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Can we delay the process of cartilage degeneration associated with Osteoarthritis: Emerging role of autophagy

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Osteoarthritis (OA) is among the most prevalent chronic human health disorders and the most common form of arthritis. Loss of chondrocyte cellularity within the articular cartilage is one of the critical events that initiate the degradation of articular cartilage during OA. However, it is still uncertain which mechanisms control the fate of chondrocytes within articular cartilage during normal versus OA conditions. Understanding the exact chondrocyte cell death/survival mechanisms could lead to several promising OA therapeutic strategies. Studies by us and others have recently shown that the process of autophagy, a form of programmed cell survival, is impaired during OA and may contribute to decreased chondroprotection, resulting in the degradation of articular cartilage. Our studies show that one of the key central factors that control autophagy mechanisms and ultimately the fate of the chondrocytes within the articular cartilage is the mammalian target of rapamycin (mTOR). mTOR is a serine/threonine protein kinase that regulates cell growth, survival and lifespan of organisms. We have shown that mTOR is overexpressed in human OA cartilage as well as mouse and dog experimental OA. Upregulation of mTOR expression co-relates with increased chondrocyte apoptosis and reduced expression of key autophagy genes during OA. Subsequently, we show for the first time that cartilage-specific ablation of mTOR (cartilage-specific mTOR knockout mice) results in increased autophagy signaling and a significant protection from destabilization of medial meniscus (DMM)-induced OA associated with a significant reduction in the articular cartilage degradation, apoptosis and synovial fibrosis. Furthermore, we show that regulation of Unc like kinase 1 (ULK1)/adenosine monophosphate-activated protein kinase (AMPK) signalling pathway by mTOR is responsible for regulating autophagy signaling and the balance between catabolic and anabolic factors in the articular cartilage. The studies provide a direct evidence of the role of mTOR and its downstream modulation of autophagy in articular cartilage homeostasis. Targeting cellular homeostatic processes, such as autophagy via inhibition of mTOR may be a promising therapeutic strategy to delay cartilage degeneration.

Biography

Mohit Kapoor is an Associate Professor and a Cartilage Biologist. His current appointments include University Health Network (Toronto, Canada) and the University of Montreal (Montreal, Canada). He completed his PhD from the University of Otago New Zealand. His research is directed towards identifying key novel mediators and signaling pathways involved in the pathophysiology of osteoarthritis. His research projects are funded by the Canadian Institute of Health Research (CIHR), Canadian Foundation for Innovation (CFI), Canadian Arthritis Network (CAN), Fonds de Recherche Sante Quebec (FRSQ)-Pfizer and is a recipient of Investigator awards from the Japan College of Rheumatology, ESCEO-AMGEN and FRSQ.

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