Osteoarthritis is predominantly associated with a progressive loss of cartilage matrix but also involves other joint components in bone turnover and the synovium. Risk factors include age and mechanical trauma, e.g. excess weight that results in inflammation. Involved in this pathophysiology is chondrocyte senescence, a pathway when altered modifies the natural history of disease in a post-traumatic murine model. This study appears important in that reduction of chondrocyte senescence by inhibition of miR204 results in recovery of cartilage matrix synthesis and suppression of articular inflammation with amelioration of osteoarthritis in mice. A therapeutic promise for a common medical problem is offered.

**Stress-activated miR-204 governs senescent phenotypes of chondrocytes to promote osteoarthritis development**

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A progressive loss of cartilage matrix leads to the development of osteoarthritis (OA). Matrix homeostasis is disturbed in OA cartilage as the result of reduced production of cartilage-specific matrix and increased secretion of catabolic mediators by chondrocytes. Chondrocyte senescence is a crucial cellular event contributing to such imbalance in matrix metabolism during OA development. Here, we identify miR-204 as a markedly up-regulated microRNA in OA cartilage. miR-204 is induced by transcription factors GATA4 and NF-κB in response to senescence signals. Up-regulated miR-204 simultaneously targets multiple components of the sulfated proteoglycan (PG) biosynthesis pathway, effectively shutting down PG anabolism. Ecopic expression of miR-204 in joints triggers spontaneous cartilage loss and OA development, whereas miR-204 inhibition ameliorates experimental OA, with concomitant recovery of PG synthesis and suppression of inflammatory senescence-associated secretory phenotype (SASP) factors in cartilage. Collectively, we unravel a stress-activated senescence pathway that underlies disrupted matrix homeostasis in OA cartilage.


**Research Corner**

Rebecca McCullough, PhD is an Assistant Professor in the Department of Pharmaceutical Sciences in Skaggs School of Pharmacy. She received her PhD in Toxicology from the University of Colorado and performed her postdoctoral fellowship at the Cleveland Clinic. Throughout her career, she has been interested in understanding the mechanisms of disease pathogenesis of chronic liver disease, with a special emphasis on alcohol-related liver disease (ALD).

Dr. McCullough’s research interests include the role of innate immunity, including complement, in contributing to end-organ damage as a result of chronic alcohol exposure. She has identified complement activation occurs both in circulation and in liver biopsies from patients with alcoholic hepatitis. This seminal work directed future studies involving genetic knockout models of certain complement components, including C1qa, C4, Factor D, C3aR and C5aR. Using murine models of ALD, she later discovered complement is required for inflammation and tissue injury after alcohol exposure, but also that it is necessary for liver regeneration, leading to the successful funding of a K99/R00 from NIH/NIAAA. Her current research is focused on understanding how complement affects innate-like T cell populations in the liver in ALD as well as developing an immunotherapy using regulatory T cells. This model serves as a platform both for additional mechanistic work on liver T cell biology, complement, and metabolic diseases but also translatable for future therapies in ALD patients. Other areas of research include organ-organ crosstalk in metabolic diseases, with a special focus on adipose-liver crosstalk. Dr. McCullough has found complement influences the impact of ethanol on adipose tissue inflammation and the secretion of soluble and extracellular vesicle (EV)-derived inflammatory factors, referred to as the “secretome”. Dr. McCullough is currently applying transcriptomic methods to identify potential factors from adipose that may be involved in hepatic sensitization and damage during ALD.
Ethics and Compliance Websites Launched

University offices dealing with federal and state regulations now have a centralized location with helpful resources when it comes to complying with the law. The Ethics and Compliance Program -- which recently launched its websites for the Denver and Anschutz campuses, respectively (http://www.ucdenver.edu/research/ORC/Ethics-and-Compliance/Pages/Denver.aspx and http://www.ucdenver.edu/research/ORC/Ethics-and-Compliance/Pages/Anschutz.aspx) -- links 24 different aspects of the University’s governmental compliance, ranging from environmental health and safety to sexual harassment to research integrity.

The University has adopted an Institutional Ethics and Compliance Program that is intended to support a culture of ethics and compliance within the University community. An effective compliance program promotes the achievement of university goals and helps avoid program disruption and financial loss that can accompany compliance failures.

Programs continue to develop in all areas involving compliance, but there has historically been little coordination among programs, and no single contact point for Institutional Compliance overall. The new Ethics and Compliance websites are designed to provide a hub – a central place to “start here” – for all sorts of compliance.

Questions? Contact Lori Hopper, Institutional Compliance and Privacy Officer lori.hopper@ucdenver.edu or 303-724-0983

The Center for Bioethics and Humanities

The Center for Bioethics and Humanities is very interested in forming a team to submit an entry into the CMS Artificial Intelligence Health Outcomes Challenge. The grand price is $1 million and an application and brief slide deck are due by June 18, 2019. For More information, please go to https://www.cmschallenge.ai/

They are looking for collaborators experienced in using claims data, Experience of participant in AI/deep learning with complex data sets, and/or experience with health care-specific data--including experience with and knowledge in hospital admissions data and measures of clinical quality. The objectives of this challenge are as follows:

Challenge Objectives

1. Use AI/deep learning methodologies to predict unplanned hospital and SNF admissions and adverse events within 30 days for Medicare beneficiaries, based on a data set of Medicare administrative claims data, including Medicare Part A (hospital) and Medicare Part B (professional services).

2. Develop innovative strategies and methodologies to: explain the AI-derived predictions to front-line clinicians and patients to aid in providing appropriate clinical resources to model participants; and increase use of AI-enhanced data feedback for quality improvement activities among model participants.

They believe they are very well positioned to fulfill Objective 2, but are in need of team members for Objective 1. Matt DeCamp will be leading these efforts, please contact him at (matthew.decamp@ucdenver.edu) or Julie Ressalam (julie.ressalam@ucdenver.edu) if you are interested.

New Commercial Venture.

We are developing a new noninvasive respiratory analysis system that visualizes detailed turbulent exhale behavior. This next generation tool will enable the medical community to diagnose and treat a broader range of respiratory and sleep related conditions and patient groups. A recent National Science Foundation ICorps grant allows us to meet physicians to better understand their needs and any shortcomings of existing technology or diagnostic tools. We are seeking 10 to 15 minute meetings with medical professionals to improve current practice and diagnostic capabilities. We are hoping that the Anschutz Medical School can put us in touch with alumni and faculty that may benefit from moving this technology forward. Please contact Min-Hyung Choi, PhD at Min.Choi@ucdenver.edu or 303-315-1404