CMSR Researcher Receives NIH Grant to Study the Role of DNA Damage in Osteoarthritis

Osteoarthritis, or OA, is the most common cause of disability among adults, and is a significant public health burden since there is currently no treatment to prevent disease progression following the onset of symptoms. While OA is primarily characterized by a loss of articular cartilage, it also affects all tissues within the joint including bone, meniscus and synovium. The result is disabling pain and loss of mobility requiring many patients to eventually undergo total joint replacement.

Historically, OA has been attributed to "wear and tear" in response to mechanical load over time. More recently, OA is understood to be an active disease process involving altered tissue metabolism and local inflammation. Advanced age is the most important risk factor for the development of OA, however, the mechanisms driving the onset of disease during the aging process are unclear and understudied. Thus, to better understand how the aged joint environment is predisposed to the onset of OA, Dr. Jennifer Jonason's laboratory in the CMSR is investigating whether the cartilage-producing chondrocytes themselves, are the primary source of factors that lead to cartilage degradation and inflammation in age-related OA.

Articular chondrocytes are a long-lived, quiescent cell population that experiences increased oxidative stress with age, and oxidative stress can cause DNA damage in the form of double-strand breaks (DSBs). DNA DSBs, in turn, can activate NF-κB and Interferon Regulatory Factor (IRF) transcription factors via a protein known as Stimulator of Interferon Gene, or STING, resulting in expression of proinflammatory cytokines and chemokines that drive an innate immune response. Dr. Jonason's lab has found evidence that aged articular chondrocytes have DNA DSBs as well as increased activation of both NF-κB and IRF transcription factors. Further, the lab has found that activation of NF-κB signaling specifically in chondrocytes can accelerate the onset of an early stage age-related OA phenotype in mice.

To continue this work, Dr. Jonason will receive a 5-year grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The ~$2M grant will support further study on the role of DNA DSBs in articular chondrocyte fate and OA development, as well as defining the specific mechanisms by which DNA DSBs induce NF-κB and IRF transcription factors in chondrocytes leading to their development of a proinflammatory secretory phenotype. These studies will also determine whether inhibition of STING could be a novel approach to prevent NF-κB signaling and OA onset in aging joint tissues, thus, adding important clinical relevance to this highly mechanistic project.