



Canadian Arthritis Research Conference Poster Abstracts

Tuesday February 25, 6:30-8:00 PM
Upper Pavilion Room

**Fairmont Empress &
Victoria Conference Centre**
721 Government Street
Victoria, BC

Listed in alphabetical order by last name

DR. ALI AKRAM BIO

Dr. Ali Akram got his M.Sc. and Ph.D. from the University of Toronto from the Department of Immunology and The Institute of Medical Science. During his graduate studies he worked on deciphering factors contributing to immunodominance following viral infection (i.e., Influenza and HIV-1) in relation to arthritis. He is well published in many high impact journals. Following his graduation, he went on to do a postdoctoral fellowship at the University Health Network/UC Berkeley before joining the lab of Dr. Ali Abdul Sater at York University to conduct his current research on the role of TRAF1 in relation to arthritis.



ABSTRACT: The role of TRAF1 in arthritis

Background: Excessive inflammation is the root cause of arthritis. It's essential to identify the mechanisms that keep inflammation in check. Our lab recently reported a novel role of TRAF1, a signaling adapter protein, in controlling inflammation. We showed that people with a genetic variation in their TRAF1 make less TRAF1 protein, which loosens the "brakes" on inflammatory cells (e.g. monocytes) and increases Rheumatoid Arthritis (RA) risks. However, therapies targeting TRAF1 in RA are complicated because TRAF1 plays additional, often opposing, roles in lymphocytes. Here we aimed to dissect the disparate roles that TRAF1 plays in regulating NF- κ B signaling and its importance in chronic inflammatory diseases.

Hypothesis: Genetically changing TRAF1's expression and its ability to interact with its complementary protein(s) will affect the overall inflammation level in models of inflammatory diseases on a cell type specific basis.

Methods: Using CRISPR-Cas9 technology we designed TRAF1-specific guides to knock-out (KO) TRAF1 expression in THP-1 cells (i.e., monocytes) and Jurkat cells (i.e., T lymphocytes) by electroporation. Upon confirmation of TRAF1's absence by western blot, these cells were stimulated with LPS (100ng/ml) to determine the level of inflammation compared to non-transfected LPS-stimulated cells. These in vitro experiments will be expanded to studies involving rodents lacking TRAF1 expression.

Results: We expect to see increased levels of proinflammatory cytokines (e.g., as detected by IL-1 β and IL-6 expression levels by ELISA) in TRAF1-KO THP-1 cells compared to non-TRAF1-KO cells. Levels of proinflammatory cytokine expression will also be investigated in vivo using LPS infected TRAF1 KO mice.

Conclusion: TRAF1 is an integral component of the inflammatory pathway and it plays an essential role in the pathogenesis of many diseases including rheumatoid arthritis (RA). Its dual role as both an inhibitor and an activator of the inflammatory pathway, depending on the cell type, is critical and determining the exact mechanisms of how TRAF1 achieves this dual function is crucial to developing future therapies aimed at treating diseases such as RA.

KEYWORDS

Inflammation, Arthritis, TRAF1, knock-out, Monocytes vs. T lymphocytes

Dr. S. Amanda Ali

BIO

Dr. Shabana Amanda Ali completed her PhD (2014) in the Institute of Medical Science at the University of Toronto with Dr. Benjamin Alman, studying the role of Hedgehog signaling and cholesterol homeostasis in osteoarthritis pathophysiology. She completed her first Postdoctoral Fellowship (2016) at the University of Western Ontario with Drs. Joy MacDermid and Marita Kloseck, exploring community-based management strategies for osteoarthritis. She completed her second Postdoctoral Fellowship (2019) in the Krembil Research Institute at the University Health Network with Drs. Mohit Kapoor and Rajiv Gandhi, identifying microRNA biomarkers for early detection of osteoarthritis. She is currently an Assistant Scientist in the Bone and Joint Center at the Henry Ford Health System, with a research program focused on understanding the early genomic changes occurring at both local and systemic levels in osteoarthritis.



ABSTRACT: Circulating microRNA signatures identified in early versus late knee osteoarthritis

AUTHORS: Shabana Amanda Ali, Rajiv Gandhi, Pratibha Potla, Sareh Keshavarzi, Osvaldo Espin-Garcia, Konstantin Shestopaloff, Chiara Pastrello, Dylan Bethune-Waddell, Starlee Lively, Anthony Perruccio, Y. Raja Rampersaud, Jason S. Rockel, Igor Jurisica, Tom Appleton, Mohit Kapoor. Affiliations: Arthritis Program, Krembil Research Institute, University Health Network, Toronto, ON, Canada; 2Western University and St. Joseph's Health Care, London, ON, Canada; 3Department of Surgery and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

The authors declare no conflicts of interest. This abstract may be shared with conference attendees and online.

Background: MicroRNAs contribute to osteoarthritis (OA) pathophysiology in multiple ways, acting both locally and systemically. MicroRNAs are good candidates for biomarkers of diseases, and may be useful for categorizing OA patients. Next generation sequencing (NGS) is an advantageous approach for biomarker discovery because it offers the sensitivity and specificity to detect novel microRNAs and low abundance microRNAs that are unique to disease stages. This study uses NGS to profile signatures of circulating microRNAs in patients with early and late radiographic knee OA.

Methods: Cohorts were carefully defined where early OA included patients with Kellgren-Lawrence grade 0 or 1 (N=41), and late OA included patients with Kellgren-Lawrence grade 3 or 4 (N=50). Demographic (e.g. age, sex, race), anthropometric (e.g. body mass index), and clinical variables (e.g. pain) were collected for all patients for use in statistical analyses. RNA containing microRNAs was isolated from plasma samples (N=91) and subjected to microRNA library preparation and NGS on the Illumina NextSeq550 platform. Data were normalized by total counts and interpreted using bioinformatics and computational biology approaches.

Results: To visualize patterns in the microRNA sequencing results in an unbiased manner, principal component analysis was used. This showed a clear separation of late OA samples from early OA samples, with 58.2% of the variability explained by component 1. Among early OA patients, a greater percentage reported high pain as compared to patients with late OA ($P=0.03$), suggesting that our early OA cohort captured a clinically relevant population. Differential expression analysis identified 215 microRNAs, 97 of which were expressed at a higher level across 85% or more of the early OA samples as compared to the late OA samples. We also identified 4 novel microRNAs that were present in 50% or more of the early OA samples. Gene target analyses predicted 27 genes to be common targets of these early OA microRNAs, shedding light on the potential functions of the novel microRNAs.

Conclusion: Leveraging the sensitivity and specificity of NGS technology, we used carefully defined cohorts of radiographic knee OA patients to identify a panel of 101 microRNAs in early OA, which includes 4 novel microRNAs. To determine the utility of these microRNAs as biomarkers of disease, next steps include validation in a larger cohort and in a longitudinal cohort.

KEYWORDS

Inflammation, Arthritis, TRAF1, knock-out, Monocytes vs. T lymphocytes

Dr. Fawzi Aoudjit

BIO

Dr Aoudjit is a professor in the department of Microbiology-Immunology; Faculty of Medicine at Laval University (Québec, Canada). Dr Aoudjit received his PhD from Laval University in Molecular Endocrinology and Physiology in 1996. After two postdoctoral fellowships in Immunology/cell Biology, at the Institute Armand-Frappier (Montréal, Canada) and at the Burnham Institute (La Jolla California), he was appointed as an assistant professor in 2001 in Laval University and as a full professor in 2010. His main research interests are in the field of basic immunology, immune cell signalling, apoptosis, and in autoimmune rheumatic diseases. Specifically, Dr Aoudjit's work focuses on how cell adhesion to the extracellular matrix shapes T cell responses and influence the development of autoimmune rheumatic diseases.



ABSTRACT: $\alpha 2\beta 1$ integrin promotes methotrexate resistance of human effector T cells: Implications for rheumatoid arthritis.

AUTHORS: Amna Abderrazak, Chakib Hamoudi, Paul R. Fortin and Fawzi Aoudjit

Background: Methotrexate (MTX) is the first line in RA therapy, which acts in part by inducing apoptosis in effector T cells. However, up to 30-40% of patients treated with MTX either fail to respond or end up developing resistance. The collagen-binding integrin $\alpha 2\beta 1$ is a major costimulatory pathway of effector T cells and has been implicated in the pathogenesis of rheumatoid arthritis (RA). We designed this study to evaluate whether $\alpha 2\beta 1$ integrin can play a role in the resistance of effector T cells to MTX therapy in RA.

Methods: Human effector T cells containing Th1 and Th17 and CD4+ effector/memory T cells were respectively isolated from peripheral blood of healthy donors and RA patients. Cells were cultured on BSA or on collagen in the absence or presence of anti-CD3 and then treated with MTX. Cells apoptosis was studied after 24 h using annexin V staining and FACS analysis and by evaluating caspase-3 activation by western blot. The production of IL-17 and IFN γ was evaluated by ELISA. The expression and function of ABC drug transporters ABCC1 and ABCG2 in MTX resistance were determined by qRT-PCR and FACS analysis and by the use of specific inhibitors.

Results: Our results show that attachment of anti-CD3-activated human polarized Th17 cells to collagen but not to other major matrix proteins (fibronectin or laminin) led to a significant reduction of MTX-induced apoptosis. However, stimulation with anti-CD3 mAb alone had no effect. The anti-CD3+collagen-rescued cells still produce significant amounts of IL-17 and IFN γ upon their reactivation indicating that their inflammatory nature is preserved. Mechanistically, we found that the prosurvival role of anti-CD3+collagen involves activation of the MTX transporter ABCC1. Finally, the protective effect of collagen/ $\alpha 2\beta 1$ integrin on MTX-induced apoptosis also occurs in memory CD4+T cells isolated from RA patients suggesting its clinical relevance.

Conclusion: Our results show that $\alpha 2\beta 1$ integrin promotes MTX resistance of effector T cells, and suggest that it could contribute to the development of MTX resistance that is seen in RA. Thus, $\alpha 2\beta 1$ integrin may represent a promising new target to improve MTX resistance and failure in RA patients.

KEYWORDS

Methotrexate resistance, Rheumatoid arthritis, Apoptosis, $\alpha 2\beta 1$ integrin, Th17 cells, ABC drug transporter

Yann Becker

BIO

After a bachelor and a first masters' degree at the University of Strasbourg, Yann Becker worked for a year as a laboratory technician at the INSERM unit 770 (Hôpital du Kremlin-Bicêtre, France). Yann joined Dr Éric Boilard's laboratory (CHU de Québec) in January 2015 for a training in immunology. He is currently attending a PhD program in Molecular Medicine under the mentorship of Dr. Paul R. Fortin (Rheumatologist, CHU de Québec). Through his research project on the detection of anti-mitochondrial antibodies in systemic lupus erythematosus (SLE) and their association with disease manifestations, Yann aims to identify novel biomarkers that would allow to improve diagnosis or prognosis of the disease and/or to achieve a better stratification of the patients. In his future research career, Yann would like to keep working on the study of auto-immune diseases in order to improve medical care and to alleviate SLE outcomes on patients' quality of life.



ABSTRACT: Anti-mitochondrial autoantibodies (AMA) in systemic lupus erythematosus and antiphospholipid syndrome; advocating for the detection of AMA in a large prospective cohort

AUTHORS: Yann LC Becker, Geneviève Marcoux, Audrée Laroche, Jenifer Espinoza, Anne-Sophie Julien, Alexandra Godbout, Emmanuelle Rollet-Labelle, Tania Lévesque, Paul R. Fortin, and Éric Boilard

Corresponding author: Eric Boilard, PhD, Centre de Recherche du CHU de Québec – Université Laval,

Background: Mitochondria are intracellular organelles of bacterial origin capable of stimulating the immune system when released into the extracellular milieu by activated or damaged cells. Additionally, a humoral response to mitochondria have been reported in several conditions, including autoimmune diseases such as primary biliary cirrhosis, the antiphospholipid syndrome and SLE. We herein present the expression of anti-mitochondrial antibodies (AMA) targeting whole organelles (AwMA), mitochondrial DNA (AmtDNA) or mitochondrial RNA (AmtRNA) in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), an autoimmune condition that may be independent of, or associated with SLE.

Methods: AMA (IgG and/or IgM) were detected in patients included in two distinct cohorts, from the University of Toronto Lupus Clinic (Healthy: n=43; SLE: n=175) and the Centre de Recherche du CHU de Québec – Université Laval (Healthy n=30; SLE: n=88; APS: n=27). Mitochondria were isolated from C57BL/6J mouse livers by differential centrifugation and mitochondrial nucleic acids further isolated by alkaline lysis (mtDNA) or with the Aurum™ Total RNA Mini Kit (mtRNA). These sources of mitochondrial antigens were used to detect AMA by direct ELISA. Titers for each AMA were associated with demographic and disease characteristics.

Results: Titers in AwMA-IgG, AmtDNA-IgG, AmtRNA-IgG and -IgM were significantly elevated in SLE patients from the compared to healthy individuals (respectively: AwMAIgG: p<0.0001; AmtDNAIgG: p=0.0004; AmtRNAIgG: p=0.0002; AmtRNAIgM: p=0.0493), while only AmtDNA-IgM and AmtRNA were increased in APS patients (respectively: p=0.08; p=0.0003; p=0.003). In SLE, AmtDNA-IgG were associated to increased histories of lupus nephritis [OR(95%CI): 4.60(1.41–14.99); p=0.01] while AmtRNAIgG were associated to decreased histories of carotid plaque formation [0.14 (0.02–0.91); p=0.04] and lupus nephritis [0.02(0.00–0.68); p=0.03]. In APS, AwMAIgM, AmtDNAIgG and -IgM, and AmtRNAIgM and appeared as protective against past thrombovascular events [respectively: 0.19(0.04;0.96), p=0.045; 0.22(0.05;0.94), p=0.04; 0.22(0.05;0.91), p=0.04; and 0.22(0.05;0.99), p=0.048], while AmtDNAIgM was also associated with reduced reporting of arterial events [0.22(0.05;0.98), p=0.046].

Conclusion: Our findings suggest that autoantibodies to various mitochondrial antigens are represented within the autoantibody repertoire in both SLE and APS. AMA displayed different clinical associations in each disease, however, these results were obtained on samples from two cross-sectional cohorts and thusly only reflect AMA levels at the time of the blood draw (i.e. distinct from the clinical events). Confirmation of these results will be obtained by the detection of AMA at various time-points (i.e.: baseline, 1, 2 and 5 years) in samples from 131 healthy donors and 1024 SLE patients included in the systemic lupus erythematosus international collaborating clinics (SLICC).

KEYWORDS

Systemic lupus erythematosus (SLE), Mitochondria, Mitochondrial DNA (mtDNA), Mitochondrial RNA (mtRNA), Autoantibodies, Autoantigens, Nephritis, Biomarkers

Yvonne Brandelli

BIO

Yvonne completed her BA in Psychology at the University of Calgary. Through a summer studentship and subsequently her honours thesis, she explored what topics in group therapy led to improvements in self-efficacy and coping for women with early-stage breast cancer. Yvonne continued to hone her interests by working on various studies in Pediatrics, Oncology, and Rheumatology. Throughout each experience, she became increasingly interested in the psychosocial factors associated with pediatric health conditions. Juvenile arthritis was of particular interest, given how strongly her previous experiences with this population resonated with her. After deciding to pursue a career in Clinical Psychology, Yvonne moved to Halifax to attend Dalhousie University and work under the supervision of Dr. Christine Chambers, a Registered Psychologist studying pediatric pain. Through her training, Yvonne hopes to better understand the experience of pain in children with arthritis and to increase the dissemination of evidence-based pain-management strategies with this population.



ABSTRACT: Exploring the Relationship Between Parent Pain Perceptions and Treatment Adherence in Children with Arthritis

AUTHORS: Yvonne N. Brandelli, BA (Hons), Christine T. Chambers, PhD, Perri R. Tutelman, BHSc (Hons), Jennifer Stinson, PhD, RN-EC, CPNC, Lawrence S. Bloomberg, Adam M. Huber, MD, MSc, FRCPC, Jennifer Wilson, BA

Introduction: Juvenile Idiopathic Arthritis (JIA) affects over 1.7 million children and families worldwide, many of whom report pain as the predominant symptom. Despite the demonstrated efficacy of pharmacological and non-pharmacological interventions in managing JIA, adhering to prescribed treatment regimens is often a challenge. Previous research has demonstrated how parent pain perceptions are implicated in avoidance behaviours (e.g., restricting children's pain-inducing activities), however little research has explored their relationship to treatment adherence.

Objectives/Aims: This study examined how parent pain perceptions (i.e., pain catastrophizing and fears of pain) are associated with treatment adherence, and whether treatment barriers (e.g., difficulty taking medications) mediate this relationship.

Methods: Recruitment took place worldwide by engaging partner organizations and sharing across online and social media platforms. 216 caregivers of children with JIA aged 0-17 participated. Participants were predominantly mothers (96%) residing in North America (77%). They completed questions about their child's arthritis, a self-report Parent Adherence Report Questionnaire (PARQ), the Parent Barriers Questionnaire – JIA (PBQ-JIA), the Pain Catastrophizing Scale (PCS-P), and the Parent Fear of Pain Questionnaire (PFOPQ).

Results: All children were reportedly on some form of treatment, and 68% had experienced arthritis-related pain in the past month. Regression analyses demonstrated that lower perceived treatment adherence was associated with higher pain catastrophizing [$t=-3.21$, [Symbol]=-0.10 (-0.16, -0.04)] and greater fears of pain [$t=-3.52$, [Symbol]=-0.08 (-0.13, -0.04)]. Further analyses revealed a full indirect mediation for parent fears of pain via self-reported barriers to treatment.

Conclusions: The current study demonstrates that parent pain perceptions relate to treatment adherence in children with JIA, although this may be better understood in considering treatment barriers. Parents who fear pain may be prone to identify more barriers, thus engaging in greater nonadherence. Results suggest both parent pain perceptions and treatment barriers are important considerations in ameliorating treatment adherence in children with JIA.

KEYWORDS

Juvenile Idiopathic Arthritis, Pain, Pain-Management, Treatment Adherence, Treatment Barriers, Medication, Parent

Dr. Dieter Brömme

BIO

Dr. Brömme received his PhD from Martin Luther University Halle-Wittenberg/GDR in 1983 and developed a life-long interest in protease research. Before joining the University of British Columbia as a Professor and Canada Research Chair in 2004, he had academic and industrial careers at the NRC Biotechnology Research Institute in Montreal, Khepri Pharmaceuticals in South San Francisco, and the Mount Sinai School of Medicine in New York. He has supervised over 80 trainees and published nearly 200 papers including book chapters and several patents with an overall H-index of 60. His main research interest is in the identification of cathepsins as drug targets in various pathologies including arthritis and osteoporosis, and the development of substrate-specific inhibitors less prone for side effects.



ABSTRACT: Ectosteric inhibitor of cathepsin K attenuates rheumatoid arthritis in mice

AUTHORS: Preety Panwar and Dieter Brömme

Rheumatoid arthritis (RA) is an autoimmune disease caused by the aberrant immune responses against self-tissues for protection against infection. Cathepsin K (CatK) is a validated drug target for musculoskeletal diseases. Active site-directed inhibitors of CatK have demonstrated efficacy in osteoporosis and osteoarthritis human clinical trials but were never approved due to significant safety concerns. Side effects were likely caused by on-target effects due to the inhibition of the entire activity of this multifunctional protease. To avoid side effects, we developed the ectosteric inhibitor concept that specifically allows blocking the disease relevant collagenase activity of CatK. Using the collagen-induced arthritis (CIA) mouse model, we demonstrated that the orally applied ectosteric CatK inhibitor tanshinone IIA sulfonate (T06) effectively reduced joint inflammation and erosion. T06 markedly inhibited cartilage degradation and also had significant effects on bone destruction and pannus formation. Serum biochemical assays confirmed that T06 reduced collagen I and II degradation markers and prevented the expression of various inflammatory markers such as TNF, IL-6, and IL-1. No systemic toxicological effects were observed. In contrast, odanacatib, a highly potent active site-directed CatK inhibitor, had a weaker effect on inflammation and joint preservation. Moreover, odanacatib had no significant effect on the inflammatory cytokines and careful histological tissue examination revealed fibrotic alterations in several organs, which also reflected some of the safety issue in the clinical trials. The T06 treatment did not show any of these adverse effects. These data support that T06 inhibits immune-receptor signalling, has direct antiresorptive activity, and suggest that T06 might represent a promising therapeutic drug for patients with rheumatoid arthritis and warrants further investigation.

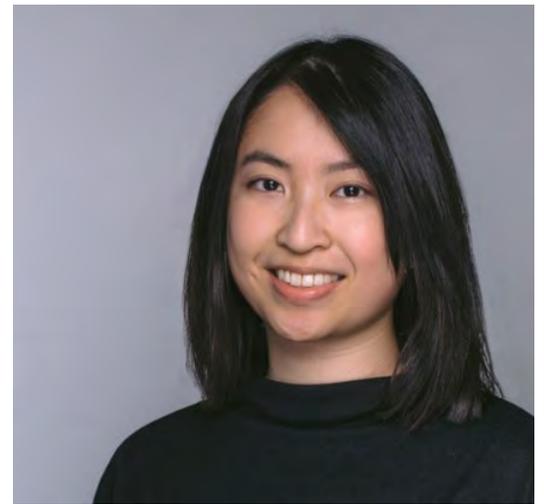
KEYWORDS

proteases, cathepsins, protease inhibitors, natural products, collagen, elastin, extracellular matrix, arthritis, osteoporosis

Mable Wing Yan Chan

BIO

Mable is currently a fourth year PhD student in Biomedical Engineering at the University of Toronto. She received her HBSc in 2016 at the University of Toronto, majoring in Pharmacology. Her research interests are in cell therapy and regenerative medicine, particularly for inflammatory diseases such as arthritis.



ABSTRACT: An optimized human osteoarthritis joint explant model reveals monocyte/macrophage-related changes in inflammation and cartilage degradation

AUTHORS: Mable Wing Yan Chan, Rajiv Gandhi, Nizar Mahomed, K Wayne Marshall, Sowmya Viswanathan

Purpose: Osteoarthritis (OA) can present as many phenotypes; there are many extrinsic and intrinsic factors that affect OA pathophysiology and presentation. Its development has been associated with all the tissues of the joint as well as infiltrating immune cells. In order to capture these key aspects for therapeutic discovery, we have developed a new human OA joint explant model. This model uses human osteoarthritic cartilage and synovium to accurately represent the endogenous OA human extracellular matrix and immune conditions. Our aim is to demonstrate that our human OA joint explant model maintains the viability and morphology of in vivo tissue while responding to inflammation-modulating treatments.

Methods: Cartilage and synovium are obtained from late-stage OA knee replacement. Full-depth punch-cut cartilage and minced synovial tissue are randomly distributed by wet weight into 24-wells or transwells inserts for 48 hours before co-culture. Pro-inflammatory cytokines (OSM+IL-1) are used as positive control. Treatment groups of 48-hour cytokine-polarized CD14+ peripheral blood monocytes/macrophages (IFN- +LPS, pro-inflammatory; IL-10+TGF-1, inflammation-suppressing) are co-cultured with the joint explants for 2 days. Explant conditions are evaluated by cartilage, synovium, and conditioned medium harvest: tissue gene expression (RT-qPCR), secreted cytokine/protease (immunoassay), and proteoglycan (GAG) content (dimethylmethylene blue) and loss (Safranin-O histology). Conditions are compared by principal component analysis for gene panels and analysis of variance for single dependent variable assays.

Results: 48-hour cartilage gene expression demonstrates distinct clusters between the pro-inflammatory cytokine control and cartilage alone control conditions within a 26-gene panel (selected based on OA literature) capturing catabolic, anabolic, and inflammatory/chemotactic genes (N=14). Addition of pro-inflammatory monocytes/macrophages elicited a similar effect, whereas inflammation-suppressing co-culture promoted upregulation of anabolic genes such as TIMP-1 (N=6). TIMP-1 protein levels matched gene observations (N=3). GAG loss into the medium was significantly increased with the pro-inflammatory positive control at 2 days (N=14). The mean GAG loss is higher in the synovium-cartilage co-culture but is not statistically significant; addition of monocytes/macrophages did not affect this result.

Discussion/Conclusion: Our human OA joint explant model demonstrates relevant changes in inflammation and matrix degradation in response to pro-inflammatory insult. It was then also shown to exhibit differential effects between addition of pro-inflammatory versus inflammation-suppressing monocytes/macrophages. We are currently limited by tissue donor variability. Our current results support that our model is a viable platform to test OA therapies with multifactorial mechanisms of action ranging from small molecule modulators to cell-based therapies.

KEYWORDS

osteoarthritis, monocytes, macrophages, explant, cartilage, synovium, inflammation

Dr. Hosni Cherif

BIO

Hosni Cherif received his bachelor's degree of science in Biochemistry from Université du Québec à Montréal in 2009. Afterwards, he started his graduate work at the Université de Montréal in the laboratory of Pr. Jean-François Bouchard. Hosni was awarded his doctorate degree in Vision Science/Cell and Molecular Biology in 2016. His thesis project demonstrated, for the first time, the involvement of G-protein coupled receptors (GPCRs) in the growth and guidance of axons of ganglion cells retina during the establishment of the visual circuitry. Since 2017 and as a postdoctoral fellow, he works to identify novel therapeutic targets for the treatment of spine disorders and new biomarkers that could enhance classic treatments. Hosni received a Vision Network recruitment grant, a joint PhD scholarship from the Faculty of Graduate Studies and the School of Optometry (FESP-EOUM), five scholarships from the Vision Sciences program. During his postdoctoral training, he received the Cole Foundation, Mitacs-Accelerate, McGill University Health Center, McLaughlin, Oral and Bone Health Research Network and Arthritis society Fellowships. He presented his project in several national and international scientific conferences and the excellence of his work was underlined by the subsequent receipt of several awards for the best poster presentation and for the best publication.



ABSTRACT: Ex-vivo evaluation of potential therapeutics to reduce painful intervertebral disc degeneration.

AUTHORS: Hosni Cherif, Daniel Bisson, KaiSheng, Lisbet.A.Haglund

Background: The accumulation of senescent cells in the tissue of intervertebral disc (IVDs) suggests a crucial role in the initiation and development of painful IVD degeneration. The aim of this research is to determine the effects of eliminating senescent cells as a potential treatment to remove senescent cells, reduce inflammation and promote overall matrix production by the remaining cells in human IVDs.

Methods: Monolayer, cell pellets or intact IVDs were cultured in the presence or absence of RG-7112 and o-Vanillin. Viability and cytotoxicity were studied using Alamar blue assay. Following treatment, gene expression of 90 senescence and inflammatory markers was evaluated by real-time q-PCR and the Ingenuity pathway analysis software. Protein expression of p16, Ki-67 and Caspase-3 was evaluated by immunohistochemistry. Proteoglycan content in intact IVDs was evaluated by MRI (7T Bruker BioSpec 70/30), Safranin O staining and DMMB assay. Pellet and disc media were analyzed using the RayBio Human Cytokine Antibody Array C5 and concentrations were measured by Luminex® immunoassay. Paired t tests and the Kruskal-Wallis test were used to identify statistical differences.

Results: By immunofluorescence, we observed co-labelling of senescent cells (p16^{INK4} positive) with apoptotic cells (Caspase-3 positive) while proliferative cells (Ki-67 positive) did not overlap with caspase 3 or p16^{INK4}. No cytotoxicity was observed, instead disc cells showed a significant increase in metabolic activity following treatment. RG-7112 and o-Vanillin both downregulated mRNA expression of senescence and inflammatory genes and increased the expression of apoptotic and proliferative genes. Following treatment, protein levels of SASP factors were decreased with RG-7112 and o-Vanillin treatment compared to untreated groups. Senolytic treatment of intact human IVDs improved proteoglycan deposition. In addition, immunohistochemical assessment of p16^{INK4} showed significantly less senescent cells and a slight non-significant increase of proliferation in both RG-7112 and o-vanillin treated IVDs. Both cytokine arrays and Luminex® assays confirmed the decrease of inflammatory factors release from treated IVDs. Discussion: This work demonstrates the potential of two senolytic compounds to remove senescent IVD cells, reduce the inflammatory environment and enhance the IVD matrix production. Both compounds showed similar senolytic activity with a slightly higher regenerative effect for o-vanillin.

Conclusion: Elucidation of the complex relationship between disc degeneration, tissue inflammation and disc cell senescence appears to be critical to improve current ineffective therapies. Removal of senescent cells could lead to improved therapeutic interventions and ultimately decrease pain and provide a better quality of life of patients living with axial arthritis.

KEYWORDS

axial arthritis, intervertebral disc, degeneration, inflammation, pain, senescence, senotherapeutics

Kelsey Chomistek

BIO

Kelsey is pursuing a Master of Science in Medical Science at the University of Calgary under the supervision of Dr. Heinrike Schmeling and Dr. Cheryl Barnabe. Kelsey received a Bachelor of Arts in Communications and Culture with a minor in Health and Society at the University of Calgary. Kelsey has been involved in rheumatology research since 2013. Her research interests include chronic disease self-management and rheumatic diseases such as juvenile idiopathic arthritis. For her Master's thesis, she developed and evaluated the acceptability of an adolescent self-management program for juvenile idiopathic arthritis.



ABSTRACT: Development and Acceptability of an Adolescent Self-management Program for Juvenile Idiopathic Arthritis

AUTHORS: Kelsey Chomistek, BA, Cheryl Barnabe, MD, MSc, Katie Birnie, PhD., Julia Brooks, PT, BMRPT, Tracey Clancy, RN, MN, CCNE, Syeda Farwa Naqvi, BCr, Researcher, Nadia Luca, MD, Maggie Mercer, RN, Maria Santana, PhD, Jennifer Stinson, RN-EC, PhD, CPNP, Aynsley Wennberg, BMR (OT), Heinrike Schmeling, MD, PhD

Background: Needs assessments have revealed an urgent need for disease information, self-management skills, and peer support for patients with juvenile idiopathic arthritis (JIA). Our aim was to develop and test the acceptability of an in-person and teleconference self-management program (SMP) to address these needs.

Methods:

Development phase: The SMP was developed through Lorig's self-management theory, needs assessments of patients with JIA, and the existing evidence-base for effective SMPs. Additional input was obtained from adolescents with JIA and pediatric rheumatology team members. **Acceptability phase:** A qualitative study with semi-structured focus groups was conducted to determine the acceptability of the SMP. Purposive sampling was used to recruit patients meeting the following inclusion criteria: a) ages 12-17, b) confirmed diagnosis of JIA according to the International League of Associations for Rheumatology classification criteria, c) receiving rheumatology care at the Alberta Children's Hospital, and d) sufficient English skills. Two groups of 4 adolescents with JIA (n = 8, mean age = 13.5, SD = 0.8) participated in 4 focus groups. Content analysis was used to analyze the data.

Results:

Development phase: The SMP structure consists of four, 1.5-hour group sessions designed to be delivered in-person or by teleconference by pediatric rheumatology health professionals. The sessions are titled: 1) Overview and diagnosis of JIA; 2) Daily living and exercise; 3) Coping strategies; and 4) Treatment and lifestyle management. Each session includes a power point presentation, interactive activities, and discussions.

Acceptability phase: Participants supported a group-based SMP delivered in-person and/or via teleconference, reflecting it would provide the opportunity for peer support in a small-group setting. Participants advised that a rheumatology healthcare provider should facilitate the session to increase the trustworthiness of the information provided and answer questions. Participants felt the content was appropriate and would be effective in supporting self-management of their JIA. Potential barriers to participation included distance and availability, but the option for teleconference-based participation was an appropriate solution. Adolescents provided suggestions for improvement (e.g. improved efficiency by reducing content to three sessions, providing additional time for discussions). Minor changes have been made to reflect these recommendations.

Conclusion: This is the first evidence-based in-person/teleconference JIA SMP in Canada. The SMP was well received by the adolescents and the inclusion of a teleconference option was an innovative solution to improve accessibility. This study proved the acceptability of the SMP prior to conducting a randomized controlled effectiveness trial, with the ultimate aim of widespread program implementation.

KEYWORDS

juvenile idiopathic arthritis, self-management

Keith Colaco

BIO

Keith holds a BSc in Biomedical Sciences from the University of Waterloo and a MSc in Global Health from McMaster University. He is currently a PhD student at the University of Toronto, conducting clinical research at Women's College Hospital and Toronto Western Hospital. Keith's primary research focus is on individuals with psoriasis, an inflammatory skin disease, and psoriatic arthritis, an inflammatory joint disease. He is developing a tool to predict risk of developing cardiovascular events, such as heart attack and stroke, in these populations.



ABSTRACT: Trends in Mortality and Cause-specific Mortality among patients with Psoriatic Disease in Ontario

AUTHORS: Keith Colaco, Jessica Widdifield, Jin Luo, Cheryl F. Rosen, Raed Alhusayen, J. Michael Paterson, Willemina Campbell, Karen Tu, Sasha Bernatsky, Dafna D. Gladman, Lihi Eder

Objective: To compare overall and cause-specific mortality rates among Ontarians with psoriasis, psoriatic arthritis (PsA) and general population comparators without psoriatic disease.

Methods: We performed a population-based study using health administrative data among adult Ontario residents between 1996 and 2016. Patients diagnosed with psoriasis (from 1996 onward) and PsA (from 2008 onward) were identified using validated case definitions and compared with individuals without psoriatic disease. All-cause and cause-specific age- and sex-standardized mortality rates, standardized mortality ratios (SMRs) and excess mortality rates were computed for the years 1996 to 2016.

Results: In 2016 we identified 176,858 Ontarians diagnosed with psoriasis and 15,430 diagnosed with PsA. A total of 2,524 psoriasis patients and 221 PsA patients died in 2016. All-cause mortality rates were greater among patients with psoriasis and PsA compared with the general population. The standardized mortality rate (per 1000 (95% Confidence Interval [CI]) in 2016 was 8.26 (7.92, 8.62) among those with psoriasis and 9.25 (7.97, 10.69) among those with PsA compared to 6.82 (6.78, 6.86) in the general population. Patients with psoriasis and PsA had excess mortality rates of 1.44 (95% CI 1.14, 1.76) and 2.43 (95% CI 1.19, 3.83), respectively. All-cause SMRs in 2016 were elevated for psoriasis: 1.18 (95% CI 1.13, 1.23); and PsA: 1.34 (95% CI 1.16, 1.52). Standardized mortality rates decreased by approximately 30% over the study period in both disease groups, but remained elevated compared to the general population.

The leading causes of death (%) and relative excess mortality (computed as SMRs) in psoriasis patients were cancer (28%) (SMR 1.11, 95% CI 1.03-1.20), diseases of the circulatory system (28%) (SMR 1.12, 95% CI 1.04-1.21), respiratory conditions (13%) (SMR 1.32, 95% CI 1.17-1.48), and mental/behavioural disorders (13%) (SMR 1.18, 95% CI 1.01-1.34). In those with PsA, circulatory disease (25%) (SMR 1.35, 95% CI 1.00-1.70) was the leading cause of death, followed by cancer (20%) (SMR 0.96, 95% CI 0.69-1.23), respiratory conditions (12%) (SMR 1.69, 95% CI 1.06-2.32), and mental/behavioural disorders (6%) (SMR 1.09, 95% CI 0.50-1.68).

Conclusions: Mortality rates in psoriasis, PsA and the general population have decreased over time, but remain significantly elevated in psoriasis and PsA compared to the general population. Leading causes of death among people with psoriasis and PsA were circulatory diseases, cancer, respiratory conditions and mental/behavioural disorders.

KEYWORDS

psoriatic arthritis; psoriasis; mortality; epidemiology; administrative data

Dr. Maria Fernandes

BIO

I am an associate professor in the department of Microbiology-Infectiology and Immunology (Faculty of Medicine) at Université Laval in Québec City. After my PhD at McGill University in molecular genetics, I pursued two post-doctorates (Thomas Jefferson University and Université Laval) during which I cloned genes that code for myeloid C-type lectin receptors, studied neutrophil biology and developed an interest in arthritis. The research in my laboratory brings all of these fields of research together into one main theme: to decipher the role of C-type lectin inhibitory receptors in the immunopathogenesis of arthritis. A key discovery made by laboratory is the involvement of the inhibitory receptor CLEC12A in the pathogenesis of gout and rheumatoid arthritis. We are currently using a multidisciplinary approach to gain insight into how CLEC12A functions with the ultimate goal of eventually transferring our findings to the clinic.



ABSTRACT: Characterization of the CLEC12A Inhibitory Pathway in Human Neutrophils: Implications for Gout

AUTHORS: Julien Vitry, Guillaume Paré, Myriam Vaillancourt, Xavier Charest-Morin, François Marceau, Kenneth R. McLeish, Michael L. Merchant, Sabine Elowe, Mireille H. Lahoud, Paul H. Naccache, Maria J. Fernandes

Background: CLEC12A is a C-type lectin receptor that negatively regulates myeloid cell function. In response to monosodium urate crystals (MSU), the causative agent of gout, human neutrophils diminish their expression of CLEC12A resulting in an enhancement of their activation. Similarly, an exacerbated inflammatory reaction is observed in CLEC12A knock-out mice injected with MSU. Moreover, CLEC12A knock-out mice with collagen antibody-induced arthritis also exhibit a more severe phenotype suggestive that CLEC12A is a global negative regulator of inflammation. The molecular mechanisms underlying CLEC12A function remain, however, incompletely characterized. Our previous work shows that CLEC12A modulates the release of IL-8 by MSU-activated neutrophils but not IL-1 production. The objective of this study was to identify the signaling pathways targeted by CLEC12A to negatively regulate neutrophil activation.

Methods: The CLEC12A signalling pathway was investigated in human neutrophils stimulated with MSU after inducing a decrease in its cell-surface expression with a specific antibody. Cells were then analysed by Western blot, immunoprecipitation and flow cytometry. Phosphoproteomic analysis was also performed. The role of the cytoskeleton role in CLEC12A signalling was studied with similar techniques and microscopy after incubation of cells with compounds that disturb the integrity of various cytoskeletal components. Structure-function studies were performed in 293T cells transfected with CLEC12A variants containing mutations in residues predicted necessary for receptor oligomerization, glycosylation and/or phosphorylation.

Results: In human neutrophils, the engagement of cell-surface CLEC12A receptor with a specific antibody induced its translocation to detergent resistant membranes (DRMs), its Src-dependent phosphorylation and its internalization. CLEC12A antibody-induced internalization relied partly on intermediate filaments. Moreover, we provided evidence for the regulation of the PI3K and p38 pathways by CLEC12A in human neutrophils. Structure-function studies identified a cysteine residue and glycosylation site that are crucial for the function of this receptor.

Discussion: We identified intracellular targets of CLEC12A in MSU-stimulated neutrophils, namely, the PI3K and p38 pathways. These findings are highly relevant to gout since these pathways play a key role in neutrophil migration, survival, the production of cytokines and reactive oxygen species. Furthermore, the PI3K-Akt pathway has not previously been associated with CLEC12A in human neutrophils. Our structure-function studies reveal that CLEC12A shares similarities with other inhibitory receptors including the phosphorylation of its signalling motif and its translocation to DRMs. These results provide insight into the molecular mechanisms underlying the role of CLEC12A in gout and identify potential pathways that could be targeted to dampen activation of neutrophils by MSU.

KEYWORDS

inhibitory receptors, C-type lectins, gout, inflammation, neutrophils, signalling

Dale Fournier

BIO

As a graduate trainee, my research and teaching interests have been linked closely with human anatomy, particularly as it relates to the spine. An unique arthritis of the spine, diffuse idiopathic skeletal hyperostosis (DISH), is poorly understood and there are no disease-modifying or symptom-reducing treatments. My M.Sc. research allowed me to investigate and characterise DISH using advanced microcomputed tomography imaging and histological techniques. My current combined M.PT./Ph.D. program allows me to translate our basic research findings into the clinical setting and to address important gaps in our understanding of DISH to improve early diagnosis, identify therapeutic targets, and better understand patient needs.



ABSTRACT: Diffuse Idiopathic Skeletal Hyperostosis (DISH): Quantitative MicroCT and Histological Analyses in Humans

AUTHORS: Dale E. Fournier, Ryan J. Beach, Patti K. Kiser, S. Jeffrey Dixon, and Cheryle A. Séguin

Background: Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory spondyloarthropathy characterised by ectopic mineral formation along the anterolateral aspect of the spine. The prevalence of DISH is estimated to be 15-25% of North Americans over 50 years and is listed by The Arthritis Society as the second most common form of arthritis. Classically, the clinical diagnosis of DISH is based on radiographic features of flowing mineral along at least four contiguous motion segments (four intervertebral discs [IVDs] and adjacent vertebra) and preserved IVD space. Importantly, these criteria limit the diagnosis of DISH to advanced cases and the etiology of DISH is unknown; underscoring the need to characterise the tissue types and cellular changes associated with ectopic mineralisation.

Methods: Intact spines (cervical-thoracic) were dissected from 19 embalmed cadavers (6 females and 13 males; range 65-94 years) and scanned by microCT. Images were used to diagnose DISH using the current clinical criteria and to quantify radiographic features of ectopic mineralisation. Six spines with DISH were then evaluated using histology and physical techniques. Individual motion segments (15 total) were isolated from regions of the thoracic spine. Sections were stained with haematoxylin & eosin and Masson's trichrome for histopathological analysis. Scanning electron microscopy, energy dispersive X-ray spectroscopy, and X-ray diffraction were used to evaluate the elemental composition and mineral content of DISH.

Results: 53% of the cohort met the diagnostic criteria for DISH (3 females and 7 males; range 72-94 years). Histological examination revealed two distinct characteristics of ectopic mineral. First, features of mature lamellar bone were evident outside of the IVD, consistent with heterotopic ossification. Second, isolated regions of amorphous calcified material within the anterior longitudinal ligament, annulus fibrosus and/or fibrocartilage extensions of the IVD, inconsistently stained and granular in appearance, consistent with dystrophic calcification. Both calcifications and ossifications showed similar physical characteristics—a high content of calcium and phosphorus and a crystalline diffraction pattern matching hydroxyapatite. Although similar in radiographic appearance, calcifications could be differentiated by radiodensities exceeding bone using microCT.

Discussion: Our findings demonstrate that ectopic mineral associated with DISH is formed by both dystrophic calcification and heterotopic ossification of spinal tissues. These features are both captured by the current clinical criteria for DISH, but these distinct processes may reflect stages of disease and hence the pattern of disease progression within the spine. Ongoing studies will investigate the spatiotemporal relationship between dystrophic calcification and heterotopic ossification in the pathogenesis of DISH.

KEYWORDS

diffuse idiopathic skeletal hyperostosis (DISH), heterotopic ossification, dystrophic calcification, microcomputed tomography, X-ray diffraction, human (cadaver), vertebral column (spine), intervertebral disc

Luiza Grazziotin

BIO

I earned a M.Sc. in Cardiovascular Sciences and a B.Sc. in Pharmacy from the Federal University of Rio Grande do Sul, Brazil. I developed a foundational expertise in Health Technology Assessment (HTA) during my Master's degree and completing a one-year HTA specialization course concurrently. I also worked as a Research Associate at a hospital-based HTA unit, in which I gained practical experience in health services research by developing, coordinating and conducting HTA projects, systematic reviews, and observational studies. I am currently a Health Economics PhD candidate at the University of Calgary. My PhD project is focused on juvenile idiopathic arthritis personalized care using simulation modeling and cost-effectiveness analysis.

I am passionate about different health economics modelling approaches and their applicability in describing complex health processes, evaluating new interventions, and ultimately, informing decision making.



ABSTRACT: Treatment pathways in childhood arthritis in the biologic era

AUTHORS: Luiza Grazziotin Lago, MSc, Gillian Currie, PhD, Michelle MA Kip, PhD, Maarten J Jzerman, PhD, Marinka Twilt, MD, MSCE, PhD, Deborah A Marshall, PhD

Background: Juvenile idiopathic arthritis (JIA), an umbrella term for seven heterogeneous subtypes of arthritis, is the most common rheumatic disease in children. JIA causes joint inflammation with daily pain and stiffness that can severely impact childhood development and cause permanent joint damage. Therefore, JIA can dramatically affect the quality of life of children and their families. Clinical practice patterns to treat JIA are complex; they involve a variety of drug treatments, including biologic therapies. These complex care pathways lead to significant expenditure for the Canadian health care system, with biologic therapies alone accounting for a large component of the cost. However, the lack of description of real-world clinical practice patterns, including recent treatment types and sequence in Canada constitutes an important gap in the literature.

Methods: First, a JIA cohort of newly diagnosed patients from 2011 to 2018 (n=400) attending the Pediatric Rheumatology (PR) clinic at the Alberta Children's Hospital was identified using a validated case ascertainment algorithm for administrative health data and using chart review to confirm JIA diagnosis. Second, an on-going data extraction using the PR clinical charts will retrieve demographic and clinical information (e.g. JIA subtype, biomarkers test results). The identified cohort will then be linked to the Alberta administrative database Pharmaceutical Information Network to obtain information regarding medications dispensed. A descriptive analysis of the variables will be conducted using frequency measures and treatment pathways will be represented using a novel graphic approach.

Expected results: We will report the proportion of patients in the cohort to have received at least one disease modifying anti-rheumatic drugs, such as methotrexate, and the proportion of patients to have received at least one biologic therapy. Based on preliminary data, we expect approximately 30% to have received at least one biologic, the most common biologic being etanercept. We expect biologic therapies to be used as third line of treatment after non-steroidal anti-inflammatory drugs and methotrexate. Significant variability in drug prescription patterns is anticipated, especially among different disease subtypes, as JIA is a heterogeneous group of diseases and JIA clinical guidelines have changed over time. Treatment-sequence visualization can help to effectively illustrate the complexity of treatment patterns and patient outcomes in JIA.

Impact on research: The evaluation of patient-level JIA type and sequence of drug treatments observed in the retrospective cohort can be used to inform future guidelines on JIA drug treatment and other health economic models.

KEYWORDS

juvenile idiopathic arthritis, childhood arthritis, drugs, disease modifying anti-rheumatic drugs (DMARD), biologic therapies

Carly Jones

BIO

Carly is a PhD student in the department of Biomedical Engineering at UBC. She completed her undergraduate degree in Engineering Physics in 2017, also at UBC. Her research is based out of the Centre for Hip Health and Mobility (a UBC biomechanics research lab), where she has been working under the supervision of Dr. David Wilson since 2014. While working as an undergraduate research assistant she published two papers on the topic of modelling hip range of motion in Slipped Capital Femoral Epiphysis (SCFE), a childhood hip disorder. After completing her graduate studies, she plans to pursue a professorship. In her free time, she enjoys singing, powerlifting, gardening, and outdoor sports such as biking, hiking and skiing.



ABSTRACT: dGEMRIC is Reduced in Hips with Bone Marrow Lesions

AUTHORS: Jones C.E., Qian H., Zhang H., Guo Y., Russell D., Forster B.B., Wong H., Esdaile J.M., Cibere J., Wilson D.R., and the IMPAKT-HiP study team

Background: Bone marrow lesions (BML) are associated with painful and progressive OA. Quantitative MRI has been used to study early cartilage degeneration in knees with BML, but similar work has not been done in the hip. Further work is needed to understand the connection between BML and cartilage degeneration in the hip. The objective of this study was to compare mean dGEMRIC values (T1Gd) in hips with BML to mean T1Gd in hips without BML in a population-based study. Reduced T1Gd suggests depleted GAG. Our hypothesis was: mean T1Gd is lower in hips with BML compared to hips without BML.

Methods: Study participants (n=128) were recruited from the Investigations of Mobility, Physical Activity, and Knowledge Translation in Hip Pain (IMPAKT-HiP) study, which is a cross-sectional population-based study of 500 subjects aged 20-49 years with and without hip pain in Vancouver, Canada. dGEMRIC and proton-density (PD) weighted MRI scans of one hip from each of the 128 participants who completed the dGEMRIC protocol were used for this analysis. BML were identified from PD-weighted fat-suppressed images by a MSK radiologist using the Hip OA MRI Scoring System (HOAMS). Hips with at least one BML in any region were treated as the BML group. Acetabular and femoral cartilage were manually segmented as a single object by an imaging scientist to determine mean T1Gd. We applied a sampling-weighted linear regression model to determine the association of the presence of BML with mean cartilage T1Gd (significance: $p < 0.05$). The model was adjusted for age, sex, BMI and physical activity. Sampling weights accounted for non-response of eligible participants and for poststratification to match the population of a large city (n=1,016,990).

Results: 36 of the 128 participants (28%) had at least one BML. Subjects with BML and without BML had similar weighted characteristics on age, BMI, physical activity, and hip pain. Mean T1Gd was 83ms (95% CI: [-152, -14], $p=0.02$) (10%) lower in the BML compared to the no-BML group.

Conclusion: Our result that the estimated difference in overall mean T1Gd between the BML and no-BML groups was 10% suggests cartilage in hips with BML have a lower GAG content than hips without BML, which is consistent with previous studies. These results suggest that BML are associated with cartilage degeneration in the hip. This work motivates further study of BML in the hip and the relationship between BML and cartilage degeneration.

KEYWORDS

osteoarthritis, bone marrow lesions, bone, cartilage, dgemric, mri, biomechanics, population-based

Christina Le

BIO

Christina Le is a PhD candidate in Rehabilitation Sciences in the Faculty of Rehabilitation Medicine and physiotherapist at the Glen Sather Sports Medicine Clinic, University of Alberta in Edmonton, Canada. Motivated by clinical and personal experiences with knee injuries, Christina's research aims to better understand the role of health-related quality of life (HRQOL) on the development of osteoarthritis following a youth sport-related knee injury and factors that impact HRQOL. Ultimately, Christina's research seeks to inform rehabilitation strategies aimed at optimizing HRQOL, preventing osteoarthritis, and ensuring lifelong well-being of youth that suffer knee injuries. Find her on Twitter as @yegphysio or online at www.yegphysiotherapy.com.



ABSTRACT: Health-Related Quality of Life Following an Acute Sport-Related Knee Injury in Youth: Implications for Preventing Post-Traumatic Osteoarthritis

AUTHORS: Christina Y. Le PT, PhD Candidate, Jackie L. Whittaker PT, PhD

Background: Youth who suffer a sport-related knee injury are at increased risk of developing osteoarthritis (OA) and various related physical, psychological, and social consequences. Despite this, the impact of these injuries on health-related quality of life (HRQOL) is unknown. A better understanding of the relationship between youth sport-related knee injuries and HRQOL may inform rehabilitation strategies that prevent OA in this at-risk population and promote long-term health. This preliminary analysis examines and compares outcomes related to HRQOL and its domains between youth who have suffered a traumatic, sport-related knee injury and age-, sex-, and sport-matched uninjured controls.

Methods: We examined the first 57 matched pairs from an ongoing inception prospective cohort study, including 57 youth (11-19 years old) who sustained a sport-related knee injury within the previous four months and 57 age-, sex-, and sport-matched uninjured controls. A knee injury was defined as a clinical diagnosis of a ligament, meniscus, or other intra-articular tibiofemoral or patellofemoral injury requiring medical attention and resulting in time-loss from sport. Health-related quality of life outcomes included the Knee injury and Osteoarthritis Outcome Score (KOOS) knee-related quality of life (QOL) subscale and Anterior Cruciate Ligament QOL (ACL QOL) questionnaire. Physical outcomes included body mass index (BMI; stadiometer), knee symptoms (KOOS symptoms), and weekly minutes of moderate-to-vigorous physical activity (MVPA; accelerometer). Psychological outcomes included fear of movement (Tampa Scale for Kinesiophobia-11; TSK-11). Descriptive statistics [median (range), proportion (95%CI), and mean within-pair differences (95%CI)] were calculated for all participant characteristics and outcomes by study group (injured or uninjured).

Results: The median age of participants was 16.6 years (range 10.9-20.1) and 68% were females. The injured group reported poorer HRQOL [mean within-pair difference (95%CI): KOOS QOL -63 (-69,-56) and ACL QOL -49 (-61,-37)] than the uninjured group. The injured group also demonstrated less MVPA [weekly minutes -85 (-167,-3)], more self-reported symptoms [KOOS symptoms -31 (-36,-26)], and greater fear of movement [TSK-11 5 (3,7)] compared to the uninjured group. No between-group differences in BMI were found.

Discussion: These findings suggest youth who suffer a sport-related knee injury experience clinically relevant differences in HRQOL compared to uninjured peers in the first four months following injury. Less engagement in MVPA, increased symptoms, and heightened fear of movement following a youth sport-related knee injury may interfere with recovery and contribute to an elevated risk of OA. Rehabilitation of these individuals must acknowledge deficits in HRQOL and address outcomes across all HRQOL domains.

KEYWORDS

quality of life, physical activity, symptoms, fear of movement

Ze Lu

BIO

Mr. Ze Lu is the second year PT-PhD combine program student under the supervision of Dr. Joy MacDermid in the School of Rehabilitation Science at McMaster University. He also works as a clinical research assistant in St Joseph's Hospital London site. His passion is on clinical outcome measures specialized for the upper extremity orthopedic surgery.



ABSTRACT: The Clinical Outcome Of Physiotherapy After Anatomical Total Shoulder Arthroplasty

AUTHORS: Ze Lu, Goris Nazari, Pedro H Almeida, Joy C MacDermid, Kenneth Faber

Background/purpose: The anatomic total shoulder arthroplasty surgery (TSA) has been considered as the standard treatment for the patients suffering from glenohumeral osteoarthritis, proximal humeral fracture. TSA has been utilized widely in worldwide with an increasing trend in the past decade. However, there is a paucity of evidence concerning the published studies on TSA which have focused on post-surgery complications and have neither specifically assessed clinical outcomes such as pain, function or range of motion, nor have provided or described in detail the postoperative rehabilitation administered. The purpose of this systematic review was to analyze the current literature on the clinical outcomes of PT program after total shoulder arthroplasty (TSA) and to summarize the improvements in this population.

Methods: A search was performed for the current systematic review in 4 databases (MEDLINE, EMBASE, PUBMED, GOOGLE SCHOLAR) until November 2019. Eligible articles were qualitatively synthesized to report findings of the included articles based on study designs (case-series, case-controls, retrospective/prospective cohorts and randomized controlled trials), clinical outcomes and physiotherapy protocols. We reported descriptive statistics (means and standard deviations) pertaining to each study to provide the magnitude of intervention effects.

Results: There were 15 eligible studies with the sample sizes ranging from 10 to 374 patients. Included studies demonstrate substantial improvement in patients after TSA surgery who completed PT rehabilitation in terms of the clinical outcomes of pain, function and range of motion outcomes. All 15 studies included in the current review contains a short follow-up period (<5 years). Of all 12 TSA studies, 5 papers provided patients with a standardized clinic or hospital- based PT program, 4 studies utilized the home-based PT protocol, and other 3 articles did not state the type of PT program.

Conclusions: Within the current body of the literature, rehabilitation was considered as the important element to optimize the clinical outcomes and achieve the best clinical practice. High-quality RCTs are required to provide more conclusive results. The home-based rehabilitation program requires update by incorporating a unified platform facilitating teleconference, measurement of AROM, online-based outcome measurement, exercise education, and real time feedback.

KEYWORDS

systematic review, total shoulder arthroplasty, clinical outcome, functional outcome, physiotherapy protocol.

Darren Mazzei

BIO

Darren has six years of clinical experience as a physiotherapist and is also undertaking a PhD in Health Economics under the supervision of Dr. Deborah Marshall at the University of Calgary. Darren wants to investigate the socioeconomic impacts of osteoarthritis management with the goal of improving patients' access to evidence-based services. Darren's thesis is centered around the cost-effectiveness analysis and budget impact assessment of the Good Life with Osteoarthritis Denmark (GLA:DTM) program that is being offered at community rehabilitation clinics in Alberta. GLA:DTM is an internationally recognized eight-week standardized education and exercise program designed to provide evidence-based core treatments to people living with osteoarthritis.



ABSTRACT: Economic Evaluation for Group-Based Exercise Therapy in Comparison to Usual Care for Hip and Knee Osteoarthritis in Alberta

AUTHORS: Darren Mazzei, Dr. Deborah Marshall, Dr. Jackie Whittaker, Dr. Peter Faris, Tracy Wasylak

Background: Osteoarthritis (OA) affects 15% of Canadians^{1,2}. OA clinical guidelines recommend exercise and education as primary interventions, but there is low uptake of these treatments^{3,4,5}. Researchers developed an 8-week evidence-based education and exercise class: Good Life with osteoarthritis in Denmark (GLA:DTM)⁶. In clinical trials GLA:DTM demonstrated improved quality of life and reduced pain in comparison to usual care⁶. To implement GLA:DTM in Alberta, decision-makers must weigh the health benefits and resource demands. This economic evaluation will inform decision-making about the value and affordability of implementing GLA:DTM in Alberta.

Objectives

1. Evaluate health outcomes of GLA:DTM in comparison to usual care for people with hip or knee OA
2. Estimate the cost-effectiveness of GLA:DTM in comparison to usual care for people with hip or knee OA
3. Describe how implementing GLA:DTM across Alberta will impact the health care budget

Research Plan: A case-control study design will compare participants with moderate to severe hip and knee OA (age > 50 years) attending the GLA:DTM program to a matched control group using a 2:1 ratio to control for age, sex, BMI, affected joint and geography. Patient-reported outcome measures include the 5-level version EQ-5D (EQ-5D-5L), Knee Injury and Osteoarthritis Outcome Score, Hip Injury and Osteoarthritis Outcome Score, self-reported pain and a cost questionnaire. Outcome measures will be collected at baseline, 3, 6, and 12-months via telephone or online questionnaire. Health-related QOL over 1 year, measured by EQ-5D-5L, will be used in an area under the curve calculation to produce quality adjusted life years (QALYs).

Cost-effectiveness is evaluated using a cost-utility analysis to calculate the difference in QALYs and difference in cost between GLA:DTM and usual care. Costs will be calculated from administrative data and patient-reported costs. Costing, evaluated from the societal perspective, will include hospital stays, ambulatory services, diagnostic imaging, physician claims, out-of-pocket costs and productivity loss. If appropriate, an incremental cost-effectiveness ratio will be calculated and compared to the decision-makers willingness to pay for added health benefits or a threshold commonly reported in the literature. A probabilistic sensitivity analysis will evaluate parameter uncertainty. The affordability of implementing GLA:DTM will be evaluated using a budget impact assessment to quantify the expected changes in health outcomes and healthcare expenditures in Alberta. Results will be extended over an entire budget cycle.

Impact: This study will inform decision-makers about the value and affordability of publicly funding GLA:DTM in Alberta.

KEYWORDS

arthritis, education, exercise, evidence-based practice, community-based services, chronic disease management budget impact assessment, cost-effectiveness, implementation, public and private funding

Dr. Natalie McCormick

BIO

Natalie's research uses large datasets to help providers, policymakers, and patients better manage the extra costs of treating and living with inflammatory arthritis.

Natalie also works to enhance public understanding about this type of research.

Supported by a CIHR Doctoral Award, she completed her Ph.D. in 2018 at The University of British Columbia and Arthritis Research Canada where she investigated the direct medical costs, and lost paid and unpaid work costs, of lupus, systemic sclerosis, Sjogren's, vasculitis, and other systemic autoimmune rheumatic diseases.

Natalie is now a CIHR-funded post-doctoral fellow in the Clinical Epidemiology Program at Massachusetts General Hospital. Supervised by epidemiologist/rheumatologist Dr. Hyon Choi, she is extending her analyses to other types of inflammatory arthritis, including gout, and techniques for causal inference.

Natalie has been involved with the Canadian Arthritis Trainee Association since 2016, helping re-launch the BC Chapter and now serving as Treasurer on the National Executive Committee.



ABSTRACT: Decomposition Analysis of Spending and Price Trends for Biologic Disease-Modifying Anti-Rheumatic Drugs by Public Payers in Canada and the United States

AUTHORS: Natalie McCormick, Zachary S. Wallace, M.D., M.Sc., Chana A. Sacks, M.D., M.P.H, John Hsu, M.D., M.S.C.E., M.B.A., Hyon K. Choi, M.D., Dr. P.H.

Background/Purpose: Biologics (bDMARDs) are among the highest-spend drugs in Canada and USA, and spending keeps rising. We characterised changes in total spending and unit-prices for bDMARDs in Canadian and US public drug programs and quantified major sources of spending increases in each setting.

Methods: We accessed aggregated drug spending data from British Columbia (BC=Canada's third-largest province) and USA for years 2012-2017. BC data included all bDMARD claims accepted by Pharmacare, BC's public drug program, for public reimbursement or towards patients' deductibles (~79% of bDMARD sales in BC). US data included bDMARD claims for all >42 million Medicare Part B fee-for-service, Part D, and Medicaid enrollees. bDMARDs covered by Pharmacare and Medicare/Medicaid for >1 rheumatic disease through December 2015 were eligible. For each bDMARD and calendar-year we extracted total spending, and numbers of recipients, claims, and doses dispensed, and calculated drug unit-price (average cost/dose). We calculated six-year changes in total spending and unit-prices for each bDMARD, adjusting for general inflation to 2017\$. We then performed standard decomposition analyses to isolate the contributions of four sources of spending growth (unit-prices, recipient numbers, treatment intensity [# doses/claim], and annual # claims/recipient) for each bDMARD and in-aggregate. For BC, we examined total spending (publicly-reimbursed and patient-paid components) and publicly-reimbursed spending alone. For USA we included statutory Medicaid rebates, and both excluded and included time-varying Medicare rebates (range 20-30%).

Results: Eight bDMARDs met inclusion criteria. From 2012 to 2017, combined public-payer and patient bDMARD spending increased by 54% in BC (from \$185 million to \$284 million CDN); publicly-reimbursed component increased by 64% (\$131 to \$215 million). US spending nearly doubled: \$5.6 to \$11.1 billion USD.

BC and USA had similar utilisation patterns and trends: oldest bDMARDs (e.g., adalimumab, infliximab, etanercept) incurred the greatest spending in both settings, and adalimumab, certolizumab, and golimumab had the largest increases in recipients.

In BC, vast majority (87%) of bDMARD spending growth was from increased numbers of recipients; unit-price increases accounted for just 1.7%. Conversely, price hikes accounted for 63% of US public-payer spending growth (59% with time-varying rebates); median six-year bDMARD price increase in Medicare/Medicaid was 59% (post-rebate price increase=41%).

Discussion/Conclusion: Provincial and pan-Canadian negotiations with drug manufacturers likely helped BC (and other provinces) avoid the steep post-market price hikes faced by US public-payers. However, further measures (i.e. expanded use of lower-priced biosimilars) are needed to help manage ongoing rises in public spending from increasing numbers of bDMARD recipients.

KEYWORDS

biologic DMARDs, drug prices, drug spending, decomposition analysis, public drug programs, pharmacare, medicare, trans-national comparisons, health services research, health policy

Dr. Arielle Mendel

BIO

Dr Arielle Mendel completed her rheumatology training at McGill University and thereafter has pursued a Master's degree in Quality Improvement and Patient Safety at the Institute for Health Policy, Management and Evaluation at the University of Toronto, during which she is also completing two years of fellowship training in vasculitis at Mount Sinai Hospital. She will be starting her academic appointment at McGill University in July 2020, where her research will focus on interventions to improve the safety and effectiveness of care for patients with systemic rheumatic disease.



ABSTRACT: Delayed glucocorticoid tapering in large vessel and ANCA-associated vasculitides: experience from a tertiary referral centre

AUTHORS: Arielle Mendel, Daniel Ennis, Shirley Lake, Simon Carette, Christian Pagnoux

Background/Purpose: Glucocorticoids (GC) are required in the initial treatment of ANCA-associated (AAV) and large vessel vasculitides (LVV) but can cause significant toxicity when maintained at high doses. We aimed to assess GC tapering trajectories, compared to existing tapering recommendations, among patients referred for AAV or LVV, and identify possible contributing factors to 'delayed' tapering.

Methods: Newly referred patients assessed July 2017-August 2019 at a tertiary vasculitis clinic for AAV (GPA, EGPA, MPA) and LVV (Giant Cell Arteritis, Takayasu arteritis) who were taking GC at their first visit were included. 'Delayed' GC tapering was defined as a prednisone dose >10 mg above target based on existing tapering recommendations. Referral specialty, diagnosis, clinic wait time, initial GC dose and duration were compared among patients with 'delayed' and 'appropriate' tapering. Chart reviews and referring physician surveys were conducted to determine potential causes of delayed tapering.

Results: 161 patients (97 AAV, 64 LVV) were taking GC at their first visit with a mean duration of 126 days (SD 124). Mean prednisone start dose was 52 mg (SD 15). 'Delayed' tapering occurred in 43 (27%) patients (22 AAV, 21 LVV). Mean prednisone dose at the first clinic visit was 40.7 mg (SD 15) in the 'delayed' group compared to 23.2 mg (SD 16) in the 'appropriate' group ($p < 0.0001$). 'Pulse' GC were administered to 20/43 (47%) patients with 'delayed' tapering compared to 23/119 (19%) with 'appropriate' tapering (difference in proportion 28% [95% CI 12-43]). Among patients with 'delayed' tapering, chart reviews identified persistent patient symptoms in 9 (21%), lack of tapering prescriptions at hospital discharge in 5 (12%), and explicit deferral of tapering to the vasculitis clinic in 3 (7%) as potential contributing factors. Mean wait times to the vasculitis clinic were similar in 'delayed' and 'appropriate' groups. Surveyed physicians ($n=15$) felt more confident tapering GC in GCA (73% "very comfortable"), but less in systemic AAV and Takayasu arteritis (40% and 20%, respectively). The most commonly cited challenges to GC tapering were managing the risk of disease relapse (80%) and differentiating active disease from damage or non-vasculitic symptoms (67%).

Discussion/Conclusion: Among patients referred for LVV or AAV taking GC, tapering was slower than recommended in over one quarter. 'Pulse' GC at treatment onset was associated with 'delayed' tapering, the reasons for which warrant further study. Strategies for improvement should address referring physician confidence with timely tapering and prioritization of high-risk referrals.

KEYWORDS

glucocorticoid tapering, giant cell arteritis, takayasu arteritis, anca-associated vasculitis, quality improvement, patient safety

Isobel Mouat

BIO

As a fifth year PhD student in Dr. Marc Horwitz' lab at UBC, Isobel uses mouse models to investigate the mechanisms by which EBV contributes to rheumatoid arthritis and multiple sclerosis. In particular, she is interested in how B cells may contribute to disease in both protective and pathogenic manners.



ABSTRACT: Latent MHV68 infection enhances collagen-induced arthritis in part through the skewing of age-associated B cells

AUTHORS: Isobel Mouat, Zach Morse, Jessica Allanach, Iryna Shanina, Marc Horwitz

Epstein-Barr virus (EBV) is thought to contribute to the development of rheumatoid arthritis (RA), though the mechanism remains unknown. Currently there does not exist a sufficient *in vivo* model to examine how EBV contributes to RA. Our aim is to utilize and expand existing *in vivo* models of EBV and RA to examine potential mechanisms of immune contribution. Results indicate that infection with latent gammaherpesvirus 68 (MHV68), a homolog and accepted *in vivo* model of EBV, leads to an enhanced clinical and immunological course of collagen induced arthritis (CIA), a common *in vivo* model of RA. Mice latently infected with MHV68 display more severe CIA clinical symptoms compared to uninfected CIA mice. Further, the immune profile of MHV68-infected CIA mice is shifted towards a proinflammatory Th1 profile, while maintaining the canonical Th17 response, compared to uninfected CIA. We propose that this immune profile bears greater semblance to that of RA patients than CIA alone. To further examine the role of the latent MHV68 infection we utilized AC-RTA MHV68, a recombinant strain of MHV68 in which genes responsible for latency have been deleted, resulting in clearance of the virus following acute infection. No clinical or immune enhancement of CIA is observed following infection with AC-RTA MHV68, indicating that the MHV68-enhancement of CIA depends on the development of latency. A major question is the mechanism(s) by which EBV contributes to disease. We propose that age-associated B cells (ABCs) are a subset impacted by latent infection that contributes to disease. ABCs are known to be increased in RA patients and following viral infection, though their contribution to disease remains unknown. We observe that ABCs (CD19⁺CD11c⁺Tbet⁺) in MHV68-infected CIA mice are increased and display an altered proinflammatory phenotype compared to ABCs in uninfected CIA. We have utilized mice that are genetically deficient in ABCs (Tbet^{flox}^{+/+} x CD19^{Cre}^{+/-}) to examine their contribution to disease. ABC deficiency results in a diminished clinical course in MHV68-infected CIA mice, indicating their pathogenicity. Alternatively, knocking out ABCs in uninfected CIA mice does not alter CIA clinical course, demonstrating that latent MHV68 infection licenses ABCs for pathogenicity during CIA. This project establishes that latent MHV68 infection enhances CIA and is a viable model for examining mechanisms of EBV's contribution to RA. Further elucidating the contribution of EBV to RA will provide opportunities to improve existing therapeutics, develop novel treatments, and offer a better understanding of RA.

KEYWORDS

viral infection, arthritis, mouse model

Dr. Mohammad Movahedi

BIO

Dr Mohammad Movahedi is an assistant professor in Institute of Health Policy, Management and Evaluation, University of Toronto. He graduated from medical school at the University of Tehran in 1992. He has since developed an interest in epidemiology and public health and received his PhD in clinical epidemiology from the University of Leeds in 2005. Between 2005 and 2011, he held an Assistant Professor faculty position at Tehran universities where he taught "Principles of Epidemiology", "Research Methods", and "Systematic Review" courses for MSc and PhD programs. He worked as a post-doc researcher in pharmacoepidemiology at Arthritis Research UK Centre for Epidemiology, the University of Manchester by 2015. Since then he has been conducting epidemiologic and statistical data analyses on clinical data of Rheumatoid Arthritis (RA) patients collected by the Ontario Best Practice Research Initiative (OBRI) registry at University Health Network.



ABSTRACT: Time to Discontinuation of Tofacitinib and TNF inhibitors in Rheumatoid Arthritis Patients with and without Methotrexate: Data from A Rheumatoid Arthritis Cohort

AUTHORS: Mohammad Movahedi, Angela Cesta, Xiuying Li, Edward Keystone, Claire Bombardier, and OBRI investigators

Background/purpose: Tofacitinib (TOFA) is an oral, small molecule drug used for rheumatoid arthritis (RA) treatment and is prescribed alone or with methotrexate (MTX). Tofa can be used as an alternative to biologic disease modifying antirheumatic drugs (bDMARDs) including tumor necrosis factor inhibitors (TNFi). We aimed to evaluate the discontinuation rate of this drug, with and without concurrent MTX in comparison with TNFi, in patients with RA in the Ontario Best Practices Research Initiative (OBRI).

Methods: RA patients enrolled in the OBRI initiating their TOFA or TNFi (adalimumab, certolizumab, etanercept, golimumab, and infliximab) within 30 days prior to or any time after enrolment between 1st June 2014 (TOFA approval date in Canada) and 31st Dec 2018 were included. Time to discontinuation (due to any reason) were assessed using Kaplan-Meier survival (adjusted for propensity score using inverse probability of treatment weight) to compare patients with and without MTX use at initiation of TOFA or TNFi.

Results: A total of 565 patients initiated TOFA (n=208) or TNFi (n=357). Of those, 106 (51%) and 222 (62%) were treated with MTX in the TOFA and TNFi group, respectively and mean (SD) disease duration were 13.1 (9.4) and 9.5 (9.4) years. In the TOFA group, 86% were female and mean (SD) age at treatment initiation was 60.4 (10.6) years. In the TNFi group 82% were female and mean age (SD) at treatment initiation was 57.0 (12.6) years. The TOFA group was more likely to have prior biologic use (61.5%) compared with the TNFi group (31%). At treatment initiation, the mean (SD) clinical disease activity index was 24.8 (12.1) in the TOFA group and 21.8 (12.0) in the TNFi group.

Over a mean of 17.3 month follow-up, discontinuation was reported in 75 (36%) and 103 (29%) of all TOFA and TNFi patients, respectively. After adjusting for propensity score, patients treated with TNFi and MTX remained on treatment longer than those treated without MTX (Logrank p=0.002) while there was no significant difference in TOFA discontinuation in patients with and without MTX (Logrank p=0.31).

Discussion/Conclusion: In this real world data study, we found that TOFA retention is similar in patients with and without MTX, while patients treated with TNFi and MTX remained on treatment longer than those treated without MTX. Merging data with other RA registries in Canada is proposed to increase study power and to provide more robust results.

KEYWORDS

discontinuation, tnfi inhibitors, tofacitinib, mtx, ra, real world data

Dr. Mohammad Movahedi

BIO

Dr Mohammad Movahedi is an assistant professor in Institute of Health Policy, Management and Evaluation, University of Toronto. He graduated from medical school at the University of Tehran in 1992. He has since developed an interest in epidemiology and public health and received his PhD in clinical epidemiology from the University of Leeds in 2005. Between 2005 and 2011, he held an Assistant Professor faculty position at Tehran universities where he taught "Principles of Epidemiology", "Research Methods", and "Systematic Review" courses for MSc and PhD programs. He worked as a post-doc researcher in pharmacoepidemiology at Arthritis Research UK Centre for Epidemiology, the University of Manchester by 2015. Since then he has been conducting epidemiologic and statistical data analyses on clinical data of Rheumatoid Arthritis (RA) patients collected by the Ontario Best Practice Research Initiative (OBRI) registry at University Health Network.



ABSTRACT: Differences Between Early and Established Rheumatoid Arthritis in Time to Achieving CDAI but not Fatigue Low Disease Activity and Remission: Data from the OBRI Registry

AUTHORS: Janet Pope, Emmanouil Rampakakis, Mohammad Movahedi, Angela Cesta, John S. Sampalis, Claire Bombardier, and other OBRI investigators

Background/purpose: Previous studies have shown that early diagnosis and treatment of rheumatoid arthritis (RA) is important for achieving comprehensive disease control and have identified established disease as an independent predictor of worse clinical outcomes. However, it is not clear whether these differences are driven by patient-reported or objective outcome measures. The aim of this analysis was to compare the time to achieving low disease activity (LDA) and remission based on both objective and patient-reported outcomes in people with early vs. established RA followed in routine clinical care.

Methods: RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) registry that were not in a low disease state at baseline based on the CDAI, SJC28, PtGA, pain and fatigue criteria below, and had at least six months of follow-up, were included in the analysis. LDA was defined as CDAI \leq 10, SJC28 \leq 2, TJC28 \leq 2, PtGA \leq 2cm, pain \leq 2cm, fatigue \leq 2cm, and MDGA \leq 2cm; remission was defined as CDAI \leq 2.8, SJC28 \leq 1, TJC28 \leq 1, PtGA \leq 1cm, pain \leq 1cm, fatigue \leq 1cm, and MDGA \leq 1cm. Between group (early vs. established) differences in time to first LDA/remission were assessed with Kaplan-Meier survival analysis and the log-rank test.

Results: A total of 986 patients were included, 347 (35%) with early RA and 639 (65%) with established RA. At baseline, patients with early RA were significantly younger (55.8 vs. 58.3 years) and were less likely to have a comorbidity (94.5% vs. 97.5%) or an erosion (26.7% vs. 62.6%), be RF-positive (65.6% vs. 74.2%), use bDMARDs (7.5% vs. 26.6%), and be non-smokers (38.9% vs. 47.3%).

Time to achieving LDA based on CDAI (HR [95%CI]: (1.23 [1.07,1.43]), SJC28 (1.32 [1.15,1.51]), TJC28 (1.18 [1.02,1.36]), MDGA (1.28 [1.10,1.49]), PtGA (1.23 [1.05,1.44]), and pain (1.29 [1.09,1.52]) were significantly shorter in early RA compared to established RA. Similarly, time to achieving remission based on CDAI (HR [95%CI]: (1.50 [1.22,1.84]), SJC28 (1.35 [1.17,1.55]), MDGA (1.25 [1.06,1.47]), PtGA (1.22 [1.02,1.47]), and pain (1.37 [1.14,1.65]) were significantly shorter in early RA. However, no differences were observed in time to remission based on TJC28 (1.12 [0.96,1.31]) and either LDA or remission based on fatigue (LDA (1.10 [0.94,1.30]); remission (1.09 [0.92,1.31])).

Adjustment for age, gender, presence of comorbidities, and baseline scores did not alter the results.

Discussion/conclusion: Time to achieving low disease state or remission based on various objective and patient-reported measures is significantly shorter in early compared to established RA with the exception of fatigue.

KEYWORDS

remission, clinical disease activity index, patient report outcome, pain, ra, real world data

Zeynab Nosrati

BIO

Zeynab Nosrati obtained her Bachelor's and Master's degrees in Medical Radiation Physics (BSc'09, MSc'12). Currently, she is doing her PhD in Pharmaceutical Sciences at University of British Columbia. Zeynab has conducted various research projects in areas of magnetic targeting, targeted drug delivery and radiopharmaceuticals. Her current research is about developing a theranostic nanomedicine platform that can target and treat difficult to reach diseases, such as rheumatoid arthritis.



ABSTRACT: Theranostic Nanomedicine for Imaging and Treatment of Multiple Joints in Rheumatoid Arthritis

AUTHORS: Zeynab Nosrati, Tullio V. Esposito, Marta Bergamo, Cristina Rodriguez-Rodriguez, Katayoun Saatchi, and Urs O. Häfeli, Corresponding authors; (Pillar 1)

Background: Many Rheumatoid arthritis (RA) patients fail to respond satisfactorily to frequently given anti-arthritis drugs or experience side effects. The main reason for non-ideal treatment is that insufficient drug doses reach the joints, therefore higher and more frequent doses needed. To improve drug pharmacological profile and direct the anti-inflammatory activity to the inflamed joints, we synthesized a pro-drug to deliver more of the drug specifically to inflamed joints, to maintain appropriate drug concentration thereafter, and to avoid side effects in other organs.

Methods: Our methods encompass the chemical syntheses of the polymeric prodrugs and the investigation of their stability and release kinetics. The pharmacokinetics of the prodrug was established after radiolabeling with In-111, and preclinical SPECT/CT imaging in an RA mouse model. The efficacy of the prodrugs is also established in the same RA model and compared to the free drug given in the same form/ timing as it is currently administered to patients. In vitro stability measurements of the prodrugs in human synovial fluid from rheumatoid arthritis patients is ongoing to better understand the impact of the local environment of an inflamed joint and how that influences drug release.

Results: Delivering methotrexate (MTX) bound to a carrier polymer produces a significant increase in drug uptake in the inflamed joints. When MTX was delivered as a prodrug, a 2 to 4 times lower dose given every two weeks was just as effective as two standard dosages per week of free MTX. In addition, attaching folic acid (a targeting ligand that selectively binds to folate receptors) to the polymeric carrier helped to keep the active drug longer in the targeted lesion.

Conclusion: In this study, using SPECT/CT we show our prodrug approach delivers higher concentrations of anti-arthritis drugs to inflamed joints than has previously been possible, despite lower and less frequent drug doses.

KEYWORDS

rheumatoid arthritis, macromolecular prodrug, targeting inflammation, drug delivery

Dr. Liam J. O'Neil

BIO

Liam O'Neil is an assistant professor at the University of Manitoba. He is a member of the Manitoba Centre for Proteomics and Systems Biology, and his research focuses on understanding the biological events that occur prior to the development of Rheumatoid Arthritis. He previously trained at the National Institutes of Health (Bethesda, MD) where he elucidated a mechanism linking neutrophil extracellular trap (NET) formation and autoantibody responses in RA. He will continue his work in Manitoba by investigating citrullinated proteins and NET formation in the context of pre-clinical autoimmunity.



ABSTRACT: A Serum Proteomic Signature predicts Rheumatoid Arthritis onset in at-risk individuals

AUTHORS: Liam J. O'Neil, Victor Spicer, Irene Smolik, Xiaobo Meng, Rishi R. Goel, Vidyand Anaparti, John Wilkins and Hani S. El-Gabalawy

Background: Anti-citrullinated protein antibodies (ACPA) are currently the primary biomarker for identifying individuals at increased risk for future RA development. However, we have recently shown in a prospective study that most unaffected ACPA+ individuals do not develop RA. We hypothesized that abnormalities in the serum proteome may serve as additional biomarkers in the prediction risk for future disease onset. The aim of our study was to mine the serum proteome of individuals who ultimately developed RA to detect biomarkers that predict disease onset.

Methods: Using the SOMAscan (slow off-rate modified aptamer) array, SomaLogic, Boulder Co, we generated quantitative levels of 1307 proteins in serum samples from seventeen first-degree relatives (FDR) of Indigenous North American (INA) RA patients who developed inflammatory arthritis (IA) synovitis after having been followed prospectively for a mean of 3.2 years. All were ACPA+ at time of IA diagnosis. We also analyzed samples from ACPA+ FDR (n = 63) and ACPA- FDR (n = 47) who did not develop inflammatory arthritis. We applied a machine learning lasso regression model to identify a minimum set of proteins that classified patients who progress into clinical arthritis.

Results: Differential expression of 669 proteins (260 upregulated, 409 downregulated) were identified between pre-Progression samples and ACPA negative FDR. ITGA2B and HIST1H3A were the highest upregulated proteins in pre-Progression samples, while protease inhibitors SERPINA5 and ITIH4 were downregulated. A lasso regression model identified a 23-marker panel that classified pre-Progression samples from the larger pool of ACPA+ and ACPA- FDR serum samples. In a validation cohort (n = 34), the model correctly classified 31/34 samples (91.2% accuracy) with a sensitivity of 95.6% and specificity of 85.7%. Area under the curve (AUC) was 0.931 for the model. Progression scores were extracted from the model, which were higher in ACPA+ FDR compared to ACPA- FDR (p < 0.001). There were no differences in Progression score comparing pre-Progression samples that were remote or close to the time of IA onset. Network analysis implicated the activation of toll like receptor 2 (TLR2) and production of TNF and IL1 as key events that precede progression.

Conclusion: Compared to at-risk individuals who did not develop IA, clear and reproducible differences in the serum proteome are demonstrable in the serum samples of individuals who ultimately developed IA, even several years before the onset of clinically evident disease. Our findings suggest that the serum proteome provides a rich source of biomarkers that may serve both to classify at-risk individuals and to identify molecular pathways involved in the development of clinically detectable RA.

KEYWORDS

rheumatoid arthritis, pre-clinical, biomarkers, proteomics

Dr. Manoj Paul

BIO

I completed my PhD at the University of Mysore, India. During my PhD, I worked on signaling pathways associated with drug induced platelet apoptosis. Later, I moved to Vancouver to start as a Post-Doctoral Fellow in the lab of Dr. Hugh Kim, University of British Columbia, Canada. Here, I'm interested to gain a better understanding of platelet signaling in the context of juvenile arthritis. This could, in turn, lead to improved approaches for diagnosis and treatment of this serious and debilitating disease.



ABSTRACT: Pro-inflammatory platelet signaling in juvenile arthritis

AUTHORS: Manoj Paul and Hugh Kim

Background: Juvenile idiopathic arthritis (JIA) is a serious disease that affects ~24,000 Canadian children and teenagers resulting in pain, reduced mobility and a risk of long-term disability. All forms of JIA are characterized by joint inflammation and destruction caused by the recruitment of leukocytes that signal the release of tissue-degrading matrix metalloproteinases (MMPs) from resident chondrocytes in the joints. There is currently a lack of prognostic markers to identify children with JIA at risk for more severe and/or progressive disease.

Platelets are recognized as immune-competent cells with an important yet incompletely defined role in chronic inflammatory diseases including arthritis. Platelet factor 4 (PF4/CXCL4) is a pro-inflammatory chemokine secreted by activated platelets. Preliminary data from our laboratory show that PF4 promotes the release of MMP-1 and MMP-13 from cultured juvenile chondrocytes, thus pointing to PF4 as a potential prognostic marker for JIA.

Hypothesis: PF4 promotes MMP release in the joints of children with JIA, and is a potential biomarker for identifying JIA patients at risk for severe and/or progressive disease.

Experimental approaches:

1. Test the efficacy of PF4 antagonism in a cell culture model. PF4 upregulates MMP expression in juvenile chondrocytes; this effect should be nullified by the PF4 inhibitory antibody (RTO). Juvenile chondrocytes will be stimulated with recombinant PF4 in the presence or absence of RTO. The release of MMP-1, MMP-3 and MMP-13 from juvenile chondrocytes will be measured in cell culture supernatants by ELISA; MMP gene transcription will be quantified by real-time PCR.

2. Evaluate PF4 in plasma as a prognostic biomarker in JIA. Blood samples will be collected from newly diagnosed JIA patients as well as control samples from healthy children. Platelets will be isolated from whole blood and activated in vitro. The amount of secreted PF4 will be quantified by ELISA and correlated with clinical assessments of disease severity, determined by Juvenile Arthritis Disease (JADAS) scores.

Significance: The clinical management of JIA is a drain on health care resources and an important cause of child and youth morbidity in Canada. There is an urgent need to better understand the pathophysiology of JIA and to develop new and more effective risk assessments and management strategies.

KEYWORDS

juvenile idiopathic arthritis; matrix metalloproteinases; inflammation; cytokines; platelets; platelet factor 4.

Dr. Razieh Rabani

BIO

I am a senior post-doctoral fellow at university health network (UHN), Toronto. My research interest focuses on cell therapy approaches for treatment of osteoarthritis and other inflammatory diseases. I did my PhD in experimental medicine at McGill university working on signal transductions in neutrophils. My first postdoc at Saint Michael's hospital, Toronto involved investigation of mechanism of action of mesenchymal stromal cells in pre-clinical model of sepsis. This sparked my interest and enthusiasm in building a career in clinical and translational research. So, in 2018, I started my second post-doc at arthritis program at UHN, Toronto to elucidate the pathology of osteoarthritis as well as therapeutic efficacy of mesenchymal stromal cells in treatment of osteoarthritis.



ABSTRACT: Understanding the molecular mechanism governing therapeutic efficacy of MSCs in OA

AUTHORS: Rabani Razieh, Chan Mable Wing Yan, Chahal Jaskarndip, Mahomed Nizar, Marshall K. Wayne, Gandhi Rajiv, Viswanathan Sowmya

Background: Osteoarthritis (OA) is a joint disease affecting > 5 million Canadians and patients have limited palliative and joint-replacement surgical options. Stromal cell therapy is emerging as a compelling treatment for OA. Our first-in-Canada Ph1/2 trial with bone marrow mesenchymal stromal cells (MSCs) in OA patients showed significant improvements in patient outcomes. Pro-inflammatory monocytes/macrophages (M s) were reduced in the synovial fluid (SF), suggestive of a clinical MSC anti-inflammatory action.

Although, MSCs showed beneficial effects in all the patients, we found variabilities in MSCs efficacy among participants. The goal of this study is to identify novel mechanisms governing therapeutic efficacy of MSCs in OA focusing on identification of novel microRNAs (miRs) regulating the efficacy of MSCs and understanding the role of IL6 (one of top cytokines secreted by MSCs) in interaction of MSCs and M s.

Methods: We conducted unbiased miR sequencing on our clinical trial MSCs exposed to SF from OA patient followed with differential expression and pathway analysis. To explore the role of IL6, we co-cultured M s with OA-MSCs in the presence of OA-SF; or in the presence of IL6 antibody. M s cell surface markers and secreted factors were assessed by flow cytometry and ELISA, respectively.

Results: A multiplex screen of MSCs exposed to OA SF identified IL6 as a top cytokine; higher IL6 secretion by MSCs is associated with positive patient outcomes. Controversially, IL6 is known to be associated with OA severity. IL6 antibody abrogated MSCs-induced anti-inflammatory polarization of M s. Further, the effect of MSCs on M s polarization was attenuated in the presence of late OA-SF compared to early OA-SF, presumably due to enhanced IL6 trans-signaling (pro-inflammatory) in late-OA SF. To discriminate between classical vs. trans-signalling, we are using soluble gp130, a decoy receptor which complexes IL6-sIL6R. Preliminary result showed that sgp130 enhanced the expression of CD163 in M s exposed to OA SF.

Further, we have identified 25 miRs differentially expressed between MSCs from responder (5/ out of 5 KOOS sub-scale responses are clinically significant) and mild responder (2-3/5 KOOS sub-scale responses are clinically significant) participants. Interestingly, the identified miRs are associated with immune response, fibrosis and OA pathology. We are verifying the miRs by qPCR to better understand and predict potent MSCs, and/or OA patients that are responders to MSC therapies.

Conclusions: Understanding therapeutically relevant mechanism of action of MSCs will help to develop enhanced MSCs, and define potency criterion for screening effective MSCs in OA patients.

KEYWORDS

osteoarthritis, mesenchymal stromal cells, clinical trial, microrna, il6, macrophage

Matthew Veras

BIO

Matthew Veras is a PhD Candidate in his final year in the Department of Physiology and Pharmacology at Western University. He is also affiliated with the Bone & Joint Institute at Western University where he has served as the Chair of the Trainee Leadership Committee. Matthew's PhD project is investigating regulators of ectopic calcification in a mouse model of Diffuse Idiopathic Skeletal Hyperostosis (DISH). This project has involved the integration of transcriptomic, proteomic, and metabolomic datasets in addition to behavioral assays of pain. To date, he has co-authored 4 publications related to intervertebral disc degeneration and DISH.



ABSTRACT: Behavioral assessment of mobility and pain in a mouse model of diffuse idiopathic skeletal hyperostosis (DISH)

AUTHORS: Matthew A. Veras, Dale E. Fournier, Diana Quinonez, Magali Millecamps, Laura S. Stone, Cheryle A. Séguin

Background: Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory spondyloarthropathy characterized by ectopic calcification of spinal tissues affecting 15-25% of North Americans. Literature is conflicting on whether pain is a symptom of DISH and the lack of longitudinal studies evaluating the symptomology associated with DISH is attributed to radiographic diagnostic criteria limited to late stage detection. Preclinical animal models are therefore vital to better understand the pathobiology of DISH.

We have shown mice lacking equilibrative nucleoside transporter 1 (ENT1^{-/-}) develop ectopic calcifications with remarkable resemblance to human DISH through radiography and histology. This study was a comprehensive longitudinal assessment of pain and stiffness in the ENT1^{-/-} mouse model to correlate spine calcification with behavioral assays and molecular analysis. We aimed to evaluate if the ENT1^{-/-} mouse recapitulates symptoms associated with DISH and determine if pain is a feature of early disease.

Methods: 40 C57Bl6 mice were used in the study: n=20 ENT1^{-/-} and wild-type (WT). We assessed behavioral indicators of axial discomfort, and locomotor capacity longitudinally at 2, 4, and 6 months-of-age using the grip force strength, FlexMaze, tail-suspension, and open-field locomotion assays. Mice were scanned by μ CT at each time point to correlate behavioral changes with radiographic features. At endpoint (6.5 months-of-age), spinal cords were isolated for immunohistochemical analysis of pain-related peptides (CGRP).

Results: Increased spine calcification (with age) was associated with significant changes in the FlexMaze assay (mice must undergo lateral flexion to explore the maze). By 6 months-of-age, both sexes of ENT1^{-/-} mice showed reduced exploration speed compared to WT. These data, paired with reduced self-supporting behavior in the tail-suspension assay, suggest that ENT1^{-/-} mice experience significantly more flexion-induced discomfort compared to WT. Both sexes of ENT1^{-/-} mice showed less rearing behavior in the open field compared to age-matched WT, potentially attributed to increased pain and/or stiffness without axial stretch. ENT1^{-/-} mice of both sexes at 6 months-of-age also showed reduced forelimb grip strength compared to WT. Immunohistochemistry showed increased CGRP-immunoreactivity in the spinal cords of ENT1^{-/-} mice compared to WT, suggesting an increase in nociceptive neurons.

Discussion/conclusion: Taken together, these data strongly suggest that ENT1^{-/-} mice show signs of discomfort and stiffness similar to DISH in humans. This study demonstrated that pathological changes associated with spinal calcification correlate with symptomatic measures of pain and stiffness in the ENT1^{-/-} mouse, validating its utility as a preclinical model to assess candidate pain and disease-modifying interventions for DISH.

KEYWORDS

diffuse idiopathic skeletal hyperostosis, ectopic calcification, behavioural assays of pain, mouse models

Salem Werdyani

BIO

Salem Werdyani obtained his B.Sc. in 1998 from the UAE University, UAE. Then he moved to Canada and completed a bioinformatics graduate certificate program at Centennial College, Toronto, Canada. In 2016, Salem accomplished his Master of Science in Medicine and started his PhD at the Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, Canada. Mr. Werdyani's PhD project aims to apply genomics and metabolomics approaches to identify novel biomarkers for osteoarthritis development and progression, which can improve our understanding of the pathogenesis of the disease and suggest novel targets for developing disease-modifying therapies. Salem was awarded the Arthritis Society Training Graduate PhD Salary Award 2019. He plans to achieve some innovative research results and produce several high-quality research manuscripts, write scientific abstracts, and present his results in national and international conferences that will contribute to improve the quality of life for individuals with arthritis and their families.



ABSTRACT: Genes related to muscle strength, behavioral trait, pain response, and inflammation are associated with poor outcome of the total joint replacement therapy in primary osteoarthritis patients

AUTHORS: Salem Werdyani, Ming Liu, Andrew Furey, Zhiwei Gao, Proton Rahman, Guangju Zhai

Purpose: Total joint replacement (TJR) is considered as the most effective treatment for end-stage OA patients. Majority of patients achieve joint pain reduction and function improvement following to TJR. However, about 22% of them do not improve or get worse after surgery. The aim of this study was to identify genetic variants associating with poor outcome of TJR in primary OA patients by a genome-wide association approach (GWAS).

Methods: Study participants were total knee or hip replacement patients due to primary OA that were recruited to the Newfoundland Osteoarthritis Study (NFOAS) before 2016 in St. John's, NL. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess pain and functional impairment pre- and 3.99±1.38 years post-surgery. Participants with a change score less than 7 of 20 points for pain were considered pain non-responders; and those with less than 22 of 68 points for function were classified as function non-responders. DNA samples were extracted from patients' blood and genotyped using the genome-wide Illumina HumanOmni2.58 microarray. SNP data underwent strict quality control filtering; genotype imputation was performed using IMPUTE2 with multiple population reference data from 1000 Genome Project. Imputed data was used to test association with non-responders to TJR using the additive genetic model.

Results: In total, 39 responders and 44 non-responders were included in the analysis. Four chromosomal regions on chr1, 5, 7, and 8 were significantly associated with pain non-responding. The lead SNP (rs1537693, $p=4.4 \times 10^{-5}$) on chr1 is located in intron one of PLXNA2 gene functioning in neurotransmission. The top SNP (rs17118094, $p=4.4 \times 10^{-5}$) on chr5 is adjacent to SGCD gene acting in muscular strength. The SNP (rs71572810, $p=4.7 \times 10^{-5}$) on chr7 is nearby IMMP2L gene which associates with behavioral abnormalities. The SNP (rs6992938, $p=5.8 \times 10^{-5}$) on chr8 is close to TRPA1 gene that has a central role in the pain response to endogenous inflammatory mediators. Three loci were significantly associated with function non-responding. The lead variant (rs9729377, $p=1.7 \times 10^{-5}$) on chr1 falls between CTBS and MCOLN2 genes linked to inflammation and the immune response. Other top SNPs on chr2 and 10 harbor CCDC93, INSIG2, and KLF6 genes associating with heel bone mineral density, hypercholesterolemia, and obesity.

Conclusion: This project was the first study that investigated the association between genetic factors and TJR non-responders. Our results demonstrated that genes related to muscle strength, behavioral trait, pain response, and inflammation play a significant role in poor outcome of TJR, warranting further investigation.

KEYWORDS

total joint replacement, pain and function on-responders, genome-wide association approach, genotyping, genotype imputation, chromosomal region, single nucleotide polymorphism (snp), muscle strength, behavioral trait, inflammation.

Brian Wu

BIO

Brian Wu is a graduate trainee working towards a degree in Laboratory Medicine and Pathobiology at the University of Toronto. He currently is working under Dr. Mohit Kapoor at the Krembil Research Institute in Toronto Western Hospital with the aim of elucidating the mechanisms that drive pathological fibrosis in disease. While he is currently using an animal model of lung fibrosis, the Kapoor lab aims to adapt the findings from his current work towards better understanding potential mediators for fibrosis that may apply to the synovial joint. In particular, synovial fibrosis is a pathological outcome in many forms of arthritis including osteoarthritis and rheumatoid arthritis.



ABSTRACT: Biomedical Research Abstract for the Arthritis Society

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Background: Fibrosis can cause the loss of tissue function, organ failure and death through excessive deposition of extra cellular matrix. Currently there is unclear etiology and limited treatment for complete pathology resolution. We recently identified fibroblast-derived ephrin B2 as a pro-fibrotic mediator and *Efnb2* knockout (KO) in fibroblast yielded partial protection against the development of fibrosis in lung and skin. Incomplete protection suggests that ephrin B2 may have other cellular sources, and it is known that ephrin B2 can be expressed in the endothelium.

Methods: To understand the role of endothelial-derived ephrin B2 in fibrosis, we generated endothelial ephrin B2KO mice and subjected them to bleomycin-induced lung fibrosis. Further, ephrin B2 is known to interact with ephB4 receptor during fibrosis, but the role of ephB4 remains unclear. To elucidate the role of ephB4 receptor in fibrosis development, We have generated fibroblast-or endothelial-KO *Ephb4* mouse lines.

Results: We have found that ablation of both endothelial-*Efnb2* and fibroblast-*Ephb4* KO is protective against fibrosis development. We found that fibroblast *Ephb4* deletion to have substantially stronger protective effects.

Discussion: Current therapies for fibrosis are broad targeting and do not completely resolve disease activity. The understanding of ephrin B2 and ephB4 interaction as a potential disease mediating signaling pathway may uncover novel and specific therapeutic targets.*

KEYWORDS

fibrosis, ephb4, fibroblast, myofibroblast, extracellular matrix