J Musculoskel Neuron Interact 2004; 4(4):393-395

Hylonome

Perspective Article

Interface and bulk regions in the repair, regeneration, and replacement of articular cartilage

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Keywords: Articular Cartilage, Superficial Zone Protein/PRG4/Lubricin, Tissue Engineering, Integration

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[1]. 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[2]. 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[3,4], at various depths from the articular surface[5], and in various joint locations[6], 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[3,4] 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[7].

Surface properties are critical to the low-friction behavior of articular cartilage. While many lubrication mechanisms are operative in articular cartilage and joints[8], boundary lubrication function and failure may be critical to the damage that is evident at the articular surface[9]. 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)[10], may be needed to restore or achieve the low-friction articular surface of cartilage. Similarly, cartilage resurfacing strategies may also utilize cells synthesizing PRG4[11]. The role of PRG4 and other proposed components of the boundary layer of cartilage remain to be fully elucidated[12,13]. The cells in the superficial zone of articular cartilage appear to be of particular interest since they have properties of progenitor cells[14].

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

The author has no conflict of interest.

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Accepted 4 August 2004

bone[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[16]. Tailoring the cartilaginous implant and host tissue may facilitate integration, recapitulating the reparative milieu of immature cartilage[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[18]. Appropriate formation of such an interface can occur in osteochondral repair procedures[19], and directing this process to be consistent *in vivo* and also *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[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[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[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 *in vivo* models and clinical practice.

References

1. Sah RL, Klein TJ, Schmidt TA, Albrecht DR, Bae WC, Nugent GE, McGowan KB, Temple MM, Jadin KD, Schumacher BL, Chen AC, Sandy JD. Articular cartilage repair, regeneration, and replacement. In: (ed) Arthritis and Allied Conditions: A Textbook of Rheumatology, 15th Ed, ed by Koopman WJ, Lippincott Williams and Wilkins, Philadelphia; 2004:2277-2301.
2. Caplan AI, Goldberg VM. Principles of tissue engineered regeneration of skeletal tissues. Clin Orthop 1999; 367S:12-6.
3. Williamson AK, Chen AC, Masuda K, Thonar EJ-MA, Sah RL. Tensile mechanical properties of bovine articular cartilage: variations with growth and relationships to collagen network components. J Orthop Res 2003; 21:872-880.
4. Williamson AK, Chen AC, Sah RL. Compressive properties and function-composition relationships of developing bovine articular cartilage. J Orthop Res 2001; 19:1113-1121.
5. Schinagl RM, Gurskis D, Chen AC, Sah RL. Depth-dependent confined compression modulus of full-thickness bovine articular cartilage. J Orthop Res 1997; 15:499-506.
6. Temple MM, Bae WC, Rivard KL, Sah RL. Age- and site-associated biomechanical weakening of human articular cartilage of the femoral condyle: relationship to cellularity and wear. Trans Orthop Res Soc 2002; 27:84.
7. Asanbaeva A, McGowan KB, Masuda K, Klisch SM, Thonar EJ-MA, Sah RL. Mechanisms of cartilage growth: alteration and function and composition *in vitro* by deposition of collagen and proteoglycan matrix components. Trans Orthop Res Soc 2004; 29:554.
8. Wright V, Dowson D. Lubrication and cartilage. J Anat 1976; 121:107-118.
9. Meachim G. Light microscopy of Indian ink preparations of fibrillated cartilage. Ann Rheum Dis 1972; 31:457-464.
10. Klein TJ, Schumacher BL, Schmidt TA, Li KW, Voegtline MS, Masuda K, Thonar EJ-MA, Sah RL. Tissue engineering of articular cartilage with stratification using chondrocyte subpopulations. Osteoarthritis Cartilage 2003; 11:595-602.
11. Schmidt TA, Schumacher BL, Klein TJ, Voegtline MS, Sah RL. Synthesis of proteoglycan 4 by chondrocyte subpopulations in cartilage explants, monolayer cultures, and resurfaced cartilage cultures. Arthritis Rheum 2004; 50:2849.
12. Hills BA, Crawford RW. Normal and prosthetic synovial joints are lubricated by surface-active phospholipid: a hypothesis. J Arthroplasty 2003; 18:499-505.
13. Jay GD, Harris DA, Cha CJ. Boundary lubrication by lubricin is mediated by O-linked beta (1-3)Gal-GalNAc oligosaccharides. Glycoconj J 2001; 18:807-815.
14. Dowthwaite GP, Bishop JC, Redman SN, Khan IM, Rooney P, Evans DJ, Haughton L, Bayram Z, Boyer S, Thompson B, Wolfe MS, Archer CW. The surface of articular cartilage contains a progenitor cell population. J Cell Sci 2004; 117:889-997.
15. Ahsan T, Sah RL. Biomechanics of integrative cartilage repair. Osteoarthritis Cartilage 1999; 7:29-40.
16. DiMicco MA, Sah RL. Integrative cartilage repair: adhesive strength correlates with collagen deposition. J Orthop Res 2001; 19:1105-1112.
17. DiMicco MA, Waters SN, Akeson WH, Sah RL. Integrative articular cartilage repair: dependence on developmental stage and collagen metabolism. Osteoarthritis Cartilage 2002; 10:218-225.
18. Flachsmann R, Broom ND, Hardy AE, Moltschaniwskyj G. Why is the adolescent joint particularly susceptible to osteochondral shear fracture? Clin Orthop 2000; 381:212-221.
19. Shapiro F, Koido S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of

articular cartilage. J Bone Joint Surg Am 1993; 75-A:532-553.
20. Hunziker EB, Quinn TM, Hauselmann H. Quantitative structural organization of normal adult human articular cartilage. Osteoarthritis Cartilage 2002;10:564-572.
21. Jadin KD, Wong BL, Li KW, Bae WC, Williamson AK, Schumacher BL, Price JH, Sah RL. Depth-associated variation in chondrocyte density in bovine articular cartilage during growth and maturation. Trans Orthop Res Soc 2003; 28:469.
22. Sah RL. The biomechanical faces of articular cartilage. In: Kuettner KE, Hascall VC (eds) The Many Faces of Osteoarthritis. Raven Press, New York; 2002:409-422.
23. Albrecht DR, Sah RL, Bhatia SN. Geometric and material determinants of patterning efficiency by dielectrophoresis. Biophys J 2004; 87:2131-2147.