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Editorial
Can the meniscus affect the nature of a chondrocyte?

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It is well understood that proper joint kinematics and loading are important factors in maintaining the health of the articular cartilage of the knee. This state of normal, physiologic loading facilitates a balance between anabolic and catabolic processes resulting in low level, homeostatic cartilage matrix turn-over and remodeling. In this way articular cartilage can function throughout an entire lifetime without loss of its load bearing or lubricating characteristics. However, situations that dramatically alter knee joint biomechanics, such as chronic disuse or overuse[1–4], anterior cruciate ligament (ACL) injury[5,6], or damage to the fibrocartilaginous menisci[7–11], can result in progressive cartilage degradation and strongly correlate with the onset of osteoarthritis (OA).

Much has been learned in the past decades about the biology and biochemistry of menisci and ligaments in the knee as well as their role in stabilizing the joint and facilitating cartilage function. However, the underlying mechanisms by which these adjacent soft tissues may interact with cartilage and regulate chondrocyte behavior, *via* mechanical and/or biological pathways, are not well understood. To complicate the picture, cartilage structure and composition are known to vary with depth and also topographically across the joint surface. The prevailing hypothesis is that these variations in cartilage properties develop *in vivo* in response to different local mechanical loading environments. On one hand, cartilage structural heterogeneity presents difficulties to the investigator and adds complexity to experimental design. But an understanding of the origin of this heterogeneity may yield profound lessons in chondrocyte mechanobiology and the role of interactions between cartilage and adjacent soft tissues in health and disease.

In this issue of Osteoarthritis and Cartilage, Bevill *et al.*[12] report on gene expression in cartilage explants harvested from different regions of the tibial plateau: both the central region not covered by the meniscus, and the peripheral region fully covered by the meniscus. Selected genes involved in both anabolic and catabolic processes were analyzed *via* real time reverse transcription polymerase chain reaction (RT-PCR). Immediately following tissue harvest, baseline gene expression for type II collagen and aggrecan was higher in central region explants, suggesting constitutive differences in chondrocyte activity in these distinct areas. But there were no topographically dependent differences in transcription of the non-extracellular matrix (ECM) genes studied, including matrix metalloproteinases (MMPs), aggrecanases, tissue inhibitor of metalloproteinases (TIMPs) and tumor necrosis factor-alpha (TNF-α). Then, after 48 h of free-swelling culture, the transcriptional response to 6 h of continuous load-controlled dynamic compression was investigated. Expression of type II collagen, aggrecan, MMP-3, and TIMP-2 was upregulated in the central explants, but only type II collagen and TIMP-2 in the peripheral explants; additionally, the magnitude of mechanically induced changes in expression were more pronounced in the central region explants. Finally, to address a question of experimental methodology regarding the consequences of the authors' compression protocol on cartilage explant deformation, separate experiments confirmed that load-controlled dynamic compression also caused a continually increasing "static" creep compression reaching nearly 20% in peripheral explants by the end of the 6 h loading period, approximately two-fold higher than that in central explants.

This study brings forward an important added perspective of the whole joint to chondrocyte mechanobiology and cartilage pathophysiology. The observation that gene expression levels in the central and peripheral regions of tibial plateau cartilage became equivalent after 48 h of free-swelling culture suggest that the local mechanical environment in the joint mediates ECM transcription. The finding that chondrocytes in these distinct regions respond differently to similar loading conditions also suggests that there may be retained phenotypic differences in response to the local mechanical environment. And the differences in the creep compression response to dynamic loading reflect markedly lower stiffness of peripheral compared to central tibial plateau cartilage. Taken together, it is possible that after meniscal damage or surgery, cartilage from the central and peripheral regions may be differentially susceptible to degradation, further complicating the situation as the mechanical and biochemical properties of the cartilage become more regionally disparate.

Moving forward, several issues and new directions are highlighted by this study. First, as the authors and other investigators have emphasized, gene expression does not necessarily correlate with protein synthesis; heavily glycosylated macromolecules involving post translational

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modification, such as aggrecan[13], can exhibit opposite trends of transcription and biosynthesis in response to the same load. Therefore, further studies would be instructive to quantify biosynthesis rates of a broad array of proteins and proteoglycans relevant to cartilage homeostasis. Secondly, since clinical problems may result from chronic alterations to the kinematic environment in the joint following meniscus or ligament injury, an extended period of on/off dynamic loading cycles could be of interest. Time dependent changes in transcription and biosynthesis following the onset of altered load (from minutes to days) may reveal adaptation or the potential for failure. Based on the literature, one could also incorporate estimates of the change in load magnitude and distribution following partial or total menisectomy[8].

At the same time, joint injury involving damage to the ACL, meniscus, synovium and other tissues, also involves critically important biological sequelae superimposed on altered joint kinematics. Joint injury is known to involve the immediate release of a broad array of inflammatory cytokines[14] and proteases[15] into the synovial fluid that can dramatically alter the catabolic/anabolic balance within cartilage even in the absence of changes in loading profile. Thus, the additive and synergistic effects of altered loading in the presence of catabolic agents may have more severe consequences than alterations in either loading or cytokine levels alone, changes that can be explored using a systems approach (proteomic[16] as well as genomic[17]). The combined effects of overload and cytokine insult may also vary markedly with age. Interestingly, Bevill *et al.*[12] used juvenile cartilage. While some investigators may question the relevance of using immature cartilage in studies ultimately relevant to OA, injuries to juvenile/immature joints are common[18], and often responsible for initiating the cascade of inflammatory events and altered kinematics that may ultimately progress to OA.

At a complementary level, the authors' methodology also highlights the challenges in creating *in vitro* systems to model complex *in vivo* problems and, specifically, the mechanisms responsible for chondrocyte response to static vs dynamic cartilage deformation in the joint. The choice of load control (vs displacement control) is often motivated by the desire to mimic *in vivo* joint loading. However, the resulting sustained static (creep) compression of cartilage disks may have very different effects on transcription and biosynthesis than those caused by dynamic compression. Indeed, the authors state that the suppressive effects of the cumulative creep compression in their study (rather than the stimulatory effects of dynamic compression) may explain the observed "regional effects" on gene expression reported here. Thus, displacement control can be used in a complementary manner to enable mechanistic interpretation of the separate effects of static and dynamic compression. Regardless of the approach, it is important to measure and report both the load and displacement waveforms in any such experiment in order to clearly interpret the results and to be able to compare with other data in the literature.

The human knee joint is a complex system of tissues that must function cooperatively for effective and pain-free movement. Studying any one component in isolation in a manner that is also relevant to a clinical outcome can be challenging. Studies such as that of Bevill *et al.*[12] suggest that normal function and maintenance of tissues in the knee (e.g., tibial cartilage and the menisci) may be interdependent, and therefore research focused on resolving how each of these tissues may influence the others would be intriguing. By incorporating aspects of molecular, cell and tissue-level biology, mechanical behavior, and clinical disease progression, future work can extend our fundamental understanding of joint mechanobiology, ultimately leading to better disease prevention and treatment.

Conflict of interest

The authors have no potential conflicts of interest to declare.

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