Biomaterials for Cartilage Regeneration

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Osteoarthritis (OA), rheumatoid arthritis (RA) or cartilage damage resulting from severe injuries are among the most prevalent chronic conditions that may lead to disability, resulting in high healthcare costs and a major economic burden to society.[1] Current articular or hyaline cartilage repair therapies include nonsteroidal anti-inflammatory drugs, such as cyclooxygenase-2 inhibitors, for pain relief; chondroprotective agents to stimulate chondrogenesis and chondrocyte synthesis of collagen and proteoglycans (eg, hyaluronan, chondroitin sulfate, glucosamine);[2] and surgical approaches (eg, microfracture, mosaicplasty, osteochondral autologous transplantation, autologous chondrocyte implantation, matrix-induced autologous chondrocyte implantation).[3,4]

The major challenge in selecting a cartilage regeneration technique for clinical applications is to find a method that demonstrates significant advantage over the others for improving joint function. However, so far, clinical outcomes have not produced histologically comparable cartilage that mimics the complex zonal architecture of native hyaline cartilage with optimal long-term implications.[4-7] Ideally, cartilage regeneration techniques must be cost effective, single stage, and patient friendly.[4] Biomaterials are an interesting choice because they not only provide in situ three dimensional space-filing properties to facilitate regeneration in medium or large-sized cartilage defects, but they also can be tailored to increase cell-anchorage sites by incorporating biophysical/biochemical cues for cell guidance.[1,5] In addition, mechanical compatibility is another crucial criterion that plays an integral role in stimulating chondrocytes to deposit cartilaginous extracellular matrix (ECM). Therefore, scaffolds are valuable in maintaining the mechanical integrity of constructs during the regeneration process. Furthermore, functional scaffolds have been designed to induce chondrogenic differentiation through a cascade of signaling events and regulatory cytokines.[1] All of these key factors demonstrate that biomaterials possess advantageous characteristics that set them apart from other competitors in the field of articular cartilage regeneration.

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Research on tissue-engineered products for hyaline cartilage regeneration is ongoing. In 2011, the market size of surgical procedures for cartilage regeneration reached €25 billion (US$33.5 billion) worldwide.[8] In the United States alone, 250,000 to 300,000 symptomatic cartilage injuries receive surgical treatment every year; 70% of these injuries are treated with lavage/débridement, 20% with microfracture, and 10% with other methods (eg, autologous chondrocyte implantation, allografts, autografts).[9,10] To date, collagen, alginate, fibrin, chitosan, hyaluronic acid (HA), and synthetic polymers have been the main components of commercial products used for cartilage regeneration. Therefore, based on their success rate, collagen-based scaffolds, commercially known as Carticel (collagen I/III; Genzyme) and CaReS (collagen I; Arthrokinetics) have been widely used to improve

Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

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Dr. Ge or an immediate family member is an employee of Novartis. Neither Dr. Mujeeb nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

J Am Acad Orthop Surg 2014;22:1-3

http://dx.doi.org/10.5435/JAAOS-22-09-001

the structural and biologic performance of grafts.[11,12]

HA alone as a chondroprotective agent has excellent viscoelastic properties, with the ability to promote chondrocyte phenotype via CD44 molecular markers; nonetheless, when injected into the defect site, it degrades rapidly. However, commercially available HA-based biomaterials including Hyalograft-C (Anika Therapeutics) and Hyalgan (Fidia Pharma), have been shown to promote the regeneration of cartilage with improved mobility.[5,13] Cartipatch (Xizia Biotech), composed of alginate/agarose hydrogel, has been clinically proven to regenerate hyaline cartilage.[14] In addition, synthetic polymers, such as the TruFit plug (composed of PLGA/calcium sulfate/PGA fibers; Smith & Nephew)) and chondrotissue (composed of PGA/HA sponge; BioTissue) have been used for filling osteochondral defects with satisfactory outcomes. All the abovementioned commercial products are approved by the FDA and the Medical Devices Directorate in the EU.

Unmet Expectations of Biomaterials and Future Perspectives

Biomaterials are designed to be flexible in order to take the shape and size of the defect site upon implantation or injection.[5] Apart from satisfying the fundamental requirement of biocompatibility, scaffolds must also mimic the in-depth heterogeneity of native cartilage and simultaneously promote cell adhesion, proliferation, and ECM deposition in situ.[15] Hydrogels and sponges have been shown to have interconnected pores or fibers (optimum pore size, 150 to 250 μm),[16] through which diffusion of nutrients and other biologic signaling molecules can facilitate complete integration with the host cartilage and subchondral bone.[17] Lack of integration may deteriorate regenerated cartilage.[18] In addition, altering mechanical properties (including strength, stiffness, and roughness) has also been shown to have an effect on the stability of the scaffold.[19,20] Various studies have shown cell-seeded scaffolds to aid deposition of cartilaginous ECM; however, lack of maturation has led to inferior qualities and subsequent clinical failure.

Summary

Although researchers have been successful in restoring the surface of articular cartilage via preloaded growth factors (eg, transforming growth factor–β) and cells in situ, constructing fully functional cartilage is still in progress.[21] Henceforth, using extrinsic biologic, chemical, structural, and mechanical cues, intensive research is now under way to fabricate new biologically inspired materials.[19] If these fundamental parameters are met, tissue engineered scaffolds will be able to restore cartilage functions more efficiently and effectively for clinical applications.

References

1. Ge Z, Li C, Heng BC, Cao G, Yang Z: Functional biomaterials for cartilage regeneration. *J Biomed Mater Res A* 2012;100(9):2526-2536.
2. Johnson K, Zhu S, Tremblay MS, et al: A stem cell-based approach to cartilage repair. *Science* 2012;336(6082):717-721.
3. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L: Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 1994;331(14):889-895.
4. Redman SN, Oldfield SF, Archer CW: Current strategies for articular cartilage repair. *Eur Cell Mater* 2005;9:23-32.
5. Khan IM, Gilbert SJ, Singhrao SK, Duance VC, Archer CW: Cartilage integration: Evaluation of the reasons for failure of integration during cartilage repair: A review. *Eur Cell Mater* 2008;16:26-39.
6. Hangody L, Ráthonyi GK, Duska Z, Vásárhelyi G, Füles P, Módis L: Autologous osteochondral mosaicplasty: Surgical technique. *J Bone Joint Surg Am* 2004;86(suppl 1):65-72.
7. Hangody L, Kish G, Kárpáti Z, Udvarhelyi I, Szigeti I, Bély M: Mosaicplasty for the treatment of articular cartilage defects: Application in clinical practice. *Orthopedics* 1998;21(7):751-756.
8. Bock AK, Ibarreta D: *Rodriguez-Cerezo*. JRC Scientific and Technical Reports IPTS European Communities, 2003, pp 1-62.
9. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG: Cartilage injuries: A review of 31,516 knee arthroscopies. *Arthroscopy* 1997;13(4):456-460.
10. Reza M: *Annual US Biomaterials Business Intelligence Reports*. Millennium Research Group, 2012.
11. Gikas PD, Bayliss L, Bentley G, Briggs TW: An overview of autologous chondrocyte implantation. *J Bone Joint Surg Br* 2009;91(8):997-1006.
12. Schneider U, Rackwitz L, Andereya S, et al: A prospective multicenter study on the outcome of type I collagen hydrogel-based autologous chondrocyte implantation (CaReS) for the repair of articular cartilage defects in the knee. *Am J Sports Med* 2011;39(12):2558-2565.
13. Grigolo B, Lisignoli G, Piacentini A, et al: Evidence for redifferentiation of human chondrocytes grown on a hyaluronan-based biomaterial (HYAff 11): Molecular, immunohistochemical and ultrastructural analysis. *Biomaterials* 2002;23(4):1187-1195.
14. Selmi TA, Verdonk P, Chambat P, et al: Autologous chondrocyte implantation in a novel alginate-agarose hydrogel: Outcome at two years. *J Bone Joint Surg Br* 2008;90(5):597-604.
15. Sharma B, Williams CG, Kim TK, et al: Designing zonal organization into tissue-engineered cartilage. *Tissue Eng* 2007;13(2):405-414.
16. Zhang Q, Lu H, Kawazoe N, Chen G: Pore size effect of collagen scaffolds on cartilage regeneration. *Acta Biomater* 2014;10(5):2005-2013.
17. Zhang J, Wu Y, Thote T, Lee EH, Ge Z, Y: The influence of scaffold microstructure on chondrogenic differentiation of mesenchymal stem cells. *Biomed Mater* 2014;9(3):1-11.
18. Huey DJ, Hu JC, Athanasiou KA: Unlike bone, cartilage regeneration remains

elusive. *Science* 2012;338(6109):917-921.

19. Murphy WL, McDevitt TC, Engler AJ: Materials as stem cell regulators. *Nat Mater* 2014;13(6):547-557.

20. Stevens MM, Qanadilo HF, Langer R, Prasad Shastri V: A rapid-curing alginate gel system: Utility in periosteum-derived cartilage tissue engineering. *Biomaterials* 2004;25(5):887-894.

21. Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ: Regeneration of the articular surface of the rabbit synovial joint by cell homing: A proof of concept study. *Lancet* 2010;376(9739):440-448.