Mechanical Signals as Regulators of Cartilage Degeneration and Regeneration

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Several studies have reported that altered mechanical loading of synovial joints results in a spectrum of conditions resulting in structural and functional deficiency of the joint. However, few studies have elucidated the coordination of intricate molecular signals that result in these pathophysiologic processes in a highly dynamic environment within the joint. A better understanding of these pathways will aid the development of new physical or pharmacologic therapies for joint disease.

In response to mechanical loading of the joint, the articular cartilage and chondrocytes are exposed to a complex array of stress, strain, fluid flow, osmotic changes, and other physical phenomena; however, under hyperphysiologic loading conditions, large deformations may lead to structural tissue damage, cell signaling, and pathologic anabolic and catabolic responses. The effect of mechanical stimuli on articular cartilage has been studied from morphologic and compositional perspectives, but an understanding of the molecular pathways involved in cellular signaling remains incomplete.

Although mechanical loading is necessary for normal cartilage maintenance, several in vivo studies suggest that abnormal mechanical forces appear to stimulate chondrocytes to produce inflammatory mediators,[1] many of which are normally produced by macrophages during response to injury or infection.[2] This response alters the delicate balance between anabolic and catabolic signaling, which can result in tissue damage and loss of function. Studies have further demonstrated that injurious compression can stimulate the production of reactive oxygen species and nitric oxide,[3,4] which depolymerizes hyaluronic acid[5] and kills chondrocytes[6] and suggests that the antioxidative status of the cartilage might be essential for the prevention of mechanically induced cell death. Chondrocyte apoptosis with an altered pattern of aggrecan expression (along with changes in CD44 level and NITEGE) following injurious loading recently has been reported in mice,[7,8] which can be reversed by inhibiting nuclear factor-κB (NF-κB) signaling.[9] Furthermore, autophagy—a key factor for cell homeostasis—is also suppressed by mechanical loading.[9] In addition to changes in the cartilage, the synovium can be affected by mechanical injury.[7,8] Increased expression of inflammatory genes and NF-κB signaling lead to synovitis. Little is known about the molecular signaling in other tissues; additional research in this area is needed to fully understand the crosstalk among various knee joint tissues in conjunction with loading and injury.

The mechanisms by which mechanical factors alter the pathophysiology of chondrocytes or other cells within synovial joints likely involve complex interaction among genetic, epigenetic, and (transcription-level) molecular influences. Chondrocytes perceive physical signals from their environment using a variety of mechanisms, including ion channels, primary cilia, and integrin-mediated connections to the extracellular matrix that involve membrane cytoskeletal and intracellular deformation. Therefore, an

improved understanding of the mechanisms by which cells sense and respond to mechanical signals may provide novel targets for the development of disease-modifying osteoarthritis drugs.[10] In cases in which mechanotransduction is mediated directly via mechanically gated ion channels, mechanical stimulation causes an ionic flux, generally involving calcium ion (Ca^{2+}) as an intracellular messenger. Given the relevance of mechanotransduction in health and disease, it is therefore surprising that the identification of specific mechanically gated ion channels has remained elusive, especially in mammals.

Recent evidence has confirmed the presence of several physically gated ion channels on the chondrocyte surface that may act as transducers of physiologic or pathologic mechanical loads.[11] Of note, the transient receptor potential (TRP) family of ion channels have emerged as critical regulators of cellular responses to a wide range of physical and chemical signals, including mechanical loading, osmolarity, and temperature. In particular, the TRP vanilloid 4 (TRPV4) channel has been found to be expressed and functionally relevant in several musculoskeletal tissues, including cartilage, bone, and synovium.[12] The critical role of the channels in joint development and health has been shown by the identification of a variety of *TRPV4* gene mutations that cause musculoskeletal diseases in humans.[13] The mechanisms by which the TRPV4 channel influences joint health have been studied both in vivo and in vitro. This channel appears to regulate the anabolic response of chondrocytes to mechanical loading, likely secondary to osmotic changes engendered in the local microenvironment of the chondrocytes.[14] Global knockout of the channel in mice has been shown to result in severe, accelerated osteoarthritis,[15] whereas cartilage-specific knockout of the channel is protective against age-related joint degeneration.[16]

Recent studies suggest, however, that the response of chondrocytes to high, potentially pathologic strains is not mediated by TRPV4 but rather by a newly discovered set of mechanosensitive ion channels named the "Piezos."[17] *Piezo1* and *Piezo2* genes are expressed and functional in articular chondrocytes, and they exhibit mechanical compression-mediated Ca^{2+} influx that underlies the injury response to mechanical stress. In cartilage explants, inhibition of Piezos using the toxin peptide GsMTx4 greatly attenuated mechanically induced cell death.[18]

Mechanical factors also may serve as signals that promote chondrogenic differentiation and cartilage regeneration,[19] and in vitro studies have provided several insights into how mechanical forces affect cell differentiation and behavior. It is important to appreciate that the stimulation required to enhance chondrogenic matrix production in chondrocytes may not be the same that induces chondrogenesis of mesenchymal stem cells (MSCs). Uniaxial compression of chondrocytes enhances matrix synthesis and deposition.[20] However, it has also been shown that although uniaxial compression of MSCs can increase glycosaminoglycan accumulation, expression of type II collagen does not occur in the absence of initial transforming growth factor-β (TGF-β) stimulation.[21] However, multiaxial load has been shown to induce chondrogenesis of human bone marrow–derived stem cells and articular–derived chondroprogenitor cells in the absence of exogenous TGF-β.[22] This is the result of the induction of endogenous TGF-β expression under complex load combined with a mechanical activation of the latent TGF-β.[23,24] The mechanical removal of the noncovalently bound latent associated protein has also been demonstrated using shearing of synovial fluid through a narrow-gauge needle.[25] Taken together, this would indicate that shear is a critical component of mechanically induced MSC chondrogenesis, whereas compression alone is sufficient for the redifferentiation of chondrocytes.

In summary, these findings provide evidence for a complex array of cellular machinery responsible for mechanotransduction under physiologic or pathologic conditions. A more thorough understanding of the detailed mechanisms involved in these processes may lead to novel approaches for enhancing tissue growth, or attenuating the mechanically driven processes that lead to osteoarthritis.

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