Articular chondrocytes transduce mechanical signals through the Wnt pathway

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Since at least the late 1980s, there has been clear evidence showing that mechanical stimulation of chondrocytes and cartilage can result in matrix synthesis. In 1989, Sah et al demonstrated that cyclical compression of cartilage explants resulted in incorporation of radiolabels to both collagen and glycosaminoglycan (GAG) fractions [1]. Cyclical tensile stretching of chondrocytes increases collagen and GAG synthesis in primary OA chondrocytes [2]. Several additional studies find that cyclical compression of chondrocytes results in synthesis of cartilage matrix molecules [3-5]. In contrast, static compression of cartilage explants and chondrocytes appears to result in matrix degradation and inhibition of matrix synthesis [6, 7]. These *in vitro* observations are consistent with several *in vivo* studies. For example, aged marathon runners have thicker cartilage than aged non-marathoners [8] and increased physical activity levels are associated with fewer OA symptoms [9, 10].

However, relatively few mechanisms of chondrocyte mechanotransduction are known. While there are challenges to studying chondrocyte mechanotransduction such as dedifferentiation, limited cell sources, and others, ion channels have been identified as a clear mechanism of chondrocyte mechanotransduction. For example, TRPV4 (transient receptor potential vanilloid 4) is a calcium permeable channel that is osmotically sensitive, and inhibition of TRPV4 reduces mechanically-induced expression of anabolic genes [11]. Cyclical tensile stretching of chondrocytes increases collagen and GAG synthesis in primary OA chondrocytes [2], and JAK inhibition can counteract cyclical-tension-induced gene expression [12]. Furthermore, several studies implicate the cytoskeleton in chondrocyte mechanotransduction [13-16]. Yet there remain several missing links between cyclical mechanical stimulation of articular chondrocytes and matrix synthesis.

In osteocytes, Wnt signaling is clearly established as an in vivo mechanism of cellular mechanotransduction. Expression of the Wnt antagonist sclerostin decreases with increased bone strain *In vivo,* and reduced loading results in increased sclerostin levels [17]. Sclerostin is a potent inhibitor of bone formation, and a subsequent study showed that maintaining approximately constant sclerostin expression in osteocytes during increased loading results in decreased bone formation [18]. This suggests a direct role for Wnt signaling in load-induced bone formation, and contrasts with the likely effects of Wnt signaling in articular chondrocytes.

There is a balance of Wnt-signaling required for joint homeostasis, as both inhibition [19]and activation [20] of beta-catenin in articular chondrocytes result in OA-like degeneration. There are several other results implicating the Wnt pathway in both joint homeostasis and OA. Upregulation of WNT16 is protective of articular cartilage after DMM [21]. Mice expressing the

Wnt inhibitor sclerostin display reduced histopathological degeneration compared to wild-type controls 16 weeks after compressive overload injury [22]. In a rabbit model of TMJ osteoarthritis, intra-articular administration of a Wnt inhibitor results in mild reductions in histopathological OA [23]. Wnt inhibitor DKK3 is upregulated in human adult OA cartilage, synovium, and synovial fluid, and in vitro culture with recombinant DKK3 resulted in decreased cytokine-induced degradation [24].

Intracellular WNT effectors are also important in osteoarthritis. Beta-catenin is elevated at the protein level in OA chondrocytes compared to normal, and cyclical hydrostatic pressure results in decreases in beta-catenin in OA, but not normal chondrocytes [25]. Furthermore, both microgravity and cyclical hydrostatic pressure increased activated beta-catenin compared to controls in pellet culture of rat chondrosarcoma cells [26]. Finally, in a global microarray, AXUD1 (AXIN1 up-regulated 1, Wnt pathway member) was upregulated by compression [27].

In this issue, Castro-Viñuelas *et al* studied Wnt signaling in cartilage and chondrocyte mechanotransduction [28]. Using a small-molecule Wnt activator, this study applied physiological cyclical compressive loading of to both OA and non-OA cartilage explants. These samples were from aged donors undergoing hip replacement for osteoporosis. The results show that the activation of Wnt signaling prior to mechanical loading of non-OA samples results in decreased expression of chondrogenic and matrix genes along with increased expression of proteolytic genes. These data suggest that Wnt signaling impairs the ability of chondrocytes to upregulate matrix synthesis following cyclical compression.

This finding paves the way for future studies seeking to harness chondrocyte mechanotransduction for cartilage repair and regeneration. However, several questions remain. Does blocking Wnt signaling result in increased matrix synthesis in response to cyclical mechanical stimuli? Is the magnitude of this potential matrix synthesis sufficient for cartilage repair? Do articular chondrocytes have access to sufficient pools of carbon sources to generate sufficient matrix? Are the mechanical properties of this neotissue similar to those of endogenous articular cartilage? While much progress remains, the study of Castro Viñuelas et al is an important step toward using mechanical stimuli to drive matrix synthesis for cartilage repair.

Author Contributions

The sole author conceived, wrote, and edited this editorial.

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Conflict of Interest

Dr. June is a co-founder of and owns stock in Beartooth Biotech and OpenBioWorks. Neither company was involved in the preparation of this editorial.

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