Skin Research Group *Of* Canada

6th Annual Conference

PROGRAM & ABSTRACTS

June 26 – 27, 2019
Hyatt Regency
Calgary, Alberta

The Skin Research Group of Canada 2019

Welcome to the 6th Annual meeting of the Skin Research Group of Canada (SRGC). The SRGC Scientific Organizing Committee is delighted to invite you to the 2019 Annual Meeting in Calgary.

This year will be our 2nd joint meeting with the Canadian Dermatology Association (CDA), a collaboration that will undoubtedly help bring Canadian basic science, translational and clinical skin research expertise under one roof. The 2019 SRGC program will showcase recent advances in skin research, and facilitate collaborations and knowledge translation. The meeting will help build critical connections between scientists, clinicians, patient alliance/patient advocacy groups, and industry partners to answer important questions to improve diagnosis and management of skin diseases.

Our joint meeting will be equally beneficial to clinicians, basic scientists and industry partners engaged in skin research and will bolster our efforts to understand the pathophysiological mechanisms underlying skin diseases such as psoriasis, eczema, skin cancer, autoimmune diseases, wound healing, skin regeneration and many other topics. At least 25 % of the conference time is dedicated to interactive sessions.

Learning objectives:

- Participants will get acquainted with molecular pathogenesis of a number of skin diseases including psoriasis, atopic dermatitis, acne, vitiligo, scleroderma, epidermolysis bullosa, cutaneous lymphomas, melanoma, non-melanoma skin cancers and chronic wound healing.
- Participants will be able to learn of recent advances in research on these diseases and will gain knowledge on how targeted therapies can be used to treat these conditions.
- Participant will also be able to critically evaluate how future research on these conditions can improve their diagnosis and management.

We need your participation to make this meeting a success!

Sincerely,
Annual Conference Scientific Organizing Committee,

Ivan V. Litvinov MD, PhD

Anie Philip, PhD

Stéphane Roy PhD

The Skin Research Group of Canada 2019

Organizing Committee

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Veronique Moulin, PhD
Professor
Department of Surgery
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Université Laval

Skin Research Group of Canada

6th Annual Conference

2019 Program

WEDNESDAY, 26 JUNE			
8:00 - 9:00am	**Registration & Poster Set Up**		***Grand Foyer***
8:30 - 9:50am	**Plenary Session I** Moderators: *Julie Fradette & Candice Diaz*	**Wound Healing**	***Stephen Room***
8:30am	"Integrating Adipose Tissue Engineering for The Production of a More Complete In Vitro Reconstructed Skin" *Julie Fradette*		
8:50am	"Fibulin-4 And Latent Transforming Growth Factor-B Binding Protein-4 In Wound Healing" *Hana Hakami*		
9:00am	"Injury-Responsive Dermal Fibroblasts Acquire Divergent Fates Dependent on Their Location Within the Wound" *Elodie Labit*		
9:10am	"A Novel Approach to Reduce Post-Surgical Fibrosis" *Layla Nabai*		
9:20am	"Inhibition of NLRP3 Inflammasome Post-Burn Impairs Wound Healing" *Roohi Vinaik*		
9:30am	"Gene Therapy and Tissue Engineering: A Strategy to Treat Recessive Dystrophic Epidermolysis Bullosa" *Martin Barbier*		
9:40am	"Combination Treatment with Tissue-Engineered Dressings and Hyperbaric Oxygen Therapy to Promote Wound Healing in Murine Irradiated Skin" *Candice Diaz*		
10:00 - 10:50am	**Plenary Session II** Moderators: *Jeff Biernaskie & Brian Wu*	**Basic Sciences**	***Stephen Room***
10:00am	"Transcriptomic Analysis of Fibrotic Versus Regenerative Skin Wound Healing" *Jeff Biernaskie*		
10:20am	"Dysfunction of Hair Follicle Mesenchymal Progenitors Is Associated with Age Related Hair Loss" *Wisoo Shin*		
10:30am	"Fibulin-4 Exerts A Dual Role in Ltbp-4 Mediated Matrix Assembly and Function" *Heena Kumra*		
10:40am	"Role of Endothelial Ephrin-B2 Signaling in Pulmonary Fibrosis" *Brian Wu*		

11:00 - 12:00pm	**Plenary Session III** Moderators: *An-Wen Chan & Ahmed Mourad*	**Translational Research**	***Stephen Room***
11:00am	"Dermatologic Assessment Is Associated with Improved Melanoma Outcomes: Population-Based Cohort Study" *An-Wen Chan*		
11:20am	"CD109 Drives Tumorigenesis and Metastasis by Modulating The EGFR/AKT Signaling in Squamous Cell Carcinoma" *Shufeng Zhou*		
11:30am	"Granzyme K: Potential Role in Inflammation and Psoriatic Disease" *Katlyn Richardson*		
11:40am	"Oral and Intra-Incisional Antibiotic Prophylaxis in Mohs Surgery: A Systematic Review and Meta-Analysis" *Ahmed Mourad*		
11:50am	"Transglutaminase 1 Replacement Therapy Successfully Mitigates the Arci Phenotype in Full-Thickness Skin Disease Models" *Sarah Hedtrich*		
12:00 - 1:00pm	**Lunch and Visit Our Sponsor Booths and Posters**		***Grand Foyer***
1:00-1:30pm	*SRGC State-of-the-art Lecture* ***Dr. Youwen Zhou*** "Therapeutic Targeting of Pathogenic Drivers of Cutaneous T Cell Lymphoma" *Moderator: Ivan V Litvinov*		***Stephen Room***
1:40 - 3:00pm	**Translational Research Roundtable Discussions**		***Stephen Room***
3:15-4:00pm	*SRGC Excellence in Skin Research Lecture* ***Dr. Lucie Germain*** "Tissue-Engineered Skin Substitutes Preserving Stem Cells for Fundamental Studies and Clinical Applications" *Moderator: Anie Philip*		***Stephen Room***
4:00 - 6:00pm	**Come See My Poster (Moderated Poster Walks)** **Visit Our Sponsor Booths**		***Grand Foyer***
6:30 - 9:00pm	**SRGC Welcome Reception**	**Achieving Excellence in Clinical Research Workshop (By Invitation Only)**	
	Thomson Room		
6:00pm	**Poster Takedown**		***Grand Foyer***

THURSDAY, 27 JUNE			
8:00 - 8:30am	**30 Career Tips In 30 Minutes**		***Imperial Room***
8:40 - 9:50am	**Concurrent Sessions**		
	Cutaneous Lymphoma Moderators: *Ivan V Litvinov & Raed Alhusayen* *Walker Room*	**Eczemas and Atopic Dermatitis** Moderators: John Elliott & *Christopher Turner* *Bannerman Room*	
8:40am	"Revisiting the Role of Phototherapy In CTCL" *Raed Alhusayen*	"Patients Allergic to Disperse Blue 106/124 Likely React to A Diverse Set of Molecules All Containing A Specific Structural Motif" *John Elliott*	
9:00am	"Significance of Ectopic Expression of Meiosis Regulatory Genes in Cutaneous T-Cell Lymphomas (CTCL)" *Jennifer Gantchev*	"A Novel Approach for Treatment of Atopic Dermatitis: Topical Application of An Immunomodulatory Peptide Inhibitor in A Mouse Model" *Fatima Hubaishi*	
9:10am	"How to Best Communicate Prognosis in Mycosis Fungoides? A Systematic Review and Meta-Analysis" *Ahmed Mourad*	"Aberrant T Cell Responses to Bacterial Inhibitory Signals in Atopic Dermatitis" *Vladimir Andrey Gimenez Rivera*	
9:20am	"Neoantigens In Mycosis Fungoides: Whole Exome Sequencing Discovery of Immunotherapeutic Targets" *Arunima Sivanand*	"Keratinocyte Carcinoma Risk in Patients with Atopic Dermatitis: A Systematic Review" *Lily Wang*	
9:30am	"Cutaneous T-Cell Lymphoma Is A Genetically and Clonotypically Heterogeneous" *Aishwarya Iyer*	"Fibroblasts from Atopic Dermatitis Patients Impair the Epidermal Homeostasis of Skin Equivalents" *Sarah Hedtrich*	
9:40am	"Human T-Cell Lymphotropic Virus-1 Infection Prevalence in Canada" *Ivan Litvinov*	"Granzyme B Inhibition Reduces the Severity of Atopic Dermatitis in Mice" *Christopher Turner*	
9:55 - 12:00pm	**Skin Science for All (CDA Program)**		***Imperial Room***

12:00 - 1:00pm	**Lunch with Industry Sponsors & Presentations** *Moderator: Veronique Moulin*	***Stephen Room***
12:30pm	"Hypertrophic scar myofibroblasts generate proangiogenic microvesicles" *Veronique Moulin*	
12:40pm	"Essential role for integrin-linked kinase in melanoblast colonization of the skin" *Lina Dagnino*	
1:00-1:30pm	*SRGC State-of-the-art Lecture* ***Dr. Kim A. Papp*** "The Role of JAK/STAT Signaling in Inflammatory Skin Diseases" *Moderator: Ivan V Litvinov*	***Stephen Room***
1:30 - 2:30pm	**CDF 50th Anniversary Program** *Harvey Lui & Regine Mydlarski*	**SRGC Job Career Forum for Graduate Students and Post-doctoral Fellows**
		Stephen Room
2:30-3:00pm	*SRGC Frontiers in Science Lecture* ***Dr. Aziz Ghahary*** "Past, Present and Future Skin Research Innovation and Commercialization" *Moderator: Anie Philip*	***Stephen Room***
3:00 - 3:25pm	**Canadian Dermatology Foundation Lecture** *Lidia Rudnicka*	
3:00 - 3:30pm	**SRGC Session** *Moderator: Dieter Reinhardt*	***Stephen Room***
3:00pm	"Targeting the Microenvironment in Fibrotic Conditions" *Andrew Leask*	
3:15pm	"Targeting CD109 In Fibrosis and Cancer: A Double-Edged Sword" *Anie Philip*	
3:35 - 4:00pm	**Journal of Cutaneous Medicine and Surgery Lecture** *Charles Lynde*	
4:00 - 5:00pm	**Closing & Awards Ceremony**	***Stephen Room***

SKIN RESEARCH GROUP *of* CANADA

6th Annual Conference

Presents

SRGC
State-of-the-art Lecture

Wednesday
JUNE 26, 2019
(1:00 – 1:30 PM)
Stephen Room

"Therapeutic Targeting of Pathogenic Drivers of Cutaneous T Cell Lymphoma"

Youwen Zhou, MD, PhD
Professor
Department of Dermatology and Skin Science
University of British Columbia

Dr. Youwen Zhou is a professor and Director of Research of the Department of Dermatology and Skin Science at University of British Columbia. A certified dermatologist in Canada and US. Dr. Zhou received his MD from University of Toronto and PhD from Downstate Medical Center in New York. He serves on the editorial board of JAAD and other dermatology journals. He has received numerous national and international awards and has served on the Advisory Board of CIHR-IMHA Institute. His is the president of Canadian Melanoma Foundation and past president of Canadian Society of Investigative Dermatology. As a clinician scientist, Dr. Zhou discovered numerous molecular mediators and pathogenic drivers of cutaneous T cell lymphoma (CTCL) and other skin diseases. His current research is focused on developing next-generation diagnostic tools and targeted therapies for patients with skin inflammation and skin cancers.

SKIN RESEARCH GROUP *of* CANADA

6th Annual Conference

Presents

SRGC
Excellence in Skin Research Lecture

Wednesday
JUNE 26, 2019
(3:15 – 4:00 PM)
Stephen Room

"Tissue-engineered Skin Substitutes Preserving Stem Cells for Fundamental Studies and Clinical Applications"

Lucie Germain, PhD

Full Professor, Department of Surgery, Faculty of medicine
Université Laval, Quebec, QC, Canada
Canada Research Chair (Tier 1) on Stem Cells and Tissue Engineering Scientific Director, LOEX
Researcher, CHU de Québec – Université Laval Research Centre

Dr. Lucie Germain holds a Ph.D. and pursues a career in regenerative medicine as full professor at Université Laval.

Her work at the Tissue Engineering Laboratory/LOEX, a research Centre of the Université Laval is dedicated to post-natal stem cells and the reconstruction of human tissues for experimental and clinical applications.

Dr. Germain published more than 155 peer-reviewed articles, 67 book chapters and review articles. She gave more than 135 invited seminars and conferences.

Her sustainable contribution to health research was recognized by the foundation scheme of Canadian Institutes of Health Research (CIHR), which allowed her a financial support for 7 years. Within the CHU de Québec-Université Laval Research Centre, she was Director of the Regenerative Medicine Division until 2014. The Canada research chair program recognized Dr. Germain as a world leader in the field of stem cells and regenerative medicine by granting her a junior Tier-2 chair in 2001 and a senior Tier 1 chair in 2015. Dr. Germain was named Member of the Canadian Academy of Health Sciences in 2013. Between 2014 and 2018, she was appointed Vice-Dean of Research and Graduate Studies at the Faculty of Medicine of Université Laval. In 2005, Dr. Germain received one of the six Quality of Life Research Awards from the IMHA of CIHR. In 2009, she was recognized as Visionary by Châtelaine.

SKIN RESEARCH GROUP *of* CANADA

6th Annual Conference

Presents

SRGC
State-of-the-art Lecture

Thursday
JUNE 27, 2019
(1:00 – 1:30 PM)
Stephen Room

"The Role of JAK/STAT Signaling in Inflammatory Skin Diseases"

Kim A. Papp, MD, PhD, FRCPC
Director of Research
President
Probity Medical Research

Dr. Kim Papp is a Member of the College of Physicians and Surgeons of Ontario, a Fellow of the Royal College of Physicians and Surgeons of Canada, and a Fellow of the American Academy of Dermatology.

The Waterloo, Ontario, Canada based dermatologist has over 25 years' experience as a Principal Investigator, and has conducted over 170 psoriasis studies in which he closely supervised and assessed over 2750 subjects. Dr. Papp is an internationally renowned Key Opinion Leader in clinical research who conducts clinical trials on a wide range of dermatological disorders.

Dr. Papp, with the support of Probity Medical Research, an organization for which he serves as Founder and President, has earned the distinction of top enrolling investigator in over 70 international dermatology studies.

SKIN RESEARCH GROUP *of* CANADA

6th Annual Conference

Presents

SRGC
Frontiers in Science Lecture

Thursday
JUNE 27, 2019
(2:30 – 3:00 PM)
Stephen Room

"Past, Present and Future Skin Research Innovation and Commercialization"

Aziz Ghahary, PhD

Director, BC Professional Fire Fighters' Burn and Wound Healing Research Group

Professor, Division of Plastic Surgery, Department of Surgery, Faculty of Medicine, University of British Columbia

Associate Member, Dermatology and Skin Sciences, Faculty of Medicine, University of British Columbia

Dr. Aziz Ghahary received his Ph.D in Medical Physiology from the University of Manitoba in 1988 and after 2 years as post - doctoral training, he accepted an assistant professorship position in the Department of Surgery at the University of Alberta in 1990. He was then promoted to associate and full professor in 1996 and 2003, respectively. In 2005, he was then recruited by the Department of Surgery/ Plastic Surgery as a full professor and the director of the BC professional Firefighters' Burn and Wound Healing Research Group. During the last 12 years, 14 Ph.D. and 5 master students have been successfully graduated from his lab.

Funding and publications:

Dr. Ghahary has been awarded more than 52 research grants from local, national and international granting agencies. He is one the well-funded investigator in UBC. He has published or co-published over 185 peer reviewed articles, presented over 220 abstracts and major presentations at national and international conferences.

Discovery and Patents:

Dr. Ghahary has 7 patents from which one is related to a protein called stratifin also known as 14-3-3 sigma. He then found a very high level of eta isoform of 14-3-3 protein in sera of patients with rheumatoid arthritis. This biomarker has now been patented and licensed to the biggest diagnostic company in US and Canada, Quest Diagnostic and Lifelab, respectively. The early RA diagnostic test called JOINTstat, is now available in Canada and US. This has been approved for diagnosis in Europe, Australia, Japan and New Zealand.

PLENARY SESSION I

Wound Healing

Moderators: *Julie Fradette & Candice Diaz*

Stephen Room

WEDNESDAY, 26 JUNE **8:30 - 9:50AM**

PLENARY TALK

DR. JULIE FRADETTE

PRESENTERS

Hana Hakami

Elodie Labit

Layla Nabai

Roohi Vinaik

Martin Barbier

Candice Diaz

Wednesday, 26 June
Plenary Session I Wound Healing
8:30 - 9:50am

JULIE FRADETTE **8:30 – 8:50am**

INTEGRATING ADIPOSE TISSUE ENGINEERING FOR THE PRODUCTION OF A MORE COMPLETE IN VITRO RECONSTRUCTED SKIN

Julie Fradette
Centre de recherche en organogénèse expérimentale de l'Université Laval/LOEX, CHU de Québec Research Center - Université Laval and Department of Surgery, Faculty of Medicine, Université Laval, Québec, QC, Canada

Stromal/stem cells extracted from human adipose tissue (ASCs) offer the potential for new applications in tissue engineering, including cutaneous reconstruction. We have previously shown that ASCs could be used to produce a connective tissue using a self-assembly strategy. By combining this technique with a concomitant step of adipogenic differentiation, we recreated a functional human adipose tissue which is representative of the skin's deepest layer: the hypodermis. Our hypothesis is that ASCs could be advantageous for skin tissue engineering to produce enhanced substitutes devoid of exogenous biomaterials. Our objective is to reconstruct both bilayered, as well as more complete trilayered skin substitutes as models to study the influence of adipocytes in cutaneous biology and wound healing. Dermis was reconstructed by the self-assembly technique using human dermal fibroblasts as a comparison. Bilayered skin constructs were obtained by seeding keratinocytes directly onto either a dermis, a connective tissue layer made of non-differentiated ASCs or an adipose tissue layer. A trilayered substitute was also produced by apposing an adipose layer (hypodermis) under a bilayered skin containing dermal fibroblasts or ASCs. Each reconstructed skin was cultured at the air-liquid interface for 14 days and compared through various analyses. A properly regulated epidermal stratification was observed for both bilayered and trilayered reconstructed skin substitutes. Immunolabelings revealed an appropriate pattern of epithelial differentiation, with expression of K14 in the basal layer, K10 in the suprabasal layers and transglutaminase in the granular layer. The presence of a dermo-epidermal junction (laminin 5, collagen IV), which is important for strong cohesion between the compartments, was also detected for all types of reconstructed skin. We thus suggest that easily accessible and expandable ASCs can be used as an alternative cell source for dermal reconstruction. These new engineered skin represent enhanced autologous substitutes for great burn victims or patients with chronic ulcers.

Hana Hakami **8:50 – 9:00am**

FIBULIN-4 AND LATENT TRANSFORMING GROWTH FACTOR-β BINDING PROTEIN-4 IN WOUND HEALING

Hana Hakami1,2, Véronique Moulin3, Nathalie Lamarche-Vane1,4, Dieter P. Reinhardt1,5 *1Faculty of Medicine, McGill University, Montreal, Canada, 2Faculty of Sciences, King Saud University, Riyadh, Saudi Arabia, 3Centre of Research in Experimental Organogenesis of Laval University (LOEX), Quebec, QC, Canada, 4Cancer Research Program, Research Institute of the MUHC, Montreal, Quebec, Canada, 5Faculty of Dentistry, McGill University, Montreal, Canada*

Introduction:
Wound healing is a highly complex process producing only partially functional scar tissue. This tissue lacks the integrity of organized elastic fibers as well as of collagen fibers, which contributes to the stiffness of scar tissue. Fibulin-4 (FBLN4) and latent transforming growth factor beta binding protein-4 (LTBP4) are required for elastic fiber formation. FBLN4 also plays a significant role in collagen fiber assembly. Knockdown of LTBP4 in skin fibroblasts isolated from systemic scleroderma patients prominently reduced downstream collagen type 1A1 and 1A2 mRNA levels. Additionally, mutations in FBLN4 and LTBP4 cause autosomal recessive cutis laxa (ARCL) type B and C, respectively. On the molecular level, it is not known how FBLN4 and LTBP4 function in wound healing.
Methods:
Using immunofluorescence, we analyzed normal and scar skin samples for their elastic fiber protein profile. To investigate the roles of FBLN4 and LTBP4 in the proliferation phase of wound healing, cell proliferation and cell migration assays were performed. To further investigate the role of FBLN4 and LTBP4 in cell migration, focal adhesion and actin filaments were analyzed in skin fibroblast cultures seeded on FBLN4 or

LTBP4. Collagen gel contraction assays were conducted to evaluate the function of FBLN4 and LTBP4 in the contractility of myofibroblasts, a key cell type in wound healing.

Results:

In normal and scar skin tissues, FBLN4 and LTBP4 localized specifically to elastic fibers and collagen fibers. FBLN4, but not LTBP4, elevated skin fibroblast proliferation. Both, FBLN4 and LTBP4 enhanced skin fibroblast migration. Both proteins stimulated focal adhesion kinase phosphorylation through RhoA activation. The presence of FBLN4 and LTBP4 increased significantly the contraction of myofibroblast-cellularized collagen gels.

Conclusions:

The results suggest that FBLN4 and LTBP4 have important roles in wound healing since they promote cell migration, focal adhesion formation and myofibroblasts contractility.

Learning objectives:

To analyze the expression of two elastic fiber proteins, FBLN4 and LTBP4, in normal and scar skin tissues from different ages. - To explore differences in skin fibroblast proliferation, cell migration and focal adhesion formation caused in the presence of FBLN4 and LTBP4. - To track the pathway underlying FBLN4 and LTBP4 focal adhesion promotion.

Takeaway Message:

Patients affected by skin scarring suffer from long-term physical and psychological challenges. Basic knowledge about wound healing is required to improve current treatments. FBLN4 and LTBP4 are elastic fiber proteins that potentially have important roles in wound healing.

Elodie Labit **9:00 – 9:10am**

INJURY-RESPONSIVE DERMAL FIBROBLASTS ACQUIRE DIVERGENT FATES DEPENDENT ON THEIR LOCATION WITHIN THE WOUND

Labit E, Sinha S, Abbasi S, Biernaskie J

University of Calgary

Introduction:

Few mammals can completely regrow a damaged tissue – a process known as tissue regeneration. Instead, humans and most other mammals repair injuries by producing scar tissue, which has different properties compared to the original tissue it replaces. In mice, an interesting model combines regeneration and fibrosis; after large wounds, regeneration occurs in the center zone. However, the mechanisms driving regeneration in the central zone is unclear.

Methods:

We hypothesize the dermal progenitor cells recruited to the central regenerative zone are different from those in the peripheral scar zone.

Results:

To test this hypothesis, we used Hic1-tdTomato-lineage to trace the dermal progenitors to either the central or peripheral zone. We compared centre and peripheral cells using single-cell RNA (scRNAseq) sequencing 14 days after injury. Interestingly, our data showed that fibroblasts from regenerative zone reacquired some development cells fate (like Crabp-1 expression) and they seem to activate some specific transcription factors like Runx-1 whereas scar fibroblasts expressed specific scar transcription factor such as Dlk1, known as fibrosis marker. However, center and peripheral fibroblasts share a lot of common markers and transcription factors. Indeed, their inducibility to become regenerative or scar fibroblasts seems to be dependent on the micro-environment signals. Precisely, we found, thanks to negative Hic1-tdTomato scRNAseq analysis, that epithelial and immune compartment are very different within the two zones and could be responsible for the specific signal in the centre by switching the fibroblasts in regenerative fibroblasts. In addition, we validated that neutrophils and reactive oxygen species (ROS) production were two times higher in the regenerative part than in the scar part.

Conclusions:

Our next study will be to test the effect of the neutrophil depletion and ROS production inhibition on fibroblasts fate, then skin repair (scar vs regeneration). The comprehension of regeneration process could benefit millions patients suffering from severe skin injuries.

Learning objectives:

1. Mesenchymal cells and micro-environment interactions 2. Innate immune cells and skin regeneration 3. Modulation of scar 4. Single cell SEQ analysis and gene regulatory networks

Takeaway Message:
Understand i) the wound micro-environment (immune and epithelial component) and ii) the dialogue between micro-environment and dermal fibroblasts is necessary and essential to improve skin regeneration from skin injuries, such as burn and severe skin trauma.

Layla Nabai **9:10 – 9:20am**

A NOVEL APPROACH TO REDUCE POST-SURGICAL FIBROSIS

Layla Nabai, Malihe-Sadat Poormasjedi-Meibod, Ryan Hartwell, John Jackson, Aziz Ghahary
University of British Columbia

Introduction:
Fibrotic scar formation following surgical procedures or medical device implants is a clinically challenging problem with no satisfactory preventive or therapeutic modality. Our group has previously shown that kynurenic acid (KynA), a tryptophan metabolite, has an anti-fibrogenic effect both in vitro and in vivo. Here, we hypothesized that controlled delivery of the KynA to the wound bed can prevent post-surgical fibrosis
Methods:
Poly lactic-co-glycolic acid (PLGA), a biocompatible, biodegradable polymer, was used to fabricate microspheres loaded with KynA. The morphology, encapsulation efficiency, and release profile of the microspheres were determined. The efficacy of the controlled release microspheres was tested in a validated animal model of fibrosis. Pre-cut poly vinyl alcohol (PVA) sponges alone or loaded with polymer only (empty) or KynA containing microspheres were implanted subcutaneously on the back of the rats. Samples were harvested after 35 and 66 days. Collagen deposition inside the PVA sponges was evaluated both by histology and hydroxyproline assay. The expression of α-smooth muscle actin(α-SMA) was determined by immunohistochemistry (IHC) and qPCR.
Results:
Our results showed that addition of 17% methoxy polyethylene glycol-block-poly (D, L-lactide) (MePEG-b-PDLLA) to PLGA was needed to improve release kinetics of the microspheres without affecting encapsulation efficiency. Masson's trichrome staining and hydroxyproline assay revealed that collagen deposition in PVA+ KynA microspheres was significantly reduced in comparison with PVA or PVA+ empty microspheres. Also, the expression of α-SMA was significantly decreased in PVA+KynA microspheres group in comparison with PVA alone
Conclusions:
The results of our study shows that KynA can efficiently be encapsulated in and released from FDA approved polymer, PLGA. Implantation of the controlled release, KynA- loaded microspheres in wound bed reduces the post- surgical fibrosis in vivo.
Learning objectives:
At the end of the presentation participants will be able to 1- Identify a new strategy to prevent post surgical fibrosis. 2- Describe the process of preparing controlled release kynurenic acid microspheres. 3- Describe the process of testing in vivo efficacy. 4- Evaluate the results of the study based on the data provided.
Takeaway Message:
Controlled delivery of the anti-fibrosis agent, kynurenic acid, to wound bed can reduce post-surgical fibrosis. This can be achieved by encapsulation of kynurenic acid in FDA approved polymer microspheres and embedding the fabricated microspheres in wound bed before suturing.

Roohi Vinaik **9:20 – 9:30am**

INHIBITION OF NLRP3 INFLAMMASOME POST-BURN IMPAIRS WOUND HEALING

Roohi Vinaik, Abdikarim Abdullahi & Marc G. Jeschke
University of Toronto

Introduction:
Survival of burn patients is contingent on effective wound healing, a complex process that requires coordinated responses of myeloid cells and inflammatory pathways. NLRP3 inflammasome, which serves as a platform for secretion of pro-inflammatory cytokines, is implicated as a central regulator of wound healing. However, its role during the acute dermal and epidermal regeneration in the context of burns is unknown.
Methods:

Wild-type (WT), NLRP3-/-, and glyburide (NLRP3 blocker) treated mice were exposed to a 30% TBSA scald burn. Mice were sacrificed at 3 and 7 days post-burn. Gene expression was conducted via RT-PCR. Trichrome staining assessed collagen deposition and granulation tissue formation. F4/80 staining compared macrophage infiltration. Flow cytometric analysis characterized macrophage distribution and profile.

Results:

NLRP3, IL1β, and IL18 expression was upregulated in skin post-burn, and these changes were non-existent in NLRP3-/-. NLRP3-/- skin demonstrated significantly less macrophage infiltration and higher expression of M2 anti-inflammatory macrophage markers Arg1 and Fizz1 compared to WT. Trichrome staining of NLRP3-/- skin showed decreased collagen deposition. Administration of the anti-hyperglycemic glyburide, which is also an NLRP3 blocker, resulted in similar changes and impaired wound healing.

Conclusions:

NLRP3-/- and glyburide-treated mice demonstrate impaired wound healing, indicating that NLRP3 is protective in burn wounds via production of inflammatory mediators, macrophage recruitment and polarization to M1 pro-inflammatory phenotype. Post-burn activation of NLRP3 in skin plays a central role in mediating inflammatory processes leading to improved wound healing.

Learning objectives:

1. NLRP3 inflammasome is upregulated in human and murine skin during the acute phase post-burn. 2. Lack of NLRP3 impairs infiltration of pro-inflammatory M1 macrophages. 3. M1 macrophages during the acute phase are necessary for appropriate wound healing. 4. NLRP3 blockers should not be given in early phase after a burn injury.

Takeaway Message:

NLRP3 inflammasome activation and acute post-burn inflammation is necessary for wound healing. NLRP3 blockers such as anti-hyperglycemic glyburide should not be given during the acute post-burn phase.

Martin Barbier **9:30 – 9:40am**

Gene therapy and tissue engineering: a strategy to treat recessive dystrophic epidermolysis bullosa

Martin Barbier1,3, Angela Dakiw Piaceski1,3, Sébastien Larochelle1,3, Michael Boivin Welch1,2,3, Alex Larose1,3, Danielle Larouche1,3, Karim Ghani2,3, Véronique Moulin1,3, Elena Pope4, Manuel Caruso2,3, Lucie Germain1,3.

1Centre de Recherche en organogénèse expérimentale de l'Université Laval/LOEX (Québec, Canada), 2 Centre de Recherche sur le cancer de l'Université Laval (Québec, Canada); 3CHU de Québec-Université Laval Research Center (Québec, Canada). 4Hospital for Sick Children and University of Toronto (Toronto, Canada).

Introduction:

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic disease in which minor mechanical stress in the skin causes the formation of blisters and erosions. RDEB is caused by mutations in the COL7A1 gene – encoding type VII collagen (Col7), which leads to defective anchoring fibrils at the dermal-epidermal junction (DEJ) ultimately resulting in a loss of adhesion between the epidermis and the dermis. Production of autologous skin substitutes from genetically corrected patient's cells, and their subsequent graft, has the potential to be a suitable treatment to the permanent skin lesions of RDEB patients.

Methods:

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic disease in which minor mechanical stress in the skin causes the formation of blisters and erosions. RDEB is caused by mutations in the COL7A1 gene – encoding type VII collagen (Col7), which leads to defective anchoring fibrils at the dermal-epidermal junction (DEJ) ultimately resulting in a loss of adhesion between the epidermis and the dermis. Production of autologous skin substitutes from genetically corrected patient's cells, and their subsequent graft, has the potential to be a suitable treatment to the permanent skin lesions of RDEB patients.

Results:

We observed that viral particles infected the keratinocytes and fibroblasts of this RDEB patient with a transduction rate up to 40% and 70% respectively. Up to 80% of keratin 19-expressing keratinocytes were successfully transduced and maintained in culture. Skin substitutes were produced from the transduced cell populations and we observed the restoration of Col7 at the DEJ. The adhesion of the epidermis to the dermis was also restored compared to skin substitutes produced from RDEB cells.

Conclusions:

We developed an efficient method to restore Col7 production in a RDEB patient's cells using a SIN COL7A1 retroviral vector. Stem cell keratinocytes were effectively transduced and observed in the epidermal layer of the skin substitutes. Adhesion of the epidermis to the dermis was also restored compared to controls. In conclusion, our results indicate that this method might be suitable for the permanent treatment of RDEB skin lesions.

Learning objectives:

Recessive Dystrophic Epidermolysis Bullosa incidence and clinical manifestations. Structure of self-inactivating retrovirus for gene therapy. Methodology to produce tissue-engineered skin substitutes using the self-assembly approach.

Takeaway Message:

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe genetic disease for which there is no cure. We developed, using gene therapy and tissue-engineering, a promising strategy for the permanent treatment of RDEB skin lesions.

Candice Diaz **9:40 – 9:50am**

COMBINATION TREATMENT WITH TISSUE-ENGINEERED DRESSINGS AND HYPERBARIC OXYGEN THERAPY TO PROMOTE WOUND HEALING IN MURINE IRRADIATED SKIN

Diaz C1, Hayward CJ1, Paquette C1, Langevin J2, Galarneau J2, Archambault L1, Pollock NW1, Fradette J1

1 Université Laval 2 Cégep de Ste-Foy, Québec, Canada

Introduction:

Radiotherapy for cancer treatment can result in radiodermatitis and incapacitating hard-to-heal skin wounds. Such chronic wounds can benefit from daily sessions of hyperbaric oxygen therapy (HBOT) over several weeks. We have previously engineered biological dressings from human adipose-derived stem-cells (ASCs) recognized for their therapeutic secretome. Our goal is to develop a murine model recreating radiodermatitis following local irradiation in order to assess various treatments. Our hypothesis is that serial HBOT sessions combined with our biological dressings would accelerate healing in a murine model of excisional wounds on irradiated tissues.

Methods:

The dorsal murine skin received a single dose of 45 Grays (Gy). Four weeks after irradiation, full-thickness splinted excisional wounds (8 mm) were created in irradiated and non-irradiated areas. The impact of HBOT session (20 sessions) and weekly changes of engineered biological dressings, alone or in combination, have been evaluated using macroscopic images and histological analyses.

Results:

Skin alterations (epidermal hyperproliferation, increased dermal myofibroblast content) were noticeable 4 weeks after irradiation. Global wound closure evaluation revealed delayed healing in irradiated tissues (60% vs 90% healed surface area after 33 days, $P<0.007$). A course of HBOT could potentially promote wound closure in irradiated tissues, administered alone (79% vs 60%, $P<0.06$) or combined with ASCs dressings (85% vs 60%, $P<0.0083$). Detailed characterization will determine the impact of HBOT and ASCs dressing on scar quality (neoepidermis, granulation tissue neovascularization). Irradiation decreased tissue vascularity, which was increased (1.8 fold) after being treated with HBOT combined with biological dressings.

Conclusions:

We established a murine model to assess various therapeutic protocols for the treatment of radiodermatitis.

Learning objectives:

• Describe the impact of irradiation on murine skin • Discuss the kinetics of global wound healing between irradiated and normal skin in our model • Describe the impact of HBOT and biological dressings, alone or in combination, on global wound closure and scar quality in a model of healing compromised by irradiation

Takeaway Message:

These preclinical studies will provide an evidence-based evaluation of the efficacy of two treatments (HBOT and biological dressings), separately and in combination, to improve the quality of life for patients affected by radiodermatitis and chronic wounds developing after radiotherapy.

PLENARY SESSION II

Basic Sciences

Moderators: *Jeff Biernaskie & Brian Wu*

Stephen Room

WEDNESDAY, 26 JUNE **10:00 - 10:50AM**

PLENARY TALK

DR. JEFF BIERNASKIE

PRESENTERS

Wisoo Shin

Heena Kumra

Brian Wu

Wednesday, 26 June
Plenary Session II Basic Sciences
10:00 - 10:50am

Jeff Biernaskie **10:00 – 10:20am**

TRANSCRIPTOMIC ANALYSIS OF FIBROTIC VERSUS REGENERATIVE SKIN WOUND HEALING

Jeff Biernaskie
Calgary Firefighters Burn Treatment Society Chair in Skin Regeneration and Wound Healing
Dept of Comparative Biology and Experimental Medicine, Faculty of Veterinary Medicine
Hotchkiss Brain Institute and ACHRI
Cumming School of Medicine
University of Calgary

Abstract not available

Wisoo Shin **10:20 – 10:30am**

DYSFUNCTION OF HAIR FOLLICLE MESENCHYMAL PROGENITORS IS ASSOCIATED WITH AGE RELATED HAIR LOSS

Wisoo Shin, Nicole L. Rosin, Holly Sparks, Sarthak Sinha, Waleed Rahmani, Matt Workentine and Jeff A. Biernaskie
University of Calgary

Introduction:
Age-related effects on hair follicle epithelial stem cell (HFSC) function have been shown to contribute to the loss and thinning of hair. The mesenchymal components however, which act as critical regulators of HFSC function, have been largely overlooked in relation to aging. Previous work identified a stem/progenitor population within the connective tissue sheath cells (CTS), named hair follicle dermal stem cells (hfDSCs), which provide supplementary cells to enlarge the dermal papilla (DP) during HF regeneration. Here, we hypothesized that age-related HF dysfunction is associated with the loss of endogenous hfDSCs function.
Methods:
To test this, we employed a series of age-dependent in vivo lineage tracing techniques and single-cell RNA sequencing analyses.
Results:
First, we performed a long-term lineage trace of hfDSCs for over 24 months. We observed significant declines in both the number of hfDSCs and their differentiated mesenchymal progeny with advanced age. In vivo clonal analysis of hfDSCs in 2mo vs. 18mo old mice showed that aged hfDSCs exhibit impairment in self-renewal capacity and preferentially differentiate into CTS cells. Proliferation assays performed on prospectively isolated hfDSCs from the same timepoints, revealed a reduction in colony number and size in aged hfDSCs suggesting a cell autonomous dysfunction. Finally, single-cell RNA-seq of young versus aged HF mesenchyme showed a loss of the hfDSC population in aged skin and identified a number of distinct subpopulations within adult HF mesenchyme.
Conclusions:
Our findings identify a previously underappreciated function for hfDSCs and suggest that their dysfunction contributes to the pathogenesis of hair loss.
Learning objectives:
To highlight the role of mesenchymal fibroblasts/stem cells in tissue regeneration. To contribute to the understanding of tissue regeneration and wound healing. To connect basic science research with possible clinical applications
Takeaway Message:
Here, we highlight the critical role of hair follicle mesenchymal stem cells in maintaining an inductive dermal papilla for hair follicle regeneration throughout life. The dysfunction of these stem cells largely contributes to age-associated hair loss.

Heena Kumra **10:30 – 10:40am**

FIBULIN-4 EXERTS A DUAL ROLE IN LTBP-4 MEDIATED MATRIX ASSEMBLY AND FUNCTION

Heena Kumra*, Valentin Nelea*, Dieter P. Reinhardt (*Co-first authors)
McGill University

Introduction:
Elastogenesis is a hierarchical process by which cells form functional elastic fibers, providing elasticity and the ability to regulate growth factor bioavailability in skin, among other tissues. This process requires accessory proteins, including fibulin-4 and -5 and latent transforming growth factor binding protein (LTBP)-4. Mutations in these proteins cause cutis laxa and related disorders resulting in deficient elastic fibers and function.

Methods:
We used recombinant fibulin-4 and LTBP-4 proteins in combination with atomic force microscopy and dynamic light scattering to study structural aspects. Protein interactions were determined by surface plasmon resonance spectroscopy. Consequences on elastogenesis was studies by indirect immunofluorescence of fibroblasts.

Results:
Our data demonstrate novel molecular mechanisms in elastogenesis, focusing on the interaction and functional interdependence between fibulin-4 and LTBP-4 and its impact on matrix deposition and function. We show that LTBP-4 is not secreted in the expected extended structure based on its domain composition, but instead adopts a compact conformation. Interaction with fibulin-4 surprisingly induced a conformational switch from the compact to an elongated LTBP-4 structure. This conversion was only induced by fibulin-4 multimers associated with increased avidity for LTBP-4, fibulin-4 monomers were inactive. The fibulin-4-induced conformational change caused functional consequences in LTBP-4 in terms of binding to other elastogenic proteins, including fibronectin and fibrillin-1, and of self-assembly. A transient exposure of LTBP-4 with fibulin-4 was sufficient to stably induce conformational and functional changes, a stable complex was not required. These data define fibulin-4 as a molecular extracellular chaperone for LTBP-4, a novel paradigm in the field. The altered LTBP-4 conformation also promoted elastogenesis, but only in the presence of fibulin-4, which is required to escort tropoelastin onto the extended LTBP-4 molecule.

Conclusions:
Altogether, this study provides a novel dual mechanism for fibulin-4 in i) inducing a stable conformational and functional change in LTBP-4, and ii) promoting deposition of tropoelastin onto the elongated LTBP-4. This novel fundamental finding is essential to understand the pathogenesis of skin diseases associated with mutations in elastogenic proteins.

Learning objectives:
1) We learn that LTBP-4 is not secreted into the extracellular space in its fully functional conformation. 2) LTBP-4 requires an extracellular chaperone (FBLN-4) that promotes structural and functional changes. 3) Elastogenesis in skin fibroblasts requires both, the extended LTBP-4 and FBLN4 as an adapter.

Takeaway Message:
The data define fibulin-4 as a novel molecular extracellular chaperone for the structure and consequently the function of LTBP-4.

Brian Wu **10:40 – 10:50am**

ROLE OF ENDOTHELIAL EPHRIN-B2 SIGNALING IN PULMONARY FIBROSIS

Brian Wu, Sayaka Nakamura, David Lagares, Evgeny Rossomacha, Akihiro Nakamura, Poulami Datta, Riyadh Asrafuzaman, Philippe Monnier, Jianping Wu, Boris Hinz and Mohit Kapoor
University Health Network, University of Toronto

Introduction:
Fibrosis of the lungs and skin is a prominent feature of many diseases and mechanisms to explain the cause or development of fibrosis are unclear. We have previously identified the ephrin-B2 ligand as a novel mediator of skin and lung fibrosis (1). We showed that the conditional knockout (KO) of Efnb2 in collagen I expressing cells, including fibroblasts, partially protects mice against bleomycin-induced lung and skin fibrosis. This suggests that other cells, potentially endothelial cells through their interaction with fibroblasts, could contribute to tissue fibrosis through ephrin-B2 signaling. Therefore, this study aims to identify the contribution of endothelial-derived ephrin-B2 in the development of tissue fibrosis.

Methods:
With tamoxifen-induced Tie2-Cre genetic KO model on C57BL/6J background, we generated conditional Efnb2 KO mice. 4 week old mice underwent tamoxifen treatment (1mg/day; 5 days) or corn oil as control, and then treated with bleomycin sulphate (1.2 U/kg) at 6 weeks of age. Pulmonary fibrosis was assessed through histology 14 days post-treatment. Quantification of Gomori's One-Step Trichome was performed (50 fields at 20X); images were processed with ImageJ Color Deconvolution and quantified with Threshold Calculation. Percent of lung collagen was calculated using total lung tissue area as baseline.

Results:
The successful generation of Efnb2 KO mice post tamoxifen treatment was confirmed via genotyping for exon 1 deletion product. Through histomorphometric assessment, we found that endothelial Efnb2 KO exhibited significant protection against bleomycin-induced pulmonary fibrosis.

Conclusions:
Our results thus far suggest that endothelial-derived ephrin-B2 may play a key role in either development or progression of pulmonary fibrosis.

Learning objectives:
The goals of this work are to (1) understand the role of ephrin B2 signaling within the context of tissue fibrosis, (2) understand the mechanism of how endothelial ephrin B2 may promote fibrosis, and (3) elucidate interactions between endothelial cells and fibroblasts during fibrosis.

Takeaway Message:
The role of ephrin B2 in the development of tissue fibrosis remains unclear in cell-specific contexts. It is now evident that both fibroblast-derived and endothelial-derived ephrin B2 expression participates in fibrosis development.

PLENARY SESSION III

Translational Research

Moderators: An-Wen Chan & Ahmed Mourad

Stephen Room

WEDNESDAY, 26 JUNE **11:00 - 12:00PM**

PLENARY TALK

DR. AN-WEN CHAN

PRESENTERS

Shufeng Zhou

Katlyn Richardson

Ahmed Mourad

Sarah Hedtrich

Wednesday, 26 June
Plenary Session III Translational Research
11:00 - 12:00pm

An-Wen Chan **11:00 – 11:20am**

DERMATOLOGIC ASSESSMENT IS ASSOCIATED WITH IMPROVED MELANOMA OUTCOMES: POPULATION-BASED COHORT STUDY

Patrick Fleming, Kinwah Fung, An-Wen Chan
University of Toronto

Introduction:
The US Preventive Services Task Force does not recommend routine skin cancer screening, while melanoma guidelines recommend dermatologic follow-up at least annually after diagnosis. There are limited data on whether dermatologic assessment leads to better melanoma outcomes.

Methods:
Using linked, population-based, administrative data, we conducted a retrospective inception cohort study of patients diagnosed with primary invasive melanoma in Ontario, Canada from 2010-2013 with follow-up until Dec 31, 2015. We fit two multivariable models that adjusted for potential confounders: a) logistic regression to assess whether seeing a dermatologist between 3-24 months prior to diagnosis was associated with earlier melanoma stage; and b) cause-specific hazard regression to estimate the association between melanoma patient adherence to annual dermatologic assessments (time-varying exposure) and melanoma-specific death, accounting for the competing risk of non-melanoma death.

Results:
Among 10,067 patients with melanoma who survived at least 1 year (mean follow-up 3.6 years), 2,151 (21%) saw a dermatologist between 3-24 months prior to diagnosis and 628 (6.2%) died of melanoma. Seeing a dermatologist 3-24 months prior to diagnosis was associated with a 58% reduction in the odds of subsequently being diagnosed with Stage II-IV melanoma (adjusted odds ratio 0.42, 95% CI 0.33-0.53). After diagnosis, adherence to annual dermatologic assessments for at least 75% of the observation time was associated with a 44% reduction in melanoma-specific death compared with adherence levels below 75% (adjusted hazard ratio 0.56, 95% CI 0.47-0.66). After diagnosis, the median proportion of time spent in adherence was 67% (inter-quartile range 0-100%). Older age, lower income, and rural residence (but not melanoma stage) were risk factors for non-adherence.

Conclusions:
Dermatology visits before and after melanoma diagnosis may promote better patient outcomes. Strategies are needed to improve adherence rates to dermatologic assessment.

Learning objectives:
1) To understand the patterns of dermatologic follow-up after melanoma diagnosis. 2) To appreciate the risk factors associated with regular dermatologic follow-up among melanoma patients. 3) To understand the association between dermatologic follow-up and melanoma outcomes.

Takeaway Message:
Dermatology visits before and after melanoma diagnosis may promote better patient outcomes.

Shufeng Zhou **11:20 – 11:30am**

CD109 DRIVES TUMORIGENESIS AND METASTASIS BY MODULATING THE EGFR/AKT SIGNALING IN SQUAMOUS CELL CARCINOMA

Shufeng Zhou 1, Sebastien Tabaries2, , Peter M. Siegel2 and *Anie Philip1
1 Division of Plastic Surgery, Department of Surgery, McGill University, Montreal, Quebec;
2 Rosalind and Morris Goodman Cancer Research Centre - McGill University

Introduction:
CD109, a member of the a2-macroglobulin (a2M)/C3, C4, C5 family, is a glycosylphosphatidylinositol (GPI)-anchored cell surface glycoprotein that is frequently overexpressed in many cancers including squamous cell carcinoma (SCC), and this overexpression is associated with malignant transformation. While CD109 is well known to be a negative regulator of TGF-beta, recent evidence suggests CD109 is also involved in the EGF pathway. As of yet, the essential role of CD109 in the development of human SCC and metastasis has not been determined. We therefore hypothesized that CD109 is one of the key effectors that regulate SCC progression by modulating both TGF-beta and EGFR pathways, the two major pathways that implicate in cancer progression and metastasis.

Methods:
We used Crispr/Case9 technology to generate CD109 KO A431. In vivo tumor xenograft formation and tail vein assay were employed to determine the tumorgenicity and metastasis ability of A431 cells. Co-immunoprecipitation and Western blot were performed to detect the interaction between CD109 and EGFR. Immunofluorescence microscopy was applied to detect the colocalization of EGFR and CD109.
Results:
In this study, we report that CD109 drives tumorgenicity and metastasis by modulating both the TGF-beta and EGFR signalling in SCC cells. We found that the loss of CD109 abrogated the tumorigenicity and metastatic ability of A431 SCC cells. We demonstrate the interaction between CD109 and EGFR and colocalization of the two molecules in parental A431 cells' membrane. However, the loss of CD109 diminished EGFR expression and abolished the interaction between EGFR and CD109, which suggests that the GPI-anchored membrane CD109 protein is necessary to maintain the EGFR expression. We further demonstrated that the loss of CD109 impaired EGFR/AKT signalling, which lead to diminish tumorigenesis and metastasis of SCC cells.
Conclusions:
CD109 acts as a driving force of tumorigenesis and metastasis in SCC by modulating EGFR /AKT activities.
Learning objectives:
To delineate the function of CD109 in SCC progression.
Takeaway Message:
Our research establishes the oncogenic role of CD109 by demonstrating that CD109 acts as a driver of tumorgenicity and metastasis in SCCs.

Katlyn Richardson **11:30 – 11:40am**

GRANZYME K: POTENTIAL ROLE IN INFLAMMATION AND PSORIATIC DISEASE

Katlyn C. Richardson, Christopher T. Turner, Sho Hiroyasu, Matthew R. Zeglinski, Richard I. Crawford, Angela Burleigh, David J. Granville
University of British Columbia

Introduction:
Psoriasis is a common skin disease characterized by skin inflammation and increased epidermal proliferation forming thick, scaly plaques. Current therapies are not completely effective and present with a number of side effects. Thus, to allow for the development of new therapeutic options, a deeper understanding of the pathological mechanisms associated with psoriasis are necessary. Granzyme K (GzmK) is a serine protease recently elucidated as a mediator of cutaneous inflammation. GzmK is upregulated in sepsis, allergic asthma and burns. The pathological role of GzmK in psoriasis remains unknown. In the present study, we hypothesize that GzmK contributes to the onset and progression of psoriasis through the augmentation of inflammation and/or epidermal proliferation.
Methods:
GzmK expression was evaluated histologically in tissue from psoriasis patients and compared to healthy skin controls. The role of GzmK was investigated in a murine model of psoriasis, comparing GzmK-/- to WT mice. Psoriasis severity was assessed macroscopically for onset and severity of erythema and plaque formation. Psoriatic tissue was examined histologically for epidermal thickness GzmK expression, collagen organization (Masson's Trichrome, picosirius red, Collage I/III), inflammation (markers of T-cells, macrophages, NK cells), angiogenesis (CD31) and fibrosis (α-SMA). To elucidate a mechanistic role, we are currently culturing keratinocytes with GzmK for assessment of epidermal proliferation, cytokine expression and the GzmK degradome.
Results:
GzmK positive cells were markedly elevated in lesional skin from psoriasis patients compared to healthy control skin. Lymphocytes and dendritic cells were identified as the predominant cell type responsible for GzmK expression. Preliminary data suggest that GzmK-/- psoriasis mice have reduced erythema and plaque formation compared to WT mice.
Conclusions:
GzmK, an important mediator of cutaneous inflammation, is elevated in human psoriatic tissue and may contribute to psoriasis lesional development.
Learning objectives:
1. GzmK promotes inflammation in the skin. 2. GzmK is expressed in lymphocytes and dendritic cells in psoriatic tissue. 3. GzmK-induced inflammation may contribute to psoriasis pathogenesis.

Takeaway Message:
GzmK is elevated in psoriasis and may contribute to increased disease severity. As such, the present studies will provide key rationale for pursuing GzmK-targeted inhibitors for the treatment of psoriasis.

Ahmed Mourad **11:40 – 11:50am**

ORAL AND INTRA-INCISIONAL ANTIBIOTIC PROPHYLAXIS IN MOHS SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ahmed Mourad1, Robert Gniadecki2, Muba Taher2
1Faculty of Medicine & Dentistry, 2Division of Dermatology, University of Alberta, AB, Canada

Introduction: Antibiotic prophylaxis is used to prevent surgical site infections (SSIs) that can cause significant morbidity from pain, delayed wound healing and impaired cosmesis. High-risk patients including those with prosthetic heart valves and implantable devices are often given antibiotic prophylaxis. Evidence with respect to oral and intra-incisional antibiotic prophylaxis is nebulous, and previous studies regarding this have shown inconsistent results.

Methods: A comprehensive literature search of the EMBASE(Ovid), Scopus, Web of Science, and PubMed databases was performed using the MeSH terms "antibiotic", "dermatology", "surgery" and "prophylaxis" to include eligible studies that investigated rates of SSIs vs. placebo following administration of oral or intra-incisional antibiotic prophylaxis in Mohs surgery. Calculated risk ratios were used to compare SSI rates following antibiotic prophylaxis vs. placebo. A pooled meta-analyses of these risk ratios was performed using a random-effects model using Review Manager, version 5.3 (The Cochrane Collaboration, Oxford, UK). Heterogeneity was assessed using I2 values determined from the meta-analysis. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool.

Results: The initial search strategy yielded a total of 421 articles. After the screening of the titles and abstracts, 37 articles were reviewed in full. Five randomized controlled trials (RCTs) with 2,919 patients receiving Mohs Micrographic Surgery (MMS) met the inclusion criteria for the current study. Three of the five studies were RCTs (n= 839) that investigated oral antibiotic prophylaxis versus placebo in MMS for the ear and nose. The meta-analysis revealed no difference between oral antibiotic prophylaxis and placebo for SSI reduction (pooled RR: 0.81 (95% CI: 0.31-2.11), I2=70%). Two of the five included RCTs (n= 2080) reported data for pre-operative intra-incisional antibiotic prophylaxis in MMS at various sites. Both studies showed statistically significant reductions in the SSI following intra-incisional antibiotic prophylaxis (pooled RR: 0.18 (95% CI: 0.05-0.71), I2=26%).

Conclusions: Our meta-analysis showed no statistically significant reduction in SSI following oral antibiotic prophylaxis vs. placebo. Intra-incisional antibiotic prophylaxis, a methodology that is not widely used, may be a viable prophylactic option given the significant reduction compared to placebo in the pooled analysis. The current study suggests that routine oral antibiotic prophylaxis should be cautioned due to the development of microbial resistance to antibiotics and antibiotic related adverse events. Thus, as per the Advisory Statement on Antibiotic Prophylaxis in Dermatological Surgery (2008), prophylaxis in Mohs surgery should be considered for patients who are at high-risk for serious complications and increased morbidity following surgical site infections.

Learning objectives: 1. To discuss the risks and merits for providing antibiotic prophylaxis in Mohs surgery. 2. To outline the results of this meta-analysis regarding the reduction of surgical site infections following oral and intra-incisional antibiotic prophylaxis. 3. To discuss the results of this meta-analysis was to assess if oral and intra-incisional antibiotics provided significant improvement of SSI.

Takeaway Message: Intra-incisional antibiotic prophylaxis may be a viable prophylactic option for reducing surgical site infections in Mohs Surgery. Routine oral antibiotic prophylaxis should be cautioned due to the development of microbial resistance to antibiotics and antibiotic related adverse events. As per guidelines, prophylaxis in Mohs surgery should be considered for patients who are at high-risk for serious complications and increased morbidity following surgical site infections.

Sarah Hedtrich **11:50 –12:00pm**

TRANSGLUTAMINASE 1 REPLACEMENT THERAPY SUCCESSFULLY MITIGATES THE ARCI PHENOTYPE IN FULL-THICKNESS SKIN DISEASE MODELS

Guy Yealland* Roswitha Plank *, Enrico Miceli, Marcelo Calderón, Hans Christian Hennies, Sarah Hedtrich1,3

1Institute for Pharmacy, Pharmacology & Toxicology, Freie Universität Berlin, Germany

2Faculty of Pharmaceutical Sciences, University of British Columbia

Introduction:

TGM1 mutations causing a loss of Transglutaminase 1 function are the most common known cause of ARCI, a group of monogenic skin diseases that cause disruptions to normal skin differentiation. Patient skin becomes dry and "scaled" with notable detriments to barrier function, resulting in increased transepidermal water-loss, both of which can prove fatal to neonates where sepsis can be a particular threat. Here we build on previous work in which protein loaded thermoresponsive nanogels were successfully used to deliver proteins into barrier deficient skin models or excised human skin. Full thickness skin models were generated from fibroblasts and KC derived from an ARCI patient carrying mutations in TGM1 or KCs and fibroblasts from control persons. These were fully characterised and then treated topically with functional Transglutaminase 1 in PBS or loaded in thermoresponsive dendritic polyglycerol-poly(N-isopropylacrylamide) and exposed to a temperature ramp emulating the temperature gradient found across the human skin.

Methods:

Here we build on previous work in which protein loaded thermoresponsive nanogels were successfully used to deliver proteins into barrier deficient skin models or excised human skin. Full thickness skin models were generated from fibroblasts and KC derived from an ARCI patient carrying mutations in TGM1 or KCs and fibroblasts from control persons. These were fully characterised and then treated topically with functional Transglutaminase 1 in PBS or loaded in thermoresponsive dendritic polyglycerol-poly(N-isopropylacrylamide) and exposed to a temperature ramp emulating the temperature gradient found across the human skin.

Results:

ARCI skin models demonstrated altered histology and loss of Transglutaminase 1 activity effectively emulated key features of the ARCI phenotype in vitro, and were successfully used as a therapeutic testing platform. The permeation of Testosterone was significantly increased in the ARCI models. Successful delivery of functional Transglutaminase 1 to the viable epidermis, as mediated by thermoresponsive nanogels, was capable of improving the barrier function of ARCI skin models in a dose dependent manner, without apparent cytotoxic induction.

Conclusions:

With further optimisation, this strategy may prove promising as a new therapeutic avenue in the treatment of ARCI.

Learning objectives:

Is topical delivery of biomacromolecules feasible? Are human-based disease models suitable for preclinical studies? Is a protein replacement therapy feasible for monogenic diseases?

Takeaway Message:

A local protein replacement therapy is a promising novel approach for the treatment of monogenic skin diseases such as ARCI.

CONCURRENT SESSIONS

Cutaneous Lymphoma

Moderators: *Ivan V Litvinov & Raed Alhusayen*

Walker Room

Eczemas and Atopic Dermatitis

Moderators: *John Elliott & Christopher Turner*

Bannerman Room

THURSDAY, 27 JUNE **8:40 - 9:50AM**

PRESENTERS

DR. RAED ALHUSAYEN

Jennifer Gantchev

Ahmed Mourad

Arunima Sivanand

Aishwarya Iyer

Ivan Litvinov

DR. JOHN ELLIOTT

Fatima Hubaishi

Vladimir Andrey Gimenez Rivera

Lily Wang

Sarah Hedtrich

Christopher Turner

Thursday, 27 June
Concurrent Session: Cutaneous Lymphoma
8:40 - 9:50am

Raed Alhusayen **8:40 – 9:00am**

REVISITING THE ROLE OF PHOTOTHERAPY IN CTCL

Raed Alhusayen
Sunnybrook Research Institute; Division of dermatology, University of Toronto

Abstract not available

Jennifer Gantchev **9:00 – 9:10am**

SIGNIFICANCE OF ECTOPIC EXPRESSION OF MEIOSIS REGULATORY GENES IN CUTANEOUS T- CELL LYMPHOMAS (CTCL)

Jennifer Gantchev, Amelia Martínez Villarreal, Pingxing Xie, Philippe Lefrançois, Scott Gunn, Elena Netchiporouk, Denis Sasseville and Ivan V. Litvinov
Research Institute of the McGill University Research Centre

Introduction:
Cancer testis (CT) antigens, under normal circumstances are uniquely expressed in testicular germ cells. Recent research has shown that meiosis-specific CT antigens are ectopically expressed in cutaneous T-cell lymphoma (CTCL) and may contribute to increased genomic instability. The aberrant activation of meiosis genes in a mitotic cell is now recognized as a distinctive process, "meiomitosis". We have previously demonstrated the ectopic expression of several meiotic CT (meiCT) genes in 9 patient-derived CTCL cell lines and in expanded peripheral T lymphocytes isolated from Sézary Syndrome patients.

Methods:
In this study we examined the expression of 5 meiCT proteins in formalin-fixed, paraffin-embedded (FFPE) lesional samples from CTCL patients. We also analyzed the transcriptional expression of these genes using publicly-available RNA sequencing (RNA-Seq) data from Sézary Syndrome patients and healthy controls.

Results:
Our work demonstrates the heterogenous expression in atypical lymphocytes of meiosis genes involved in initiation (STRA8), sister chromatin cohesion (STAG3, SGO2), homologous chromosome synapsis (SYCP3) and homologous recombination (DMC1). Additionally, our observations in FFPE samples were validated in a cohort of RNA-Seq data of Sézary Syndrome patients, where STAG3, SGO2, SYCP3 and DMC1 exhibited significant differential gene expression when compared to healthy controls.

Conclusions:
Our results build upon our previous work to further solidify the concept that CTCL malignant cells undergo the process of cancer meiomitosis, as opposed to a characteristic mitotic division. The ectopic expression of meiosis genes together with further investigation of cancer meiomitosis will help build a foundation to develop novel diagnostic tests to distinguish CTCL from benign skin conditions and will set a precedent to develop more targeted therapies for patients with this malignancy.

Learning objectives:
1. To assess the ectopic expression of meiCT genes in CTCL lesional samples. 2. To correlate the expression of meiCT genes to RNA-sequencing data on Sézary Syndrome patients.

Takeaway Message:
Due to the ectopic expression of meiCT genes across CTCL samples, it is no longer feasible to consider CTCL lymphocytes as mitotic, but instead we should be discussing the implications of meiomitosis in lymphomagenesis.

Ahmed Mourad **9:10 – 9:20am**

HOW TO BEST COMMUNICATE PROGNOSIS IN MYCOSIS FUNGOIDES? A SYSTEMATIC REVIEW AND META-ANALYSIS

Ahmed Mourad1, Robert Gniadecki2
1Faculty of Medicine & Dentistry, 2 Division of Dermatology, University of Alberta, AB, Canada

Introduction:
Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma, which confers significant mortality in advanced stage disease. Although stage-specific survival data are available from different cohorts, there have been no attempts to combine existing overall survival (OS) data in this disease. Moreover, the hitherto published OS data are presented as Kaplan-Meier curves and mortality risks which are of limited utility for the patients, who prefer to have an estimate of their chances of survival. The patients prefer prognostic information in terms of survival, not mortality, e.g. "the chance to live 5 years" or "the longest (best case) survival".

Methods:
We performed a formal meta-analysis of OS for the various stages of MF (Stage IA – IV). Hazard ratios were then estimated from the pre-specified disease stages (Stage IIB-IV) which compared to Stage IA disease at 5 years. Stage-specific pooled 5-year OS rates were calculated using the pooled HRs and their respective ±95% confidence intervals (CI).

Results:
The initial search strategy yielded a total of 2137 articles and 59 studies were reviewed in full. Ten studies (n=6279) were included in the meta-analysis. Disease stage determined the overall survival in MF. The development of tumors (progression from stage I to IIB) and extracutaneous spread (stage IV) had a powerful, negative impact on survival. This is evidenced by the stark increase in the pooled HRs for Stage IB (HR: 2.34 (95% CI: 1.82 – 3.00) and Stage IIB (HR: 7.24 (95% CI: 5.91 – 8.86)) disease.

Conclusions:
We postulate that the information presented in this study could be readily used by clinicians to communicate prognostic information to patients with stage IB-IV mycosis fungoides. The survival values calculated by us represent "best case" and median overall 5-year survival which are intuitively understandable and can be used directly in communicating prognosis to the patients.

Learning objectives:
1. To outline the importance of having more robust measures of prognostic data for mycosis fungoides. 2. To outline the statistical methodology used to pool overall survival data on mycosis fungoides. 3. To discuss the results of this meta-analysis of overall survival in mycosis fungoides including pooled 5-year overall survival rates with best- and worst- case survival for each stage of this disease.

Takeaway Message:
Advanced stage mycosis fungoides (stage >IIB) predicts significantly worsened mortality compared to early stage disease. The pooled hazard ratios of overall survival determined from this meta-analysis were used to calculate pooled 5-year overall survival rates with best- and worst- case survival for each stage of disease. This novel data could serve as an effective and intuitive tool for communicating prognosis to patients with mycosis fungoides.

Arunima Sivanand **9:20 – 9:30am**

NEOANTIGENS IN MYCOSIS FUNGOIDES: WHOLE EXOME SEQUENCING DISCOVERY OF IMMUNOTHERAPEUTIC TARGETS

Arunima Sivanand, Dylan Hennessey, Aishwarya Iyer, Robert Gniadecki
Division of Dermatology, University of Alberta, AB, Canada

Introduction:
Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, has a dismal prognosis in advanced stages. The success of immune checkpoint inhibitors (ICI) in treating advanced malignancies has not extended to MF. There is an urgent need to identify predictive biomarkers, and to advance immunotherapies in MF. Neoantigens are 'new' peptides, generated by somatic mutations in tumour cells, that evoke an immune response. As tumour-specific markers, neoantigens are an attractive immunotherapeutic target. A high neoantigen burden across multiple cancers has been associated with higher overall survival after ICI treatment. Neoantigens have never previously been studied in MF, and our objective was to characterize their identity and number in MF.

Methods:
9 samples (3 plaques, 3 tumours, 3 controls) were selected from ongoing analysis of 108 whole exome sequences (WES) at 200X depth. RNA-seq was available for 3 samples, and used to validate expression of predicted peptides. Bioinformatics pipelines utilized included Mutect2 for mutation calling, OptiType for HLA typing and MuPeXi to predict peptides (8-11 amino acids long) and binding affinities to HLA types.
Results:
An average of 3303 non-synonymous mutations were identified, resulting in 5907 putative neoantigens. 569 were strong binders (<0.05%rank), 1244 intermediate binders (<0.15%rank) and 4094 weak binders (<0.5%rank). 83% of predicted peptides were expressed according to available RNA-seq.
Conclusions:
We describe the use of WES with high sequencing depth to successfully identify neoantigens in MF for the first time. MF has a high tumour mutation burden, resulting in a neoantigen burden markedly greater than highly mutagenic cancers such as melanoma and lung cancer. The paradoxically poor ICI response may be attributed to challenges in using T-cell based therapies to target T-cell malignancies, and intratumour genetic heterogeneity resulting in subclonal neoantigens. This suggests a role for the development of immunotherapies targeting specific neoantigens.
Learning objectives:
1) To be introduced to the concept and utility of neoantigens. 2) To become familiar with the neoantigen landscape in mycosis fungoides. 3) To learn about how neoantigens can be used as predictive biomarkers for immunotherapy, and as a basis for developing targeted immunotherapies.
Takeaway Message:
MF is a highly mutated tumor producing high numbers of neoantigens.

Aishwarya Iyer **9:30 –9:40am**

CUTANEOUS T-CELL LYMPHOMA IS A GENETICALLY AND CLONOTYPICALLY HETEROGENEOUS

Aishwarya Iyer, Dylan Hennessey, Sandra O'Keefe, Jordan Patterson, Weiwei Wang, Gane Ka-Shu Wong and Robert Gniadecki
Division of Dermatology, University of Alberta, AB, Canada

Introduction:
Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) primarily arising in the skin. 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 main objective of this study is to address the presence of intratumor heterogeneity in MF.
Methods:
To determine whether MF is a monoclonal process we performed laser microdissection of atypical tumor cells in skin biopsies and performed simultaneous whole exome (WES) and transcriptome sequencing (WTS) to identify the T-cell clonotypes and the genetic architecture of the samples.
Results:
Multiple clonal and subclonal cell population was observed within individual tumor/plaque sample, based on the single nucleotide variations (SNV) and copy number aberrations (CNA) providing evidence of intratumor genetic heterogeneity. Also, T-cell receptor oligoclonality was observed for the sequences obtained from WES, indicating the presence of multiple tumor T-cells along with reactive T-cells.
Conclusions:
Intratumor heterogeneity is correlated with the prognosis of solid cancers and their response to immunotherapy. Heterogeneity in CTCL does not only provide better insights into tumor origin and disease progression but may also be a source of prognostic biomarkers.
Learning objectives:
To identify for presence of any- 1. T-cell heterogeneity 2. Intratumor heterogeneity 3. Genetic differences in early and late stage MF
Takeaway Message:
Cutaneous T-cell lymphoma indicates genetic and T-cell clonotypic heterogeneity

Ivan Litvinov **9:40 –9:50am**

HUMAN T-CELL LYMPHOTROPIC VIRUS-1 INFECTION PREVALENCE IN CANADA

Laetitia Amar, Michelle Le, Feras M. Ghazawi, Elham Rahme, Amanda Segal, Elena Netchiporouk, Gizelle Popradi, Linda Moreau, Osama Roshdy, Denis Sasseville, Ivan V. Litvinov
Division of Dermatology, McGill University Health Centre

Introduction:
Human T-Cell Lymphotropic Virus-1 (HTLV-1) is estimated to affect ~20 million people worldwide and in up to ~5% of carriers it produces Adult T-Cell Leukemia/Lymphoma (ATLL). While active surveillance and programs to decrease HTLV-1 vertical transmission are in place in Japan, in the United States and Canada this virus remains mostly neglected by medical regulatory authorities. In Canada, HTLV-1 is known to be endemic in the northern native communities (i.e. First Nations). Currently, the prevalence of HTLV-1 infection in Canada is not known.

Methods:
In this report we for the first time estimate the actual prevalence of HTLV-1 in Canada based on the findings of ATLL incidence during 1992-2010 that we obtained from the Canadian Cancer Registry and Le Registre Québécois du Cancer.

Results:
Our findings confirm that HTLV-1 is endemic in Nunavut First Nations communities with an estimated prevalence of ~200 individuals per 100,000 population. Overall, we estimate that up to ~17,000 individuals are infected with HTLV-1 in Canada with almost half of these individuals (~8,100) residing in Quebec. Our study confirms that HTLV-1 remains a rare infection in Canada with 54.71 (Confidence Interval 53.90-55.54) individuals being affected per 100,000 population.

Conclusions:
In conclusion, HTLV-1 remains a rare infection in Canada even considering that this infection is endemic in the First Nations communities. This report for the first time estimates the rate of HTLV-1 infection across the country.

Learning objectives:
1. Understand the epidemiology of HTLV-1 infection prevalence in Canada. 2 Describe the rate of HTLV-1 infection in endemic regions in Canada in Nunavut and other First Nations communities. 3. Correlate the prevalence of HTLV-1 infection and incidence of Adult T-Cell Leukemia/Lymphoma in Canada.

Takeaway Message:
In conclusion, based on our findings, HTLV-1 remains a rare infection in Canada even considering that this virus is endemic in the First Nations communities. This report for the first time estimates the rate of HTLV-1 infection across the country and highlights Quebec as a province with the largest number of ATLL cases and, hence, likely a significant number of HTLV-1+ (i.e., >8,000) individuals. These combined results suggest that it may be important to raise awareness of HTLV-1 associated health risks in select provinces/territories and consider implementing programs to decrease HTLV-1 transmission, as currently in place in Japan.

Thursday, 27 June
Concurrent Session: Eczemas and Atopic Dermatitis
8:40 - 9:50am

John Elliott | **8:40 – 9:00am**

PATIENTS ALLERGIC TO DISPERSE BLUE 106/124 LIKELY REACT TO A DIVERSE SET OF MOLECULES ALL CONTAINING A SPECIFIC STRUCTURAL MOTIF

John F. Elliott, Rylee Oosterhuis, Fabricio Mosquera, Karsten Sturmay, John Vederas, Béla Reiz, Randy Whittal, Wayne Moffat, Kunimasa Suzuki
University of Alberta

Introduction:
Ryberg described that commercial disperse dyes are impure, and that many patients who patch tested positive to Disperse Blue (DB)106 and 124 also reacted strongly to a relatively lower mobility 'pink spot' seen when DB106 and DB124 were fractionated by thin-layer chromatography (TLC). A more recent report by Everitt explains that the chemical nature of the pink spot is unknown.

Methods:
We fractionated DB106 and DB124 over silica columns and patch tested all fractions on a single patient who was highly allergic to both blue dyes. Multiple fractions gave a positive response, and all of these were analyzed by high-resolution LC-MS.

Results:
We noted that all of the active fractions contained as a probable constituent at least one molecule with a single sulphur. This suggested that the patient might be responding to a family of molecules all structurally related to DB106/124 and containing a single sulphur atom (i.e. structurally related to the 2-azo-5-nitrothiazole portion of DB106/124). We purchased 2-amino-5-nitrothiazole from Sigma but the patient was patch test negative to this chemical. We hypothesized that the primary amino group in 2-amino-5-nitrothiazole was relatively unreactive compared to the azo group present in the corresponding position in DB106/124, and therefore used classical synthetic chemistry methods to create a simple azo derivative of 2-amino-5-nitrothiazole. Surprisingly during synthesis of the diazonium tetrafluoroborate salt a pink material was generated, which mass spec analysis showed to be a dimer of 2-amino-5-nitrothiazole joined via the same azo group present in DB106/124.

Conclusions:
The highly allergenic 'pink spot substance' present as a contaminant in Disperse Blue 106/124 preparations is very likely a dimer of 2-amino-5-nitrothiazole joined via the same azo group present in DB106/124. When reacting with endogenous cutaneous proteins the 'pink spot substance' would be capable of generated exactly the same haptenated structure as would be generated by DB106/124. Other structurally related chemicals will also likely give a positive patch test response in patients allergic to DB106/124. We are currently using a chemical-structure informatics approach to discover new Disperse Blue 106/124-related contact allergens and identify their source in consumer products.

Learning objectives: See above

Takeaway Message:
The highly allergenic 'pink spot substance' present as a contaminant in Disperse Blue 106/124 preparations is very likely a dimer of 2-amino-5-nitrothiazole joined via the same azo group present in DB106/124. When reacting with endogenous cutaneous proteins the 'pink spot substance' would be capable of generated exactly the same haptenated structure as would be generated by DB106/124. Other structurally related chemicals will also likely give a positive patch test response in patients allergic to DB106/124. We are currently using a chemical-structure informatics approach to discover new Disperse Blue 106/124-related contact allergens and identify their source in consumer products.

Fatima Hubaishi **9:00 – 9:10am**

A NOVEL APPROACH FOR TREATMENT OF ATOPIC DERMATITIS: TOPICAL APPLICATION OF AN IMMUNOMODULATORY PEPTIDE INHIBITOR IN A MOUSE MODEL

Fatima Hubaishi1, Annie Beauchamp1, Louis Cyr1, Jichuan Shan2, Elizabeth D. Fixman2 & Brian J. Ward1

1 Research Institute of McGill University Health Centre 2 Meakins-Christie Laboratories, Research Institute of the McGill University Health Centre Faculty of Medicine, McGill University, Montréal, QC, Canada

Introduction:

Atopic dermatitis (AD), a common chronic inflammatory skin disease that occurs in 15-20% of children, is accompanied by intense itchiness and elevated IgE levels. AD affects the quality of life and places a social and financial burden on patients and their families. Genes, the environment, and the immune system all contribute to AD pathogenesis. The most commonly used treatments include anti-histamines and anti-inflammatory drugs (e.g. corticosteroids) that target only the symptoms but not the underlying immune pathways that drive AD pathogenesis. Acute AD is an allergic condition in which CD4+ Th2 cells producing cytokines such as IL-4, IL-5, IL-13 play a major role. Since both IL-4 and IL-13 act primarily through the STAT6 transcription factor, this is a logical target for immunomodulatory therapy. STAT6 inhibitory peptide (STAT6-IP) uses cell-penetrating peptide technology to deliver an immunomodulatory peptide designed to interfere with STAT6 signaling. When delivered to the lung, STAT6-IP reduces maladaptive Type 2-driven responses in murine models of asthma and respiratory virus infection.

Methods:

A murine model of AD-like disease was induced in 8-week-old female Balb/c mice, by topical administration of two allergens, known to induce Type 2 allergic responses in mice, i) house dust mite (HDM), ii) papain, following disruption of the skin barrier by tape striping. STAT6-IP was applied topically throughout the allergen exposure. Several experimental outcomes were assessed: i) ear thickness was measured 24 h after each allergen application; ii) total serum IgE; iii) cytokine levels produced by ex-vivo re-stimulation of auricular lymph node cells with allergen; iv) ear inflammation and edema assessed by histology; and v) mRNA levels of pro-inflammatory and Type 2 cytokines.

Results:

STAT6-IP reduced ear thickness in mice exposed to HDM, but not in mice exposed to papain. There was a trend for STAT6-IP to reduce total IgE. STAT6-IP also markedly decreased the cellularity of auricular lymph nodes in both HDM- and papain-exposed mice. Other analyses are ongoing.

Conclusions:

Significance: In summary, our data suggest that topical application of STAT6-IP has the potential to prevent increases in ear thickness and draining lymph node cytokine responses in a murine model of allergen-induced AD. We are hopeful that our new model will help us delineate the effects of STAT6-IP and its potential as a novel therapeutic for AD.

Learning objectives:

•Atopic dermatitis-like disease murine model in Balb/c upon sanitization with proteases allergens. •Murine type 2 allergic response in acute AD. •Topical application of STAT6-IP has a potential therapeutic effect to interfere with the development of AD symptoms.

Takeaway Message:

Immunomodulatory intervention provides a promising therapeutic approach for atopic dermatitis.

Vladimir Andrey Gimenez Rivera **9:10 – 9:20am**

ABERRANT T CELL RESPONSES TO BACTERIAL INHIBITORY SIGNALS IN ATOPIC DERMATITIS

Gimenez Rivera, V.A. and Jack, C.

McGill University Health Centre (RI-MUHC)

Introduction:

The skin of atopic dermatitis (AD) patients exhibits dysbiosis characterized by an overrepresentation of cutaneous Staphylococcus aureus (SA). There is a synergism between SA colonization and dysregulated Th2 milieu in AD, as Th2 skewing may contribute to the overgrowth of cutaneous SA during flares, facilitating establishment of sustained Th2 inflammation. We hypothesize that, in AD patients, aberrant T cell responses to SA components contribute to this vicious cycle.

Methods:
We have previously established an in vitro model of type 2 immune cell dysregulation. PBMC-derived T cells from AD patients or non-atopic healthy normal subjects cultured for 7 days with SA-driven inflammation signals (i.e. SEB and TSLP), results in the polarization of memory Th2 and Tc2 cells; these produce large amounts of IL-13 upon TCR re-stimulation. Exposure to an inhibitory bacterial proteoglycan NOD2 ligand (PGN-SAndi) in culture during T cell polarization can limit Th2 responses.
Results:
In this study, we demonstrate that NOD2-mediated inhibition of Th2 performed slightly better with cells isolated from normal subjects than inhibition of responses in AD patients (% reduction in IL-13 secretion: 95 ±10 in 86%, p-value < 0.01; 70 ± 7 in 75% of AD, p-value<0.01). We demonstrate that signalling through NOD2 efficiently blocked Th2 differentiation and activation, as evidenced by reduction of GATA3 expression and phosphorylation of STAT6 in T cells. Notably, when PGN-SAndi was added during TCR re-stimulation to inhibit pre-differentiated Th2 and Tc2 cells, only memory T cells from normal subjects showed a significant reduction of IL-13 ([NS] IL-13 secretion % reduction: 55 ±2, p<0.05; versus [AD] not significant). These results suggest that fully differentiated memory T cells from AD patients lack control mechanisms to limit Th2 cytokine production.
Conclusions:
Our work demonstrates mechanisms whereby aberrant memory Th2/Tc2 cell responses to SA inhibitory signals might contribute to the chronic inflammation observed in AD skin.
Learning objectives:
Human evidence for T cell activation in atopic dermatitis pathogenesis has emerged - clinical efficacy of therapeutic T cell cytokine blockade in patients, in particular IL-13/ IL-4 - Immune dysregulation dominated by type 2 cytokines strongly associated with atopic dermatitis - contributors to pathologic functional state in the skin of human AD patients are complex and poorly defined
Takeaway Message:
Dysfunctional responses to S.aureus can affect human type 2 cell pathogenic IL-13 cytokine production. Our work demonstrates mechanisms whereby aberrant memory Th2/Tc2 cell responses to SA inhibitory signals might contribute to the chronic inflammation observed in AD skin.

Lily Wang **9:20 – 9:30am**

KERATINOCYTE CARCINOMA RISK IN PATIENTS WITH ATOPIC DERMATITIS: A SYSTEMATIC REVIEW

Lily Wang, Rachel Bierbrier, Aaron Drucker, An-Wen Chan
University of Toronto

Introduction:
Atopic dermatitis (AD) is an inflammatory skin condition characterized by abnormal immune function and an impaired skin barrier. There is a potentially increased risk of cutaneous malignancy in AD due to the use of immunosuppressive medication, chronic inflammation and aberrant immune response. However, there are conflicting results on this possible association in the literature. The objective of our systematic review is to determine the risk of keratinocyte carcinoma (basal and squamous cell carcinoma) in patients with AD compared to the general population (i.e. without AD).
Methods:
Medline and EMBASE through January 3, 2019 were searched. We included observational studies (case-control and cohorts) reporting a risk estimate for keratinocyte carcinoma in patients with AD compared with a control group (general population or patients without AD). Two independent reviewers extracted relevant data and assessed risk of bias of included trials using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) assessment tool, modified for observational studies. Data were expressed as standardized incidence ratios (SIRs) or odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed (Cochrane Q) and quantified (I2 statistic).
Results:
Ten eligible studies (1 059 453 total participants) were identified: five population based cohort studies involving 1 053 271 participants, and five case control studies involving 2951 participants. Pooled effect estimates from both cohort studies (SIR 1.46, 95% CI: 1.20, 1.77) and case control studies (OR 1.53, 95% CI: 1.08, 2.18) were consistent with a positive association between AD and keratinocyte carcinoma.

Conclusions:
Atopic dermatitis is associated with an increased risk of keratinocyte carcinoma. Potential explanations include aberrant immune function related to AD itself or immunomodulatory treatments, and increased susceptibility to keratinocyte ultraviolet damage in patients with filaggrin mutations. Further investigations with more robust case definitions of AD, including AD severity, and data on the type and frequency of immunosuppressive medications used would help to elucidate the mechanism underlying this relationship.
Learning objectives:
1. Identify the relationship between atopic dermatitis and cutaneous cancer risk 2. Discuss potential mechanisms underlying the association between AD and keratinocyte cancer. 3. Recognize the clinical application of our study's results and next steps for research.
Takeaway Message:
Atopic dermatitis is associated with an increased risk of keratinocyte carcinoma. There is a role for more research to elucidate the mechanisms of this relationship. There may be a role for increased skin cancer screening in this population.

Sarah Hedtrich **9:30 –9:40am**

FIBROBLASTS FROM ATOPIC DERMATITIS PATIENTS IMPAIR THE EPIDERMAL HOMEOSTASIS OF SKIN EQUIVALENTS

Anna Löwa, Andrej Kováčik, Kateřina Vávrová, Sabine Kaessmeyer, Sarah Hedtrich
Faculty of Pharmaceutical Sciences, University of British Columbia,

Introduction:
Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disease. However, its pathogenesis is still not fully understood. Further, although it is widely accepted that fibroblasts exert significant effects on the epidermal regeneration in normal and diseased states of the human skin, little is known about the impact of fibroblasts on AD pathogenesis so far. Here, we report on the impact of AD patient-derived fibroblasts on the epidermal differentiation, maturation and inflammation of full-thickness skin equivalents in the presence and absence of activated CD4+ T cells.
Methods:
Fibroblasts were isolated from plucked scalp hair follicles of healthy volunteers and AD patients and subsequently screened for the presence of common gene mutations in filaggrin (FLG; R501X, 2282del4, R2447X, S3247X) using Taqman allelic discrimination assays. Afterwards, full-thickness skin equivalents were generated using hair follicle-derived fibroblasts from AD patients (n = 6), healthy donors (n = 6) and normal interfollicular keratinocytes. The skin equivalents were also exposed to human CD4+ T cells. Subsequently, the equivalents were comprehensively characterized with regard to differentiation, skin barrier function and inflammatory responses.
Results:
Skin equivalents generated from AD fibroblasts were characterized by hyperproliferation, epidermal thickening and increased levels of the pro-inflammatory keratinocyte-derived cytokine thymic stromal lymphopoietin (TSLP) as well as PAR-2 expression. Further, dysregulated expression of differentiation markers such as filaggrin have been observed. Exposure to activated CD4+ T cells to skin equivalents generated from AD fibroblasts resulted in TSLP-triggered T cell migration into the dermis equivalent which has not been observed in normal control models.
Conclusions:
These findings clearly indicate the impact fibroblast on skin homeostasis and that fibroblasts may significantly promote and maintain AD-related characteristics.
Learning objectives:
(1) Which impact may patient-derived fibroblasts have on skin homeostasis? (2) Do fibroblasts contribute to AD phenotypes? (3) Which effects are mediated or triggered by fibroblasts?
Takeaway Message:
Fibroblasts exert significant effects on skin homeostasis - in normal as well as in diseased states.

Christopher Turner **9:40 –9:50am**

GRANZYME B INHIBITION REDUCES THE SEVERITY OF ATOPIC DERMATITIS IN MICE

Christopher Turner, Stephanie Santacruz, Matthew Zeglinski, Christine Wang, Katlyn Richardson, Sho Hiroyasu, Hongyan Zhao, Gail Gauvreau, Hermenio Lima, Roma Sehmi and David Granville.
University of British Columbia

Introduction:
Granzyme B (GzmB) is a serine protease minimally expressed in normal skin but drastically elevated in numerous autoimmune and/or chronic inflammatory skin diseases. While often regarded as a pro-apoptotic protease, GzmB retains its activity and accumulates in the extracellular milieu during dysregulated inflammation. Within the extracellular space, GzmB can cleave extracellular matrix proteins, cell adhesion proteins and key proteins within the basement membrane zone/dermal-epidermal junction. We hypothesized GzmB contributes to the onset and progression of atopic dermatitis (AD).

Methods:
In the present study, GzmB levels were evaluated in human AD lesions and compared to healthy skin. In vitro cleavage assays were used to identify GzmB substrates pertinent to skin. Cultured keratinocytes were exposed to GzmB and the effect on barrier permeability was evaluated. Finally, a causative role for GzmB was assessed in a murine model of AD, comparing GzmB-/- and wild-type (WT) mice.

Results:
GzmB positive cells were abundant in human AD lesions compared to healthy skin. Significant reductions in inflammation, epidermal thickness and overall lesion incidence and severity, were observed in GzmB-/- compared to WT AD mice. Topical administration of a GzmB inhibitor to WT mice also reduced AD severity compared to vehicle-treated controls. Cultured keratinocyte monolayers exposed to GzmB exhibited a dose-dependent impairment of barrier function that was associated with reduced E-cadherin, desmoglein-1 and desmogelin-3. In vitro, GzmB effectively cleaved filaggrin, E-cadherin, desmoglein-1 and -3. Epidermal levels of filaggrin (stratum corneum), E-cadherin, desmoglein-1 and -3, and dermal decorin levels were all decreased in WT AD-affected mice compared to controls, while GzmB-/- and GzmB inhibitor-treated AD-affected mice displayed significantly greater levels of the aforementioned proteins.

Conclusions:
GzmB-mediated proteolytic activity contributes to reduced cell adhesion, impaired barrier function and inflammation and represents a valid therapeutic target for the treatment of AD.

Learning objectives:
Granzyme B increases the severity of atopic dermatitis in mice. Granzyme B impairs epidermal barrier function by cleaving filaggrin, E-cadherin and desmogleins. Inhibition of Granzyme B reduces the severity of atopic dermatitis in mice.

Takeaway Message:
Inhibition of Granzyme B reduces the severity of atopic dermatitis in mice, thus may provide a therapeutic option.

Thursday, 27 June
Lunch with Industry Sponsors & Presentations
12:00 - 1:00pm

Veronique Moulin	**12:30 – 12:40pm**

HYPERTROPHIC SCAR MYOFIBROBLASTS GENERATE PROANGIOGENIC MICROVESICLES

Alexandra Laberge, Mays Merjaneh, Syrine Arif, Sébastien Larochelle, and Véronique J. Moulin
Centre of Research in Experimental Organogenesis of Laval University (LOEX), Quebec, QC, Canada

Introduction:
Hypertrophic scars are a common post-surgical complication that is difficult to prevent or treat. These scars are characterized by a high production of matrix proteins by pathological myofibroblasts (Hmyos) as well as a supra-physiological vascular density. Acute wound myofibroblasts have been shown to produce microvesicles following activation by the serum protein alpha-2-macroglobulin (A2M). Our aims were to evaluate the capacity of Hmyos to produce microvesicles and to examine the role of these signaling entities in modulating angiogenesis in pathological scars.

Methods:
Hmyos isolated from six human hypertrophic scar tissue samples were cultured in the presence of 10% bovine serum, different concentrations of A2M, or two specific inhibitors of A2M receptors. Microvesicles released in the culture medium were isolated using sequential centrifugation and quantified by flow cytometry. These microvesicles were added to cutaneous microvascular endothelial cells to evaluate their effect on three different parameters related to angiogenesis.

Results:
Hmyos shed microvesicles following stimulation with serum or A2M. The A2M receptor, low-density lipoprotein receptor-related protein 1 (LRP1), was detected on the surface of Hmyos. Microvesicle production was blocked by selective inhibition of A2M-LRP1 binding. Hmyo-derived microvesicles stimulated the three major mechanisms underlying blood vessel formation: endothelial cell proliferation, migration, and capillary-like tube formation.

Conclusions:
Our results suggest that Hmyos may contribute to the excessive angiogenic response involved in hypertrophic scarring by releasing pro-angiogenic microvesicles upon stimulation by serum A2M.

Learning objectives:
• Hypertrophic scar myofibroblasts produce microvesicles; • Serum alpha-2-macroglobulin stimulate microvesicle shedding from hypertrophic scar myofibroblasts via activation of cell-surface low-density lipoprotein receptor-related protein 1; • Microvesicles generated by hypertrophic scar myofibroblasts exhibit in vitro proangiogenic properties.

Takeaway Message:
Hypertrophic scar myofibroblasts contribute to the excessive angiogenic response involved in hypertrophic scarring by releasing pro-angiogenic microvesicles upon stimulation by the serum protein alpha-2-macroglobulin.

Lina Dagnino **12:40 – 12:50pm**

ESSENTIAL ROLE FOR INTEGRIN-LINKED KINASE IN MELANOBLAST COLONIZATION OF THE SKIN

Melissa Crawford, Valerie Leclerc, Kevin Barr, Lina Dagnino
University of western Ontario

Introduction:
Melanocytes are pigment-producing cells found in the skin and other tissues. Alterations in the melanocyte lineage contribute to various human diseases, including neurocristopathies and pigmentation disorders. During embryogenesis, neural crest cell subsets give rise to the first wave of melanoblasts, which migrate dorsolaterally, homing to the skin and differentiating into melanocytes.

Methods:
We generated a novel reporter mouse model in which the gene encoding integrin-linked kinase (ILK) was inactivated specifically in the first-wave melanoblasts, using a tamoxifen-inducible system. We also developed methods to isolate, culture and target both embryonic melanoblasts and postnatal melanocytes to investigate the role of ILK in melanocytic lineage cells.

Results:
Targeted inactivation of Ilk in these melanoblasts causes defects in their ability to form long pseudopods, to migrate and to proliferate. As a result, integrin-linked kinase (ILK)-deficient melanoblasts fail to populate normally the developing epidermis and hair follicles. Defects in motility and dendricity also occur upon Ilk gene inactivation in mature melanocytes, causing abnormalities in integrin-associated cell responses to the extracellular matrix substrates collagen I and laminin 332. Significantly, the ability to form long protrusions in mutant cells in response to collagen is restored in the presence of constitutively active Rac1.

Conclusions:
ILK is a key element in a signaling nexus involving interactions between extracellular matrix substrates, integrins and Rac1, implicated in melanocytic cell establishment and functions in the skin.

Learning objectives:
1. The audience will learn key steps in melanocytic cell specification and migration during embryogenesis 2. The audience will learn and be able to apply concepts of targeted gene inactivation to study fundamental aspects of pigment cell biology 3. The audience will be able to distinguish phenotypic characteristics of normal and abnormal embryonic melanoblasts and mature melanocytes

Takeaway Message:
Integrin-linked kinase is essential for melanoblast population of the skin and proper functions of postnatal, pigmented melanocytes.

POSTER ABSTRACTS

Wound Healing

PRESENTERS

Avisa Abbasi

Yasser Almadani

Holly Sparks

Yunyuan Li

Megan Vierhout

Mohammadali Sheikholeslam

Sergio Cortez Ghio

Yanran Wang

Andrea-Kaye Datu

Avisa Abbasi **WH01**

A Novel Adipose Micro Fragments Embedded Bio-engineered Liquid Scaffold for Treatment of Large Non-Healing Wounds

Avisa Abbasi, Reza Jalili and Aziz Ghahary
University of British Columbia

Introduction:
Diabetic wounds and pressure ulcers (PU) are debilitating and serious forms of non-healing wounds that cause significant health problems. According to an analysis by the Rick Hansen Institute, the cost of treating PUs in Canada is estimated to be $365.7 million per year. Our research group has developed a shelf-ready powdered reconstitutable liquid skin substitute referred to as MeshFill to treat non-healing wounds refractory to current treatments. Recently, after obtaining the human ethics permission we treated 9 patients in our institute. Although, findings showed significant improvement in healing outcome within 4-8 weeks of MeshFill treatment, larger and wider wounds needed more time to heal possibly due to lack of new source of skin cells. It is our working hypothesis that utilizing small pieces of autologous fat tissue bearing adipose stem-cells would serve as a new source of cells in promoting the healing of chronic wounds.

Methods:
Autologous fat tissues were obtained from B6-GFP mouse in order to more accurately investigate the fate of adipose-derived cells. Minced fat fragments were mixed with liquid MeshFill and Optimized Adipose Fragments (OFA) embedded within liquid MeshFill were used to treat delayed splinted wounds generated on the back of mice and also for subcutaneous injections.

Results:
Our findings showed that Fibroblast cells migrated from fat particles both in 2D and 3D and Live and Dead Assay confirmed the viability of the cells. After evaluating the Meshfill gelation time, we tested the efficacy of the OFA + MeshFill in treatment of splinted delayed wound models in C57BL/6 mice. Acute wounds generated on C57BL/6 mice (2 wounds/mouse) and received either: 1) Meshfill only, 2) OFAs plus MeshFill or 3) OFAs only. At different time points (Days 7, 15, 30) the outcome evaluated by checking a list of criteria including: 1) Epithelialization and healing time, 2) Clinical appearance, 3) Tissue cellularity, 4) Infiltrated immune cells (CD3 and CD4 + cells), 5) ECM depositions and 6) Dermal and epidermal thickness.

Conclusions:
Findings from this study which prove faster healing, will pave the way for further pipeline development of the current skin substitute model for future clinical application combination therapy for complicated non-healing wounds.

Learning objectives:
1. A combination of adipose tissue micro fragments and MeshFill can be used to develop a composite, in situ-forming skin substitute for treatment of deep and wide wounds 2. Adipose-derived SCs, (ASCs) can be easily extracted by liposuction from adipose tissue in large quantities with minimally invasive procedure from patients and cultured on a large scale 3. ASCs can improve the healing of chronic wounds 4. ASCs display multilineage developmental plasticity 5. ASCs can be cryo-preserved for up to 6 months for future therapeutic use

Takeaway Message:
Adipose tissue which is a favourable source of stem cells and can easily be accessible from patients with non-healing wounds, would be a great option if combined with MeshFill for treatment of chronic wounds.

Yasser Almadani **WH02**

GETTING A GRIP ON CD109'S ROLE IN DUPUYTREN'S DISEASE

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Introduction:
Transforming growth factor (TGF)- β is a pleiotropic cytokine that regulates a broad range of biological processes including cellular growth, differentiation, extracellular matrix (ECM) deposition and immune modulation. TGF-β signaling is transduced by a pair of transmembrane serine/threonine kinases known as TGF-β receptor type I and type II receptors, and TGF- β co-receptors such as CD109 (a membrane-anchored protein) are known to strongly regulate TGF- β signaling in a variety of cell types. Although aberrant regulation of TGF- β signaling is known to play a key role in Dupuytren's disease (DD), the significance and expression of CD109 in DD myofibroblasts and adjacent palmar fascia is largely unknown.

Methods:
We examined whether CD109 expression in primary human DD fibroblasts is different from genetically-matched phenotypically normal fibroblasts from adjacent palmar fascia (PF), or genetically different and anatomically-matched normal fibroblasts from carpal tunnel syndrome patients (CT). Immunofluorescent staining was utilized to elucidate distinct staining patterns and subcellular location of CD109 and other GPI-anchored proteins. In addition, CD109 gene expression levels were measured by qPCR. Flow cytometry was also utilized to detect any differences in CD109 expression and other GPI- anchored proteins. Also, Levels of CD109 protein expression were assessed by western blot analysis.
Results:
Our results show that DD fibroblasts and adjacent normal PF fibroblasts display decreased levels of CD109 protein and increased alpha smooth muscle expression, when compared to normal CT fibroblasts. Interestingly, our data also demonstrate that CD109 mRNA expression and CD109 release form the cell surface are similar in DD fibroblasts, adjacent PF fibroblasts and normal CT fibroblasts, suggesting that the decrease in CD109 protein levels in DD cannot be attributed to a decrease in CD109 synthesis or excessive CD109 release. In addition, other GPI-anchored protein levels are comparable between CT, PF and DD fibroblasts.
Conclusions:
Our finding that CD109 protein levels are decreased in DD fibroblasts and adjacent PF fibroblasts as compared to normal CT fibroblasts, provides a mechanistic explanation for the increased fibrotic response in DD. Furthermore, our results showing that CD109 protein levels are decreased while the CD109 mRNA levels and CD109 release from the cell surface remain unchanged, suggest that CD109 turnover/degradation may be enhanced in DD. Together, our findings suggest that decreased CD109 function may play a critical role in increased fibrosis in DD fibroblasts and thus CD109 may represent a molecular target for therapeutic intervention in DD.
Learning objectives:
1- Uncovering the role of TGF-beta co-receptors in Dupuytren's disease. 2- Introducing a potential mechanistic explanation for the increased fibrotic responses in Dupuytren's disease. 3- Introducng CD109 as a potential early risk marker.
Takeaway Message:
CD109 strongly regulates TGF- β signaling in a variety of cell types. Therefore, decreased CD109 function may play a critical role in increased fibrosis in DD fibroblasts and thus CD109 may represent a molecular target for therapeutic intervention in DD.

Holly Sparks **WH03**

REINDEER ANTLER VELVET IS A UNIQUE MODEL OF MAMMALIAN SKIN REGENERATION

Holly D. Sparks, Peng Jiang, Hailey Robbins,Kevin Gowing, Olivia Hee, Hanna Pope, John Matyas, Ron Stewart, Robert McCorkell, Jeffrey Biernaskie
University of Calgary

Introduction:
Wound healing in adult mammals is intrinsically flawed. Rather than regenerating lost tissue, adult mammals instead repair large full-thickness wounds though the formation of poorly functional scar tissue. Despite enormous investment, the wound healing industry has failed to effectively eliminate scar and dysfunctional healing in humans. Understanding the molecular mechanisms that promote tissue regeneration is critical to the development of future wound healing therapies aimed at reducing scar formation.
Methods:
Full thickness 12mm excisional wounds and thermal injury were created in antler velvet (specialized skin covering the regenerating antler) and equivalent wounds created on the back skin of the same 4 animals. Wounds were monitored for up to 60 days to observe phenotypic healing patterns. Further, excisional wounds created on the antler and back in an additional 3 animals were collected at 4 different time points (Day 0, 3, 7, and 14) during healing. Bulk RNA Sequencing was utilized to investigate transcriptomic differences in regenerative (antler) and non regenerative (back skin) healing and confirmation of protein and cellular response was further investigated with immunohistochemical staining.
Results:
Full thickness excisional wounds created in antler velvet were found to regenerate >80% of lost appendages including hair follicles, glands, and pigmentation. Remarkably, this regenerative capacity is also sustained

following severe burn injury. Importantly, in the same animal, similar wounds created on the backskin heal through scar formation as is typically observed in other mammalian species, including humans. Marked differences were observed in immune response and molecular signaling upon immunohistochemical and transcriptomic analysis.

Conclusions:

Here, we describe Reindeer (Rangiferus tarundus) as a powerful model possessing both regenerative and non-regenerative skin. Identification of cellular and molecular differences between these healing patterns allows identification of therapeutic targets aimed at improving wound healing in mammalian skin (such as humans) toward a more regenerative phenotype.

Learning objectives:

1. To describe the Reindeer as a novel model of regenerative and non regenerative wound healing in the same animal 2. To identify key cellular differences in regenerative and non-regenerative healing in mammals 3. To describe molecular differences in regenerative and non-regenerative healing in mammals 4. To identify therapeutic targets aimed at improving wound healing in mammals

Takeaway Message:

Here, we identified Reindeer as a novel model of regenerative (antler velvet) and non regenerative (back skin) wound healing in the same large animal species. This model allows researchers to identify key differences in these two patterns of wound healing, thus allowing identification of therapeutics aimed at improving wound healing in mammals toward a more regenerative (rather than scar-forming) phenotype.

Yunyuan Li **WH04**

CONTRIBUTIONS OF MYELOID CELLS IN SKIN REPAIR AND HAIR FOLLICLE REGENERATION

Yunyuan Li, Hatem Nojeidi, Ruhangiz T. Kilani, Aziz Ghahary
University of British Columbia

Introduction:

The roles of infiltrated hematopoietic cells in wound healing have extensively been studies. However, the conversion of hematopoietic cells into skin cells and their contributions in wound healing and skin appendage regeneration have not been appreciated.

Methods:

We performed double immunofluorescent staining with antibodies for hematopoietic cells and either fibroblasts or keratinocytes to investigate hematopoietic cell conversion. We cultured GFP expressed splenocyte-derived myeloid cells, injected to healthy skin in wounded mice and traced injected cells to convert to skin fibroblasts and keratinocytes.

Results:

The result show that during the healing process, some of the CD45-positive hematopoietic cells are positive for type I pro-collagen or keratin 14, the markers of fibroblasts and keratinocytes, respectively. Further, CD11b-positive myeloid cells seem the origin of converted skin cells. Tracing injected labeled splenocyte-derived myeloid cells in skin, we confirm that myeloid cells able to convert into skin cells. Furthermore, our results from in vivo experiments provide new information on contribution of myeloid cells in hair follicle regeneration.

Conclusions:

This work highlights the myeloid cell contributions in wound repair and hair follicle regeneration in mice

Learning objectives:

1. This study provide further evidence in potential role of CD11b-positive myeloid cells in skin wound healing; 2. We are first time demonstrated that infiltrated myeloid cells can convert keratinocytes and participate in re-epithelialization 3. We demonstrated that myeloid cells can regenerate new hair follicles after skin injury

Takeaway Message:

The molecular and cellular mechanisms of skin wound healing.

Megan Vierhout **WH05**

DEVELOPMENT OF A CELLULAR AND MOLECULAR PHENOTYPING PIPELINE FOR TARGET CHARACTERIZATION IN ARCHIVED FFPE SKIN SAMPLES DERIVED FROM PATIENTS DIAGNOSED WITH SCLERODERMA

Megan Vierhout, Pavithra Parthasarathy, Anmar Ayoub, Soumeya Abed, Spencer D. Revill, Abdul Shaik, Olivia Mekhael, Manreet Padwal, Safaa Naiel, Hadyn Walker, Aaron Hayat, Anna Dvorkin-Gheva, Salem Alowami, Asghar Naqvi, Nathan Hambly, Jeremy Hirota, Martin Kolb, Nader Khalidi, Maggie Larche and Kjetil Ask

Introduction:
The identification and characterization of cellular and molecular events associated and responsible for progression of human disease is required in the development of suitable treatment strategies. We have here developed a pipeline allowing cellular and molecular phenotyping characterization of archived human samples and show feasibility of detection and quantification of alternatively activated macrophages and production of CCL18 in skin and lung biopsies derived from patients diagnosed with systemic sclerosis and compared to healthy skin as well as to other fibrotic lung diseases including sarcoidosis, Idiopathic Pulmonary Fibrosis, Rheumatoid Arthritis, Hypersensitivity Pneumonitis and non-fibrotic control lungs. All studies were approved by the Hamilton Integrated Research Ethics Board.

Methods:
Tissues were formalin-fixed and paraffin-embedded, and 1mm cores were incorporated in a tissue microarray containing over 100 cores (>30 patients). Duplex RNAscope® fluorescent in-situ hybridization (FISH) was used to detect CCL-18 and CD68 mRNA, and immunohistochemistry (IHC) was used to detect CD206, CD68, and Dectin 1 proteins. IHC was quantified using HALO image analysis software

Results:
We demonstrate that concomitant analysis of over 100 tissues allows the simultaneous characterization of alternatively activated macrophages in archived FFPE samples. As expected, colocalization of CCL18 and CD68 mRNA transcripts was shown through duplex FISH demonstrating the presence of alternatively activated macrophages in all fibrotic tissues. IHC staining of macrophage markers CD206, CD68, and Dectin-1 was also detected and associated with all fibrotic diseases contained on tissue microarray.

Conclusions:
The presence of CCL18 in CD68 positive macrophages in skin derived from patients with systemic sclerosis and fibrotic lung disease supports the notion that alternatively activated macrophages are a potential target for therapy in fibrotic disease, irrespective of the nature of the disease. The development of tissue micro arrays containing multiple diseases allows for direct comparisons between diseases at the cellular and molecular level

Learning objectives:
• Elucidate underlying mechanisms that contribute to the progression of scleroderma • Demonstrate the involvement of alternatively activated macrophages in scleroderma • Explore a novel workflow in molecular phenotyping and utilize the associated technologies to provide insight into potential targets for therapy in scleroderma

Takeaway Message:
Scleroderma, a disease of unknown etiology, requires further investigation of the molecular phenotypes involved in disease mechanism, which may shine light on methods for treatment. We demonstrated that alternatively activated macrophages may be a viable target for therapy in scleroderma, and show a pipeline that allows the examination of multiple samples at the molecular and cellular level at the same time.

Mohammadali Sheikholeslam **WH06**

GELATIN-POLYURETHANE BILAYER SKIN SUBSTITUTE

Mohammadali Sheikholeslam, Paul Santerre, Marc Jeschke

Introduction:
Wound closure is vital for survival of patients with complex wounds including burns. While auto-grafting is the gold standard for treating severe skin loss, it has its limitations, including in many cases a limited availability of skin to graft. On the other hand, current skin substitute technologies remain expensive and require significant clinical management of the skin wounds. Also, most of the commercially available products provide dermal compartment of the skin which necessitates another surgery for transplanting a split-thickness autograft. In the current study we developed a bilayer scaffold providing both dermal and epidermal components. This substitute is unique in that the same technique (electrospinning) and the same

materials (with different ratios) are used for both parts, which provides a good consistency between the two sides.

Methods:

Mixture of gelatin (G) and elastic, biodegradable polycarbonate polyurethane (PU) were spun at two different ratios: G80-PU20 for dermal side and PU80-G20 for epidermal side. SEM, cell viability and immunostaining were used for characterization of the scaffolds and seeded cells.

Results:

G80-PU20 fabricated with large pore size (10-20 μm) and a hydrophilic character provides fibroblasts adhesion, growth and infiltration, while PU80-G20 made with small pore size (2-3 μm) and a hydrophobic character help forming a monolayer of keratinocytes faster and should provide a better efficiency for hindering water loss and bacterial infection. Keratinocytes seeded on the PU80-G20 side showed not enough cell viability and proliferation, however when the scaffold was coated with laminin, an abundant protein in the basement membrane, cell compatibility was improved significantly. When PU80-G20 scaffold was compred with G80-PU20 and a commercially available collagen-based scaffold, it showed superiority in forming monolayer of keratinocytes that can lead to a faster wound closure in vivo.

Conclusions:

This bilayer scaffold worth in vivo evaluation and have a great potential for application as skin substitute in clinic.

Learning objectives:

1) Making different fiber and pore sizes by playing with gelatin/PU ratio and electrospinning parameters 2) Feasibility of making bilayer skin substitute using the same materials and method, but providing two distinct layers 3) Making a biocompatible environment for keratinocytes

Takeaway Message:

Bilayer skin substitute can support enhanced keratinocyte adhesion, proliferation and migration toward a faster wound healing than a dermal scaffold

Sergio Cortez Ghio **WH07**

EPITHELIAL STEM CELL FUNCTION PRESERVATION IN TISSUE-ENGINEERED BILAYERED SKIN SUBSTITUTES: A SYSTEMATIC REVIEW OF CLINICAL STUDIES

Sergio Cortez Ghio, Danielle Larouche, and Lucie Germain
Université Laval

Introduction:

Over the last 25 years, multiple tissue-engineered bilayered skin substitutes comprising both a dermis and an epidermis have been developed to treat large wounds from full thickness burns, persistent ulcers, and tumor removal. To ensure long-term graft survival and restoration of the epithelial barrier function, engineered skin substitutes must provide a microenvironment capable of sustaining epithelial stem cell retention. The objective of our study was thus to compare these engineered substitutes and determine how important this emulated microenvironment is for long-term epithelial tissue survival and function restoration.

Methods:

For this systematic review of the literature, we used PubMed and EMBASE to identify and compare clinical trials and case studies reporting the use of autologous tissue-engineered bilayered skin substitutes which were grafted in a single-step surgery to act as permanent skin replacement published in the last 25 years. Twenty-one studies were identified by 2 reviewers and all data pertinent to epithelial stem cell retention through culture and substitute production, procedure success rate, and post-engraftment follow up were extracted and compiled into a comprehensive table.

Results:

Most groups used biomaterial scaffolding populated with autologous fibroblasts for the dermal component of their substitutes. Seeding densities of both dermal and epithelial cells were similar across studies. Only a few groups achieved subjectively long-term high graft survival after a single procedure. Grafted tissue survival varied significantly both intra- and inter-study. We believe these discrepancies might be largely attributable to culture conditions (media, feeder layer, cytokines, etc.).

Conclusions:

Clinical observations compiled in this study support the idea that some of the engineered bilayered skin substitutes can provide the microenvironment necessary for epithelial stem cells to maintain their proliferative potential and differentiation capabilities. However, culture conditions prior to and after substitute assembly seem to be play a bigger part in stem cell retention than dermis properties.

Learning objectives:
This is a global portrait of advances in clinical tissue-engineered autologous bilayered skin substitutes. Systematic reviews are a powerful tool for basic science research, namely for hypothesis generation.
Takeaway Message:
Epithelial stem cells must be preserved in engineered skin substitutes in order to achieve long-term tissue survival and barrier function restoration. Culture conditions play a large role in their preservation.

Yanran Wang **WH08**

INVESTIGATING THE THERMAL RESISTANT MECHANISM IN STEMS CELLS DERIVED FROM BURNED SKIN

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Introduction:
Burned-derived mesenchymal stem cells (BD-MSCs) isolated from severely burned skin represent a promising new source of skin stem cells for potential use in the clinic for skin regeneration and wounding healing. It is intriguing that these BD-MSCs remain viable even when exposed to high thermal heat after a burn injury. It is likely that there is a mechanism that allows BD-MSCs to survive heat stress.
Methods:
BD-MSCs and control groups were incubated at the pre-determined heat treatment condition to simulate the burn injury. The cells were then analysed for cell viability using Trypan blue exclusion assay, necrosis and apoptosis using Annexin V and propidium iodide for flow cytometric analysis. Cell lysates were collected for the following SDS-PAGE and silver gel staining to detect the difference of protein expression.
Results:
At 44°C for 1hr, BD-MSCs showed the most profound difference of heat shock protein (HSP70) expression compared to control groups, which indicates the strongest heat response, thus this to be the optimal condition to study the underlying mechanisms. Preliminary results showed that apoptosis and necrosis are changed following the heat stress in BD-MSCs compared to control groups through flow cytometry. Mass spectrometry will be performed on targeted bands to identify specific proteins, thus gives insight to the underlying mechanisms.
Conclusions:
Further investigation is required to understand the novel mechanism that allows BD-MSC's to survive heat stress. This knowledge is important to know as their application in the clinic allows enhanced wound healing.
Learning objectives:
1. Giving insight to the mechanisms of thermal stress resistance seen in dermal mesenchymal stem cells. 2. Furthering the knowledge of a novel source of stem cells: Burned-derived mesenchymal stem cells. 3. Providing the fundamental while important information for the possible application of BD-MSCs in clinic.
Takeaway Message:
Further investigation is required to understand the novel mechanism that allows BD-MSC's to survive heat stress. This knowledge is important to know as their application in the clinic allows enhanced wound healing.

Andrea-Kaye Datu **WH09**

A SURGICAL DEVICE TO STUDY THE EFFICACY OF BIOENGINEERED SKIN SUBSTITUTES IN MICE WOUND HEALING MODELS

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Introduction:
Due to the poor regenerative capacity of adult mammalian skin, there is a need to develop effective skin substitutes for promoting skin regeneration after a severe wound. However, the complexity of skin biology has made it difficult to enable perfect regeneration of skin. Thus, animal models are used to test potential skin substitutes. Murine models are valuable but their healing process involves dermal contraction.
Methods:
We have developed a device called a dome that is able to eliminate the contraction effect of rodent skin while simultaneously housing a bioengineered skin graft. The dome comes in two models, which enables

researchers to evaluate the cells that contribute to wound healing from neighboring intact tissue during skin healing/regeneration.

Results:

One model provides a physical barrier to minimize contraction, while the other model has additional perforations in the barrier to allow cellular contribution from the surrounding intact skin. We evaluated the two models and their effects on granulation tissue formation, the extent of vascularization, and the transition to myofibroblastic phenotype.

Conclusions:

This protocol simplifies grafting of skin substitutes, eliminates the contraction effect of surrounding skin, and summarizes a simple method for animal surgery for wound healing and skin regeneration studies.

Learning objectives:

1. To bring to light the difficulties and problems in using animal models when studying skin and wound healing. 2. To further elucidate our device and how it can help with difficulties. 3. Show data to illustrate the positive effects of the device.

Takeaway Message:

The device our lab has created remedies the contraction effect of surrounding skin and other difficulties included with skin regeneration studies in animals. It can be used to help researchers to carry out experimental studies with more precision and consistency.

POSTER ABSTRACTS

Basic Sciences

PRESENTERS

Hana Hakami

Yunyuan Li

Maude Vaillancourt-Audet

Philip Surmanowicz

Alexe Grenier

Hana Hakami **BS01**

FIBULIN-4 AND LATENT TRANSFORMING GROWTH FACTOR-B BINDING PROTEIN-4 CELL INTERACTIONS IN ELASTOGENESIS

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Introduction:
Elastogenesis presents a cell surface located hierarchical process that requires the recruitment of several proteins, including fibulin-4 (FBLN4) and latent transforming growth factor beta binding protein-4 (LTBP4). Previously, we showed that FBLN4 interacts with fibroblasts. Cell interaction with LTBP4 has also been demonstrated. However, the cell receptors for FBLN4 and LTBP4, and the respective molecular mechanisms in elastogenesis remain unknown. In this study, we aimed to identify the FBLN4 and LTBP4 cell receptors, and to determine the functional consequence of their cell interactions in elastogenesis.

Methods:
Initially, we have recombinantly produced FBLN4 and LTBP4 full length proteins and FBLN4 deletion mutants. FBLN4 multimers and monomers were separated using gel filtration chromatography. Skin fibroblast interactions with FBLN4 and LTBP4 were assessed using cell binding assays. Heparan sulfate deficient cells and siRNA knockdowns were used to identify the FBLN4 and LTBP4 cell receptors. Immunofluorescence was used to examine elastic fiber formation in skin fibroblast cultures after knocking down the FBLN4 and LTBP4 cell receptors.

Results:
Skin fibroblasts bind strongly to FBLN4 and LTBP4. FBLN4 multimers exclusively interact with cells, but not monomers. We identified two cell interaction epitopes on FBLN4, one located in cbEGF2-3 and a second one in the C-terminal domain. Additionally, we have investigated FBLN4 and LTBP4 cell receptor(s). In the presence of heparin, cell binding to FBLN4 was entirely abolished, and reduced to LTBP4. Treating cells with heparinases reduced cell attachment to both proteins. Heparan sulfate deficient cells did not bind to FBLN4. Both syndecan-2 and -3 knockdowns in fibroblasts abolished interaction with FBLN4, whereas only syndecan-3 knockdown abolished interaction with LTBP4. Syndecan-2 and -3 knockdowns in cultured skin fibroblast resulted in compromised elastic fiber assembly.

Conclusions:
FBLN4 contains two cell interaction sites mapped to cbEGF2-3 and the C-terminal domain. FBLN4 interacts with syndecan-2 and -3, whereas LTBP4 interacts with syndecan-3.

Learning objectives:
To create an effective design for deletion mutants for studying protein functions including cell interaction. - To analyze cell interaction with extracellular elastogenic proteins (FBLN4 and LTBP4). - To use gene knockdown using siRNA for identifying FBLN4 and LTBP4 cell surface receptors. - To determine relevant changes in elastic fiber assembly by skin fibroblasts using immunofluorescence.

Takeaway Message:
Skin elasticity is due to the abundance of elastic fibers. Elastogenesis constitutes a hierarchical process that requires several proteins, including FBLN4 and LTBP4. FBLN4 and LTBP4 interact with skin fibroblast through syndecans. Their cell interactions are essential for proper elastogenesis.

Yunyuan Li **BS02**

DEVELOPMENT OF A NOVEL APPROACH IN INDUCTION OF ALOPECIA AREATA IN MICE AND EVALUATING THE POTENTIAL ROLE OF MYELOID CELLS IN HAIR LOSS AND SKIN INFLAMMATION

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University of British Columbia

Introduction:
Alopecia areata (AA) is an autoimmune skin disease characterized by hair loss and local skin inflammation. The molecular and cellular mechanisms of AA are still unknown. Several methods have been developed previously to induce AA in mice. However, these methods need more complicated procedures, high cost and achieve low AA induction rate.

Methods:
In this study, we have developed a novel approach in inducing both the patchy and alopecia universalise in C3H mice. We simply isolated a mixture of skin cells from AA-affected skin of mice by collagenase digestion and directly injected these cells to mice. We also cultured this mixture of cells in vitro. The attached and suspended cells were separately dermally injected to the dorsal skin of healthy C3H/HeJ mice.
Results:
Using our method, a double successful rate in AA induction in mice was achieved. The induction rate of AA in mice received either attached cells or suspended cells were almost the same. However, mice received attached cells developed patchy while mice received suspended cells developed universalise. Examination of attached cells indicated they mainly included fibroblasts, keratinocytes and CD11b+ myeloid cells. To exclude the possible skin fibroblasts and keratinocytes can induce AA, we isolated skin cells from normal mice and injected the same number of cells to healthy mice. Result showed that none of mice developed to AA. In consistent with this finding, dermal injection of splenocyte-derived myeloid cells could also induce hair loss and skin inflammation in C3H/HeJ mice and C57/BL mice.
Conclusions:
These findings confirmed the reproducibility of inducing AA in C3H/HeJ mice by our new approach without previously used AA skin grafting or injecting a cocktail of cytokine treated T cells. Further, CD11b+ myeloid cells from AA-affected skin may play a potential role in induction of alopecia areata.
Learning objectives:
1. This study introduces a simple method to induce alopecia areata. 2. This study introduce a new information about myeloid cells 3. This study provide information for mechanisms of chronic skin dieases.
Takeaway Message:
What type of cells cause hair loss and skin inflammation based on our findings?

Maude Vaillancourt-Audet **BS03**

INFLUENCE OF CHRONIC ULTRAVIOLET (UV) RADIATION ON MIGRATION OF THREE PRIMARY MELANOMA POPULATIONS

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Université Laval

Introduction:
Exposure to solar light is the main etiologic factor in the initiation of the cutaneous melanoma. The carcinogenic effect of solar light is caused by the capacity of ultraviolet B (UVB) radiation to generate highly mutagenic cyclobutane pyrimidine dimers (CPDs) in DNA and by the produced oxidative stress. While the role of UV in cancer initiation is already well established, its influence on the primary melanoma progression to metastatic state remains fragmentary. Our hypothesis is that chronic UV exposure stimulates the metastatic progression of melanoma. The aim of this study is thus to determine the effect of UV radiation on melanoma cells migration as a proof of concept.
Methods:
Melanoma cell lines (A375, WM983a and SK-MEL-28) were grown as spheroids and treated with chronic UV radiation directly or indirectly. Direct exposure consists of 5 minutes of irradiation (570J/m2) every 12h for 7 days with a solar simulator. As a control for DNA damages, spheroids have been fixed 24h after the last irradiation and the presence of CPDs was assessed by immunofluorescence. Indirect exposure was achieved by spheroid exposition to a conditioned medium of keratinocytes previously chronically irradiated with UVB (75J/m2) every 12h for 7 days. Irradiated or not-irradiated spheroids were then embedded in collagen I matrix with or without the keratinocyte conditioned medium and the radial cell migration was evaluated as well as the number of invading cells. In parallel, spheroids were set to migrate in an inverted Boyden chamber in order to quantify the number of invading cells towards the keratinocyte conditioned medium.
Results:
Chronic UV irradiation generated residual DNA damages in primary melanoma spheroids. The migration of WM983a and SK-MEL-28 grown as spheroids was increased toward the keratinocyte conditioned medium.
Conclusions:
Chronic UV exposure has an effect on the migration of primary melanomas and could induce a greater metastatic power.

Learning objectives:
1. Optimization of primary melanoma spheroids formation. 2. Observation of primary melanoma spheroids migration in a 3D environment with a qualitative and quantitative method. 3. Understanding the effect on migration of direct UV exposure via chronic irradiation. 4. Understanding the effect on migration of indirect UV exposure via keratinocyte conditioned medium with chronic UVB irradiation. The effects of UV light on the metastatic power of primary melanoma is unknown. Our study highlights the potential effects of chronic UVs irradiation via direct DNA damages or discharge cytokine interactions on the migration of primary melanomas.

Takeaway Message:
The effects of UV light on the metastatic power of primary melanoma is unknown. Our study highlights the potential effects of chronic UVs irradiation via direct DNA damages or discharge cytokine interactions on the migration of primary melanomas.

Philip Surmanowicz **BS04**

β3-TUBULIN KNOCKDOWN INTERFERES WITH MICROTUBULE DYNAMICS, CELL-CYCLE REGULATION, AND MICROVESICLE RELEASE IN HUMAN MELANOMA CELLS

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Introduction:
Microvesicles (MVs), ranging in size from 100 nm to 1000 nm, play an important role in carcinogenesis by promoting angiogenesis and tumor metastasis, interfering with anti-tumor immunity, and inducing multidrug resistance. The release of MVs requires structural changes in microfilaments, intermediate filaments, and microtubules. Class III β-tubulin (β3-tubulin), one of the seven β-tubulin isotypes, is a microtubule component involved in malignant transformation and cancer development. Herein, we characterize the effects of β3- tubulin knockdown on microtubule dynamics, cell cycle regulation, and MV formation in human melanoma cells.

Methods:
Human malignant melanoma cells (A375, ATCC, Manassas, USA) were cultured following manufacturer's recommendations. Using a lipofectamine RNAiMAX (Thermo Fisher Scientific, Massachusetts, USA) protocol, A375 were transfected with either β3-tubulin siRNA (Santa Cruz Biotechnology, Dallas, USA) or FlexiTube Lamin A/C non-targeting siRNA (Thermo Fisher Scientific, Massachusetts, USA). Western blot analysis, RNA isolation, immunofluorescent microscopy, and MV purification were performed 48 hours after transfection. Cell cycle analysis was conducted 24 and 48 hours post-transfection.

Results:
The A375 cells were found to constitutively express β3-tubulin mRNA and protein. Knockdown of β3-tubulin in A375 cells impaired microtubule dynamicity, induced cell cycle arrest, activated apoptosis signaling pathways, and inhibited MV release.

Conclusions:
Taken together, the data suggest that β3-tubulin knockdown interferes with microtubule dynamics, cell-cycle regulation, and MV release in human melanoma cells. By understanding the significance of β3-tubulin in carcinogenesis, the dermatologist will gain diagnostic, prognostic, and therapeutic insights essential for the management of melanoma patients.

Learning objectives:
1. To review the hallmarks of carcinogenesis. 2. To discuss the role of MVs in cancer development. 3. To explore the effects of β3-tubulin on microtubule dynamics, cell-cycle regulation, and MV formation in melanoma cells.

Takeaway Message:
By impairing microtubule dynamics, inducing cell cycle arrest, and inhibiting MV release, β3-tubulin may serve as an important biomarker and/or therapeutic target for melanoma patients.

ANTI-AGING EVALUATION OF A KALMIA ANGUSTIFOLIA EXTRACT ON HEALTHY SKIN SUBSTITUTES

Alexe Grenier, André Pichette, Jean Legault, Roxane Pouliot
Université Laval

Introduction:
Skin aging is the most visible element of the aging process, giving rise to a major concern for anyone. During this process, several changes at a cellular level occur, altering skin appearance. Among these changes, there is a decrease in the keratinocyte proliferation, in the synthesis of matrix compounds and in cutaneous hydration. Plants from the Ericaceae family, like Labrador tea and Kalmia angustifolia, another boreal forest plant, generally have anti-inflammatory and antioxidant potentials. Thus, this project is based on the hypothesis that Kalmia angustifolia should have an anti-aging cosmetic potential that is comparable, and even better than Labrador tea, which has a well-established anti-aging effect. The objectives aimed to evaluate the safety and anti-aging efficacy of the extract by comparing it to a Labrador tea extract.

Methods:
The safety evaluation of the extracts was performed using a MTT cytotoxicity test, while the efficacy was determined on healthy skin substitutes reconstructed according to the LOEX self-assembly method and analyzed by histochemistry, with a Masson's trichrome staining, and immunofluorescence, with elastin, collagen-1, collagen-3 and aquaporin-3 stainings.

Results:
Toxicity tests established the low concentrations safety of the two extracts, as well as their optimal concentration for further experiments (between 25 and 50 µg/mL). Histological and immunohistochemical analyses performed on the skin substitutes treated with the extracts revealed an increase in the dermis (statistically significant) and the living epidermis thickness compared to control. Moreover, the extracts positively influence the elastin, collagen-1, collagen 3 and aquaporin-3 expression, usually decreased during skin aging.

Conclusions:
The results obtained suggest that Kalmia angustifolia extract could have a promising anti-aging effect, especially on dermis extracellular matrix, comparable to Labrador tea.

Learning objectives:
Learn more about skin and dermatology research in Canada and advances in skin aging 2) Learn about the work of other researchers to eventually create new collaborations 3) Learn more about the job perspectives in the field, the background of workers, etc.

Takeaway Message:
The boreal forest is full of unexplored resources that can lead to the development of cosmetic active ingredients such as Kalmia angustifolia, which has a great anti-aging potential as demonstrated in this study.

POSTER ABSTRACTS

Clinical Research

PRESENTERS

Sho Hiroyasu

Holly Sparks

Abdulhadi Jfri

Vijay Sandhu

Sho Hiroyasu **CS01**

GRANZYME B: A NOVEL TARGET FOR PEMPHIGOID DISEASES

Sho Hiroyasu, Valerio Russo, Matthew R. Zeglinski, Hongyan Zhao, Yoan Machado, Anika Kasprick, Chiharu Tateishi, Wataru Nishie, Angela Burleigh, Peter A. Lennox, Nancy Van Laeken, Nick J. Carr, Richard I. Crawford, Hiroshi Shimizu, Daisuke Tsuruta, Christopher M. Overall, Ralf J. Ludwig, and David J. Granville

University of British Columbia

Introduction:

Proteases play important roles in both the afferent and efferent phases of the pemphigoid diseases (PD) through the cleavage of hemidesmosomal proteins. However, to date, clinical trials targeting specific proteases have been limited. In this study, we investigated the role of the serine protease, granzyme B (GzmB), in PD pathology. We hypothesized that GzmB contributes to both the afferent and efferent phases of the diseases through the cleavage of hemidesmosomal proteins.

Methods:

Skin biopsies and blister fluids were collected from patients with bullous pemphigoid (BP) or inflammatory epidermolysis bullosa acquisita (EBA). Tissue and blister fluids were assessed for GzmB using immunohistochemistry and ELISA, respectively. Hemidesmosomal proteins in the lesional tissues were also assessed by immunohistochemistry. GzmB-mediated hemidesmosomal protein cleavage and cell attachment assays were performed. To test its function in the efferent phase of the PD, a passive transfer model of EBA on GzmB-deficient mice was analyzed with clinical score, histological blistering score, immunohistochemistry, and western blotting. Finally, to test the role of GzmB in the afferent phase, cleavage sites of collagen XVII by GzmB were analyzed using western blotting or mass spectrometry.

Results:

Abundant GzmB and loss of hemidesmosomal proteins were identified on the PD patient lesional samples. GzmB cleaved hemidesmosomal proteins (collagen XVII, □6□4 integrin) to reduce cell attachment strength. GzmB-deficient mice with EBA exhibited a reduction in affected-body surface area, histological blisters, neutrophil infiltration, and hemidesmosomal-protein loss, compared to the wild-type mice with the disease. Cleavage analyses of collagen XVII suggested that GzmB cleavage occurs in the NC16a domain, which is the pathological-autoantibody recognition site.

Conclusions:

GzmB contributes to PD pathology through the cleavage of hemidesmosomal proteins.

Learning objectives:

Granzyme B is a serine protease secreted from immune- and non-immune cells. Granzyme B is abundant in the lesional skin of pemphigoid diseases. Granzyme B cleaves hemidesmosomal proteins. Granzyme B deficiency improved a pemphigoid disease.

Takeaway Message:

We elucidated that granzyme B contributes to the pathology of pemphigoid diseases through the cleavage of hemidesmosomal proteins.

Holly Sparks **CS02**

ADULT HUMAN DERMAL PROGENITOR CELL TRANSPLANTATION IMPROVES THE FUNCTIONAL OUTCOME OF SPLIT THICKNESS SKIN GRAFTS IN A XENOGRAFT MODEL

Natacha A. Agabalyan†, Holly D. Sparks†, Samar Tarraf, Nicole L. Rosin, Katie Anker, Grace Yoon, Lindsay N. Burnett, Duncan Nickerson, Elena S. Di Martino, Vincent A. Gabriel and Jeff Biernaskie († these authors contributed equally to this work)

University of Calgary

Introduction:

Following full-thickness skin injuries, closure of the wound is critically important to minimize morbidity. The standard of care to achieve wound closure is autologous split-thickness skin grafting (STSG). Though often life-saving, patients with STSGs report chronic functional deficiencies such as chronic itch, altered sensation, fragility, hypertrophic scarring, and contractures. These negative sequelae are attributable to the absence of functional dermis, and the formation of disorganized fibrotic scar. Recent work has demonstrated the existence of dermal progenitor cells (DPCs) residing within hair follicles that function to continuously regenerate mesenchymal tissue.

Methods:
Adult human DPCs were permanently labeled using a TdTomato expressing lentiviral vector, expanded in culture, then transplanted into a full-thickness skin wound in immune-compromised mice and closed with a human STSG. Animals were followed for up to 3 months to observe graft acceptance and patient behavior. After 3 months, grafts were harvested for immunohistochemical and biomechanical testing.
Results:
At 3 months, hDPCs had successfully integrated into the graft and differentiated into various regionally-specified phenotypes, improving both viscoelastic properties of the graft and mitigating pruritus.
Conclusions:
The addition of cultured cells from adult human dermis can improve overall graft function and patient experience following split thickness skin grafting.
Learning objectives:
1. Can hDPCs be successfully isolated and expanded in culture from adult human patients? 2. Do transplanted cells survive and integrate underneath a hSTSG? 3. Can the addition of cells improve the function of a hSTSG in a xenograft model?
Takeaway Message:
Transplantation of cultured cells from adult human dermal tissue is an exciting therapeutic addition aimed at improving the function of the current standard of care in treating large wounds and burns. Future work in this field should further explore improved means of cell delivery and expansion methods for autologous cell transplant.

Abdulhadi Jfri **CS03**

PSYCHOSOCIAL IMPACT OF CLINICAL SEVERITY ON HIDRADENITIS SUPPURATIVA

Abdulhadi Jfri, Ivan V. Litvinov, Elizabeth O'Brien, Elena Netchiporouk
McGill University Health Centre

Introduction:
Hidradenitis suppurativa (HS) negatively impacts quality of life. The objective of this study was to find how HS Hurley and Severity Assessment of Hidradenitis Suppurativa (SAHS) relate to scores on Dermatology Quality of Life Index (DQLI) and Beck Depression Inventory (BDI).
Methods:
We performed a single center cross-sectional study conducted from October 2018 until February 2019. Patients were considered eligible if they were 12 years or older and had a clinical visit for HS. Patients were excluded if they declined to participate, could not read or write in English or French, or had a known diagnosis of depression or mental health disorder as defined by the DSM-5 criteria. The survey instrument included 2 patient-centric questionnaires: DLQI and BDI.
Results:
50 patients participated. Mean age: 37.94 ± 15.68 years, mostly women (n=28; 56%), mostly self-identified Caucasian (n=33; 66%). Hurley staging of the patients showed 12 (24%) stage I, 16 (32%) stage II and 22 (44%) stage III. Mean DLQI score was highest (poor quality of life) for stage III (16.95 ±8.68) followed by stage II (11.00±7.45) and stage I (5.17±4.49). One-way ANOVA analysis found no statistically significant differences in the mean BDI scores based on Hurley staging alone, $p = 0.32$. Linear regression found SAHS score had a statistically significant ($p = 0.027$) effect on BDI score, with score for severe disease (SAHS ≥ 9) significantly higher ($p = 0.04$) than for mild disease. Visual analogue scale (VAS) for pain did not reach statistical significance ($p = 0.075$) based on BDI scale. No other independent variables had a statistically significant effect. Statistically significant associations existed between DLQI and smoking history ($p = 0.04$); Hurley stage III disease ($p = 0.0004$); higher clinical severity based on pain score ($p < 0.0001$) and SAHS raw score ($p = 0.0016$). Linear regressions were used to find variables for modeling BDI and DLQI. Variables associated with higher DLQI included Hurley stage III, smoking history, and pain score; disease duration was associated with decreased DLQI. Variables associated with increasing BDI included SAHS score and smoking history, female sex and non-Caucasian origin.
Conclusions:
BDI-based depression severity does not correlate with clinical severity of HS based on Hurley stages, but advanced stages have greater impact on quality of life using DLQI.
Learning objectives:
1. Beck depression scores correlate with the HS clinical severity using Severity Assessment of Hidradenitis Suppurativa (SAHS) 2. The advanced clinical stages of HS have greater impact on patients' quality of life

using DLQI scale. 3. Higher impact on patient's life using DLQI was observed with Hurley stage III, smoking history, and high pain score using visual analogue scale (VAS)

Takeaway Message:

The advanced Hurley stages of HS have greater impact on patients' quality of life and the more severe clinical assessment scores using SAHS showed greater depressive symptoms reflected by BDI scale.

Vijay Sandhu **CS04**

WORKPLACE PRODUCTIVITY AND MENTAL HEALTH IN PATIENTS WITH HIDRADENITIS SUPPURATIVA

Vijay K. Sandhu1, Monica Shah1, Vincent Piguet2,3, Afsaneh Alavi2,3,4

Faculty of Medicine, University of Toronto, Toronto, ON, Canada1; Division of Dermatology, Department of Medicine, University of Toronto, ON, Canada2;

Women's College Hospital, Toronto, ON, Canada3; York Dermatology Center, Richmond Hill, ON, Canada4

Introduction:

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin condition associated with a marked decrease in quality-of-life (QoL), with HS patients experiencing a higher incidence of mental health comorbidity. Furthermore, HS typically starts in early adulthood, a time of immense professional growth and continues to affect patients in their most productive ages leading to challenges in maintaining meaningful employment. No Canadian studies have explored mental health and work productivity as QoL markers in HS patients.

Methods:

We conducted a prospective case series at a community dermatology clinic in Toronto, Canada. We enrolled participants with a diagnosis of HS and who were aged >18 years old. Enrolled participants completed a set of three questionnaires: i) demographic and health history questionnaire ii) Hospital Anxiety & Depression scale (HADS) and iii) Workplace Productivity and Impairment (WPAI) questionnaire. Pearson correlation tests were conducted to assess the effect size for the association between disease specific variables (age, patient-reported QoL, Hurley stage) and HADS and WPAI scores.

Results:

Forty-four participants met inclusion criteria. Anxiety & depression: The mean HADS Anxiety (HADS_A) score was 7.1 +/- 5.6, with 12 patients (27.3%) having abnormal HADS_A scores (>11). The mean HADS Depression (HADS_D) score was 9.25 +/- 4.9, with 17 patients (38.6%) having abnormal HADS_D scores (> 11). Employment: Thirty-four HS patients (77.3%) were employed. Mean work productivity loss was 45.2 +/- 34.6% and mean activity impairment was 54.32 +/- 33.7%. Higher Hurley stages were associated with higher rates of work impairment. Subjective QoL and HADS_A and HADS_D scores were the best predictors of work impairment and activity impairment.

Conclusions:

This study shows a high prevalence of anxiety and depression in HS patients. Screening for mental health challenges in HS patients is needed. Though the majority of HS patients are employed, there is considerable amount of impairment faced in the workplace. To our knowledge, this is the first study to use the WPAI in an HS population. Further studies to validate the WPAI for HS patients are needed.

Learning objectives:

1.Explain how mental health comorbidities and workplace productivity are important quality-of-life indicators in patients with Hidradenitis suppurativa. 2. Appreciate the increased burden of depression and anxiety and workplace challenges experienced by patients living with Hidradenitis suppurativa. 3. Describe a new tool for assessing workplace productivity in patients with Hidradenitis suppurativa.

Takeaway Message:

There is an increased need to screen for depression, anxiety and workplace-related challenges in patients with Hidradenitis suppurativa and additional supports for patients in these areas may be required.

POSTER ABSTRACTS

Epidemiology Research

Translational research

PRESENTERS

Ivan V Litvinov

Leila Cattelan

Philippe Lefrançois

Ivan Litvinov **ER01**

EPIDEMIOLOGY AND PATIENT DISTRIBUTION OF ORAL CAVITY AND OROPHARYNGEAL SCC IN CANADA.

Jessica Lu, Feras M. Ghazawi, Evgeny Savin, Andrei Zubarev, Peter Chauvin, Abdulhadi Jfri, Denis Sasseville, Anthony Zeitouni and Ivan V. Litvinov
McGill University Health Centre

Introduction:
Oral cavity cancers (OCC) and oropharyngeal cancers (OPC) continue to be a major source of morbidity and mortality worldwide, requiring the shared effort of numerous specialists. Tobacco and alcohol consumption have long been identified as risk factors for both OCC and OPC. In addition, HPV is gaining its position as the main causal agent for OPC.

Methods:
Data pertaining to the year of diagnosis, the patient's sex, age at the time of diagnosis, province/territory, city, and forward sortation area (first three entries of postal code) of oral cavity and oropharyngeal malignancies diagnosed in Canada during 1992-2010 were extracted from the Canadian Cancer Registry and Le Registre Québécois du Cancer using ICD-O-3 codes. Malignancy-associated mortality data was extracted from the Canadian Vital Statistics database using ICD-9 and ICD-10 codes.

Results:
21,685 cases of oral cavity and 15,965 cases of oropharyngeal malignancies were identified from 1992-2010. Of those, 84.97% were oral cavity squamous cell cancers (SCC), 88.10% were oropharyngeal SCC, and both had a male predominance. While oral cavity SCC incidence stabilized over the study period, oropharyngeal SCC continued to increase. Oral cavity SCC incidence increased with age, while oropharyngeal SCC incidence peaked in the 50-59-year age group (62.87 cases per million individuals per year). More detailed geographic distribution analysis of SCC patients at the provincial/territorial, city and postal code levels identified clustering of these patients across the country, with trends comparable to those previously reported in other countries. Notably, T2G postal code in Calgary, AB had the highest incidence of both oral and oropharyngeal cancers. Disease-specific mortality analyses also supported our incidence data, with a few exceptions to the general trend.

Conclusions:
Understanding the landscape of oral/head and neck malignancies in Canada remains crucial in informing the allocation of medical resources for the prevention, diagnosis, and management of these cancers.
Learning objectives:
1. Understand the epidemiology of oral and oropharyngeal SCC cancers in Canada. 2. Learn more about the key differences in the underlying risk factors in the pathogenesis of these malignancies. 3. Highlight changing trends with respect to incidence and mortality of these cancers across Canadian Provinces and territories.

Takeaway Message:
We identified and confirmed important epidemiological differences in trends between oral and oropharyngeal cancers, identified high incidence postal codes (e.g., T2G in Calgary, Alberta) for each malignancy and correlated incidence/mortality with known risk factors including alcohol/tobacco use and HPV infections, therefore, enabling a more comprehensive understanding of these cancers in Canada.

Ivan Litvinov **ER02**

PENILE SQUAMOUS CELL CARCINOMA: ANALYSIS OF INCIDENCE, MORTALITY TRENDS AND GEOGRAPHICAL DISTRIBUTION IN CANADA

François Lagacé, Feras M. Ghazawi, Michelle Le, Evgeny Savin, Andrei Zubarev, Mathieu Powell, Linda Moreau, Denis Sasseville, Ioana Popa, and Ivan V. Litvinov
McGill University Health Centre

Introduction:
Penile squamous cell carcinoma (SCC) is a rare disease with several known risk factors. However, few studies have assessed its incidence and temporal trends.
Methods Three independent cancer registries were used to retrospectively analyze demographic data from Canadian men diagnosed with penile SCC between 1992 and 2010.

Results:
The overall incidence rate was 5.97 cases per million males. Four provinces and several clusters of Forward Sortation Area postal codes with significantly higher incidence rates were identified. Incidence rates

increased linearly between 1992 and 2010. The overall mortality rate was 1.87 deaths per million males per year. The province of Saskatchewan and the city of Moncton, New Brunswick had significantly higher mortality rates.

Conclusions:

This study will help dermatologists recognize patient populations that are at higher risk for developing this malignancy. The identification of high-incidence areas will also act as a foundation for future studies that will seek to identify new risk factors and etiologic agents for this malignancy.

Learning objectives:

The goal of this study is to 1) analyze the epidemiology of penile SCC in Canada 2)to examine patient distribution with this cancer across Canada in order to 3) elucidate population risk factors.

Takeaway Message:

There are several known risk factors for penile SCC. The identification of high-incidence geographic clusters suggests that there are new environmental and lifestyle risk factors involved in the pathogenesis of this malignancy.

Leila Cattelan **ER03**

INVESTIGATING EPIDEMIOLOGIC TRENDS AND GEOGRAPHIC DISTRIBUTION OF ANAL SQUAMOUS CELL CARCINOMA PATIENTS THROUGHOUT CANADA BETWEEN 1992 AND 2010

Leila Cattelan1, Feras M. Ghazawi2, Michelle Le1, Evgeny Savin3, Denis Sasseville3, Kevin Waschke4, and Ivan V. Litvinov3

1Department of Medicine, McGill University, Montreal, Quebec, Canada 2Division of Dermatology, University of Ottawa, Ottawa, Ontario, Canada 3Division of Dermatology, McGill University, Montreal, Quebec, Canada 4Division of Gastroenterology, McGill University, Montreal, Quebec, Canada

Introduction:

Anal cancer is a rare disease comprising of only 0.5% of new cancer cases in the United States. The most common subtype, accounting for 85% of cases reported, is squamous cell carcinoma (SCC). Studies in several developed nations have reported an increasing incidence of anal cancer in the past decades, while various risk factors have been identified pertaining to its pathogenesis. These include HPV infection, tobacco, and immunosuppression. The epidemiologic characteristics and distribution of anal SCC patients throughout Canada however remain poorly described.

Methods:

A retrospective analysis of demographic data across Canada between 1992 and 2010 was performed using three independent population-based cancer registries. The incidence and mortality of anal SCC was examined at the levels of provinces and territories, cities and Forward Sortation Area (FSA) postal codes.

Results:

3,720 patients were diagnosed with anal SCC in Canada between 1992 and 2010; 64% were female. The overall national incidence rate was 6.27 cases per million individuals per year. The age standardized incidence rate was of 5.86 cases per million individuals per year, with the average age of diagnosis being 60.42 years. The incidence of anal SCC increased steadily over this period of time, with significantly high provincial incidence rates documented in British Columbia and Nova Scotia (9.31 cases per million individuals each). Closer examination revealed high incidence areas in various urban areas including Vancouver, Windsor, Hamilton, Toronto, Ottawa, and Montreal. The analysis of mortality rates throughout the nation corroborated these findings. Finally, clustering of anal SCC down to the FSA postal code level is presented to shed light onto novel avenues of research for potential environmental etiologies and to identify susceptible populations.

Conclusions:

This study, for the first time, provides a comprehensive analysis of the burden of anal SCC in Canada, revealing geographic clustering trends.

Learning objectives:

To outline the demographic characteristics and geographic distribution of anal SCC patients across Canada to utilize geographic clustering trends as a tool to direct further research in order to identify more specific risk factors and etiologies of anal SCC To identify patient populations at higher risk of anal SCC with the aim of better directing healthcare resources to these areas

Takeaway Message:
This study highlights areas of clustering of anal SCC throughout Canada; characterizing epidemiologic trends will serve to better direct healthcare resources to populations at risk for more efficacious prevention and diagnosis.

Philippe Lefrançois **TR01**

IN SILICO ANALYSES OF THE TUMOR MICROENVIRONMENT IN BASAL CELL CARCINOMA HIGHLIGHT THE IMPORTANCE OF TH2 CYTOKINE PROFILE, TUMOR-ASSOCIATED MACROPHAGES AND ACQUISITION OF MESENCHYMAL STEM CELL-LIKE PHENOTYPE IN ADVANCED AND TREATMENT-RESISTANT TUMORS

Philippe Lefrançois M.D., Ph.D., Pingxing Xie M.D., Ph.D., Scott Gunn B.Sc., Jennifer Gantchev, M.Sc., Amelia Martinez Villareal, B.Sc., Denis Sasseville M.D., FRCPC and Ivan V. Litvinov M.D., Ph.D., FRCPC.
McGill University Health Centre

Introduction:
Basal Cell Carcinoma (BCC) represents the most common form of all cancers. BCC is characteristically surrounded by a fibromyxoid stroma. Previous studies have suggested a shift towards a Th2 response, an increase in T regulatory lymphocytes and the presence of cancer-associated fibroblasts in the BCC tumor microenvironment.
Methods:
In this study, we aimed to further characterize the BCC tumor microenvironment in detail by analyzing previously published BCC RNA-Sequencing data and correlating it with clinically-relevant features. We performed immune cell type deconvolution by CIBERSORT and cell type enrichment by xCell.
Results:
Using immune cell type deconvolution by CIBERSORT, we have identified a brisk lymphocytic infiltration, and more abundant macrophages in BCC tumors compared to normal skin. Using cell type enrichment by xCell, we confirmed the observed immune infiltration in BCC tumors compared to normal skin. In addition, as they are more abundant in low-risk BCC than in high-risk BCC, gamma-delta T lymphocytes may play a protective role against BCC by restricting its growth. Tumoral inflammation induced by macrophage activity was associated with advanced BCC. In advanced and vismodegib-resistant BCC, more mesenchymal stem cells were observed. Particularly in vismodegib-resistant BCC, fibroblasts and adipocytes were found at high number, which ultimately may contribute to the decreased drug delivery to the tumor.
Conclusions:
In conclusion, this study has revealed notable BCC tumor microenvironment findings that are associated with important clinical features.
Learning objectives:
Appreciate the advantages of in silico RNA deconvolution to study the tumor microenvironment in cancer genomics from clinical samples Understand how immune-related findings in BCC correlate with clinical findings Discover how cell type abundances relate to BCC pathogenesis
Takeaway Message:
In silico RNA deconvolution enables robust characterization of BCC tumoral microenvironment according to important clinical features.

Philippe Lefrançois **TR02**

THE TRANSCRIPTIONAL LANDSCAPE OF BASAL CELL CARCINOMAS: NOVEL SIGNALING PATHWAYS AND ACTIONABLE TARGETS

Philippe Lefrançois M.D., Ph.D. (1), Pingxing Xie M.D., Ph.D. (1), Scott Gunn (1), Denis Sasseville M.D., FRCPC (1), and Ivan V. Litvinov M.D., Ph.D., FRCPC (1).
McGill University Health Centre

Introduction:
Basal Cell Carcinoma (BCC) represents the most common form of all cancers. Except for the well-established role of the Sonic hedgehog (Shh) pathway, the transcriptional landscape of BCC remains largely unknown.

Methods:
Using bioinformatics analyses on previously published BCC RNA-Sequencing (RNA-Seq) data, we searched for novel differentially-expressed genes and pathways in BCC correlating with clinically-relevant features.

Results:
Potentially targetable pathways in all types of BCC include Wnt/β-catenin, IL-17, cadherins, and integrins. In high-risk BCC with Mohs histopathological subtypes, upregulated genes include AIM2, BCAT1 and CDKN2A. For vismodegib-resistant BCC, potential therapeutic avenues include antagonizing specific Wnt/β-catenin pathway members and PDGF signaling. For advanced BCC, upregulated pathways include TLR, IL-17, Akt/PI3K, integrins and protein degradation. In the end, we validated some target genes in our BCC patient samples.

Conclusions:
In conclusion, these analyses have revealed new pathways implicated in BCC tumorigenesis, clinically-applicable biomarkers and potential drug targets for local and systemic therapies.

Learning objectives:
Discover new biomarkers and biological targets in basal cell carcinomas Appreciate the advantages of RNA-Sequencing in cancer genomics from clinical samples Understand the importance of ectopically-expressed genes in carcinogenesis

Takeaway Message:
This study tripled the number of potentially actionable pathways in BCC. Potential molecules include already-approved biologics (drug repurposing) and targeted agents under clinical trials.

POSTER ABSTRACTS

Psoriasis

PRESENTERS

Navjeet Gill

Mélissa Simard

Sophie Morin

Ahmed Mourad

Geneviève Rioux

Vijay Sandhu

Raymond Milan

Meital Yerushalmi

Navjeet Gill **PS01**

RISK OF INFLAMMATORY BOWEL DISEASE IN PSORIASIS PATIENTS TREATED WITH ANTI-INTERLEUKIN-17 AGENTS: A BAYESIAN META-ANALYSIS

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2. Department of Mathematical & Statistical Sciences, Faculty of Science,
University of Alberta, Edmonton, AB

Introduction:
There is growing evidence supporting the association of Interleukin-17A (IL-17A) inhibitors, such as Secukinumab and Ixekizumab, and inflammatory bowel disease (IBD). Currently, the Food and Drug Administration recommends avoiding IL-17A inhibitors in patients at risk for IBD and screening for IBD before initiation of IL-17 inhibition. To assess the absolute risk of IBD in patients treated with IL-17 inhibitors, we performed a Bayesian meta-analysis and determined the number needed to harm (NNT) for IBD flare during IL-17 inhibitor therapy.

Methods:
Our literature review identified three risk factors for IBD in addition to psoriasis: smoking, hidradenitis suppurativa, and having a first-degree relative with IBD. Point estimates for population prevalences of these risk factors were found through a MEDLINE search. Applying Bayes' Formula, the prevalence of IBD was estimated in four groups: the general psoriasis population, the group with positive risk factors including psoriasis (worst-case scenario controls), the general psoriasis population receiving IL-17 inhibitor therapy, and the positive risk factor group receiving IL-17 inhibitor therapy.

Results:
The probability of developing Crohn's disease (CD) or ulcerative colitis (UC) in the general psoriasis population was 0.24%, but this increased substantially (to 36.67% and 41.10%, respectively) when all risk factors were present. In the general psoriasis population, the probability of developing CD or UC during IL-17 inhibitor therapy was only marginally increased (to 0.25% and 0.51%, respectively). However, IL-17 inhibition increased the absolute risk of CD by 0.88% and the absolute risk of UC by 18.90% in patients with positive risk factors, translating to a NNT of 114 for CD and 5.3 for UC.

Conclusions:
In patients with positive IBD risk factors, therapy with IL-17 inhibitors results in a substantially increased risk of UC exacerbation and a smaller risk of CD exacerbation. In patients with no risk factors, the probability of IBD flare during anti-IL17 treatment is negligible.

Learning objectives:
1. Impact of individual IBD risk factors on IBD risk in psoriasis patients receiving Interleukin-17A inhibition therapy. 2. Comparison of IBD risk associated with IL-17 inhibition therapy in the general psoriasis population versus psoriasis patients with positive IBD risk factors 3. Use of Bayesian analysis to inform clinical decision making

Takeaway Message:
Interleukin-17 inhibition therapy should be avoided in psoriasis patients with positive IBD risk factors due to substantially increased risk of IBD flare.

Mélissa Simard **PS02**

EFFECTS OF OMEGA-3 ON A PSORIATIC SKIN MODEL PRODUCED BY TISSUE-ENGINEERED

Mélissa Simard1,2; Sophie Morin1,2; Julie Fradette1,3; Roxane Pouliot1,2
1 Centre de recherche en organogénèse expérimentale de l'Université Laval / LOEX intégré au Centre de recherche du CHU de Québec-Université Laval ; 2 Faculté de Pharmacie, Université Laval ; 3 Département de chirurgie, Université Laval.

Introduction:
Psoriasis is a dermatosis characterized by a marked thickening of the epidermis, due to keratinocyte hyperproliferation, and abnormal epidermal differentiation. Clinical studies have shown that supplementation of the diet with omega-3 fatty acids could improve the symptoms of psoriatic patients. However, the mechanisms involved are still poorly understood. The aim of this study was to investigate the effects of α-linolenic acid (ALA) on the keratinocyte proliferation and differentiation of a psoriatic skin model.

Methods:
Healthy (HS) and psoriatic skin substitutes (PS) were produced according to the LOEX self-assembly method, using culture media supplemented with 10 µM ALA. After 56 days of production, the skin substitutes were analyzed by gas chromatography, histology, indirect immunofluorescence and Western Blot.

Results:
The added ALA was efficiently incorporated into the phospholipid and triglyceride fractions of the epidermis, as levels of EPA (7x) and DPA (3x) were significantly higher (p-value<0,001) in phospholipids of PSALA+ than in PS-. The epidermis of PSALA+ was more organized and was significantly thinner than the epidermis of PS- (p-value<0,001). Moreover, addition of ALA decreased keratinocytes proliferation, as less cells were stained with Ki67 in PSALA+ epidermis than in PS- epidermis. Finally, expression of both filaggrin and keratin 14 were increased after supplementation with ALA, thus, showing a restored differentiation in PSALA+.

Conclusions:
Taken together these results show that omega-3 fatty acids decrease the pathologic phenotype of psoriatic skin substitutes by normalizing keratinocytes proliferation and differentiation.

Please include 3 - 5 learning objectives (60 words) - Define omega-3 role in psoriasis. - Meet experts in dermatology. - See the latest advances in the field.

Takeaway Message:
Omega-3 fatty acids decrease the pathologic phenotype of psoriatic skin substitutes by normalizing keratinocytes proliferation and differentiation.

Sophie Morin **PS03**

STUDY OF ANTI-PSORIATIC EFFECTS OF ISOPROTERENOL ON LESIONAL SKIN SUBSTITUTES

Sophie Morin (1,2), Mélissa Simard(1,2), Roxane Pouliot(1,2)

1Centre de recherche en organogénèse expérimentale de l'Université Laval/LOEX intégré au Centre de recherche du CHU de Québec-Université Laval, QC, Canada. 2Faculty of Pharmacy, Laval University, Quebec

Introduction:
Psoriasis is an inflammatory skin disease characterized by the emergence of thick plaques caused by the hyperproliferation of epidermal cells. Our team has developed a unique psoriatic human skin model reconstructed according to the self-assembly method, which is totally autologous. Isoproterenol is an analog of epinephrine and is already known to serve as a good topical treatment for psoriasis. Indeed, in vitro studies with dibutryl cyclic AMP and isoproterenol demonstrated that the epinephrine-cyclic AMP cascade could modified the proliferation of epidermal cells. The aim of this study was therefore to evaluate the anti-psoriatic capacity of isoproterenol on lesional skin substitutes.

Methods:
Psoriatic skin substitutes of different conditions were produced according to the self-assembly method; tests were performed on two different lesional cell populations. Isoproterenol (10-6 M) was added directly to the serum of the culture media (DMEM with Ham's F12, 5% Fetal Clone II serum) from the seeding of the fibroblasts.

Results:
The substitutes produced with isoproterenol presented a more uniform surface with a better dispersion of the cells compared with the controls, which showed irregularities, thicker and thinner skin areas. Histological analyses also demonstrated that the living epidermis of skin substitutes with isoproterenol was thinner than isoproterenol-free substitutes, indicating that the psoriatic phenotype was less important. Moreover, the expression of differentiation proteins was modified between the two culture conditions.

Conclusions:
The use of isoproterenol for the growth of keratinocytes appeared to reduce the psoriatic characteristics of lesional skin substitutes.

Learning objectives:
Introduce the benefits of in vitro reconstructed skin models using the self-assembly method -Demonstrate that psoriatic substitutes correctly reproduce key characteristics of the pathology -Demonstrate that isoproterenol improves cell differentiation of psoriatic keratinocytes

Takeaway Message:
Isoproterenol appears to have promising potential to decrease the magnitude of psoriatic lesions

Ahmed Mourad **PS04**

BIOLOGIC DRUG SURVIVAL IN PSORIASIS: A SYSTEMATIC REVIEW AND COMPARATIVE META-ANALYSIS

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Introduction:
Drug survival is defined as the time until treatment discontinuation and has been widely applied to measure real-world therapeutic effectiveness of biologics in psoriasis. The current study adapted statistical methodology by Tierney et. al (2007) to pool the overall drug survival rates for ustekinumab (UST), adalimumab (ADA), etanercept (ETA), and infliximab (INF) at 2 years and 5 years. This was completed in order to determine which biologic had superior drug survival rates and to calculate clinically significant pooled overall survival rates for each biologic with best- and worst- case survival rates.
Methods:
A comprehensive systematic search of the literature was completed to identify drug survival studies of biologics in psoriasis. The estimator curves for each biologic were compared in a pair-wise manner to yield comparative hazard ratios (eg: hazard ratio for ustekinumab vs. adalimumab). Hazard ratios for each comparison were pooled in a random effects meta-analysis for data at 2 years and 5 years. The corresponding pooled ±95% confidence intervals for each comparison were used to calculate best- and worst- case drug survival rates. 786 studies were identified after duplicates were removed. Evaluation of these articles led to the inclusion of 22 studies.
Results:
Ustekinumab had superior biologic persistence to any other biologic at 2 years and 5 years. Adalimumab was superior to etanercept and infliximab drug survivals at 5 years. Pooled 2-year drug survival rates for adalimumab, etanercept, and infliximab were 58.9%, 47.6%, and 48.9%, respectively. The pooled drug survival rates for these biologics at 5 years were 45.1%, 34.3% and 33.4%.
Conclusions:
This meta-analysis utilized novel statistical methodology to demonstrate ustekinumab's superior drug survival compared to TNF-α inhibitors. Estimated pooled 2- and 5- year drug survival rates for ustekinumab, adalimumab, etanercept, and infliximab were calculated. Data from this study could serve as a useful tool for treatment decision-making and patient communication.
Learning objectives:
1. To discuss the merit of drug survival in assessing real-world effectiveness of biologics. 2. To discuss the relative real-world effectiveness and superiority of ustekinumab compared to TNF-α inhibitors. 3. To outline the best- and worst- case overall drug survival rates for each biologic using the hazard ratio data from the pooled meta-analysis.
Takeaway Message:
This meta-analysis utilized novel statistical methodology to demonstrate ustekinumab's superior drug survival compared to TNF-α inhibitors.

Geneviève Rioux **PS05**

DEVELOPMENT OF A T-CELL ENRICHED SKIN MODEL TO STUDY AN AUTOIMMUNE DISEASE: PSORIASIS

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Introduction:
Psoriasis is a chronic inflammatory dermatosis that affects approximately 2% of the world's population and for which no cure has emerged. This skin disorder is characterized by an increased proliferation of keratinocytes resulting in thickening of the epidermis, an increased angiogenesis and a leukocyte infiltrate. Psoriasis is mediated by T cells through the IL-23/IL-17 axis. IL-17A, the hallmark cytokine of the Th17 cells, activates keratinocytes leading to the secretion of various chemokines responsible for leukocytes infiltration, thus producing an activation loop leading to the chronicization of the psoriatic lesions.

Methods:
T cells were isolated from whole blood by negative selection with the EasySep Direct Human T cell isolation kit (StemCell technologies) and activated with phorbol 12-myristate 13-acetate (PMA) and ionomycin. T cells isolated from blood were characterized using flow cytometry analysis and then co-cultured with psoriatic keratinocytes for 14 days. Supernatants were harvested to evaluate IL-17A production by ELISA assays.
Results:
Flow cytometry analysis showed that the CD3+CD69+ population increased from 2.34% to 95.5% after the activation period. Furthermore, in comparison with the activation method using CD3-CD28 beads, T cells activated with PMA and ionomycin secreted IL-17A and this production is maintained over time.
Conclusions:
The presence of IL-17A in the psoriatic skin model will bring us closer to the physiopathological conditions observed in vivo. Optimization of culture conditions is currently underway to integrate these T cells into the 3D psoriatic skin model.
Learning objectives:
Possible collaborations to use this psoriatic skin model enriched with T-cell to test molecules with anti-psoriatic potential. - Meet experts in the field of skin immunity. - See the latest advances in tissue engineering and skin models (healthy and pathological).
Takeaway Message:
Th17 are major players in psoriasis. The presence of this cell type in our 3D psoriatic skin model could reproduce the inflammation obtained in psoriatic skin. This model could be used to tests immunosuppressive drugs for the treatment of psoriasis.

Vijay Sandhu **PS06**

NARROWBAND ULTRAVIOLET-B TREATMENT FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS: THE IMPACT ON PATIENT QUALITY-OF-LIFE

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Introduction:
Psoriasis is an inflammatory skin condition, with a worldwide prevalence of 1.3% to 8.5%. It has a marked impact on quality-of-life (QoL), with psoriasis patients typically scoring high on the Dermatology Life Quality Index (DLQI). Narrowband ultraviolet-B (NBUVB) phototherapy is a well-established therapy for moderate-to-severe psoriasis. However, data on the impact of NBUVB on patient QoL is limited. This study aimed to assess the efficacy and safety of NBUVB and its impact on patient QoL.
Methods:
We treated patients with moderate-to-severe plaque psoriasis with NBUVB three times per week for 10 weeks. Patients were included if they had a Psoriasis Area Severity Index (PASI) of ≥ 10 and had not used systemic or biologic treatment in the last four weeks. Concomitant topical treatments were permitted, but systemic and biologic agents were not. Body surface area (BSA), PASI, and DLQI scores were collected at the start and end of treatment. Efficacy was measured by the proportion of patients achieving PASI75. Safety was measured by recording reported adverse events (AEs). A clinically meaningful improvement in DLQI was defined as a score decrease of $\geq$5-points or a post-treatment score of 0.
Results:
Overall, 29 patients were included. Twenty-six patients (90%) achieved PASI75, 3 (10%) of which stopped treatment at week 6 due to earlier skin clearance. Common AEs were discomfort (34%), erythema (31%) and pruritus (7%). No serious AEs were noted. The mean improvement in DLQI was 73% ($p < 0.01$), with 16 of 21 patients (70%) achieving a clinically meaningful change of $\geq$ 5-point improvement or final score of 0.
Conclusions:
Our findings showed that NBUVB therapy led to a clinically significant improvement in psoriatic plaques and a clinically meaningful improvement in DLQI in most patients. Though our sample size was small, NBUVB phototherapy may be a suitable alternative for patients for whom systemic or biologic agents are contraindicated or infeasible.

Learning objectives:
1. Recognize the role of NBUVB phototherapy in the treatment paradigm for patients with moderate-to-severe plaque psoriasis. 2. Describe the efficacy of NBUVB phototherapy in patients with moderate-to-severe plaque psoriasis. 3. Describe the common and serious adverse events associated with NBUVB phototherapy for psoriasis patients. 4. Recognize the impact of NBUVB phototherapy on quality-of-life for patients with moderate-to-severe plaque psoriasis.

Takeaway Message:
NBUVB phototherapy is a reasonable treatment option for moderate-to-severe plaque psoriasis, with a marked improvement in patient quality-of-life. Given the favourable side effect profile, NBUVB therapy may be a suitable alternative to systemic medications in patients with multiple comorbidities or other contraindications to systemic therapy.

Raymond Milan **PS07**

FACTORS ASSOCIATED WITH BIOLOGIC AGENTS' USE IN PATIENTS WITH MODERATE-TO-SEVERE PSORIASIS

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Introduction:
Biologic agent use in psoriasis has not been previously described in Canada, although management of psoriasis has changed dramatically with the introduction of these agents. We sought to identify predictors of biologic agent use among patients with moderate-to-severe psoriasis who were being treated with conventional systemic agents (CSA).

Methods:
A retrospective cohort study using Quebec health administrative databases was conducted. Patients (19-85years) with a psoriasis diagnosis in 1997-2015 were identified. Those newly dispensed a CSA after June 1, 2008 (date when the first biologic agent was listed for psoriasis on the provincial drug formulary) were selected at the first CSA dispensing date (index date). Patients were followed from index date until their first biologic agent dispensation date, death, or December 2015, whichever occurred first.

Results:
This cohort included 2,073 psoriasis patients (mean age 61± standard deviation, SD 14 years, 46.7% male) of whom, 60.6% were prescribed their first CSA by a dermatologist. Most patients (54.7%) received methotrexate at index date. During follow-up, 276 (7.5%) patients received a biologic agent with a mean time to the first biologic dispensation of 1.72±1.57 years. Of patients who received a CSA from a dermatologist, 89% also received their biologic agent from a dermatologist. In multivariate Cox regression models, the hazard ratio (HR) of receiving a biologic agent decreased with age (HR for 5 years age increase 0.82; 95% confidence interval, CI: 0.77-0.86), and was higher among those with prior visits to a gastroenterologist (1.50; 1.08-2.07), those with psoriatic arthritis (1.70; 1.28-2.25) and those using antihypertensive medications (1.41, 1.06-1.87). When only CSA prescribed by a dermatologist were considered (N=1,256), younger age and the presence of psoriatic arthritis were predictors of biologic agents use.

Conclusions:
In patients newly prescribed a CSA, younger individuals and those with psoriatic arthritis were more likely to receive biologic agents.

Learning objectives:
What is Treatment pattern for psoriasis patients treated with biologic agents - When to prescribe a biologic agent - What are the socio-demographic characteristics of patients receiving a biologic agent - What are the clinical characteristics of patients receiving a biologic agents

Takeaway Message:
In most cases, dermatologists are prescribing CSA and biologic agents to patients with moderate-to-severe psoriasis. Knowing the demographic and clinical characteristics of patients receiving a biologic agent will help guide healthcare professionals in their decision of prescribing these agents.

MORE THAN SKIN DEEP: THE MICROBIOME OF PSORIASIS AND PSORIATIC ARTHRITIS

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Introduction:

Psoriasis is a common inflammatory skin disease affecting 1-3% of the Canadian population. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that affects 30% of psoriasis patients. Despite much progress in the study of these diseases their pathogenesis is not fully understood, inspiring an interest in the role the microbiome. Here, we characterize the cutaneous microbiome of psoriatic plaques and compare it between psoriasis and PsA patients, and between the different phenotypic classes of PsA (peripheral or axial).

Methods:

Skin swabs were obtained from an extensor psoriatic lesion (elbow or knee), and from unaffected skin on the contralateral joint in psoriasis and PsA patients satisfying CASPAR classification criteria. Control samples were taken from matched sites in healthy subjects. Bacterial DNA was isolated from the swab samples and subjected to high-throughput 16S ribosomal DNA sequencing. Blood was obtained for HLA Class I typing, and a standard protocol used by a rheumatologist to evaluate peripheral and/or axial joint involvement in PsA. All study subjects were Caucasian.

Results:

We recruited 34 healthy controls, 56 psoriasis patients, and 137 PsA patients. Consistent with our previous reports, there was a higher proportion of infections requiring antibiotics in the PsA group compared to psoriasis, albeit not statistically significant. Baseline Psoriasis Area and Severity Index [PASI] scores were comparable between the groups. Of the patients with available clinical data in the PsA group (n=94), 27 had axial disease. Currently, statistical and bioinformatic analyses are being conducted to sequencing data to decipher whether microbiome differences exist between the different genetic and clinical groups.

Conclusions:

The study will provide insight into the potential role of the skin microbiome in psoriatic disease severity and contribute to the development of a pathogenetic model for PsA that includes genes, environmental factors and the skin microbiome.

Learning objectives:

1. Functions of the skin microbiome; application in dermatology (what is known in psoriasis, atopic dermatitis, etc) 2. Methodologies of skin microbiome studies: DNA collection, isolation, sequencing 3. Skin microbiome study design: importance of microenvironments; preparation and exclusion criteria 4. Genetics and clinical presentation of psoriasis and psoriatic arthritis 5. Outcome measures in microbiome research

Takeaway Message:

This project is the first to investigate the role of skin bacteria in psoriasis and psoriatic arthritis (PsA), an inflammatory joint disease associated with psoriasis, in the context of the patient's immune- and skin-barrier genes. Results from this study may inform further investigations into the causal link(s) between skin bacteria and PsA, as well as studies into new treatments that will ultimately lead to improved care of patients with PsA worldwide.

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