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hnRNPK a Possible Mechanosensitive Gene: Its Function in Chondrocytes and Osteoarthritis

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Abstract: Mechanical stimulation contributes to the development, homeostasis, integrity and functionality of the articular cartilage by modulating several cellular activities including production and remodeling of extracellular matrix (ECM), chondrocyte differentiation, proliferation and apoptosis. On the other hand, abnormal mechanical strain play a critical role in osteoarthritis (OA) pathogenesis by inducing ECM degradation and chondrocyte apoptosis. Furthermore, deleterious mechanical loading can also stimulates the production of pro-inflammatory mediators such as interleukin 1β (IL-1β) that promote to cartilage degradation, chondrocyte hypertrophy and inflammation [1]. Heterogeneous nuclear ribonucleoprotein K (hnRNPK), a member of the hnRNP family, is implicated in the expression, stabilization and organization of the cytoskeleton in neurons and fibroblast, suggesting that it might be involved in the regulation of cellular mechanical properties and mechanotransduction[2, 3]. However, it is still unclear whether hnRNPK participates in chondrocyte response to mechanical stimuli and osteoarthritis progression. The current study aimed to investigate the role of hnRNPK in chondrocyte mechanotransduction and establish its link in osteoarthritis development and progression. Here, we used cyclic tensile stress (CTS) method to examine the hypothesis that mechanical stimulation of chondrocytes alters the expression of hnRNPK. Furthermore, we studied the effect of hnRNPK siRNA on chondrocyte response to IL-1β and mechanical stimulation in chondrocytes. To validate its involvement in osteoarthritis, hnRNPK expression in chondrocytes isolated from normal and osteoarthritis cartilage was also investigated. hnRNPK is differentially expressed in normal and osteoarthritis chondrocytes and its expression is altered following CTS loading and IL-1β exposure. Chondrocyte cytoskeleton proteins (F-actin and vimentin), chondrogenic markers (type II collagen and aggrecan) and proteinase (matrix metalloproteinase 13(MMP-13) and A disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS4)) were identified as hnRNPK- regulated genes. Furthermore, downregulation of hnRNPK increased chondrocyte sensitivity to IL-1β, which was demonstrated by increased chondrocyte apoptosis and the expression of catabolic and hypertrophic markers. In conclusion, hnRNPK plays an essential role in maintaining chondrocyte phenotype and survival, and the regulation of ECM production and remodeling. Finally, mechanical loading and inflammation might promote osteoarthritis progression through the downregulation of hnRNPK.

Keywords: Mechanosensitive gene; hnRNPK; IL-1β; chondrocytes; osteoarthritis

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