. 25% (28/113) of patients had DXA imaging ordered by the rheumatologist within the first 6 months. 16% (18/113) received calcium, vitamin D, pharmacotherapy, and completed BMD study. Multivariate analysis was performed looking at variables associated with utilization of GIOP measures.

CONCLUSIONS

Rheumatologists at our centre appear to have higher implementation rates of GIOP preventative care compared to studies of administrative databases of the general population. We will explore variables associated with rates of GIOP care in order to identify populations in which to target further interventions.

Supervisor: Dr. Carrie Ye

Chronic fatigue in vasculitis: a systematic review

van Laar GG, Cohen Tervaert JW, Clifford A, Yacyshyn E
Supervisor: Dr. Jan Willem Cohen Tervaert

INTRODUCTION

Objective - This study aims to review chronic fatigue in patients with vasculitis. Current knowledge of the prevalence, potential determinants and impact on quality of life (QoL) will be ascertained.

METHODS

Methods - Using a systematic Medline search, we identified studies investigating fatigue in vasculitis. Prevalence and impact on QoL were quantified. Furthermore, factors affecting or explaining fatigue were identified.

RESULTS

Results - Chronic fatigue is consistently reported in approximately 75% of patients suffering from ANCA-associated vasculitis, while in medium- and large-vessel vasculitis up to 85% of patients report "pathological" fatigue. Though studies investigating factors affecting fatigue in vasculitis are limited, a strong correlation with sleep disturbance and pain is described. In addition, an association between fatigue and dysfunctional coping strategies has been observed. Furthermore, a weak association between elevated CRP and reduced energy levels has been found, whereas no association was found with other clinical signs of active disease. Chronic fatigue is strongly associated with the impairment in physical health and QoL experienced by circa 82% of vasculitis patients; unlike other factors such as disease activity and/or vasculitic damage.

CONCLUSIONS

Conclusion - Patients with vasculitis consider physical fatigue to be the largest burden of the disease, surprisingly outranking common clinical problems related to vasculitis. The etiology of fatigue in vasculitis appears to be multifactorial, with pain and sleep disturbance being the most important factors, whereas disease activity is likely to play a much smaller role.

Supervisor: Dr. Jan Willem Cohen Tervaert

The Survival Impact of Lenalidomide Maintenance Chemotherapy in Multiple Myeloma Patients Treated with Autologous Stem Cell Transplant and Bortezomib-Based Induction; An Analysis of Real World Data

Cherniawsky, H., Sandhu, I., Chu, M., Hewitt, J., Ismail, I., Belch, A., Pilarski, L., Nikitina, T., Venner, C.

Supervisor: Dr. Christopher Venner

INTRODUCTION

Management of multiple myeloma (MM) focuses on obtaining profound and durable response. Recent large-scale phase 3 randomized trials have shown improved progression free survival (PFS) and overall survival (OS) with daily low dose lenalidomide, an oral immunomodulatory. We sought to evaluate the impact of lenalidomide maintenance in patients with MM undergoing initial bortezomib-based induction chemotherapy and autologous stem cell transplant (ASCT) in a real-world setting.

METHODS

We reviewed patients treated from December 2004 to June 2015 (to ensure 2-year follow-up) based on intention-to-treat. Maintenance chemotherapy included those on lenalidomide or lenalidomide plus bortezomib. Treatment response was assessed according to the IMWG consensus criteria with an endpoint of near CR (nCR) where CR was not confirmed by immunofixation or bone marrow biopsy.

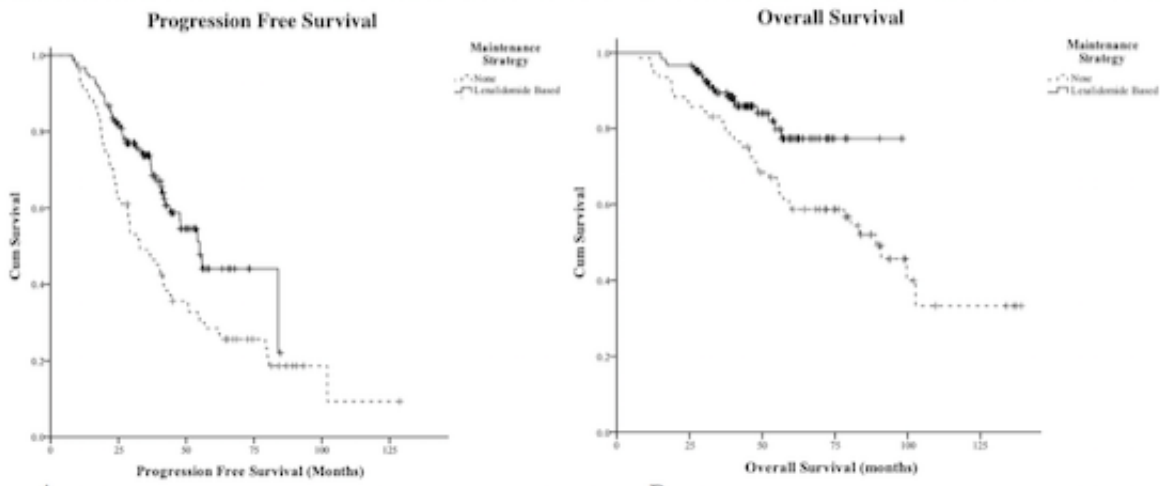
RESULTS

198 patients were analyzed. 121 received lenalidomide based maintenance and 77 received none. Median ISS score was 2 in both groups ($p=0.98$). On average, patients received 25 cycles of lenalidomide (0.5-84). 60% required dose modification due to adverse effects excluding relapse; cytopenias (29.8%), rash (10.7%), infection (9.1%) and fatigue (5.8%). 15% discontinued therapy before relapse. Thromboembolism and second primary malignancies (SPMs) were seen in 3.3% and 1.7% of maintenance patients. Estimated 3-year OS was superior in the maintenance group (88.4% vs 80.5%). Median OS was not reached in the maintenance cohort and was 89mons in the no maintenance group ($p=0.01$). Median PFS was superior in the lenalidomide group (55.0mons vs 32.9mons ($p=0.002$)). In the maintenance cohort 95.0% achieved \geq VGPR (53.7% \geq nCR) compared to 77.9% (29.1% \geq nCR) of the non-maintenance patients ($p=0.03$).

CONCLUSIONS

Our data illustrates the positive impact of lenalidomide on PFS, OS and depth of response. Treatment was well tolerated with low rates of thromboembolism and SPMs. This data supports our ongoing use of lenalidomide-based maintenance helping to further establish this approach as standard of care.

Supervisor: Dr. Christopher Venner



A.
 B.
 Figure 1. Progression free (A) and Overall (B) survival analyzed by status of maintenance therapy in patients treated with bortezomib-based induction therapy and autologous stem cell transplant.

Role of Iron Metabolism in Heart Failure: A focus on Iron-deficiency (Use of Human Explanted Heart Samples)

Hao Zhang, Dr. Gavin Y Oudit, Dr. Shaohua Wang
Supervisor: Dr. Gavin Y Oudit

INTRODUCTION

Heart failure (HF) is highly associated with systemic iron deficiency (ID). HF patients with ID are accompanied with worse physical capacity and exacerbated clinical outcomes; however, the underlying mechanism remains unknown. Intravenous iron administration evidently improves clinical endpoints. Hence, this translational medical study aims to integrate clinical information, laboratory results and experimental data from human heart tissues: 1) to recapitulate the pathophysiological role that ID plays in the progression of HF; 2) and to identify novel HF molecular signatures or potentially curative and affordable treatments to correct ID status in HF patients.

METHODS

Adult (n=165) and pediatric (n=43) failing hearts are collected per HELP protocol, and healthy hearts (n=34) are obtained per HOPE protocol. Iron levels were measured directly from the myocardium, and transmission electron microscopy was used to assess the characteristics of the mitochondria. Meanwhile, the patients' clinical information (eg. co-morbidity, medication), laboratory results (eg. eGFR, creatinine) and biomarkers (eg. BNP) were integrated into the analysis.

RESULTS

The myocardial iron content in LV is significantly lower in the HF patients with ID (ischemic cardiomyopathy (ICM): $96.8 \pm 40.2 \mu\text{g/g}$ (n=12, 7M:5F, LVEF: $32.7 \pm 16.0\%$), dilated cardiomyopathy (DCM): $113.2 \pm 56.2 \mu\text{g/g}$ (n=30, 24M:6F, LVEF: $29.2 \pm 15.6\%$) vs. non-failing control (NFC): $168.7 \pm 32.3 \mu\text{g/g}$ (n=14, 6M:8F, LVEF: $52.3 \pm 9.6\%$)) ($p < 0.05$). ID correlates weakly with systemic hemoglobin (Hb) concentration (ICM: 84g/L, DCM: $116.7 \pm 15.5 \text{g/L}$); however, renal function in DCM group is impaired (eGFR: $77.1 \pm 28.7 \text{ml/min/1.73m}^2$) indicating renal dysfunction. Mitochondrial morphology is also disrupted in iron-deficient failing hearts indicating impaired respiratory/metabolic function and altered myocardial fuel source.

CONCLUSIONS

This study demonstrates that ID is an independent predictor of unfavorable clinical outcomes for HF patients, a translational bridge linking basic research to clinical medicine.

Supervisor: Dr. Gavin Y Oudit

Patients with Primary Biliary Cholangitis (PBC) Make Proinflammatory Cellular Immune Responses to Human Betaretrovirus

Hiatem Abofayed, Dr. Andrew L. Mason
Supervisor: Dr. Andrew L. Mason

INTRODUCTION

Our laboratory is characterizing a human betaretrovirus (HBRV) infection in patients with PBC. Most patients have evidence of HBRV proviral integrations in their bile ducts and respond to anti-retroviral therapy. Peripheral blood, PCR and serological diagnostics are only capable of detecting HBRV infection in a minority of PBC patients, however. To create a diagnostic assay, we addressed the hypothesis that PBC patients' lymphocytes produce IFN- γ when stimulated with HBRV Gag and Env proteins.

METHODS

A library of overlapping 15-mer peptides covering the HBRV Gag (n=58) and Env (n=85) and the characterized mitochondrial autoantigen PDC-E2 epitope were synthesized (Mimotope). Intrahepatic lymphocytes were collected from transplant livers from PBC (n=5) and other liver diseases (n=4). ELISpot was used to measure the number of spot forming colonies (SFC) from IFN- γ producing lymphocytes (n=100,000) following stimulation with individual peptides.

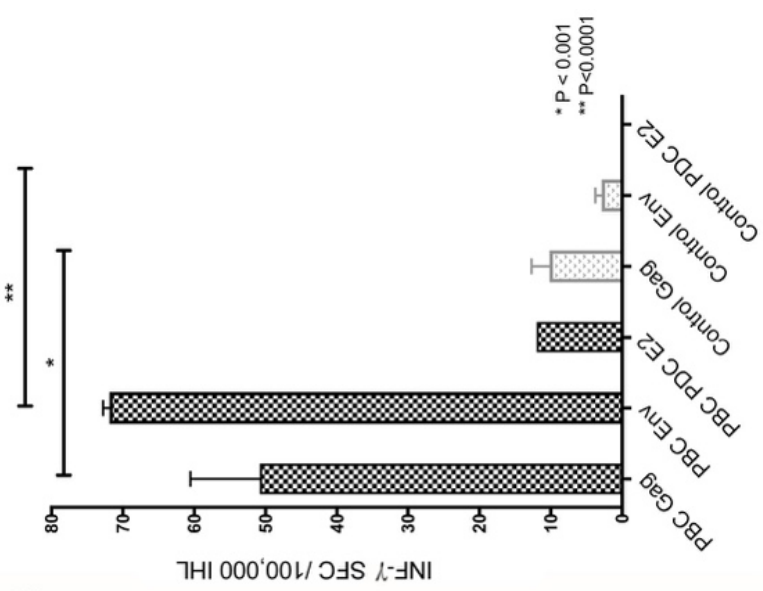
RESULTS

The analyses using 144 peptides identified 15 HBRV Gag and 21 HBRV Env peptides that stimulated the PBC patients' IHL (Figure A). The mean number of IFN- γ producing SFC stimulated with individual peptides was 51 PBC versus 10 controls for HBRV Gag and 72 PBC versus 3 controls for HBRV Env (Figure B: $P < 0.001$ and $P < 0.0001$, respectively). Using a mean cutoff level < 5 SFC, the HBRV Env peptides provided a 100% specificity and sensitivity for detecting HBRV infection, whereas HBRV was less discriminatory. Notably only one patient with PBC had detectable IFN- γ producing IHL following stimulation with the autoantigen mitochondrial autoantigen PDC-E2 peptide.

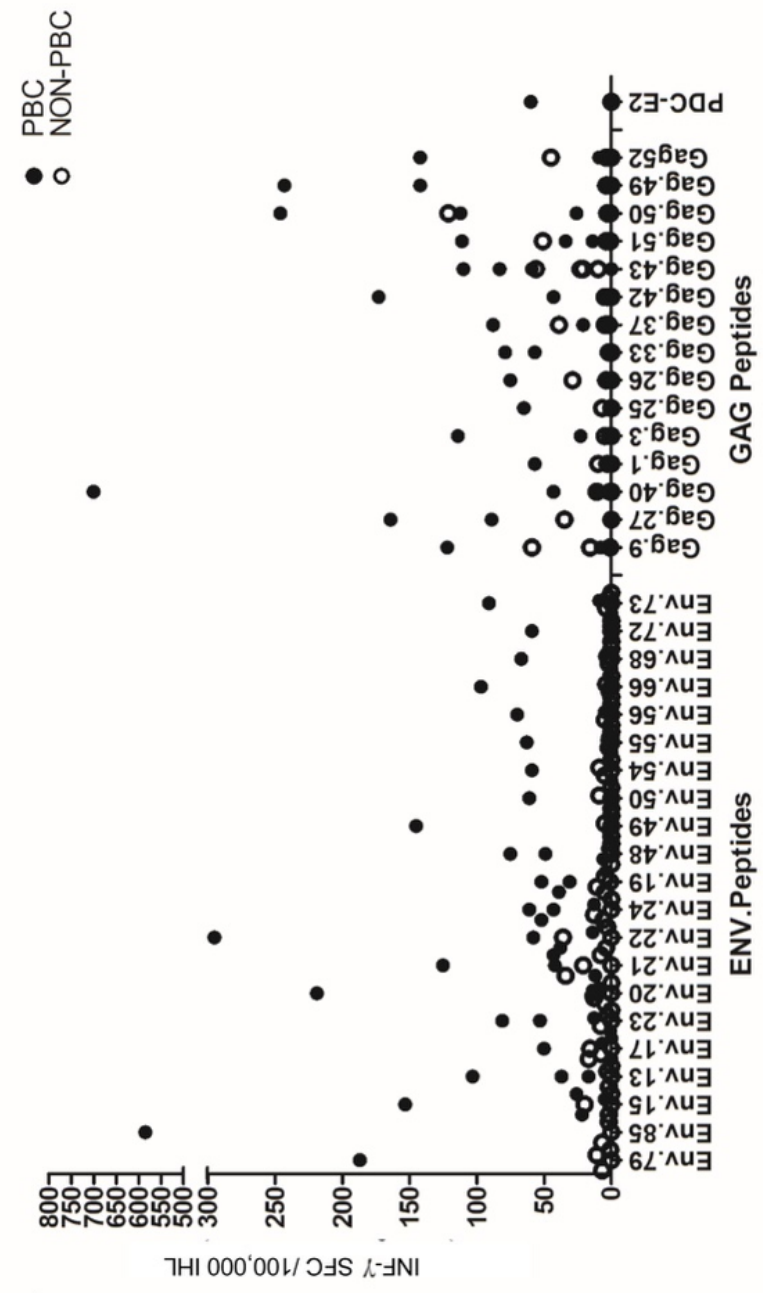
CONCLUSIONS

These are the first data to demonstrate that the intrahepatic proinflammatory cellular immune responses to HBRV greatly exceed the autoimmune response, suggesting that HBRV infection plays an important role in mediating PBC. The identified 15 HBRV Gag and 21 Env peptides are being evaluated using peripheral blood mononuclear cells to measure the IFN- γ release and construct a "Quantiferon" assay

Supervisor: Dr. Andrew L. Mason



B



A

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Alopecia areata secondary to the use of leflunomide in patients with rheumatoid arthritis: a case report and literature review

Ina Cusnir, Jill Hall, Carrie Ye
Supervisor: Carrie Ye

INTRODUCTION

Leflunomide (LEF) is a disease modifying anti-rheumatic drug (DMARD) that has been licensed for the treatment of rheumatoid arthritis since 1998. Commonly reported adverse effects include diarrhea, nausea, hypertension, headache, transient hair loss, and hepatotoxicity¹.

METHODS

We describe a patient with rheumatoid arthritis treated with LEF who developed alopecia areata (AA) and will discuss similar published cases.

RESULTS

We believe the AA was due to the LEF for several reasons. First, notwithstanding the association between MTX and AA, the patient had no history of hair loss prior to initiation of LEF despite long-term use of MTX; second, it resolved following its discontinuation.

We determined this reaction to be “probable” on the Naranjo adverse drug reaction probability scale with a score of 7 out of 13.

Further, 3 similar cases have been reported in the literature.

CONCLUSIONS

LEF-induced alopecia areata appears to be very uncommon, but if identified to be culprit and discontinued, can be reversible.

Supervisor: Dr. Carrie Ye



Rheumatologic immune-related adverse events associated with immune checkpoint inhibitor therapy in cancer care: a case series from an academic center

Janet Roberts, Anna Oswald, Ina Cusnir, Jason Soo, Michael Smylie, Quincy Chu, John Walker, Michael Kolinsky, Naveen Basappa, Carrie Ye
Supervisor: Dr. Carrie Ye

INTRODUCTION

The last decade has seen an exponential increase in the use of immunotherapies in cancer treatment. Immune checkpoints are inhibitory pathways that modulate the immune response and prevent autoimmunity and have proven a successful therapeutic target. Tumor cells use immune checkpoints to their advantage, to evade the endogenous antitumor immune response. Therapeutic targets blocking these pathways, release the brakes on pivotal immune system inhibitory mechanisms, unleashing a robust antitumor response, but risking concomitant induction of a host of immune related adverse events (IRAEs). Data on rheumatologic specific adverse events remains limited.

METHODS

All rheumatologists affiliated with the University of Alberta were contacted and 12 cases, diagnosed with rheumatic IRAEs in the context of ICI therapy, were identified over an 18 month period. Following ethics approval a chart review was conducted and data including clinical presentation, treatment and outcomes collected.

RESULTS

Presentations included; arthralgias (2), arthritis (6), systemic inflammatory reaction (1), sicca (1) and myositis (2). Three patients had pre-existing autoimmune disease. Malignancy types included: metastatic melanoma (4), metastatic squamous cell (1), non small-cell lung cancer (4), urothelial (1), metastatic renal cell (1) and hepatocellular carcinoma (1). All patients received either a cytotoxic t-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1) inhibitor, either alone or in combination. All patients were antibody negative. Treatments included systemic glucocorticoids, local steroid injections and disease-modifying anti-rheumatic drugs (hydroxychloroquine, methotrexate and sulfasalazine). Nine patients discontinued immunotherapy due to adverse events. Eight patients had sustained stability of their underlying malignancy, 3 had disease progression and there was one death.

CONCLUSIONS

Rheumatic IRAEs are an important complication of ICIs. Collaboration between centers is required to identify trends in presentation, treatment and outcomes to guide the development of treatment recommendations.

Supervisor: Dr. Carrie Ye

Low incidence of device related infections with peri/post-operative antibiotic use in CRT-P/D and ICD Implants

Jessica Wijesundera, Janek Senaratne, Usha Chhetri, Diane Beaudette, Andrea Sander, Mike Hanninen, Sajad Gulamhusein, Mano Senaratne
Supervisor: Mano Senaratne

INTRODUCTION

Higher device related infections (DRI) incidence has been observed with CRT-P/D and ICD devices compared to traditional pacemakers with a 1.2% rate reported at 1 year (Europace 2012;247:71-76). DRI management in this elderly population is costly and has higher morbidity/mortality. A previous study from this institution demonstrated a significantly reduced DRI rate when peri/post-operative antibiotics were given at traditional pacemaker implantation (PACE 2014;37:947-54). This study examined DRI incidence following peri/post-operative antibiotics during CRT-P/D and ICD implantations.

METHODS

The study included all patients who underwent CRT-P/D and ICD implantations from 1996–2015. Patients received IV cephalexin/clindamycin pre- and 8-hours post-procedure followed by five days of oral therapy. Data was collected prospectively in a SPSS database.

RESULTS

There were 288 new implants (CRT-P = 107 (37.2%); CRT-D = 82 (28.5%); ICD = 99 (34.4%)). Age at implantation was 61.6 ± 0.7 years (mean \pm SEM); Males = 212 (73.6%); Females = 76 (26.4%). All patients (excluding those who moved out-of-province or died) had a minimum follow-up period of 1 year. DRI occurred in 6 patients (ICD = 4, CRT-P = 1, CRT-D = 1), amounting to a rate of 4.3/1000 device-years. Five were pocket infections while one patient had endocarditis. Times to DRI from implantation were: 1.7, 3.5, 6.7, 7.3, 7.9 and 9.2 years. All pocket infections occurred in patients with repeat procedures.

CONCLUSIONS

This study demonstrates that administration of peri- followed by post-operative antibiotics during CRT-P/D and ICD implantations is associated with a very low rate of DRI. This rate of 4.3/1000 device-years compares favorably to contemporary rates (8.9/1000 device-years for ICD implants – Arch Int Med 2007;167:669-75) with no DRI within the first year following implantation. This approach should be considered pending a definitive trial in view of the increasing incidence of DRI.

Supervisor: Dr. Mano Senaratne

Determining a stimulation paradigm using intermittent electrical stimulation as a prophylactic method for deep vein thrombosis

Kahir A. Rahemtulla, Dirk G. Everaert, Vivian K. Mushahwar
Supervisor: Dr. Vivian Mushahwar

INTRODUCTION

Deep vein thrombosis (DVT), affects approximately 45,000 Canadians a year. Of specific concern are patients who are immobilized and cannot seek the aid of anti-coagulants due to hemorrhaging risks, or compression devices due to discomfort. We propose using intermittent electrical stimulation (IES) as an alternative intervention for activating the muscle pump in the leg to increase venous blood flow and prevent stasis, an accepted cause of DVT. The objective of this study was to determine the required level of stimulation to increase venous blood velocity from baseline to a pre-determined 8-fold target to reduce stasis.

METHODS

Ten able-bodied subjects were recruited for this study. The stimulation paradigm consisted of stimulating the gastrocnemius and the tibialis anterior muscles in sequential order, with a 35 Hz biphasic pulse and a pulse width of 300 μ s, on the subject's right leg. Stimulation intensity of the gastrocnemius was modulated to produce a recruitment curve. At each stimulation intensity tested, Doppler ultrasound was used to measure the peak and baseline venous blood velocity in the popliteal vein of the right leg. During stimulation, plantarflexion forces generated by gastrocnemius contractions were measured using an in-house built apparatus. Three recruitment curves were obtained per subject. A questionnaire was used to determine the subject's comfort level.

RESULTS

An 8-fold increase in peak venous blood velocity from baseline was observed for a 30% of maximum voluntary plantar flexion contraction. This fold increase was determined to be sufficient to increase venous velocity sufficiently at the femoral vein based on previous work. The questionnaire showed discomfort to the stimulation being "very little" to "moderate."

CONCLUSIONS

A suitable increase in venous blood velocity is achieved at comfortable stimulation levels. Further research is required in rehabilitation and acute care settings to further determine the feasibility of IES as a method of prophylaxis for DVT.

Supervisor: Dr. Vivian Mushahwar

VDD Pacing in Atrio-Ventricular Nodal(AVN) Block - An Overlooked Alternative to DDD Pacing

Kalutota S Samarasinghe, Usha Chhetri, Diane Beaudette, Andrea Sander, Deb Sawyer, Deanna Moir, Sajad Gulamhusein, Mikael Hanninen, Janek Senaratne, Manohara Senaratne
Supervisor: Dr. Manohara Senaratne

INTRODUCTION

VDD pacing is an alternative to DDD pacing in patients with atrioventricular block (AVB) with preserved sinus node (SN) function. Although VDD pacing offers advantages of lower costs, shorter implantation times, lower radiation exposure and lower pneumothorax rates, it is used less often due to concerns regarding loss of atrial sensing.

METHODS

Patients with AVB and no history of SN dysfunction or recurrent atrial fibrillation were selected for VDD pacing at Grey Nuns Hospital. Only patients with a minimum follow-up of 1 year were included to ensure all early failures were captured.

RESULTS

Between 1990-2014, 316 VDD pacemakers were implanted. 283 patients were analyzed while 33 patients (10.4%) were lost to follow-up due to moving out of province. Mean follow-up duration was 5.9 ± 0.3 years (SEM) amounting to a total of 1680.5 patient-years. Death occurred in 99 patients, with a mean duration to death of 4.7 ± 0.4 yrs. No deaths occurred due to implantation complications. Reprogramming to VVIR was done in 47 patients (16.6%) due to atrial fibrillation in 21 (7.4%); atrial malsensing in 26 (9.2%) - 1 event per 64.6 patient-years. Eight (2.8%) malsensing events occurred within 3 months of implantation and 4 (1.4%) between 3-12 months. Only 1 (0.4%) patient required implantation of an atrial lead due to the development of pacemaker syndrome.

CONCLUSIONS

This study demonstrates VDD pacing can be a viable alternative to DDD pacing in patients with AVB and intact SN function. Although 7.4% required a change to VVIR due to atrial fibrillation, a similar rate would be expected in DDD pacing. The rate of reprogramming to VVIR due to atrial malsensing was low, at 1 event per 64.6 patient-years. The 4.2% atrial malsensing rate within 1 year of implantation compares favorably with the reported 3-4% rate of atrial lead malfunction/dislodgement that may necessitate reoperation.

Supervisor: Dr. Manohara Senaratne

MOLECULAR ARCHETYPE HETEROGENEITY IN ULCERATIVE COLITIS BIOPSIES

Katelynn Madill-Thomsen, Simone Withecomb, Michael Parkes, Vojislav Jovanovic, Jeffery Venner, Richard Fedorak, Philip Halloran, Brendan P. Halloran
Supervisor: Dr. Phil Halloran

INTRODUCTION

Current assessment of patients with ulcerative colitis (UC) lacks the granularity to correlate strongly with response to therapy. Utilizing a microarray based system for colonic epithelial assessment we looked for stratification of endoscopically similar UC biopsies using molecularly heterogeneous archetypes.

METHODS

Molecular data from 71 UC biopsies (61 patients) was obtained using microarrays. Top 300 transcripts correlating with the endoscopic Mayo score (2/3 versus 0/1) were used for an unsupervised analytical method called archetypal analysis (AA). Logistic regression modeling was used to compare archetype scores or cluster membership to endoscopic Mayo score and PC1 in predicting mucosal healing. A contingency table was generated to show evidence of mucosal healing within each of the archetype clusters. We assessed a subset of serial biopsies from the original 71 (selected by availability of biopsies before and after therapy) plus one IBDU case. Patients were classified as 'responders' (Mayo 2/3 to Mayo 0/1) or 'non-responders' (Mayo 2/3 that did not decrease to 0/1).

RESULTS

We found three unique clusters of biopsies using AA (A1: lack of inflammation, A2: inflammation and response to wounding, A3: inflammation). Logistic regression showed that the only models with significant predictive value (p -value < 0.05) were those that contained archetype scores or cluster membership. Response rates differed significantly between archetype clusters (Table 1), while the mayo score distribution within these clusters was similar. In our subset of serial biopsies, most initial biopsies had an A2 archetype, moving to an A1 archetype in follow-up that mirrored response to treatment (Figure 1).

CONCLUSIONS

AA suggests there is potentially important heterogeneity in UC biopsies that is not accessible by endoscopic Mayo score. Serial biopsies showed dynamic shifts in the archetype composition between biopsies. This may be a useful tool for both initially prognosticating patients and assessing response to treatment over time with increased granularity and reliability.

Supervisor: Dr. Phil Halloran

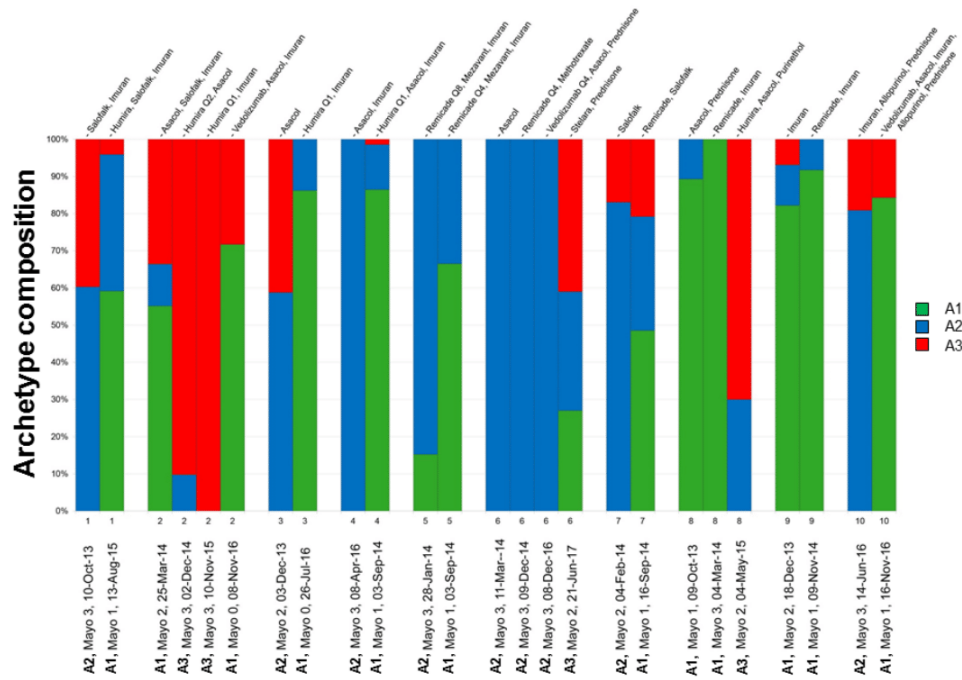


Figure 1. Changes in archetype composition over time in serial biopsies taken from 10 different UC patients with changing therapies.

| Archetype Cluster (Total cases) | # of cases improved* |
|---------------------------------|----------------------|
| A1 (4) | 4 (100%) |
| A2 (16) | 10 (62%) |
| A3 (6) | 1 (17%) |

All cases had a Mayo score of 2-3 on initial endoscopy.
 *score of 0-1 on follow up endoscopy.
 Pearson's Chi-Squared = 7.222, df = 2, p = 0.027

Significant lung injury and its prognostic significance in acute liver failure

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C.J. Karvellas⁸
Supervisor: Dr. Dean Karvellas

INTRODUCTION

Respiratory failure is a concerning complication of acute liver failure (ALF) and high oxygen requirements often preclude ALF patients from undergoing liver transplantation (LT). The aim of this study was to evaluate the association between significant lung injury (SLI) and important clinical outcomes including 21-day overall survival and transplant-free survival (TFS) and rates of LT in ALF patients.

METHODS

Retrospective cohort study of 947 ALF patients with chest x-ray (CXR) and arterial blood gas (ABG) data enrolled in the US Acute Liver Failure Study Group (US-ALFSG) from January 1998 through December 2016. ALF patients were stratified as having SLI if there was the presence of hypoxemia ($\text{PaO}_2/\text{FIO}_2 < 200$ mmHg on ABG) and abnormalities on CXR. Primary outcomes were 21-day TFS and overall survival along with listing for and receipt of LT.

RESULTS

Of 947 ALF patients, 370 had evidence of SLI while 577 did not. ALF patients with SLI (ALF-SLI) had significantly worse oxygenation than controls on admission (120 vs. 300 mmHg, $p < 0.001$) and worse biochemical derangement reflected by median bilirubin (7.3 vs. 6.3 mg/dl, $p = 0.04$), creatinine (2.3 vs. 1.8 mg/dl, $p < 0.001$), and lactate (6.1 vs. 4.6 mmol/l, $p = 0.0008$). ALF-SLI patients were less likely to receive LT (18% vs. 25%, $p = 0.02$) and had significantly decreased 21-day TFS (34% vs. 42%, $p = 0.006$) and overall survival (49% vs 64%, $p < 0.0001$). After adjusting for significant covariates, the development of SLI was independently associated with decreased 21-day TFS (OR 0.68, $p = 0.01$) in ALF patients.

CONCLUSIONS

SLI is a relatively common complication in ALF patients. SLI significantly lowers 21-day overall survival and TFS as well as rates of LT in ALF patients. SLI is an independent predictor of lower 21-day TFS in patients with ALF. This suggests that the development of SLI in ALF patients could negatively affect outcomes.

Supervisor: Dr. Dean Karvellas

A Mixed-Method, Randomized, Waitlist Control Trial for the Strength, Hope and Resourcefulness Program for People with Parkinson's (SHARP PWP)

Miyasaki, J., Larsen, D., Murdoch, K., Howell, A., Joyce, A., Edey, W., Arsenault, C., Sandham, T

Supervisor: Dr. Janis Miyasaki and Dr. Denise Larsen

INTRODUCTION

Parkinson Disease (PD) is the second most common neurodegenerative disorder in North America. Although recognized for its effect on movement, PD has several non-motor symptoms including depression, anxiety, and apathy. PD has no cure and clinical treatment is focused upon symptom management and improving quality of life. Despite this focus, virtually no research examines specific interventions to promote psychological well-being in patients. This study examines the effects of a six-session Strength, Hope, and Resources Program for People with PD (SHARP-PWP) based on principles of positive psychology. The authors aimed to answer the following research questions: (a) does SHARP-PWP (with Usual Treatment (UT)) improve overall well-being and mental health compared to a control group (UT only)? (b) what are the processes that occur in SHARP-PWP in relation to well-being?

METHODS

The authors utilized a mixed-method design to examine the effects of a randomized waitlist-controlled trial of SHARP-PWP. 31 patients with a diagnosis of PD within the last five years (average age=66; 13 men, 18 women) were eligible to participate. Multiple self-report measures to track mental health and well-being were administered to both treatment and waitlist groups. After the program, 16 participants were interviewed for qualitative analysis. A two-factor mixed ANOVA was used to analyze quantitative data while qualitative data were analyzed using Interpretive Description, a common method used in qualitative health research.

RESULTS

Preliminary qualitative findings reveal outcomes in various domains including perspective, identity, relationships, and strengths. Several processes were identified including promotion of safety and comfort, universality, comparison, resource networking, emotional release, and an intentional, active hope focus. Quantitative data analysis is currently underway but will be presented and discussed.

CONCLUSIONS

The program in this study can be taught to patient support groups to improve resilience and optimism among those newly diagnosed. This in turn, will help PD patients engage effectively in their healthcare and improve quality of life.

Supervisor: Dr. Janis Miyasaki and Dr. Denise Larsen

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Prevalence of and the influence of gender and ethnicity on depression in patients attending a cardiac rehabilitation program

Keshani De Silva, Janek Senaratne, Tracy Rai, Rhonda Lightfoot, Lena Kirincic, Wendy Reinhardt, Karen Macdonald, Mano Senaratne
Supervisor: Dr. Mano Senaratne

INTRODUCTION

Depression is known to adversely affect outcomes in patients with cardiac disease. It remains underrecognized and undertreated. The Beck Depression Inventory (BDI) has been validated to screen for depression. The purpose of the present study was to elucidate the prevalence of and factors influencing depression in patients attending a cardiac rehabilitation program, (CRP).

METHODS

Patients attending CRP from 2003-2016 at Grey Nuns Hospital were included. All patients had a BDI performed prior to CRP. Data were collected prospectively and entered into an SPSS database.

RESULTS

The BDI for the 5065 pts (mean age: 61.3 ± 0.1 years; Males = 76.2%) was: 0-9 (normal) = 3665 (72.4%); 10-18 (mild depression) = 1007 (19.9%); 19-29 (moderate depression) = 306 (6.0%); 30-63 (severe depression) = 87 (1.7%). The BDI (mean \pm SEM) for males (mean age: 60.8 ± 0.1 yrs) and females (mean age: 63.4 ± 0.3 yrs) were 7.0 ± 0.1 and 8.5 ± 0.2 ($p < 0.001$), respectively. The BDI for Caucasians (CA), South Asians (SA), and East Asians (EA) were 7.3 ± 0.1 , 8.0 ± 0.3 , and 7.0 ± 0.3 , respectively ($p = 0.01$ for CA versus SA by one-way ANOVA and least significant difference test). A BDI of ≥ 10 was observed in 26.8%, 32.0%, and 23.1% of CA, SA, and EA respectively ($p = 0.01$). The mean ages for CA, SA, and EA were 61.6 ± 0.1 yrs, 60.5 ± 0.3 yrs and 59.8 ± 0.8 yrs, respectively. The proportion of females amongst CA, SA, and EA groups were 24.0%, 22.5%, and 22.4%, respectively ($p > 0.05$).

CONCLUSIONS

The prevalence of depression is high in patients attending CRP affecting 27.6% of the population. Depression is more frequent in females and SA. The higher prevalence in SA was not accounted for by differences in age or gender. The SA group especially may warrant extra scrutiny given language barriers which may hamper diagnosis.

Supervisor: Dr. Mano Senaratne

Utilization of prophylactic Azithromycin in patients with frequent COPD exacerbations

Liu, Kevin; Hirji, Alim
Supervisor: Dr Alim Hirji

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has been identified as the 4th leading cause of death, in both Alberta and Canada , and leading cause of readmissions to hospital .

Multiple trials have shown that the use of maintenance Azithromycin reduces the frequency of acute exacerbations of COPD (AECOPD) . We hypothesize that patients who suffer from frequent AECOPDs (≥ 2 admission per year) are under-prescribed Azithromycin maintenance therapy at our institution.

METHODS

We reviewed all patients admitted to the University of Alberta Hospital with a diagnosis of COPD From September 1, 2015 to September 1, 2016. We included patients with 2 or more admissions and a minimum of 5 Emergency Department (ED) visits for AECOPD within the study period. Medication lists were gathered using discharge prescriptions and provincial medication PIN profiles.

RESULTS

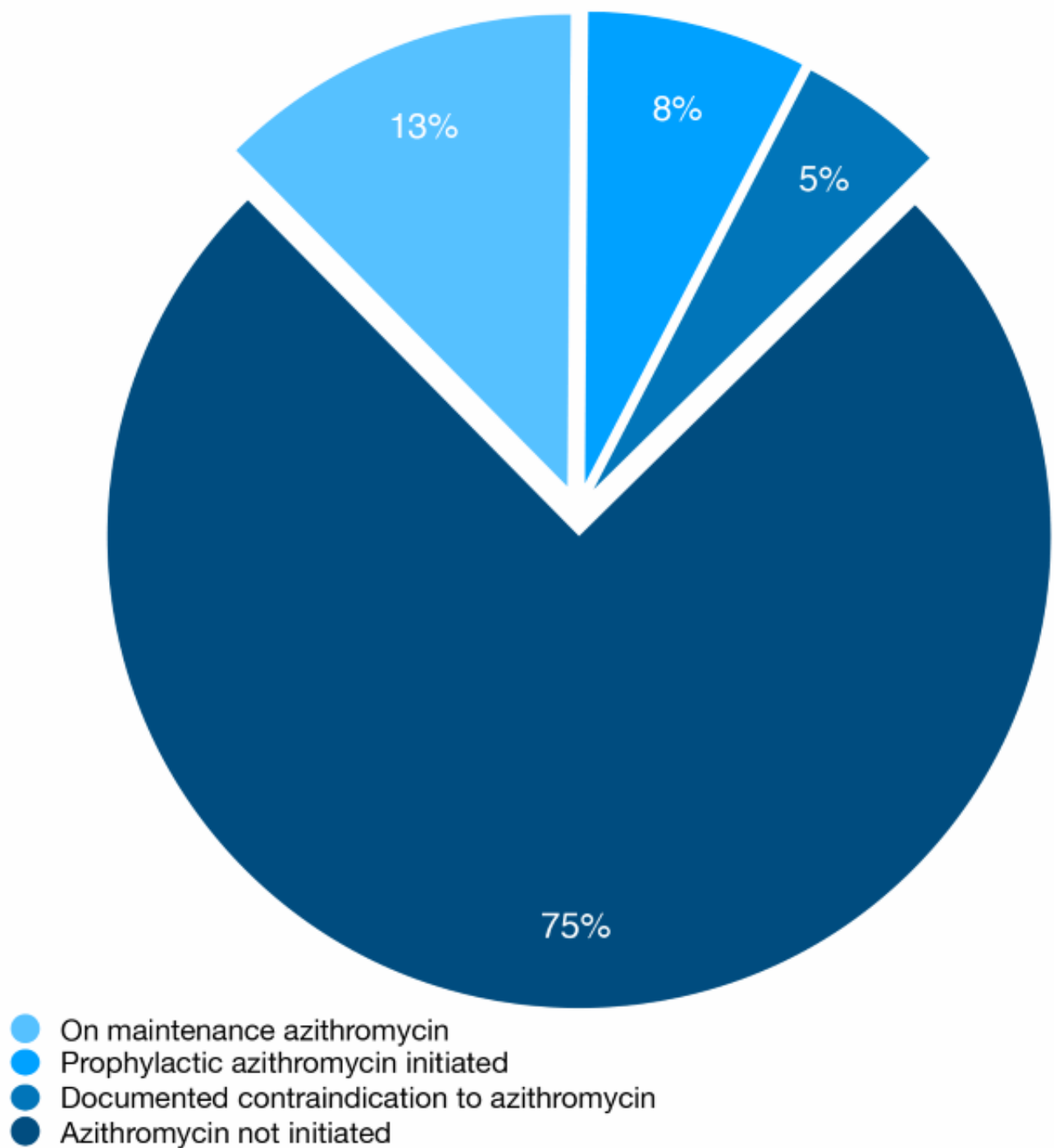
There were 496 admissions for AECOPD during the study period, including 66 patients with ≥ 2 admissions for AECOPD. 40 of these patients had at least 5 ED visits. Of this group, 5 patients (12.5%) were on maintenance Azithromycin prior to the study period. 2 patients (5%) had a documented contraindication to Azithromycin (Long QTc). 3 patients (8%) were initiated on Azithromycin therapy. For the remaining 30 patients (75%), Azithromycin prophylaxis was not prescribed despite frequent acute care visits during the 1-year period (Figure 1).

CONCLUSIONS

Despite strong evidence advocating for the use of daily maintenance Azithromycin for COPD patients with frequent exacerbations, our study cohort revealed surprisingly poor uptake of this management strategy.

Supervisor: Dr Alim Hirji

Figure 1. Maintenance azithromycin prescribing practices for patients with frequent COPD exacerbations



Cockroach Extract Proteolytic Activity Down-regulates Interleukin-13 Dependent Eotaxin-3 (CCL26) in Airway Epithelial Cells

Khadija Alzahrani, Vivek Gandhi, Cheryl Laratta, and Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Asthma is an inflammatory disease of the airways in which innate and adaptive immunity play important roles. The airway epithelium is the main barrier between the host and inhaled allergens, and its activation by allergens is a key step towards the activation of innate and adaptive immunity. Cockroach allergens can activate epithelial cells through multiple receptors and induce primarily pro-inflammatory effects. IL-13, an important mediator in asthma, also activates epithelial cells and induces a potent eosinophil chemoattractant, eotaxin-3 (CCL26). The interactions between the effects of IL-13 and cockroach allergens on airway epithelium have not been studied.

METHODS

A bronchial epithelial cell line (BEAS-2B) and normal human bronchial epithelial cells (NHBE) were cultured in pre-coated multi-well plates and stimulated with IL-13, CE or both, when 80-90% confluent. CCL26 mRNA was measured by qRT-PCR and the release of CCL26 protein by ELISA. To test the role of CE proteases, heat inactivated CE (HICE), boiled CE or CE pre-incubated with protease inhibitors were used. Western blotting used to assess STAT-6 phosphorylation and IL-13 protein degradation.

RESULTS

CE prevented IL-13-mediated up-regulation of CCL26 mRNA and protein from BEAS-2B and NHBE cells in a time and dose dependent manner. HICE and CE pre-incubated with aprotinin, an inhibitor of trypsin-like serine proteases, did not inhibit IL-13 mediated CCL26 mRNA induction. CE did not prevent the immediate activation of STAT6 by IL-13. Western blot detected early onset degradation of IL-13 protein by CE in the presence of aprotinin or with HICE but not with boiled CE.

CONCLUSIONS

CE inhibits IL-13-mediated CCL26 up-regulation. This effect is mediated by a trypsin-like protease activity in CE. Trypsin like activity inhibitors prevent CE effect to inhibit IL-13-induced CCL26 mRNA and protein expression but do not inhibit IL-13 protein degradation. So, CE trypsin like activity prevents IL-13-induced CCL26 expression in a degradation independent manner.

Supervisor: Dr. Harissios Vliagoftis

IgG-4 Related Mononeuritis Multiplex and Review of the Literature

L. Tsang and E. Yacyshyn
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

IgG4-related diseases (IgG4-RD) are uncommon but can affect the pancreas, salivary gland, and lacrimal glands, with increasing cases involving other tissues described. Features of IgG4-RD include: subacute painless swelling, dense tissue infiltration of IgG4 plasma cells and small lymphocytes, storiform fibrosis, obliterative phlebitis, tissue eosinophilia, elevated serum IgG4 levels, and responsiveness to glucocorticoid therapy.

METHODS

RESULTS

A previously healthy 47-year old male presented with mononeuritis multiplex initially with unilateral peroneal neuropathy, and rapidly progressed to include bilateral ulnar neuropathies. Imaging and laboratory investigations were unremarkable, including negative ANCA, ANA, RF, ENA, cryoglobulin screen, and normal CRP, SPEP, ACE level, and free kappa lambda chain assay. Infectious work-up including Hepatitis B and C, syphilis, HIV, and Lyme disease were negative. His electromyography demonstrated severe ulnar nerve axonal damage with complete atrophy of the abductor digiti minimi muscle, and a persistent peroneal nerve palsy. Sural nerve biopsy revealed non-specific inflammatory infiltration (lymphoid predominant) with the presence of eosinophils.

He subsequently developed recurrent episodes of pancreatitis. Computerized tomography scan of the pancreas was modestly enhanced, and concerns for primary autoimmune pancreatitis could not be ruled out.

Given his rapid progression of neuropathy, he received intravenous immunoglobulins, glucocorticoids and cyclophosphamide, then transitioned to methotrexate maintenance therapy with gradual improvement in neuropathy. Serum IgG-4 level was elevated at 1.00g/L while on methotrexate, which raised suspicion for IgG-4 RD. However, his sural nerve could not be re-stained for IgG-4 levels and a repeat biopsy was not indicated.

CONCLUSIONS

Our patient presented with possible IgG4-RD as the etiology for his mononeuritis multiplex and recurrent pancreatitis. To date, there is one confirmed cases of IgG-4 related mononeuritis multiplex reported in the literature (Ohyama et al. (2013)). Therefore, as IgG4-RD gain recognition, it should be included in the investigation of mononeuritis multiplex.

Supervisor: Dr. Elaine Yacyshyn

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Targeting STAT5 in Acute leukemic cells with siRNA

Mahsa Mohseni (a), Cezary Kucharski (b), Remant Bahadur KC (b), Hasan Uludag (b,c), Joseph Brandwein (d)*
Supervisor: Dr. Joseph Brandwein

INTRODUCTION

Development of novel acute leukemia therapy is urgently needed due to poor prognosis and high relapse rates of current therapies (1, 2). Transcription factors including Signal Transducer and Activator of Transcription (STAT)- protein family members are key molecular targets for acute leukemia, since they can activate expression of oncogenes leading to aberrant proliferation of cancer cells (1). In hematological malignancies, downregulation of STAT5 can decrease proliferation of leukemia cells (1, 2). Small interfering RNA (siRNA) mediated silencing of these targets has become a promising alternative due to its specificity and high degree of safety (3). In this study, we evaluated therapeutic role of STAT5 inhibition in acute leukemic cell lines by polymeric siRNA delivery systems.

METHODS

Acute myeloid MOLM13 and Acute lymphocytic NALM-6 leukemia cells were used. Lipid-modified low molecular weight polyethyleneimine (PEI) polymers were used as siRNA carriers. Cell proliferation was assessed by MTT assay, Cellular uptake by Flow Cytometry and STAT5 knockdown at mRNA level by RT-qPCR.

RESULTS

Specific lipid substituted 2 and 1.2 kDa PEI (2PEI and 1.2PEI) displayed excellent complexation properties with siRNAs to form nanoparticles and gave high siRNA uptake in both cells with negligible toxicity. There was a good correlation in uptake between the two cell types. Cell growth was reduced (90%) by STAT5 siRNA delivery in MOLM13 cells using 1.2PEI-lipid polymer, however, STAT5 downregulation was not enough to cause cell death in NALM6 cells. Though some polymers showed higher uptake, STAT5 gene expression was strongly downregulated (60-70%) with leading polymers and silencing effect was higher on day 6.

CONCLUSIONS

We demonstrated effective delivery of STAT5 siRNA by polymeric nanoparticles into leukemia cells, accompanied by marked inhibition of STAT5 gene. Further experiments will be directed at evaluating STAT5 protein silencing by siRNA therapy and exploring the effect of STAT5 downregulation on leukemic patient samples.

Supervisor: Dr. Joseph Brandwein

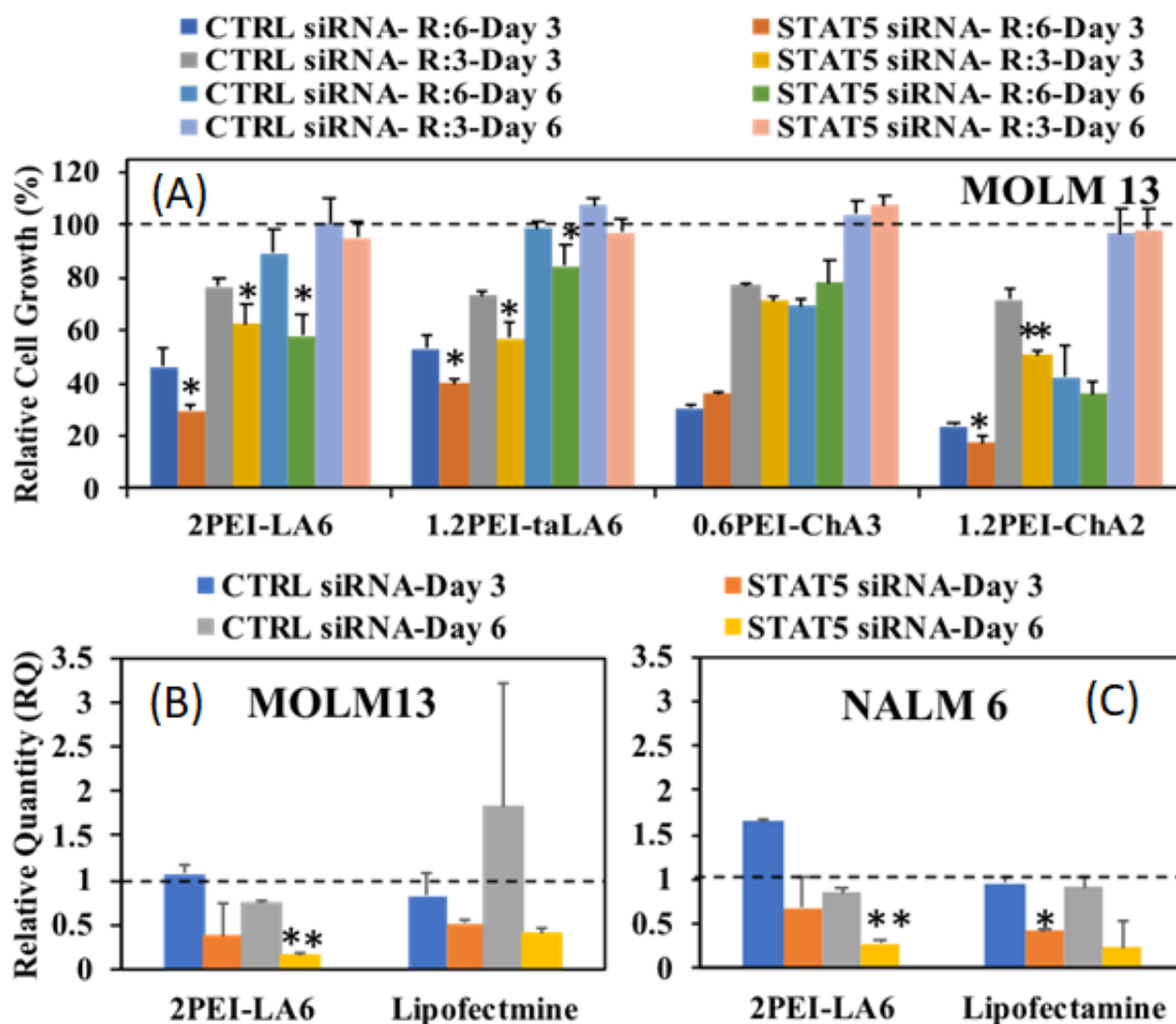


Figure: (A) Effect of siRNA/polymer complexes on proliferation of MOLM 13 cells. Cells were treated with wt/wt ratios of 6 and 3 of siRNA/polymer groups and 50 nM of Control/STAT5 siRNA for 3 and 6 days and cell growth was measured by the MTT Assay and expressed relative to non-treated cells (taken as 100%). The specific effect of STAT5 siRNA (indicated by significant differences “*” between Control and STAT5 siRNA groups) was better manifested by 2PEI-LA6 polymer delivery on both day 3 and day 6. *, $p \leq 0.04$; **, $p \leq 0.001$. (B and C) STAT5 mRNA levels after siRNA treatment. The relative STAT5 mRNA levels (relative to β -actin as an internal control) were quantified through RT-qPCR. MOLM 13 (B) and NALM 6 (C) cells were treated with 50 nM of STAT5/CTRL siRNA (with 2PEI-LA6 at ratio of 6) for 3 and 6 days and RQ values of mRNA are plotted relative to non-treatment group. Lipofectamine™ 2000 was used as a reference (commercial) delivery reagent. *, $p \leq 0.007$; **, $p \leq 0.0007$.

A Great Mimicker: Pitfalls for Rheumatologists in the Diagnosis of Whipple's Disease

Martha Decker, Bohdan Savaryn, Stan Houston, Julinor Bacani, Carrie Ye
Supervisor: Dr. Carrie Ye

INTRODUCTION

Whipple's disease is a systemic infectious disease caused by *Tropheryma whipplei* involving arthralgias, malabsorption, diarrhea, and weight loss. Articular and constitutional symptoms are common and may precede other symptoms by several years.

METHODS

We review a case of Whipple's disease which presented as fever of unknown origin (FUO) mimicking malignancy and large vessel vasculitis (LVV), puzzling multiple specialists for several years.

RESULTS

A 58 year-old woman with a 38-year history of refractory epilepsy, resulting in temporal lobectomy, was referred to our rheumatology clinic for 5 years of FUO and arthralgias after investigations for malignancy and infection were negative. A CT scan of the abdomen showed mesenteric and retroperitoneal lymphadenopathy. Two separate excisional biopsies of mesenteric lymph nodes showed no malignancy or infection. A 4.3cm ascending aortic aneurysm was seen on CT scan, suspicious for LVV.

The fevers were associated with increased seizures and repeated hospital visits. The fevers resolved on a trial of oral prednisone, but recurred with tapering doses. Prednisone was discontinued after PET scan failed to show vasculitis. CT-angiogram was negative for aortic aneurysm and on reassessment of previous imaging, this finding was due to artifact from adjacent lymphadenopathy.

Repeat core biopsy of a mesenteric lymph node revealed prominent histiocytes with periodic acid-Schiff (PAS)-positive intracellular material. Electron microscopy showed intra- and extra-cellular bacilli, consistent with *T. whipplei*. PCR for *T. whipplei* was positive from both lymph node and CSF, confirming Whipple's disease. Atypically, duodenal biopsy was negative for Whipple's disease. She was treated with ceftriaxone for two weeks then long-term doxycycline and hydroxychloroquine. The patient's epileptic control improved on therapy raising the suspicion that the seizure disorder was due to Whipple's disease.

CONCLUSIONS

Rheumatologists need to have a high index of suspicion for Whipple's disease. Potential pitfalls in diagnosis include absence of abdominal symptoms, short-term response to prednisone therapy, and the need for pathologist-led specialized testing of tissue.

Supervisor: Dr. Carrie Ye

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Mechanism of CLIC5A-dependent PI4,5P2 generation

Md. Mizanur Rahman, Laiji Li, Barbara J. Ballermann
Supervisor: Dr. Barbara Ballermann

INTRODUCTION

CLIC5A, (chloride intracellular channel 5A), activates ERM (ezrin radixin moesin) proteins in kidney glomerular podocytes and inner ear sensory hair cells. ERMs help shape cellular structures like sensory stereocilia and podocyte foot processes. Patients and mice with CLIC5A loss of function develop deafness, vestibular dysfunction and kidney disease, and CLIC5A deletion in mice potentiates hypertension-induced glomerular injury. The CLICs actually are NOT ion channels and their functions remain poorly understood. Since ERM activation requires docking on phosphatidylinositol-4,5 bisphosphate (PI4,5P2), and since we found that CLIC5A activates ERMs through Rac1-dependent PI4,5P2 generation, we investigated how CLIC5A, Rac1 and the PI4P5 kinases (PI4P5K) interact. Hypothesis:ERM-specific PI4P5K activation by Rac1 depends on CLIC5A.

METHODS

Wild-type (WT), constitutively active (Q61L) and dominant negative (T17N) GFP-Rac1, WT-CLIC5A, and HA-PI4P5K α were expressed in COS7 and HEK293 cells. Proteins were pulled from cell-, or WT- and CLIC5A-deficient mouse kidney lysates with GST-CLIC5A, or bead-immobilized PAK Binding Domain (PBD). The PBD specifically binds Rac1/GTP, but not Rac1/GDP.

RESULTS

GST-CLIC5A pulled GFP-Rac1 from cell lysates, without preference for WT, Q61L, or T17N Rac1, but CLIC5A did not interact directly with His-Rac1 or His-Rac1/GTP in vitro. GST-CLIC5A pulled HA-PI4P5K α protein and activity from cell lysates. When Rac1 was GTP γ S loaded, endogenous PI4P5K α , β and γ all associated with immobilized PBD whether CLIC5A was present or not. However, immobilized PBD pulled PI4P5K α 2 and active ERM only from WT, not CLIC5A deficient mouse kidney lysates, while PI4P5K β and PI4P5K γ associated with the PBD beads with or without CLIC5A.

CONCLUSIONS

In vivo, CLIC5A is required to form Rac1/GTP-ERM-PI4P5K α 2 complexes, but not for assembly of GTP/Rac1-PI4P5K β or -PI4P5K γ complexes. As GTP-loading of Rac1 is sufficient for its interaction with all PIP5Ks, the data suggest that CLIC5A indirectly stimulates GTP loading of the Rac1 subset that specifically activates PI4,5P2 generation by ERM-associated PI4P5K α 2.

Supervisor: Dr. Barbara Ballermann

Use of Prebiotics, Probiotics and Dietary Fibre Supplements in Inflammatory Bowel Disease

Melissa Silva, Richa Chibbar, Jens Walter, Karen J. Goodman, Ammar Hassanzadeh Keshteli, Rosica Valcheva, Levinus A. Dieleman
Supervisor: Dr. Levinus Dieleman

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory conditions of the intestines induced by abnormal immune responses to resident intestinal bacteria in genetically susceptible hosts. Probiotics, prebiotics and dietary fibres (PPF) alter the gut microbiota and have the potential to change the disease course. Although the role of these compounds in the treatment of IBD is relatively understudied, anecdotal evidence suggests widespread, undocumented use by patients. The aim of the study was to assess PPF use and awareness in IBD patients in association with disease course.

METHODS

We conducted a cross-sectional study using a self-administered 20-item questionnaire and chart review for patients with a diagnosis of IBD in the University of Alberta IBD Clinic. We ascertained demographics, disease characteristics, awareness and PPF use by questionnaire and abstracted disease diagnosis, flare frequency and fecal calprotectin (FC) as indicators of disease severity from charts.

RESULTS

276 adult participants (54% female) with a diagnosis of IBD, 66% Crohn's disease (CD), 31% ulcerative colitis (UC), completed questionnaires; 43% had fecal calprotectin data in charts and 51% had ≥ 1 flare in the last year. Nearly all (91%) patients had heard of PPF (89%); 63% had used in their lifetime; 51% continued usage over the last year. Use was more frequent in CD (62%) than in UC (38%). Increased FC (≥ 250 $\mu\text{g/g}$) was associated with PPF use in the last year (OR: 1.6, 95% CI: 0.88-3.08); lifetime use was associated with UC-subtype flaring patients in the last year (56%) than in non-flaring patients (44%) (OR: 2.3, 95% CI: 0.86-6.39).

CONCLUSIONS

This study shows that a large proportion of IBD patients with greater disease severity have used probiotics, prebiotics and dietary fibre supplements, despite the lack of well-proven efficacy. Since these microbiota-altering strategies have a potential to affect disease outcomes, it is important that clinicians and researchers document their use.

Supervisor: Dr. Levinus Dieleman

Provincial Expenditures in Rheumatic Diseases: Trends and Disparities in Medical Care Costs

Mena Bishay, MD; Elaine Yacyshyn, MD, FRCPC
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

Autoimmune and inflammatory diseases encompass a broad spectrum of presentations amongst patients. It is a growing field accruing more costs with time. Few studies examining the economic impact of these diseases exist. We look at aggregate data for health expenditures on a provincial and regional level to study trends and disparities in costs.

METHODS

Provincial health expenditure data from 2009-2016 was pulled from Alberta Health Services Analytics, Data Integration, Measurement & Reporting via their Tableau system. Data was obtained for the following disease groups: connective tissue disease and vasculitis (CTDV), rheumatoid arthritis (RA), spondyloarthropathy and other inflammatory arthropathies (SPA), crystal arthropathies (CA), and for osteoarthritis (OA) for comparison.

RESULTS

From 2009 to 2016, provincial costs have risen by 102%, 43%, 60%, and 87% respectively for CTDV, RA, SPA, and CA. The number of patients within each disease group has risen 68%, 25%, 32% and 54%, respectively. Total costs were highest in the greater Calgary and greater Edmonton regions across all diseases, making up 56-71% of total provincial expenditures. The greater Calgary region has higher average costs per patient compared to the greater Edmonton region, with differences up to \$660 per patient. In 2015-2016, the average cost per patient for CTDV ranged from \$3810-\$4958/year for most locations, but for the remote west, rural south, and remote north regions average costs were \$6256, \$7619, and \$9299/year, respectively.

CONCLUSIONS

The number of patients with autoimmune and inflammatory diseases has risen steadily since 2009. Costs have also risen, however they have done so out of proportion to the patient population growth. Consistent differences exist in the cost per patient between the two largest centers in Alberta. Inequality in the cost of care for CTDV in remote/rural regions exists, pointing to areas of potential quality improvement. The reason for these inequalities is not clear and requires further research.

Supervisor: Dr. Elaine Yacyshyn

Detecting cerebral degeneration in ALS using texture analysis: a multicentre study

Michael Chunn¹, Abdullah Ishaque^{1,2}, Daniel Ta³, Herb Yang⁴, Sanjay Kalra^{1,2}
Supervisor: Dr. Sanjay Kalra

INTRODUCTION

The diagnostic process of ALS is long and complicated. This is in part due to a lack of biomarkers for the disease. Texture Analysis (TA) is a tool used to detect and differentiate between different types of pathology. It has been used successfully in two previous studies involving ALS, and this study aims to examine its ability to detect cerebral degeneration on a multicentre scale. Furthermore, the present study will examine whether abnormal texture values correlate with clinical measures of progression.

METHODS

3D-MPRAGE images were acquired on 3T MRI systems for ALS patients (n=64) and healthy controls (n=48) at four sites across Canada. Images were realigned and bias-corrected prior to texture feature extraction, which was performed in native space using a Grey Level Co-occurrence Matrix. Texture maps were normalised to MNI standard space, then analysed using a full factorial model to examine the main effect of diagnosis on the feature autocorrelation (autoc) while controlling for age, site, and brain parenchymal fraction. Extracted autoc values from an ROI in the internal capsule were correlated with ALSFRS-R, tapping scores, and a scale of upper motor neuron (UMN) dysfunction extracted from neurological examinations done at study visits.

RESULTS

The most significant texture abnormalities were in the internal capsule of the corticospinal tract. Significant texture abnormalities in the internal capsule correlated significantly with UMN burden as measured by total UMN score. Furthermore, an ROC analysis showed strong discrimination between patients and controls, with an area under the curve (AUC) of 0.840.

CONCLUSIONS

The present study shows promising results in TA's ability to detect cerebral degeneration in ALS. This is important as extracted texture values could be used as an objective measure of degeneration. Moreover, correlation with signs of impairment seen in clinic provides a link between the clinical process of diagnosis and the disease process itself.

Supervisor: Dr. Sanjay Kalra

Barriers and facilitators to implementation of electronic consultations (eConsult) for enhanced access to specialist care: a scoping review

Mohamed A. Osman¹, Deenaz Zaidi¹, Liza Bialy², Robin Featherstone², Kara Schick-Makaroff³, Stephanie Thompson¹, Scott Klarenbach¹, Aminu K. Bello¹
Supervisor: Dr. Aminu Bello

INTRODUCTION

Excessive wait times and limited access to specialist care are significant problems in the Canadian health system particularly in remote and rural communities. There is an opportunity to mitigate these problems through the application of eHealth technologies.

In liaison with key stakeholders (Alberta Health, Alberta Health Services, Kidney Strategic Clinical Network), we have developed an electronic consultation system (eConsult) in Alberta that is being piloted to enhance ambulatory kidney care. Information on the factors that favor or hinder the adoption, scale up and sustainability of this novel care model remains unknown. We therefore aimed to conduct a scoping literature review to identify key barriers and facilitators for eConsult adoption, sustainability and scale up.

METHODS

The choice for a scoping review methodology was informed by the complex nature of the intervention (eConsult) and expected heterogeneity in the conduct and reporting of the relevant studies. We leveraged the Arksey & O'Malley's framework on conducting scoping reviews which involved five steps 1) identifying the research question; 2) identifying the relevant studies; 3) study selection; 4) charting the data; and 5) reporting the results, and an optional step of a consultation exercise with relevant stakeholders. We searched key electronic databases (Medline, Embase, Wiley Cochrane Library, CINAHL, Cochrane Library, and PsycINFO). We included both observational and experimental studies. with no restriction on date or language.

RESULTS

A total of 2562 unique records were screened by two independent reviewers. A total 196 papers were selected for full text review. Included articles were classified using Quadruple aim framework (improved quality and process of care, patient satisfaction, provider satisfaction and cost savings) to thematically described the identified key barriers and facilitators .

CONCLUSIONS

Our findings are relevant in informing the development and implementation of eConsult systems as platforms to enhance access to specialist care particularly for remote and rural communities of Alberta.

Supervisor: Dr. Aminu Bello

What impact does academic mentoring have on subsequent academic performance in medical school?

Monika Oliver BSc, MD; Hatem Alnassar, MD; Sita Gourishankar MSc ,MD, FRCP
Supervisor: Dr. Sita Gourishankar

INTRODUCTION

Academic mentoring (AM) is considered a valuable aspect of undergraduate medical education at the University of Alberta. Historically, our undergraduate program has not had a formal AM program for students experiencing academic difficulty. Subsequently, a faculty member was appointed to proactively and systematically identify struggling learners and offer one-on-one AM with the goal of improving subsequent performance.

METHODS

We performed a retrospective cohort study examining the impact of AM on academic performance of undergraduate medical students. Seventy students were flagged for academic difficulty as measured by a score of <60% on mandatory course work. Students were asked to complete a preliminary questionnaire with subsections on self-perception as a learner, sources of stress, school-life balance, study methods, and prior educational background. Results were used to guide discussion in a subsequent 60-90 minute mandatory AM session with the AM Coordinator. Success of the AM was measured by the presence or absence of ongoing academic struggle following the mentoring session.

RESULTS

Of the seventy participants, sixty-five (92.9%) experienced repeat performance deficiencies. Of this subset, sixty-three (90%) students were noted to have >2 subsequent failures suggesting persistent academic struggle post Academic Mentoring (AM). All participants expressed appreciation for the opportunity to discuss their performance candidly with a faculty member, with the majority reporting being satisfied with the AM session.

CONCLUSIONS

AM as a component of remediation is a new initiative at the University of Alberta. The high percentage of students with persistent struggles following an initial mentoring session suggests an ongoing need that requires faculty attention. The positive feedback from students implies targeted mentorship is a worthwhile component of successful remediation.

Supervisor: Dr. Sita Gourishankar

RNAseq Analyses of PBMC from PBC Patients either Responding or not Responding to Obeticholic Acid Therapy

Morteza Seifi, Juan Jovel, Andrew Mason
Supervisor: Dr. Andrew L. Mason

INTRODUCTION

In the POISE phase III trial, patients with progressive primary biliary cholangitis (PBC) were treated with obeticholic acid (OCA) and approximately 50% of patients responded to therapy. We addressed the hypothesis that genes and pathways associated with response to OCA may be detected by RNAseq transcriptional analyses of peripheral blood mononuclear cells.

METHODS

Whole blood RNA was evaluated in OCA responders (n=45) versus non-responders (n=83) using next generation sequencing to generate 5 GB per sample. Differences in transcription were evaluated using the DESeq2 R package. Pathway analyses and significance association were conducted using Gene Ontology Consortium and regression analysis, respectively.

RESULTS

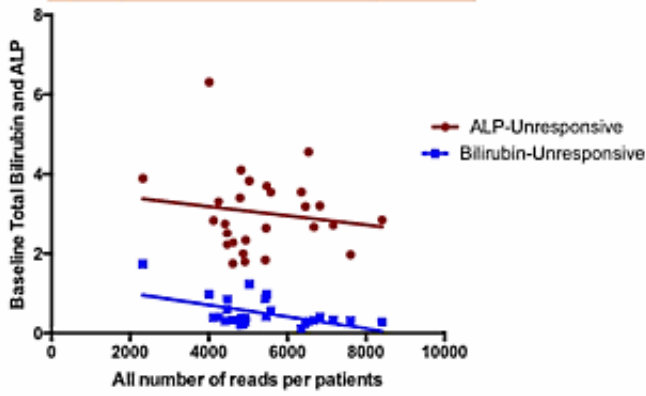
Responders to OCA demonstrated increased expression in 161 genes and decreased expression in 158 genes. The major upregulated genes in the OCA-responsive patients were associated with regulation of mRNA splicing via the spliceosome, negative regulation of inflammatory responses and viral genome replication ($p < 0.05$). The down regulated genes in the OCA responders were associated with antigen processing, regulation of interleukin-8 secretion, and endocytosis ($p < 0.05$). To assess the potential role of these transcriptional changes as potential biomarkers, a transcriptional score was calculated using either total number of reads in the upregulated genes or downregulated genes. Analyses with biochemical changes showed that bilirubin values significantly correlated with both the upregulated score and down-regulated score in non-responders only, (Figure: $p < 0.006$ and $p < 0.04$, respectively).

CONCLUSIONS

Diminished expression of proteins associated with control of splicing have been observed in prior proteomic studies of PBC patients' biliary epithelium cells. Therefore, it is of interest to observe that patients non-responsive to therapy had diminished expression of spliceosomal transcripts. Infection with a human betaretrovirus linked with PBC may be directly linked with control of splicing as the virus encodes a REM protein that acts as a chaperone that prevents splicing of the viral genome.

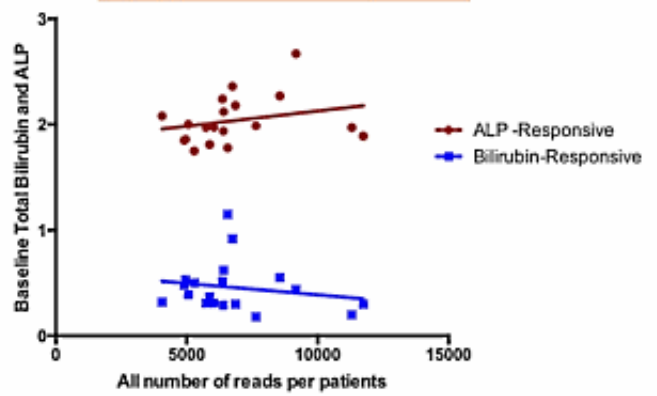
Supervisor: Dr. Andrew L. Mason

Upregulated Score Non-Responders



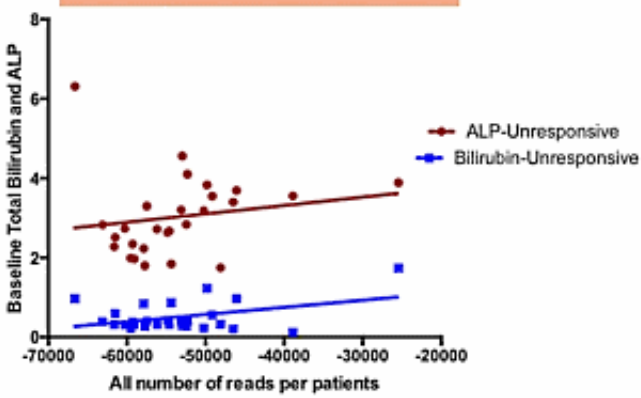
ALP: $p=0.45$; Bilirubin $p=0.0057$

Upregulated Score Responders



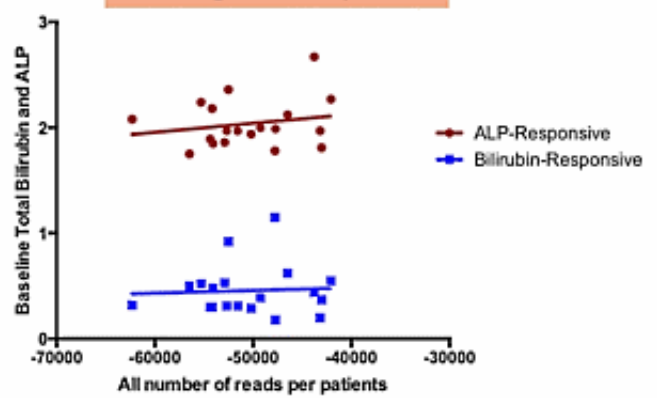
ALP: $p=0.28$; Bilirubin: $p=0.44$

Down regulated Non-Responders



ALP: $p=0.38$; Bilirubin $p=0.038$

Down regulated Responders



ALP: $p=0.41$; Bilirubin: $p=0.81$

Are cardiovascular clinical trials in the last 20 years more pragmatic or explanatory?

Nariman Sepehrvand, Wendimagegn Alemayehu, Debraj Das, Pishoy Gouda, Arjun K. Gupta, Zakariya Kashour, Anukul Ghimire, Xiaoyang A. Du, Sanaz Hatami, Sanam Verma, Hazal Babadagli, Robinder S. Sidhu, Justin A. Ezekowitz
Supervisor: Dr. Justin A. Ezekowitz

INTRODUCTION

Pragmatic trials may test interventions that are more applicable to the population in which they will eventually be applied. The aim of this study was to investigate how pragmatic or explanatory cardiovascular (CV) randomized controlled trials (RCT) are, and if this was changing over time.

METHODS

Using the six top-ranked medical and cardiology journals based on impact factors, all CV-related RCTs that were published during the years of 2000, 2005, 2010 and 2015 were included. The PRECIS-2 tool was used to evaluate the level of pragmatism, which uses a 5-point ordinal scale (ranging from very pragmatic to very explanatory) across 9 domains of trial characteristics. A cutpoint was used to divide the trials into pragmatic (≥ 3) or explanatory (< 3).

RESULTS

Mean (\pm SD) PRECIS-2 score was 3.3 ± 0.77 among 594 included RCTs. Overall, 415/594 (70%) trials were identified to be pragmatic and the rate increased over time from 55% in 2000 to 82% in 2015 (trend $p < 0.001$). There was no difference in the level of pragmatism between different sources of funding (public, industry, or both). The findings of explanatory trials were more likely to be positive for primary endpoint than that of pragmatic trials (69% vs 57%, $p=0.019$).

CONCLUSIONS

The PRECIS-2 tool can be used for appraising trials to assess their placement in the pragmatic-explanatory continuum. The level of pragmatism increased over time in CV trials. Greater focus on the design and delivery of CV trials will be required for broad application.

Supervisor: Dr. Justin A. Ezekowitz

| | All; n=594 | PRECIS < 3 (more explanatory); n=179 | PRECIS ≥ 3 (more pragmatic); n=415 | p-value |
|-----------------|---------------|--------------------------------------|------------------------------------|---------|
| Year | | | | |
| 2000 | 168 (28.3) | 75 (44.6) | 93 (55.7) | <0.001 |
| 2005 | 165 (27.8) | 47 (28.5) | 118 (71.5) | |
| 2010 | 130 (21.9) | 33 (25.4) | 97 (74.6) | |
| 2015 | 131 (22.1) | 24 (18.3) | 107 (81.7) | |
| Phase | | | | |
| I/II | 279 (50.0) | 121 (70.3) | 158 (41.0) | <0.001 |
| III/IV | 278 (49.9) | 51 (29.7) | 227 (59.0) | |
| Funding | | | | |
| Public | 187 (32.1) | 47 (26.7) | 140 (34.4) | 0.008 |
| Industry | 194 (33.3) | 52 (29.5) | 142 (34.9) | |
| Public/Industry | 92 (15.8) | 30 (17.0) | 62 (15.2) | |
| Unclear | 110 (18.9) | 47 (26.7) | 63 (15.5) | |
| Sites | 8 (1, 37) | 1 (1, 12) | 14 (2, 44) | <0.001 |
| Sample size | 266 (84, 860) | 99 (33, 303) | 377 (148, 1606) | <0.001 |
| F/U, month | 6 (2, 12) | 6 (1, 12) | 9 (3, 18) | <0.001 |

Patient reported outcomes using smartphones in rheumatology: A scoping review

Nathan Puhl and Elaine Yacyshyn
Supervisor: Elaine Yacyshyn

INTRODUCTION

Patient reported outcomes (PRO) are quantifiable subjective symptoms recounted by patients representing important measures in rheumatologic disease. There has been increased interest in electronic assessment of PROs with widespread use of smartphones. This review aims to understand how patient reported outcomes are measured with smartphones; how these measurements correlate with objective clinical scores, and development of such technology.

METHODS

Methods: EMBASE and MEDLINE databases were searched using MeSH subject headings. Keywords related to: smartphones and rheumatic disease. Articles were assessed using a standard protocol for suitability, disease, outcomes, and app development.

RESULTS

Combined bibliographic searches identified 262 articles after duplicates were removed. Titles and abstracts were then screened resulting in 43 articles. Of these, 13 were peer-reviewed papers while 30 were conference proceedings. 27 articles described PROs, with 10 of those correlated to objective disease activity scores. The remaining 16 articles focused solely on app development and feasibility. Most articles evaluated technology use in rheumatoid arthritis (26), followed by juvenile idiopathic arthritis (JIA) (7). Other diseases included spondyloarthropathy, lupus, or inflammatory eye disease.

In the 10 articles that compared PROs to disease activity measures, 5 demonstrated high correlation between the RAPID3, HAQ and patient reported tender or swollen joint counts with the DAS28, CDIA, SDAI, and physician global assessment. Passive activity was measured through step counters, trunk acceleration, and activity trackers in 7 articles, with 2 articles reporting significant correlation to DAS28.

CONCLUSIONS

This scoping review demonstrates the current literature regarding measuring PROs with smartphones is sparse, with the majority being conference proceedings. What data is available does suggest feasibility and utility incorporating PROs into practise for rheumatoid arthritis however there remains minimal standardization and validation regarding exact measures. As PROs are measured more frequently by accessible technology, validated studies need to be completed to evaluate effectiveness of these tools.

Supervisor: Dr. Elaine Yacyshyn

Determining the role of von Willebrand Factor in thrombotic post transplantation complications using Ex vivo lung perfusion system

Parnian Alavi, Sayed Himmat, Nader Aboelnazar, Nadia Jahroudi, Jayan Nagendran
Supervisor: Dr. Jayan Nagendran (Primary Supervisor), Dr. Nadia Jahroudi
(Co-Supervisor)

INTRODUCTION

An active option in treating end-stage lung diseases is lung transplantation. A major complication of transplantation is thrombosis, which may lead to allograft failure. Increased production of procoagulant molecules, such as von Willebrand factor (VWF), is a significant risk factor for thrombus formation. VWF plays a critical role in hemostasis and thrombus formation by mediating the adhesion of platelets to the endothelium. Upregulation of VWF can occur in response to an external stimulus, including hypoxia, which increases the risk of thrombosis. Organs which are going to be transplanted undergo exposure to hypoxia which may lead to upregulation of VWF. We will determine whether increased and/or altered VWF expression pattern occur in lungs undergoing transplantation; and whether this contributes to increased thrombogenicity. We will evaluate whether an innovative organ preservation method, namely ex vivo lung perfusion (EVLP), can moderate the effect of VWF upregulation and thrombus formation.

METHODS

Procured pig's lungs will be set in ex vivo perfusion, and the tissue biopsies will be obtained at the beginning and at the end of perfusion for RT-PCR, western blot and immunofluorescent analyses to investigate mRNA, protein, and vascular expression pattern of VWF, respectively. Similar analyses will be done on lungs that are preserved under the static cold condition.

RESULTS

Preliminary analyses demonstrated that VWF mRNA Levels were significantly increased in cold static preservation condition, while EVLP prevented upregulation of VWF mRNA. In addition, under EVLP, VWF protein level was markedly reduced at the end of perfusion. We expect to observe that increased VWF levels are correlated with increased platelet aggregates formation, thus demonstrating functional thrombogenicity in lungs allograft.

CONCLUSIONS

The information obtained will reveal whether EVLP will interfere with VWF upregulation and thrombus formation, and thus providing an effective anti-thrombotic approach that would be highly advantageous in organ transplant procedures.

Supervisor: Dr. Jayan Nagendran (Primary Supervisor), Dr. Nadia Jahroudi
(Co-Supervisor)

THE CHLORIDE INTRACELLULAR CHANNEL (CLIC) PROTEINS CLIC4 AND CLIC5A ARE TARGETED TO THE PLASMA MEMBRANE BY PHOSPHORYLATION

Peter Kim, Laiji Li, Barbara J. Ballermann
Supervisor: Dr Barbara J Ballermann

INTRODUCTION

The chloride intracellular channel (CLIC) family consists of six members defined by a homologous N-terminal module containing a glutathione-S-transferase fold. Initially classified as anion channels based on their method of discovery, modern evidence suggests CLICs are more likely soluble or peripheral membrane proteins. One member, CLIC5A, is chiefly expressed in the renal glomerulus, where it contributes to podocyte morphology by stimulating cytoskeletal remodeling. Imaging studies have previously demonstrated a dual plasma membrane (PM) and cytosolic localization of CLIC5A, and emerging evidence suggests CLIC5A initiates its signaling at the PM.

METHODS

The objective of the present study is to establish if CLIC5A is a PM-spanning channel or a peripheral membrane protein, and to identify the triggers that mobilize CLIC5A from the cytosol to the PM. CLIC5A-transfected COS-7 cells were used to perform biotinylated-surface protein capture and non-permeabilizing immunofluorescence to determine if CLIC5A was PM-spanning. In addition, subcellular fractionations in CLIC4- and CLIC5A-transfected cells were performed to establish their cellular localization.

RESULTS

Biotin surface protein capture and non-permeabilizing immunofluorescence detected CLIC5A under PM-permeabilizing conditions but not when the PM was intact, similar to the intracellular control GAPDH and unlike the transmembrane control N-Cadherin. Subcellular fractionations in both CLIC4- and CLIC5A-transfected cells showed that both proteins were predominantly cytosolic and only weakly PM-associated. However, treating cells with the Ser/Thr phosphatase inhibitor Calyculin A shifted both CLIC4 & CLIC5A to the PM, and this effect was abolished by the PKC inhibitor Staurosporine.

CONCLUSIONS

Our study suggests that CLIC5A does not span across the PM and thus unlikely a legitimate channel. Furthermore, the association of both CLIC4 and CLIC5A to the PM is stimulated by a PKC-dependent phosphorylation, potentially on these proteins themselves.

Supervisor: Dr Barbara J Ballermann

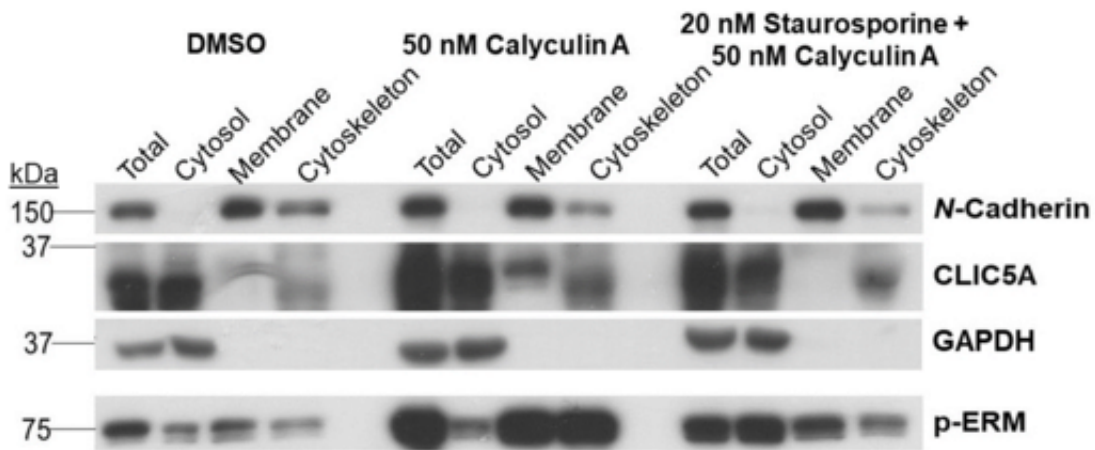


Figure. A PKC-dependent serine/threonine phosphorylation stimulates the association of CLIC5A with the plasma membrane. Subcellular fractions were obtained in CLIC5A-transfected COS-7 cells with N-Cadherin and GAPDH serving as the plasma membrane and cytosolic controls respectively. Under DMSO treatment, CLIC5A was only weakly detectable in the membrane fraction. However, treatment with the serine/threonine phosphatase inhibitor Calyculin A increased its detection in the membrane, and this effect was abolished by the PKC inhibitor Staurosporine. Phospho-ERM (p-ERM) was used as a control to determine if Calyculin A phosphatase inhibition was effective.

A role for RAC1 GTPase activation in peripheral axonal regeneration

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INTRODUCTION: Peripheral nerve damage from trauma or neuropathy is common and irreversible. Manipulation of specific molecules that influence growth cone behavior and peripheral neuron plasticity may offer therapeutic options. Rho GTPase family effectors play an important role in various aspects of neuron development and regeneration. Our previous work identified enhanced neuron growth from inhibition of RHOA, a member of this family that inhibits growth cones. However, RAC1 (Ras-related C3 botulinum toxin substrate 1), in contrast, is a family member that may support growth cone lamellipodia and hence regeneration. In particular, RAC1 has been implicated in cytoskeleton reorganization, myelination and axonal growth after nerve injury. This prompted us to probe the role of RAC1 activation in adult peripheral nerve regeneration, unexplored to date.

METHODS: Adult male Sprague-Dawley rats; Immunocyto and histochemistry; Western immunoblots; qRT-PCR; RAC/CDC42 Activator II, an epidermal growth factor (EGF) used to activate RAC1 in dissociated adult peripheral sensory neurons from dorsal root ganglia (DRGs); Neurite outgrowth *in vitro* using Neuromath Software in uninjured and injured adult sensory neurons.

RESULTS: Expression of the RAC1 protein was confirmed in intact DRGs. RAC1 mRNA levels in DRGs underwent rises after distal axon injury, indicating a role in preparing sensory neurons for enhanced plasticity during regeneration. Moreover, RAC1 expression was also confirmed in complex growth cones of regenerating axons. Adult rat DRG sensory neurons *in vitro* demonstrated a dose-related increase in neurite outgrowth and number of neurite branches when exposed to a RAC1 activator, indicating a potential ongoing functional role during adult regeneration.

CONCLUSIONS: Taken together, the findings identify an ongoing role for RAC1 in adult sensory neurons with localization both in perikarya and growth cones and evidence for functional activity. [Supported by CIHR, CDA, DoM, FoMD, UHF]

Calcineurin Inhibitors, Macrolides, and the Risk of Adverse Drug Events in Kidney Transplant Recipients

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Supervisor: Dr. Ngan N. Lam

INTRODUCTION

After kidney transplantation, calcineurin inhibitors (CNIs, cyclosporine, tacrolimus) are key components of immunosuppression but have multiple potential drug interactions. Macrolide antibiotics are often used for atypical infections. Clarithromycin and erythromycin inhibit the metabolism of CNIs, which increases the risk of CNI nephrotoxicity. In contrast, azithromycin does not affect CNI metabolism. Our objective was to determine the frequency of CNI-macrolide co-prescriptions, the proportion who receive post-prescription monitoring, and the risk of adverse drug events in kidney transplant recipients.

METHODS

We conducted a retrospective study using linked databases in Alberta, Canada to follow kidney transplant recipients (2008-2015). We identified recipients on continuous CNI who were co-prescribed either clarithromycin, erythromycin, or azithromycin. We compared outcomes in those who received clarithromycin or erythromycin vs. azithromycin. The primary outcome was a composite of all-cause hospitalization, acute kidney injury (creatinine increase $\geq 26.5 \mu\text{mol/L}$ or 1.5-times baseline), and death within 30 days of the macrolide prescription.

RESULTS

At the time of the macrolide prescription, the 293 recipients with CNI-macrolide co-prescriptions had a median age of 55 years and an estimated glomerular filtration rate of 58 mL/min/1.73 m². Almost 40% (n=112) of recipients were prescribed clarithromycin or erythromycin while the rest were prescribed azithromycin (n=181). Clarithromycin and erythromycin users were less likely to have outpatient serum creatinine monitoring post-prescription compared to azithromycin users (56% vs. 69%, p=0.03). There was no significant difference in the primary outcome between the two groups (17% vs. 11%, p=0.11); however, the risk of all-cause hospitalization was higher in the clarithromycin and erythromycin group (10% vs. 3%, p=0.02).

CONCLUSIONS

Despite drug interactions, clarithromycin and erythromycin were frequently prescribed in kidney transplant recipients on CNIs. Compared to azithromycin, clarithromycin and erythromycin users were less likely to have post-prescription monitoring of kidney function and were at higher risk of hospitalization. Further research is needed to improve safe prescribing practices in kidney transplant recipients.

Amylin receptor facilitates the release of ganglioside GM1 in exosomes: implication in Alzheimer's disease.

Rania Soudy 1, Wen Fu1, Luis Morales 2, Simonetta Sipione 2, Jack Jhamandas 1
Supervisor: Dr. Jack Jhamandas

INTRODUCTION

Exosomes are nanosized extracellular vesicles that can be released by nearly all cell types including brain cells; they facilitate intercellular communication through transfer of their cargo and eliminate unnecessary cellular material. In Alzheimer disease (AD), exosomes have been implicated in spreading pathological misfolded proteins such as beta amyloid protein (A β), thereby contributing to neuronal loss. Recent studies have highlighted a role for glycosphingolipids GM1-associated with exosomes in promoting the assembly of an exogenous soluble A β into its toxic form. Interestingly, emerging data also show that G-protein coupled receptors (GPCR) function is modulated by glycosphingolipids GM1. Our previous research has demonstrated that the deleterious effects of A β in the brain are expressed via the amylin receptor (AMY), a Class B GPCR. In the current study, our objective is to explore the role of amylin in the release of exosomes and its effects on the A β release.

METHODS

Exosomes were isolated from HEK-293 AMY3 receptor subtype transfected cells using ultracentrifugation; exosomes from wild type (Wt) HEK293 cells were used as control. Exosomes characterization was done using western blot and electron microscopy. Ex vivo and in vitro GM1 detection was done using dot blot. Cytotoxicity was done using MTT assay.

RESULTS

The levels of GM1 were higher in exosomes generated from HEK-293 AMY3 cells compared to Wt cells. Exosomes derived from A β treated HEK-293 AMY3 contained more A β compared to Wt cells. The effect of harvested exosomes from HEK-293 AMY3 on neuronal N2A cells toxicity compared to control exosomes from Wt cells is in progress. The level of brain GM1 in mouse models of AD was correlated to our in vitro results.

CONCLUSIONS

Our preliminary data highlights the role of amylin receptors in the release of exosome and studies are currently underway to determine the functional implications of these cellular events.

Supervisor: Dr. Jack Jhamandas

CHRONIC MIRIZZI SYNDROME CAUSING RECURRENT CHOLANGITIS AND SECONDARY BILIARY CIRRHOSIS: A CASE REPORT

Ravi Homenauth, Malcolm Wells, Richard Sultanian, Ali Kohansal Vajargah
Supervisor: Dr Ali Kohansal Vajargah

INTRODUCTION

Mirizzi Syndrome (MS) is an uncommon presentation in which a gallstone becomes impacted in the cystic duct or neck of the gallbladder and causes adjacent compression of the common bile duct (CBD) or common hepatic duct (CHD), with resultant biliary obstruction. Secondary Biliary Cirrhosis (SBC) refers to a chronic and progressive liver disease characterized by inflammation, fibrosis and obstruction of the intra and extrahepatic biliary tree. MS has not been described as a potential aetiology for SBC as it is typically an acute clinical presentation requiring emergent treatment.

METHODS

A literature search was performed between July 2017 and July 1997 in the PubMed using the following terms; "Mirizzi's syndrome", "chronic Mirizzi's syndrome", "secondary biliary cirrhosis", either individually or in combination. Citations among the identified publications were also reviewed.

RESULTS

A previously healthy 44-year-old female presented to the emergency department with a 15-month history of intermittent right upper quadrant pain and intermittent fevers.

Her labs at the time of presentation revealed evidence of cholangitis.

MRCP imaging intrahepatic and CBD dilation concerning for biliary obstruction.

She had an ERCP which demonstrated markedly dilated intrahepatic biliary system with a 2-cm stone in the cystic duct causing external compression of the CBD consistent with MS. (figure 1)

The Patient was then referred to hepatobiliary surgery where the diagnosis of MS was further confirmed surgically.

Intraoperatively, note was made of severe intrahepatic and peri-portal inflammation with fibrosis, suspicious for secondary biliary cirrhosis and portal hypertension.

An intraoperative liver biopsy was consistent with the diagnosis of SBC and ongoing cholangitis.

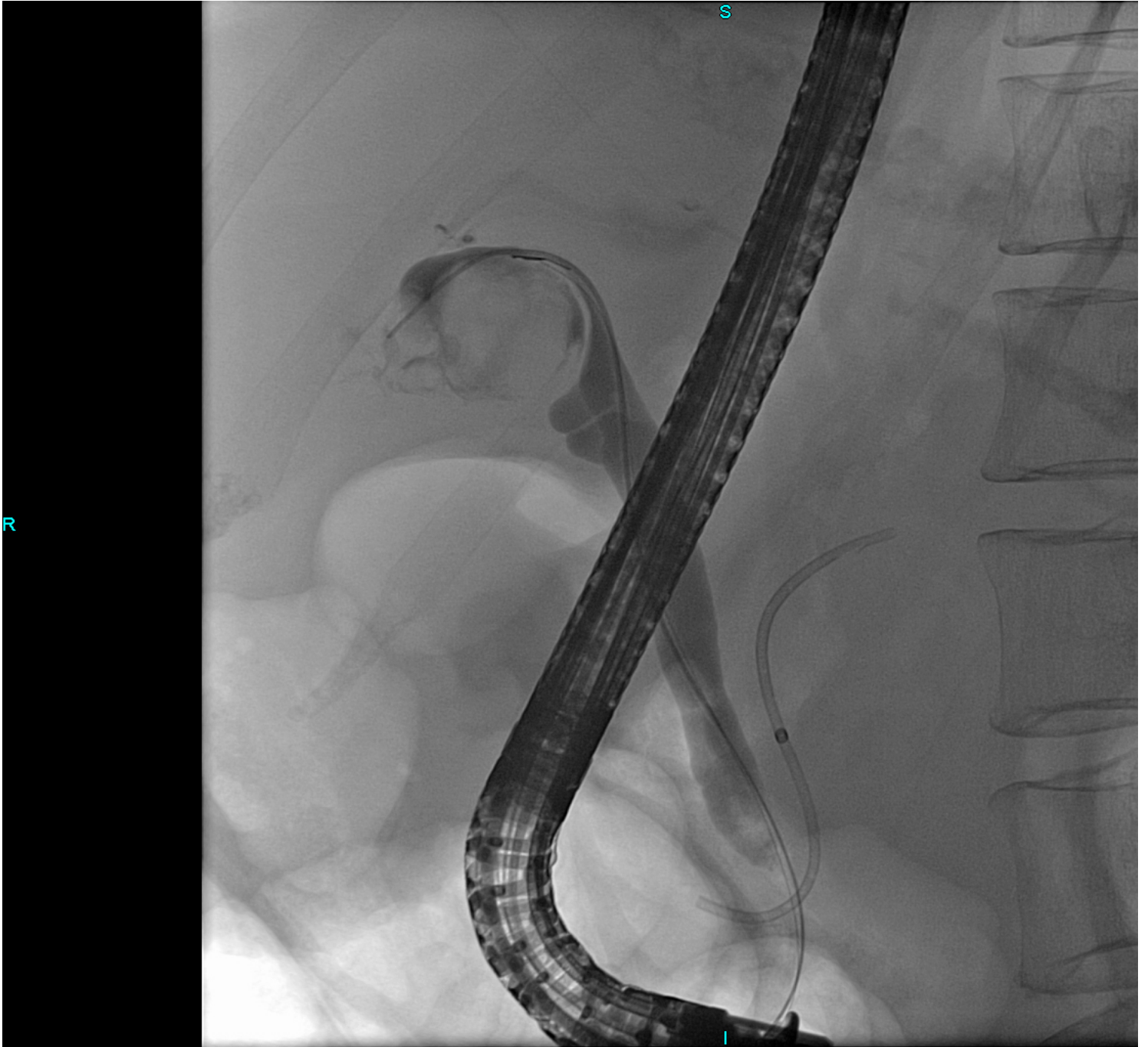
Screening workup for other causes of liver disease was negative.

CONCLUSIONS

This is a rare case of MS as a chronic presentation since patients typically require emergent treatment.

This is a unique case of chronic MS as a cause of portal hypertension with secondary biliary cirrhosis.

Supervisor: Dr Ali Kohansal Vajargah



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Low Predictive Value of Multiphase CT Angiography for CT Perfusion Defined Ischemic Penumbra

Robert Wannamaker, Harsha Kamble, Alexander Tamm, Kenneth Butcher
Supervisor: Dr. Kenneth Butcher

INTRODUCTION

Multiphase CT angiography (mCTA) has been proposed as an alternative to CT Perfusion (CTP) for identification of tPA treatable acute stroke patients. We tested the hypothesis that poor collateral patterns on mCTA are predictive of large CTP defined ischemic cores.

METHODS

Multiphase CTA was generated from CTP source images (peak arterial, +8 and +16 s). Two expert raters assessed the collateral pattern on mCTA (absent/moderate/good). An Alberta Stroke Program Early CT (ASPECT) score was also assessed on the mCTA and compared against non-contrast CT (NCCT). Suggested treatment decisions with tPA were made based on NCCT and mCTA. A semi-automated algorithm using purpose built software was used to measure penumbral and core volumes.

RESULTS

Of 141 patients, 8(6%) were found to have a large core on CTP. Three of these patients (37.5%) were found to have moderate-to-good collaterals on mCTA, with 2/8(25%) also having a NCCT ASPECTS>5. At a mismatch threshold between NCCT and mCTA ASPECTS of 2, mCTA had a sensitivity and specificity of 26.8% and 75.0% respectively for CTP-defined penumbral patterns. Specifically, when looking at patients with a large vessel occlusion (LVO), mCTA was able to identify 54.2% of patients with a penumbral pattern. There was no difference between the decision to use tPA in patients with a penumbral(68/75(91%) and non-penumbral pattern(49/60(82));p=0.136).

CONCLUSIONS

Although mCTA ASPECTS are correlated with core and total perfusion deficit, it remains only moderately sensitive for target mismatch in LVO patients. While an excellent tool, angiography remains insufficient to be used alone in the acute setting.

Supervisor: Dr. Kenneth Butcher

A Population-Based Study of Complex Device Eligibility, Utilization and Reasons for Non-Implantation in Patients at Heart Function Clinics

Rochelle Bernier, Jessica Ng, Dat Tran, Dr. Evan Lockwood, Lucy Reyes, Karen Cowan, Dr. Justin Ezekowitz, Dr. Derek V Exner, Dr Satish R Raj and Dr Roopinder K Sandhu
Supervisor: Dr. Roopinder Sandhu

INTRODUCTION

Implantable cardioverter defibrillators (ICD) reduce morbidity and mortality in patients at risk for sudden cardiac death. Yet, data regarding device eligibility and utilization in a real-world setting remains sparse. The aims of this study were to determine the rates of ICD eligibility and utilization among patients seen at heart function clinics and to identify reasons for non-implantation among eligible patients.

METHODS

As part of a quality improvement initiative, we performed a retrospective review of consecutive patients seen at two heart function clinics in Alberta from 2012-2015. A detailed chart review was performed to collect demographics, clinical indications, comorbidities and to identify reasons for non-implantation. Eligibility was determined using the 2008 ACC/AHA/HRS ICD guidelines and the 2013 CCS CRT guidelines. Logistic regression was used (odd ratio, OR and 95% CI) to identify predictors of device non-implantation.

RESULTS

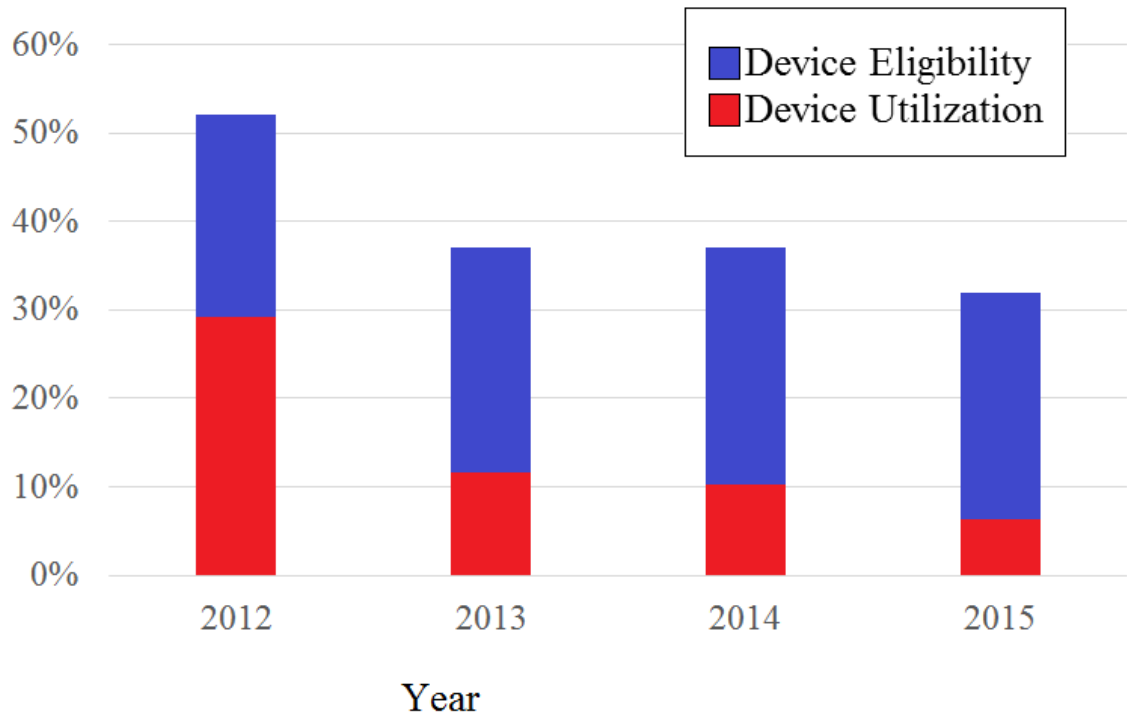
Overall, 1294 patients were seen in HF clinic, the majority were male (67%), the median age was 69(IQR 59-80) and the mean ejection fraction (LVEF) was 0.40(SD +0.15). Over the follow-up period, 53% of patients were never eligible for device therapy based on LVEF criteria. Yearly rates of eligibility and utilization ranged from 32-52% and 19-56%, respectively (Figure 1). When a reason for non-implantation was accounted for, yearly utilization rates increased to 36-64%. Among eligible patients, independent predictors of device non-implantation were age >75 years(OR 1.80, 1.23-2.63), LVEF ≤ 0.35(OR 4.69, 2.74-8.04), kidney disease(OR 1.71, 1.04-2.80) and cancer(OR 2.56, 1.23-5.34). Almost half of the time (46%), no clear documented reason for non-implantation was found. When a reason was documented, it was most commonly included patient preference (25%), technical reasons (19%) and medical reasons (10%).

CONCLUSIONS

In this population-based study, we found that less than half of eligible patients received an ICD and a reason for non-implant was often missing. Better screening and documentation is needed in order to improve ICD utilization.

Supervisor: Dr. Roopinder Sandhu

Proportion of Heart Function Population



Supporting Healthy Aging by Peer Education and Support (SHAPES) - A modified stepped-wedge cluster randomized trial

Rajabali S, Gartner S, Hunter K, Juby A, Dafoe W, Wagg A
Supervisor: Dr. Adrian Wagg

INTRODUCTION

By 2036, the proportion of older people (>65y) in the population is estimated to rise to 23–25%. Many people age with chronic medical conditions. There is evidence that self-management and an increase in health literacy leads to an improvement in health-related quality of life. This study is an innovative partnership between seniors' community organisations and faculty at the University of Alberta to provide peer delivered education and support for seniors. Objective: To assess the impact of trained health coaches on healthy aging behaviours, health literacy and health care seeking in community dwelling seniors.

METHODS

Design: A mixed methods quantitative dominant, modified stepped-wedge cluster randomized trial. Setting: Three Edmonton Senior's Centres serve as clusters. Participants: Participants (90) and health coaches (12), with no medical or psychological impairment which might seriously impair adherence to the program. Intervention: Drawing upon partnership and feedback from community organisations, a one hour workshop and three facilitated discussion sessions in the areas of healthy brain, healthy heart and healthy bones have been developed for delivery to the participants by health coaches. Outcome: Difference in change in proportion of seniors engaged in healthy aging behaviours following the intervention compared to controls. Analysis: Quantitative analysis of the primary endpoint by linear mixed effects model including fixed effects for time and intervention status at each time point. Qualitative data will be analysed by content analysis method.

RESULTS

This study is ongoing. So far, health coaches- 6 men and 6 women, mean age (SD) = 69.9 years (7.5) have been trained. Based on feedback, the modules have been modified to include more resources, simplify the language and provide clarification where needed.

CONCLUSIONS

Health coaches, drawn from community dwelling seniors, may help in educating and supporting their peers in healthy aging behaviours and self-management of chronic disease which may empower seniors whilst increasing their health literacy and appropriate use of health care.

Supervisor: Dr. Adrian Wagg

Hypoxia indirectly raises pro-angiogenic TIMAP levels in endothelial cells

Salah Aburahess, Laiji Li, Barbara J. Ballermann
Supervisor: Dr Barbara Ballermann

INTRODUCTION

Angiogenesis is a critical component of tissue remodeling, wound healing, and tumor growth. Tissue or tumor hypoxia generates angiogenic stimuli, including VEGF, which then act on blood vessels to stimulate endothelial cell (EC) sprouting into the hypoxic tissue. TIMAP (TGF β 1 inhibited membrane-associated protein) is an EC-predominant protein, discovered by our laboratory, required for in vitro angiogenesis. TIMAP binds and strongly inhibits protein phosphatase 1 β , with consequent hyperphosphorylation of AKT, that in turn signals EC survival and proliferation. Here, we wondered whether TIMAP levels in EC are regulated by hypoxia.

HYPOTHESIS: Hypoxia induces pro-angiogenic TIMAP expression in EC.

METHODS

Lung tissue and lysates from control and hypoxic mice (progressive hypoxia, 35 days) were evaluated by Western Blot (WB), TIMAP immunoprecipitation (IP) and immunofluorescence microscopy (IF). Human umbilical vein (HUVEC) and lung (hLEC) EC were grown under hypoxic and control (0.2 vs. 21% O₂) conditions for 48 and 72 hours. The EC were also grown in media containing 1% fetal bovine serum (FBS) \pm 50ng/ml or 100ng/ml VEGF165. or growth factor enriched EGM-2 medium (LONZA).

RESULTS

By WB and IP/WB, TIMAP protein abundance was significantly greater in lung lysates from hypoxic compared to control mice (n=5, p < 0.001). By IF, TIMAP expression was also higher in lungs from hypoxic vs. control mice, where it localized exclusively to EC. However, in HUVEC or hLEC cultured under hypoxic conditions TIMAP levels did not increase. Nonetheless, VEGF (50 or 100 ng/ml) or EGM-2 significantly raised TIMAP protein abundance in HUVEC and hLEC compared to the same medium without these growth factors.

CONCLUSIONS

The data suggest that the pro-angiogenic EC signaling protein TIMAP is induced in EC in hypoxic tissue. Based on the in vitro data, this response is not direct, but probably relies on growth factor release from neighboring hypoxic cells.

Supervisor: Dr Barbara Ballermann

A rare case of ANCA-associated aortitis

Saurash Reddy, Richard Owen, Elaine Yacyshyn
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

ANCA vasculitides have traditionally been characterized as small-vessel diseases, with large-vessel vasculitis classically presenting as Takayasu's Arteritis or Giant Cell Arteritis. ANCA-associated aortitis is a rare large-vessel vasculitis, with less than 25 described cases in the literature.

METHODS

A 64-year old female was diagnosed with seronegative rheumatoid arthritis after developing joint swelling in 2013. She was treated with prednisone after declining DMARD therapy. Two months later, she presented to hospital with chest pain and elevated troponins. CT imaging revealed a 6.3cm ascending aortic aneurysm with chronic Type B Dissection. After surgical repair, she was discharged on methotrexate and prednisone for management of her RA. Aortic biopsies showed no signs of vasculitis, and there were no systemic features of vasculitis either.

RESULTS

In follow-up had persistently elevated inflammatory markers despite adequate arthritis control, and serial CT scans showed re-expansion of the aneurysm, requiring another repair in 2015. A vasculitis workup was initiated, yielding a positive MPO titre with p-ANCA positivity with intermittent proteinuria and hematuria. A diagnosis of ANCA-associated large-vessel vasculitis was made based on these findings. Given that her inflammatory markers, hematuria, and proteinuria had normalized at diagnosis with no active arthritis or other vasculitis symptoms, a renal biopsy was not performed. Hydroxychloroquine was added to her previous methotrexate without pursuing induction therapy with cyclophosphamide.

CONCLUSIONS

This case highlights an unusual case of large vessel ANCA-related vasculitis. Previous cases describe large-vessel presentations in conjunction with typical manifestations of ANCA small-vessel disease (hemoptysis, hematuria, visual symptoms). Evaluation includes CT angiography to confirm aortic involvement, and both infectious and autoimmune workup for aortitis. Vessel biopsy should be pursued if possible in conjunction with evaluation for other manifestations of ANCA. Treatment typically involves induction with corticosteroids and cyclophosphamide, along with required surgical intervention. Patients should be monitored with serial inflammatory markers and imaging for relapse.

Supervisor: Dr. Elaine Yacyshyn

Lamin A forms a structural platform for protein-protein interactions of histone-modifying and metabolic enzymes: a novel link between metabolism and epigenetics

Zervopoulos SD, Haromy A, Boukouris AE, Stenson T, Sutendra G, Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Nuclear lamins form the nuclear envelope, and they also form deep intranuclear invaginations of unknown function and a nucleoplasmic network, where they interact with DNA and proteins. Recently, p300 (a histone acetyltransferase) was found in a complex with metabolic enzymes “moonlighting” in the nucleus producing acetyl-CoA [pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase complex (PDC)], used for histone acetylation. We hypothesized that lamin A provides a structural platform for histone-modifying and metabolic enzymes, facilitating interaction and promoting histone acetylation.

METHODS

We used several cell lines: A549 lung cancer, small-airway epithelial, 786-O renal cancer, proximal tubule cells and fibroblasts from healthy and progeria patients (a disease caused by lamin A mutations). We exposed them to stimuli promoting nuclear entry of metabolic enzymes and siRNAs for PDC and lamin. We used super-resolution confocal and electron microscopy, immunoblots and co-immunoprecipitation (Co-IP).

RESULTS

Mitochondria can reside within nuclear invaginations, which are found in higher number in cancer cells compared to their healthy controls. PKM2 and PDC can be seen directly crossing the nuclear envelope and colocalizing with lamin and acetylated histones in distinct microdomains. Co-IP experiments show that lamin interacts directly with PDC. Knockdown of lamin A decreases both nuclear PDC levels and histone acetylation. Progeria fibroblasts (which express a dysfunctional form of lamin) show increased nuclear PDC levels but decreased histone acetylation than healthy cells.

CONCLUSIONS

Lamin A is important for the entry and retention of nuclear PDC. It also provides a structural platform for metabolic enzymes and their co-factors to form functional complexes, promoting acetylation events. These functions may be facilitated by nuclear invaginations, which increase the functional surface area for interaction with both cytoplasmic mitochondria and intra-nuclear proteins. Their increased presence in cancer suggests that the previously unrecognized role of lamin in epigenetic regulation may be more prominent in cancer.

Supervisor: Dr. Evangelos Michelakis

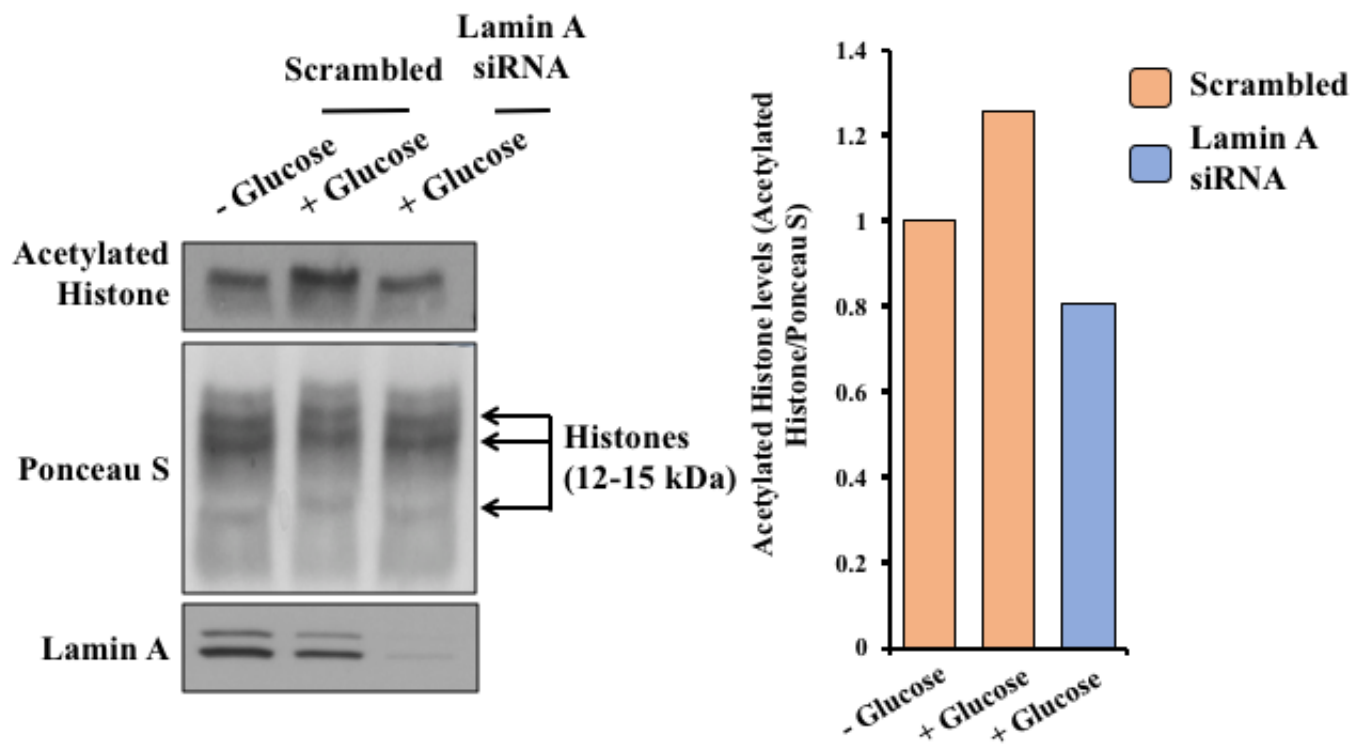


Fig. A549 lung cancer cells were treated with scrambled or lamin A siRNA prior to glucose deprivation for 24 hours; a well-described stimulus for synchronization of histone acetylation. Upon re-introduction of glucose, cells with low lamin A show decreased levels of histone acetylation compared to cells treated with scrambled siRNA.

Identification of pathways altered by MMTV in biliary epithelial cells by RNAseq: Implications for disease progression in primary biliary cholangitis.

Willows SD, Jovel J, Mason AL
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease associated with cholangitis and destruction of interlobular bile ducts. Our lab has previously characterized a retrovirus in patients with PBC called human betaretrovirus (HBRV) due to its close similarity to the betaretrovirus mouse mammary tumor virus (MMTV). When biliary epithelial cells (BEC), the target of immune destruction, are exposed to HBRV or MMTV, cells develop aberrant and increased expression of the mitochondrial protein pyruvate dehydrogenase E2, a prominent auto-antigen targeted in PBC.

METHODS

Immortalized BEC (IBEC) were exposed to MMTV and maintained for 9, 16 or 30 days and then assessed for transcriptional changes. RNAseq analyses were conducted using the Cytoscape and ClueGO to determine modulated pathways in MMTV exposed vs. control cells. RNAseq results were then compared with our previous proteomics and transcriptomics studies to determine genes and pathways that are altered in both MMTV infected cells and PBC BEC.

RESULTS

Several relevant gene ontology groups were found to be altered in MMTV exposed cells, including those related to apoptosis, mitochondrial biogenesis, cell growth and metabolism. Expression of the mitochondrial biogenesis regulator PGC-1 α and several related genes were altered in MMTV exposed cells, and further analysis revealed higher amounts of mitochondrial DNA 9 days after MMTV exposure, suggesting greater amounts of mitochondria. Changes to pathways relating to mRNA processing and export were also found in this and previous proteomics experiments. Furthermore, expression of Transferrin receptor, the receptor for MMTV in mice, was found to be modulated.

CONCLUSIONS

Exposure of IBEC cells to MMTV was found to cause significant changes in several cellular pathways with implications for disease progression. An increase in mitochondrial mass triggered by the PGC-1 α pathway, may lead to the previously described mitochondrial phenotype.

Supervisor: Dr. Andrew Mason

Healthcare providers' experiences with implementing the Conservative Kidney Management Pathway in northern and central Alberta - a qualitative study

Hussain, S., Davison, S.N.
Supervisor: Dr. Sara Davison

INTRODUCTION

Conservative kidney management (CKM) is a non-dialysis treatment option for elderly patients with end-stage kidney disease who are frail with multiple comorbidities and poor functional status. For such patients, Alberta recently launched an interactive, online CKM Pathway that standardizes CKM care and focuses on preserving kidney function, mitigating and managing symptoms and offering holistic psychosocial support to patients and families. This study aimed to assess healthcare providers' experiences in delivering CKM care with the pathway in hospital-based kidney clinics.

METHODS

This qualitative study elicited feedback on four specific aspects of CKM care: symptom guidelines, patient resources, impact on clinical practice and community engagement. Semi-structured focus groups were conducted and recorded with front-line kidney staff who manage over 150 CKM patients across Alberta. R recordings were transcribed verbatim and thematic analysis was done using line-by-line coding and reported under COREQ guidelines.

RESULTS

Five focus groups were conducted across four renal clinics in Edmonton and Red Deer with 25 clinicians including 8 nephrologists. Major themes included: 1) Renal clinic dynamics. Increased trust developed between nurses and doctors. More autonomous nurses were able to offer additional symptom support using the pathway although had challenges with time constraints and engaging some nephrologists. 2) Guidelines and patient materials. Staff were supportive of the CKM philosophy, agreed with the guidelines aimed at improving patient outcomes and found patient resources valuable as discussion aids. They all felt the pathway helped improve care. 3) Shared care. Staff felt the need to involve community partners in managing CKM patients, especially nearer the end-of-life. They had some success with coordinating care but shared perceived or experienced challenges.

CONCLUSIONS

Kidney clinic staff piloting the CKM Pathway felt it provided robust, standardized care to CKM patients but more community awareness of CKM care on the pathway is warranted.

Supervisor: Dr. Sara Davison

The Validity and Acceptability of Patient-led Self- screens for Identifying Malnutrition in Inflammatory Bowel Disease

Tannaz Eslamparast, Kamal Farhat, Lorian Taylor, Nusrat Shommu, Ankush Kumar, Quinn Fitzgerald, Karen Kroeker, Brendan Halloran, Juan G Abraldes, Mang Ma, Hisham H Ghali, Maitreyi Raman, Puneeta Tandon
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Malnutrition is common in Inflammatory Bowel Disease (IBD) and is associated with significant morbidity and mortality. Identification of high-risk patients using an efficient, and sensitive screen is the first step to dietitian referral for nutritional assessment and intervention.

Aim: To determine the validity of patient led self-screens against a dietitian-led subjective global assessment (SGA) to detect malnutrition in IBD patients.

METHODS

Adult patients were prospectively recruited from IBD clinics in Edmonton and Calgary. Patients completed 4 self-screening questionnaires: abridged Patient-generated Subjective Global Assessment (abPG-SGA), Malnutrition Universal Screening Tool (MUST), Canadian Nutrition Screening Tool (CNST) and Malnutrition Screening Tool (MST). A dietitian blinded to the results of the screens carried out a gold standard nutritional assessment using the SGA.

RESULTS

A total of 205 IBD patients, 51% male, (124 Crohn's (CD) and 81 Ulcerative colitis (UC)) were assessed. According to Harvey-Bradshaw Index and partial Mayo scores, 47% of CD and 53% of UC patients had moderate to severe disease activity. The most common symptoms affecting dietary intake in this patient population were diarrhea (25%), pain (23%), poor appetite (22%) and fatigue (18%). According to the dietitian -led SGA, 23% of patients (18% Crohn's, 31% UC) were moderately to severely malnourished. Patients classified themselves at moderate to high risk of malnutrition in 50% (MUST), 40% of cases (abPG-SGA), 18% (CNST), 21% (MST). Of the 4 screening tools, the MUST and abPG-SGA had the best test characteristics.

CONCLUSIONS

The MUST and abPG-SGA are promising nutrition screening tools in patients with IBD. They are time-efficient and can be completed by patients in the waiting room. With the high sensitivity and high negative predictive value for malnutrition detection, the majority of patients who screened at risk of malnutrition would be appropriately referred for further assessment. Future clinical practice should integrate these tools into routine IBD nutrition screening.

Supervisor: Dr. Puneeta Tandon

Table 1. Measures of validity of the abPG-SGA, MUST, CNST and MST against the dietitian-administered SGA in IBD

| Patient-led self-screens | Sensitivity (%) | Specificity (%) | PPV | NPV |
|--------------------------|-----------------|-----------------|------|------|
| abPG-SGA | 83 | 73.4 | 0.48 | 0.93 |
| MUST | 91.5 | 62.4 | 0.42 | 0.96 |
| CNST | 44.7 | 89.7 | 0.56 | 0.84 |
| MST | 54.3 | 88.4 | 0.58 | 0.86 |

abPG-SGA abridged patient generated subjective global assessment, *MUST* malnutrition universal screening tool, *CNST* Canadian nutrition screening tool, *MST* malnutrition screening tool, *SGA* subjective global assessment, *PPV* positive predictive value, *NPV* negative predictive value

Levels of agreement between patient and practitioner led malnutrition screening tools in Cirrhosis

Tannaz Eslamparast, Lorian Taylor, Nusrat Shommu, Ankush Kumar, Kamal Farhat, Quinn Fitzgerald, Juan Gonzalez Abraldes, Mang Ma, Hisham H Ghali, Puneeta Tandon, Maitreyi Raman
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Malnutrition is prevalent in cirrhosis, and tools to screen for nutrition risk are available, however, screening is seldom implemented in clinical practice. Time constraints in a clinic setting may provide one explanation for this omission. Accurate, easy to use patient-led nutrition screening tools may increase use of nutrition screening.

Research objectives:

1. To identify the agreement between a patient led and health practitioner led nutrition-screening tool, the nutrition prioritizing tool (NPT).
2. To identify agreement between the patient led NPT and registered dietitian (RD) assigned gold-standard royal free hospital subjective global assessment score (RFH-SGA assessment tool).

METHODS

A cross-sectional survey and RD-led interview were completed on 68 patients with diagnosed cirrhosis from Edmonton and Calgary cirrhosis clinics and inpatients. Patients completed the online patient led NPT, and were subsequently interviewed by a research assistant and a RD to determine the practitioner led NPT and RFH-SGA gold standard assessment score.

RESULTS

Both the practitioner led NPT (Kappa = 0.37, $p < 0.001$) and RFH-SGA (0.07, $p = 0.173$) were not in agreement with the patient led NPT results. Considering that patients with any degree of nutrition risk should be referred for further assessment, all screens were collapsed into two categories, low risk and increased risk. While this did not improve the kappa levels the sensitivity of the patient led NPT compared to the RFH-SGA was 69% and the specificity was 87%.

CONCLUSIONS

Many patients with cirrhosis (67% using RFH-SGA) would likely benefit from consultation with a RD. Patients in the 3 nutrition risk categories identified by the patient-led NPT screening tool were not in agreement with the practitioner led screening NPT categories or the gold-standard RFH-SGA, although the sensitivity and specificity of the test was acceptable. Further examination of other patient led measures with higher levels of agreement with the RFH-SGA is warranted.

Supervisor: Dr. Puneeta Tandon

Table 1. Malnutrition scores on three different scales

| Scales | Low risk % (n) | Mild to moderate Risk % (n) | High or severe risk % (n) |
|----------------------|-----------------------|------------------------------------|----------------------------------|
| Patient led NPT | 50 (34) | 9 (6) | 41 (28) |
| Practitioner led NPT | 27 (18) | 21 (14) | 53 (36) |
| RH-SGA | 34 (23) | 49 (33) | 18 (12) |

Epidemiologic risk factors of antimicrobial resistance in patients with septic shock admitted to North American critical care units: a retrospective cohort

Tayne Hewer¹ Demetrios K Kutsogiannis², Constantine J Karvellas² , Anand Kumar³ in collaboration with the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) Database working group
Supervisor: Demetrios Kutsogiannis

INTRODUCTION

Antibiotic resistance is a serious global threat resulting in a significant clinical and economic burden (\$6,000-\$30,000 USD, 2008). The examination of resistance between different epidemiological is required to identify patient populations admitted to an intensive care unit (ICU) who may be more susceptible to life-threatening infections caused by resistant pathogens; to allow for targeted treatment strategies aimed at reducing resistance and related complications, while improving outcomes and corresponding health care costs.

The specific aim of this retrospective cohort study was to determine the frequency of resistant organisms among different epidemiological sub-groups of patients within the Cooperative Anti-microbial Therapy of Septic Shock (CATSS) database.

METHODS

We conducted a retrospective review of a cohort of critically ill patients with septic shock within the CATSS database between 1996 and 2012. The presence of resistant organisms was assessed in relation to age, APACHE II, comorbidities, site of origin and acquisition of infection. Multivariable logistic regression was used to describe independent predictors of the presence of resistant organisms at the time of septic shock diagnosis.

RESULTS

In this retrospective cohort of septic patients admitted to North American ICUs, APACHE (OR 1.00 95% CI 0.99,1.01) , liver failure (OR 1.23 95% CI 1.03,1.46), ventilator dependence (OR 2.09 95% CI 1.16,3.76), diabetes (OR 1.21 95% CI 1.04,1.42), elective surgery (OR 1.33 95% CI 1.17,1.52), emergent surgery (OR 1.24 95% CI 1.05,1.48), neuromuscular disease (OR 1.54 95% CI 1.15,2.06) and nosocomial acquired infection (OR 1.70 95% CI 1.52,1.90) were independent predictors of increased odds of the presence of any resistant organism. Leukemia (OR 0.80 95% CI 0.64, 0.99) and hypertension (OR 0.87, 95% CI 0.78, 0.96) were independent predictors of reduced odds of the presence of any resistant organism.

CONCLUSIONS

Further research should focus efforts on these higher risk groups for prevention of hospital acquired antibiotic resistance and improved hospital outcomes.

Supervisor: Dr. Demetrios Kutsogiannis

ANXIETY IMPACTS HEALTH-RELATED QUALITY OF LIFE AND HOSPITALIZATIONS IN PATIENTS WITH CIRRHOSIS

ThucNhi T. Dang, M.D, Nicholas Mitchell, M.D, Kamal Farhat, BSc, Juan G Abrales, M.D., Mang Ma, M.D, Robert J Bailey, M.D., and Puneeta Tandon, M.D.

Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Depression has a significant effect on health-related quality of life (HRQoL), functional status and mortality. The effect of anxiety on HRQoL and clinical outcomes in cirrhosis is not as well understood.

Objectives

- (1) Determine the prevalence of anxiety in cirrhosis and its association with clinical outcomes
- (2) Identifying predictors of anxiety using relevant clinical variables and subcomponents of the Hospital Anxiety and Depression Scale (HADS)

METHODS

Patients 18-80 years old with cirrhosis were recruited consecutively from liver clinics in Edmonton. Individuals were excluded if they: were disoriented or had overt hepatic encephalopathy; active malignancy; hepatocellular carcinoma outside transplant criteria; end-stage renal disease on dialysis; or on antidepressants. Patients were identified as having anxiety using the Mini Neuropsychiatric Interview (MINI) modules. The HADS was completed to assess anxiety. The chronic liver disease questionnaire (CLDQ) and EQ-VAS score were used to determine HRQoL. Patient sociodemographic and clinical information were collected retrospectively then 6 months prospectively to determine if they had unplanned hospitalizations or deaths.

RESULTS

A total of 304 patients were enrolled in the study, with 17.1% having anxiety diagnosed by the MINI. Multivariate analysis revealed active smoking and 3 HADS subcomponents as independent predictors of anxiety. Anxious patients had lower HRQoL as assessed by CLDQ ($P < 0.001$) and EQ-VAS ($P < 0.001$) and were frailer by the Clinical Frailty score ($P = 0.004$). There were no statistically significant differences between anxious and non-anxious patients for hospitalizations or death within 6 months of testing ($P = 0.14$). The 8.2% of patients identified as both anxious and depressed had worse CLDQ, EQ-VAS and Clinical Frailty scores than anxious-only or depressed-only patients.

CONCLUSIONS

Anxiety is common in patients with cirrhosis and not routinely screened for or treated, despite having significant impact on HRQoL and functional status. Active smoking and three HADS subcomponents were identified as being independent predictors of anxiety.

Supervisor: Dr. Puneeta Tandon

Table 2. Association of Anxiety with Frailty, Health-related Quality of Life and Hospitalization/Death within 6 months

| | Total cohort (n=304) | Anxiety MINI (n=52) | No anxiety MINI (n=252) | P value |
|------------------------------------------|-------------------------|------------------------|----------------------------|--------------|
| CLDQ | 4.73 (1.33) | 3.61 (1.23) | 4.96 (1.23) | 0.001 |
| EQ-VAS | 62.9 (22.5) | 51.8 (22.2) | 65.2 (21.9) | 0.001 |
| CFS (continuous) | 3.3 (1.1) | 3.65 (1.03) | 3.15 (1.1) | 0.004 |
| Hospitalization or death within 6 months | 33% (97/296) | 42% (21/50) | 31% (76/246) | 0.14 |

SIX-MINUTE WALK TEST AND SARCOPENIA IN PREDICTING MORTALITY IN PATIENTS WITH CIRRHOSIS

ThucNhi T. Dang, Maryam Ebadi, Aldo Montano-Loza, and Puneeta Tandon
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Low muscle mass (sarcopenia) is associated with increased mortality in patients with cirrhosis. The association of functional performance with sarcopenia and its impact on mortality has not been well established in cirrhosis.

Objectives

- 1) Determine the association between six-minute walk test (6MWT) and sarcopenia
- 2) Assess the prognostic value of the 6MWT in patients with cirrhosis

METHODS

Patients who were assessed for liver transplant (LT) at the University of Alberta hospital were retrospectively enrolled in the study. Cross-sectional imaging within 1 year of assessment was used to quantify skeletal muscle cross sectional areas, which was then normalized to calculate the skeletal muscle index (SMI; cm²/m²). Sarcopenia was defined using pre-established cut-offs in patients with cirrhosis. Cut-offs for 6MWT to predict mortality (death or delisting for being too sick for LT) were determined using receiver-operating characteristic (ROC) curves. Cox proportional hazard models were conducted to assess associations between sarcopenia, functional performance assessed by the 6MWT, and mortality.

RESULTS

A total of 180 cirrhotic patients who were evaluated for liver transplant had a 6MWT test at the time of assessment and corresponding CT imaging. A 6MWT < 489 m was independently associated with mortality, with AUC of 0.61 (95% CI, 0.51-0.71, P=0.03) and subsequently defined as "low 6MWT." In a multivariate model, adjusted for MELD, sarcopenia (HR 2.96; 95% CI 1.59-5.51; P=0.001) and low 6MWT (HR 2.33; 95% CI 1.21-4.51; P=0.01) were independently associated with mortality. Sarcopenic patients with low 6MWT experienced a 6 times higher risk (HR 6.24; 95% CI 2.65-14.68; P<0.001) of death and survived for 25 months (95%CI, 12-38) compared to 69 months (95%CI, 27-112) in sarcopenic patients with normal 6MWT (Log Rank=0.04).

CONCLUSIONS

Sarcopenia and poor physical performance independently associate with mortality in patients with cirrhosis. Although poor physical performance was observed in more than half of the sarcopenic patients, its ability to discriminate mortality requires further investigation.

Supervisor: Dr. Puneeta Tandon

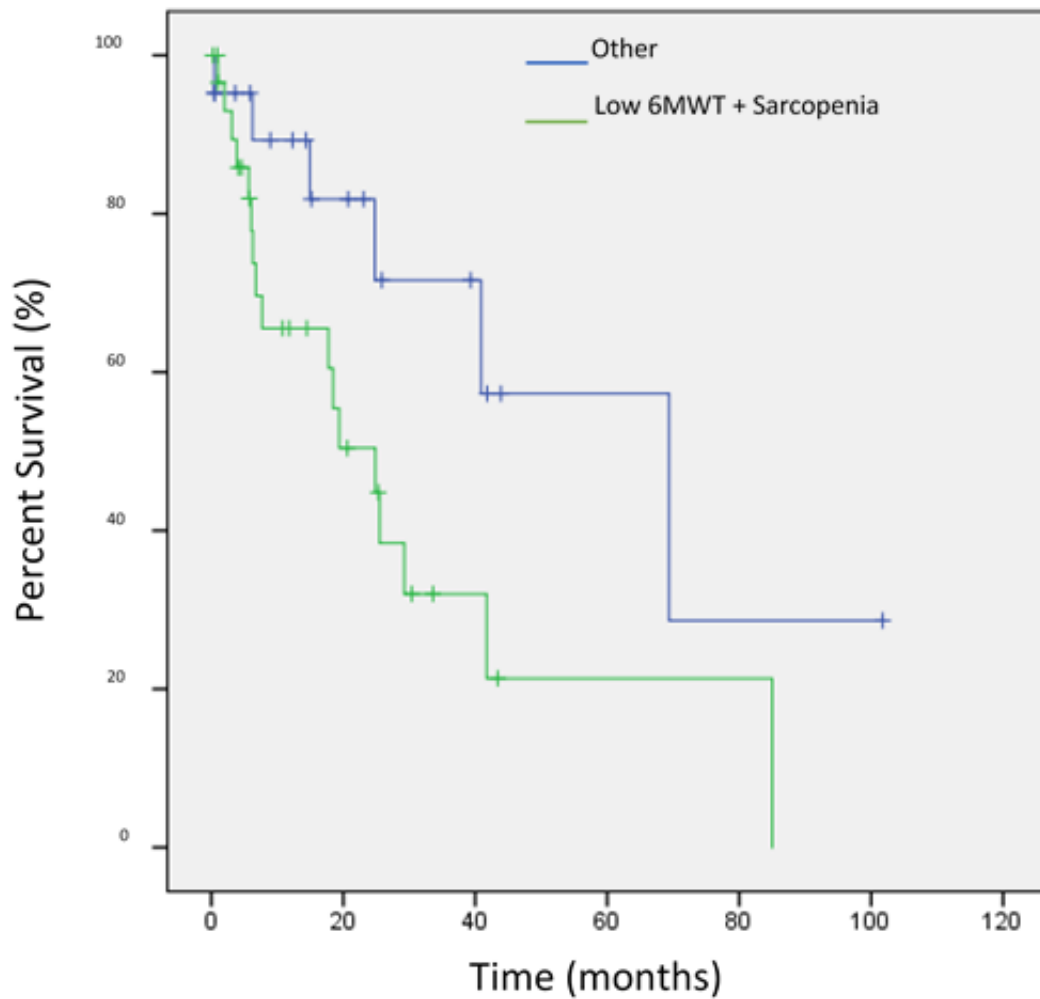


Figure 1. Sarcopenic patients with low 6MWT survived for 25 months (95%CI, 12-38) whereas median survival was 69 months (95%CI, 27-112) in sarcopenic patients with high 6MWT (Log Rank=0.04)

Multiview 3D Fusion Echocardiography Using a Novel Transducer and Respiratory Tracking Technique: First Results in Humans

Tyler Lamb, Abhilash Hareendranathan, Wanhua Su, Kumar Punithakumar, Michelle Noga, Pierre Boulanger, Harald Becher

Supervisor: Dr. Harald Becher

INTRODUCTION

While developments in ultrasound transducer technology and post-processing techniques have undoubtedly bettered 3DE, but they have failed to address inherent weaknesses of 3DE. These include a limited volume-of-view (VOV) and suboptimal endocardial definition resulting from non-perpendicular angles of ultrasound incidence relative to important structures like the left ventricle. Multi-view 3-dimensional fusion echocardiography (M3DFE) offers a solution to this dilemma by fusing 3DE datasets from complementary acoustic windows.

METHODS

Real-time M3DFE datasets were acquired from eleven volunteers during a breath-hold maneuver with i) an unmoving transducer capturing a standard apical view, ii) slight movement of the transducer to include non-standard apical views, and iii) the probe positioned at both parasternal and apical windows. Infrared cameras were used to track the 3-dimensional position and orientation of the transducer and chest markers. A range of two to five datasets were recorded per breath-hold for each of these three groups. Multi-planar reconstruction of both M3DFE and standard apical 3DE datasets was performed to generate four- and two- chamber 2-dimensional planes which were then analyzed and compared. Subjective assessments included i) successful alignment of datasets and ii) endocardial border definition (rated on a three-point scale from 0 to 2). Objective assessments included i) contrast, ii) contrast-to-noise ratio (CNR), iii) signal-to-noise ratio (SNR) and iv) % increase in VOV. Endocardial border definition, contrast, CNR and SNR were assessed for each of the standard six segments for both the apical two- and four-chamber planes.

RESULTS

At least one successfully aligned M3DFE dataset was generated for each of the three transducer position categories for all eleven volunteers. Table 1 summarizes the results.

CONCLUSIONS

This novel M3DFE technique results in successful fusion of 3DE datasets. Compared to standard 3DE datasets, M3DFE datasets demonstrate enhanced VOV and improvements in both subjective and objective measures of image quality.

Supervisor: Dr. Harald Becher

| | Contrast %Diff. in Means | CNR %Diff. in Means | SNR %Diff. in Means | EBD %Diff. in Means |
|------------------------------------------------------------|------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Unmoving Transducer: M3DFE (AVG) – SSA | -0.9% p = 0.55 | +57% p < 0.00001 | +65% p = 0.00001 | +24% p = 0.0004 |
| Unmoving Transducer: M3DFE (WAV) – SSA | +4.1% p = 0.06 | +44% p < 0.00001 | +50% p < 0.000001 | +30% p < 0.00001 |
| Unmoving Transducer: M3DFE (WAV) – M3DFE (AVG) | +4.9% p = 0.02 | +12% p = 0.25 | +18% p = 0.14 | +14% p = 0.03 |
| Moving Transducer: NSA M3DFE (AVG) – SSA | -9.4% p = 0.43 | +65% p = 0.01 | +75% p = 0.005 | 13% p = 0.054 |
| Moving Transducer: NSA M3DFE (WAV) – SSA | +0.9% p = 0.49 | +32% p = 0.03 | +42% p = 0.006 | 25% p = 0.0002 |
| Moving Transducer: NSA M3DFE (WAV) – M3DFE (AVG) | +8.6% p = 0.10 | -12% p = 0.43 | -1.4% p = 0.50 | +16% p = 0.02 |
| Moving Transducer: AP M3DFE (AVG) – SSA | -24% p = 0.99 | +17% p = 0.27 | +28% p = 0.12 | +4% p = 0.39 |
| Moving Transducer: AP M3DFE (WAV) – SSA | +0.6% p = 0.50 | +41% p = 0.009 | +55% p < 0.001 | +35% p = 0.00001 |
| Moving Transducer: AP M3DFE (WAV) – M3DFE (AVG) | +24% p = 0.0001 | +31% p = 0.07 | +42% p = 0.03 | +32% p < 0.0001 |

Table 1: Results of one-tailed ANOVA test with Tukey Honest Significant Difference post-hoc correction at end-systole. Statistically significant results which reject the null hypothesis are highlighted in green. M3DFE = Multi-view 3D Fusion Echocardiography, SSA = Single Standard Apical 3DE, AVG = fusion by voxel averaging, WAV = fusion by wavelet decomposition, NSA = non-standard apical protocol, AP = apical-parasternal protocol, CNR = contrast-to-noise ratio, SNR = signal-to-noise ratio, EBD = endocardial border definition.

The G-Protein Coupled Receptor for the Metabolite Succinate (SUCNR1) Increases in Right Ventricular Hypertrophy and Increases Contractility

Vikram Gurtu, Yongneng Zhang, Trevor Stenson, Mohammed Osman, Aristeidis Boukouris, Bruno Saleme, Sotirios Zervopoulos, Gopinath Sutendra, and Evangelos Michelakis

Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

RV hypertrophy (RVH) is characterized by an increased reliance on glycolysis versus glucose oxidation, and activation of the transcription factor hypoxia-inducible factor 1a (HIF-1a). Metabolic remodeling increases levels of metabolic intermediates, some of which are secretable, binding extracellular receptors. Recently, the receptor for succinate (SUCNR1) was described as upregulated in cardiac hypertrophy, however the mechanism of upregulation and functional role in RVH are not understood. We hypothesized that SUCNR1 would be upregulated early in RVH through HIF-1a signaling, and that its activity would acutely improve contractility.

METHODS

Sprague Dawley rats were injected with vehicle or 60mg/kg monocrotaline (MCT) to induce pulmonary hypertension and RVH. RVs were harvested weekly up to 4 weeks with RVH assessment by Fulton Index (RV to left ventricle and septum mass ratio). Isolated rat RV cardiomyocytes (RVCM) were exposed to hypoxia versus normoxia for 24 hours, or viral transduction of AdCA5 adenovirus to overexpress constitutively active HIF-1a. Cardiomyocytes were evaluated microscopically to assess contractile response to 500 μ M succinate.

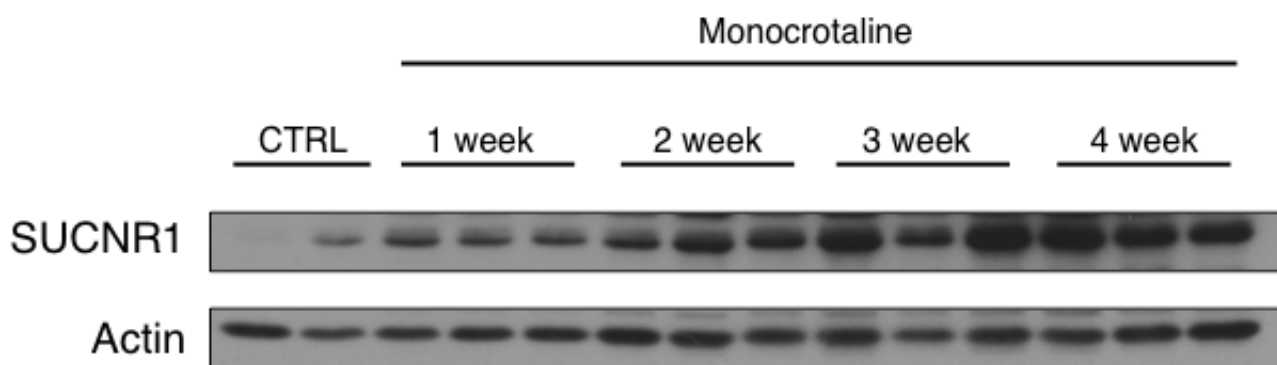
RESULTS

Although RV hypertrophy progressed starting 2 weeks after MCT (Fulton Index 0.339, 0.344, 0.451, 0.496, 0.684 for control, 1, 2, 3, and 4 week respectively), SUCNR1 expression increased as early as 1 week compared to control (Figure). SUCNR1 mRNA increased 2.22 fold in hypoxic versus normoxic RVCM, and increased 2.07 fold in AdCA5 versus control adenovirus AdGFP, suggesting HIF-1a dependent SUCNR1 transcription. In silico analysis identified a potential hypoxia response element 2987 base pairs upstream of the rat SUCNR1 gene. Chromatin immunoprecipitation of HIF-1a showed binding to this sequence. Functionally, acute succinate perfusion increased contractile response of cardiomyocytes to electrical stimulation.

CONCLUSIONS

SUCNR1 transcription increases early in RVH, and may be driven by HIF-1a signaling. The acute effects of SUCNR1 signaling on contractility indicate a role for maintaining compensation in the setting of increased RV afterload.

Supervisor: Dr. Evangelos Michelakis



The role of PAR-2 activation on airway epithelium

Yahya Fiteih and Harissios Vliagoftis

Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Our lab demonstrated that, blocking PAR-2 activation in the airways, decreased airway inflammation in mouse models of asthma. Moreover, Par-2 $-/-$ mice develop attenuated airway inflammation compared to WT mice. Furthermore, it has been demonstrated that PAR-2 mediated activation of airway epithelial cells leads to the release of critical inflammatory mediators in allergic airway inflammation such as Eotaxin and TSLP. Data mentioned above indicate that PAR-2 activation is essential for the development of allergic airway inflammation but, the exact cell/cells activated by PAR-2 activating proteinases in the airways is not clearly identified. We hypothesize that allergens possessing serine proteinases activity and/or endogenous proteinases, activate PAR-2 on airway epithelial cells, which induces the release of pro-inflammatory mediators and leads to allergic airway inflammation.

METHODS

To understand whether the development of allergic airway inflammation requires PAR-2 expression on structural cells (epithelial, endothelial cells and muscle cells) or on hematopoietic cells we performed bone marrow (BM) chimeras between WT mice and Par-2 $-/-$ mice. After BM cells transplantation the chimeric mice were sensitized and challenged with Ovalbumin. Allergic airway inflammation was assessed by measuring the number of eosinophils in the bronchoalveolar lavage fluid.

RESULTS

We demonstrated that Par-2 $-/-$ chimeric mice transplanted with WT BM cells developed attenuated airway inflammation similar to Par-2 $-/-$ chimeric mice transplanted with Par-2 $-/-$ BM cells indicating that PAR-2 expression on structural cells, possibly airway epithelium is indispensable for airway inflammation development. Also, we demonstrated reduction in allergic airway inflammation in WT chimeric mice transplanted with Par-2 $-/-$ BM cells, however, the inflammation was twice the levels in Par-2 $-/-$ chimeric mice transplanted with WT BM cells, indicating that PAR-2 expression on hematopoietic cells is essential for airway inflammation and contributes to the development of full effect.

CONCLUSIONS

PAR-2 on airway structural cells might be a novel therapeutic target for allergic airway inflammation.

Supervisor: Dr. Harissios Vliagoftis

Cardiac fibroblasts can induce a paracrine mitochondrial suppression of cardiomyocytes in hypoxia

Yongneng Zhang, Vikram Gurtu, Alois Haromy, Gopinath Sutendra, and Evangelos Michelakis

Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Cardiac fibroblasts (CFs), one of the largest cell populations in the heart, are involved in the maintenance of myocardial tissue structure and cardiac remodeling but remain understudied compared to cardiomyocytes. Our previous studies showed that the myocardium of a compensated right ventricular hypertrophy has suppressed mitochondrial function, as assessed by hyperpolarized mitochondrial membrane potential ($\Delta\Psi_m$) and low production of mitochondria-derived reactive oxygen species (mROS). We hypothesized that CFs can directly (in a paracrine manner) affect the mitochondrial function of cardiomyocytes (CMs), either at health or disease (i.e. hypoxia).

METHODS

CMs and CFs were isolated from the right ventricular myocardium of C57BL mice and Sprague Dawley rats and were studied either in isolation or in co-culture systems. $\Delta\Psi_m$ and mROS were measured by live imaging with the mitochondrial dyes TMRM and MitoSOX, respectively.

RESULTS

Hypoxia increased $\Delta\Psi_m$ and decreased mROS in both CFs and CMs (in short culture). Co-culture of CFs with CMs resulted in a further increase of hypoxia-induced $\Delta\Psi_m$ and hypoxia-induced decrease in mROS in CMs. Treatment of normoxic or hypoxic CMs with supernatant from hypoxia-treated CFs, resulted in a similar increase in $\Delta\Psi_m$ and decrease in mROS to hypoxia-treated CMs in co-culture with CFs. This suggests that in hypoxia, CFs are releasing signaling molecule(s) that result in suppressed mitochondrial function in CMs.

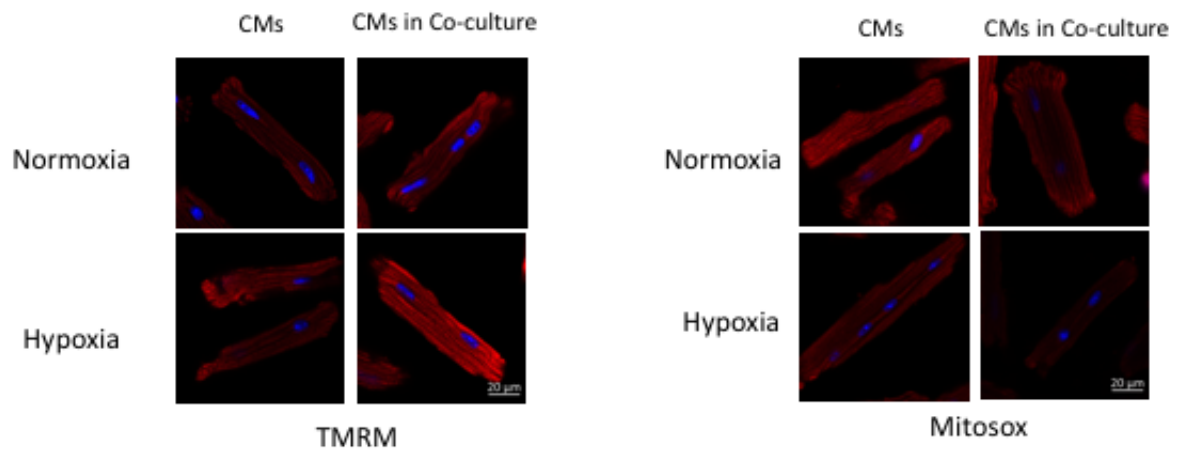
CONCLUSIONS

CFs can directly suppress mitochondrial function of CMs, in the presence of hypoxia, most likely by secreting a soluble factor. Understanding the importance of CF and CM interactions could reveal novel therapeutic targets in heart disease and specifically in the much understudied right ventricular failure.

Supervisor: Dr. Evangelos Michelakis

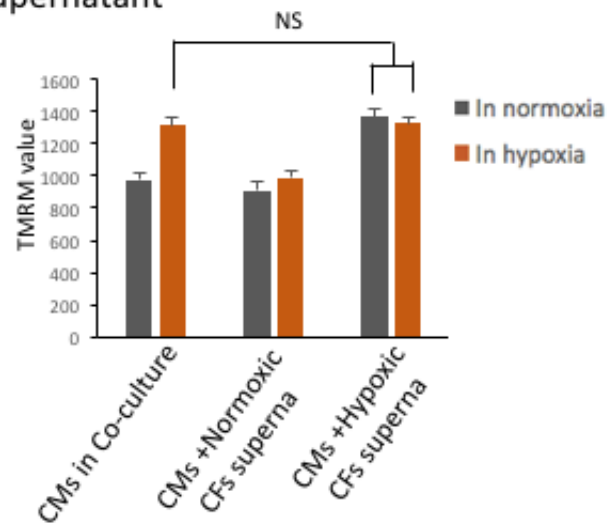
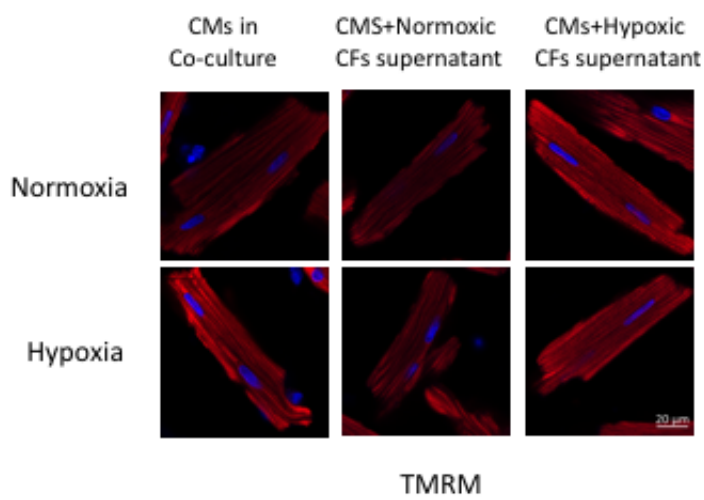
A

CMs in Co-culture



B

CMs with CFs supernatant



MSc in Medicine (Translational Medicine)

The Department of Medicine (DOM) has made **Translational Medicine (TM)** a top priority. TM facilitates the “translation” of molecular discoveries to actual patients and populations. It requires a different way of thinking at all stages of the journey from a discovery in an animal lab to the point that, following successful clinical trials, the government approves the discovered therapy for humans. TM is a critical component of **Precision Medicine**, a new discipline that aims for “custom-made” therapies for patients, as opposed to the traditional “one treatment fits all model”. This is because in order to apply an optimal therapy to a patient, one needs to understand the molecular and genetic differences that distinguish all patients from one another. Precision Medicine is now a top priority for the FOMD.

The need: To optimize the development of new “precision” therapies and diagnostic tests, a researcher studying molecules and animals needs to learn how to think as a clinician; and a clinical researcher needs to understand the principles of molecular research. This is challenging because traditional teaching models focus on one or the other, with the learners following either an exclusive molecular or clinical research career track. Although all recognize the importance of TM, there are surprisingly few examples of training programs worldwide aiming to teach this new discipline to future medical researchers and leaders.

The action: Four years ago, the DOM launched and since then supports a novel training program, teaching the attitudes and skills required to excel in TM. This is the first training program of its kind in Canada and one of few in the world.

The innovations: The TM program attracts trainees from very diverse backgrounds and levels of training. Rather than teaching principles of basic or clinical research of specific diseases, the program teaches integrative and overarching concepts and skills to address the many challenges of bringing a molecular discovery to patients with diverse diseases. Since nothing needs to be “memorized”, the final exams are “open book”. Teaching objectives include, among others, new ways to design animal experiments or clinical trials compatible with PM, strategies to attract funding including grant writing skills, effective ways to communicate cross-disciplinary research findings, understanding of regulatory rules and “quality control” principles in preclinical and clinical research. Most of these principles are not taught in traditionally structured training programs. The trainees can either get credits towards their PhD or towards a novel Masters Program with “specialization in TM”, the first of its kind in Canada.

The program uses eClass, the University of Alberta’s centrally learning management system. eClass provides a digital platform in which the reading materials are archived as well as an out-of-class forum for ongoing discussions among trainees. All sessions are recorded through the eClass multimedia environment with Adobe Connect. This allows “live” streaming of sessions from other locations; thus the lectures can be attended interactively online by residents in a remote elective rotation or by trainees from other Universities. For example, in the last year 2 residents from UBC completed the program. The ability of residents to obtain a Masters degree during busy core Internal Medicine or specialty residency is a significant advantage to our clinical training programs.

The progress: A total of 72 learners have registered to the program so far. Of these, some took credits for their PhD and some participated as “open access” students. Of the 42 trainees that

participated in the *Masters track*, there were 2 junior faculty members, 14 graduate students and 26 residents from core and 10 specialty residency programs. To complete the Masters requirements a submission of a thesis is required. So far 11 trainees have obtained their *Master's with specialization in TM* degree.

The TM program is a major investment of the DOM, with many of its faculty contributing over the years. Currently, the program is directed by Evangelos Michelakis, MD, Gopinath Sutendra, PhD, Glen Jickling, MD, PhD and Eleni Karageorgos.

Testimonials from TM program graduates



Adam Kinnaird, MD, PhD; Vanier Scholar; Urology Resident (2015):

"I would recommend this program to any graduate student or clinician who is interested in a career in translational research. The concepts that we discussed are not found in traditional basic science undergraduate, medical or post-graduate medical programs in our country. Our institution is truly on the leading edge offering this program and as such, knowledge obtained in this Master's program will give all who attend an advantage in the field of translational medicine."



Abhinav Sharma, MD; Cardiology Resident (2016):

"The Master's program in translational science gave me the tools and skills necessary to bridge the gap between basic science and clinical research. I feel more confident in examining clinical questions through a basic science lens while examining bench and laboratory work from a clinical perspective. If you are looking for a program that will allow you to interface between the bench and bedside, then this program is for you."



Tayne Hewer; Graduate Student (2017):

"...When I attended the first class I was incredibly nervous, felt overwhelmed and out of place. As the program progressed I became more confident and truly engaged in the messages brought forward with each session. In the past I took education for granted but the TM program changed this for me. While I am not sure where my career in clinical research will take me, I can honestly say that this program has changed the way I approach learning and my job..."

The TM Program class on April 19, 2018 (final exam day)



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