Articular cartilage normally functions as a remarkable low-friction, wear-resistant, and load-bearing material. The spectrum of articular cartilage damage and degeneration presents a variety of therapeutic challenges. Putative therapies often are guided by a biomimetic approach, where the goal is to re-establish key biological and biomechanical features of normal articular cartilage and joints. In the mild stage of fibrillation, surface treatments may restore damaged superficial cartilage tissue. In the moderate stage of focal full-thickness chondral and osteochondral defects, cell-based tissue replacement may fill defects and restore local cartilage function. In end-stage osteoarthritis, tissue-based biological organ replacement may restore joint function. For effective therapies of articular cartilage, there is a need to understand and control dynamic biological processes to achieve the desired tissue or joint properties in bulk tissue and also in interface regions.

Examples of the need to address bulk and interface regions are provided by repair, regeneration, and replacement strategies for an osteochondral defect. A repair strategy such as microfracture, a regeneration strategy such as cell transplantation, and a replacement strategy such as osteochondral grafting all face a number of similar challenges. Each of these strategies seeks to fill the defect with cartilaginous material that bears load in the bulk, a material that has adhesive properties facilitating integration with the surrounding articular cartilage and subchondral bone, and a material that has anti-adhesive properties facilitating maintenance of a low-friction surface. The development of these bulk and interface properties may occur in vitro, such as during fabrication of an osteochondral implant, or in vivo, such as after implantation of a formed construct.

The bulk biomechanical properties are central to the load-bearing and wear-resistant functions of cartilage. The relationships between poroelastic properties and cartilage composition and structure at various stages of development and growth, at various depths from the articular surface, and in various joint locations, provide a blueprint for inducing repair tissue and fabricating replacement cartilage tissue. The finding that cartilage mechanical properties mature rapidly in the ~8 week antenatal period suggest that an immature cartilaginous tissue may be implanted and expected, under appropriate and relatively short-term post-operative rehabilitation conditions, to deposit and remodel the proteoglycan- and collagen-rich extracellular matrix to mature into tissue with adult-like load-bearing properties. The growth of cartilage appears mediated in part by a balance between metabolism of molecules that contribute the swelling pressure of cartilage and those that contribute to the restraining collagen network.

Surface properties are critical to the low-friction behavior of articular cartilage. While many lubrication mechanisms are operative in articular cartilage and joints, boundary lubrication function and failure may be critical to the damage that is evident at the articular surface. Bioengineering cartilage tissue to be stratified and to include appropriately localized cells that form a boundary lubrication layer, including lubricin/superficial zone protein/proteoglycan 4 (PRG4), may be needed to restore or achieve the low-friction articular surface of cartilage. Similarly, cartilage resurfacing strategies may also utilize cells synthesizing PRG4. The role of PRG4 and other proposed components of the boundary layer of cartilage remain to be fully elucidated. The cells in the superficial zone of articular cartilage appear to be of particular interest since they have properties of progenitor cells.

In other areas of an implant the surface may form an interface with host tissue that requires integration, both with the surrounding articular cartilage and the subchondral bone.
bone\textsuperscript{15}. Integration of an implant to the surrounding cartilage may be mediated by metabolism of the cross-linked collagen network, driven by cells in the local vicinity of the interface\textsuperscript{16}. Tailoring the cartilaginous implant and host tissue may facilitate integration, recapitulating the reparative milieu of immature cartilage\textsuperscript{17}. The integrity of the interface with the subchondral bone is difficult to analyze, and studies of the native interface have utilized specialized fracture methods\textsuperscript{18}. Appropriate formation of such an interface can occur in osteochondral repair procedures\textsuperscript{19}, and directing this process to be consistent \textit{in vivo} and also \textit{in vitro} are important for a number of treatment strategies.

In most of the above processes, the organization of cells within native, engineered, and implanted tissues is an important factor. Such cells have a limited domain over which they typically influence their surrounding\textsuperscript{20}. The chondrocytes of cartilage are initially at very high density, and then become more dispersed as the tissue grows. In the adult, chondrocytes are organized into oriented clusters and columns in different regions of the tissue. 3-D histological-resolution imaging methods have facilitated analysis of chondrocyte organization\textsuperscript{21,22}, effectively structural bioinformatics analysis of articular cartilage at the cell micro-scale. In engineered tissues, micro-scale cell manipulation methods allow for controlling chondrocyte organization and analyzing resultant effects\textsuperscript{23}. Appropriate cell interactions, with deposition and remodeling of the appropriate molecules in the local pericellular regions and at tissue interfaces is needed for treating articular cartilage and for translating novel tissue engineering approaches into successful \textit{in vivo} models and clinical practice.

References

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