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Operative Techniques in
Orthopaedics

The Use of Biological Adjuncts

MaCalus V. Hogan, MD,[*] Ermias S. Abebe, MD,[*] Ethan J. Fraser, MBBS,[†]
Lisa A. Fortier, DVM, PhD,[‡] and John G. Kennedy, MD, MMSc, MCh, FRCS (Orth)[†]

Osteochondral lesions of the talus present unique anatomical and technical considerations to orthopaedic surgeons. Central to this clinical challenge is the current inability to restore cartilage to its native state following injury. The utilization of biological adjuncts for cartilage repair is under increased investigation across the orthopaedic surgical arena. At the core of cartilage bioengineering are 3 essential elements: chondrocytes and the application of cell sources capable of undergoing chondrogenic proliferation and differentiation; the application of biological growth factors optimal for cartilage repair; and the utilization of scaffolds optimal for cell and growth factor delivery and maturation. This review aims to highlight current basic science and clinical evidence on the use of cell sources and biological growth factors for the treatment of osteochondral lesions of the talus.
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Introduction

Osteochondral lesions (OCL) of the talus present unique anatomical and technical considerations to orthopaedic surgeons. Chondrocytes, the dominate cell type in cartilage, have little replicative capacity owing to their inability to migrate within extracellular matrix (ECM) for deposition or repair and limited vascularity.[1] Small lesions form scar or fibrocartilage tissue and are often treated by microfracture or autologous chondrocyte transfer. Talar OCLs may evolve to osteoarthritis (OA) and can lead to functional disability. Though the rate of progression is difficult to estimate, end-stage OA seen with large talar defects often ultimately requires arthrodesis or arthroplasty.

Given that cartilage cannot self-repair and sizeable or symptomatic OCL tends to fail conservative management, surgical intervention is often needed. Current paradigms aim to treat well-defined OCL by cell-based therapies, the use of autologous chondrocyte implantation, and autograft or allograft transplantation.[2] Cell-based therapies allow for the local stimulation or delivery of cells that exhibit chondrocyte function into the defect, whereas transplantation allows for the transfer of existing cartilage cells to the defect site. These techniques combine biomaterial scaffolds, with the other stem cell types, as well as inductive bioactive and bioreactive factors, to aid in defect repair. Such an approach using tissue engineering technologies for the treatment of talar OCL stands to increase as research into this arena expands.[3]

Adult-derived stem cells were traditionally believed to be housed solely within the hematopoietic system. Current evidence has expanded this definition to include "undifferentiated" cells found even in differentiated tissue: progenitor cells. In vitro studies have identified promising stem cells for potential therapeutic application in patients in the near future.[3] Thus, efforts aimed at restoring or regenerating articular cartilage to relieve pain, increase mobility, and delay or prevent the onset of arthritis are increasingly under investigation. Overall, it is hoped that, as more is learned about cartilage and the healing response, surgeons will be better able to restore an injured joint to normal structure and function.

Embryonic-Derived Mesenchymal Cells

Embryonic-mesenchymal cells (EMCs) are pluripotent stem cells derived from the early-stage preimplantation embryo.[4] Unlike adult-derived stem cells, which can only differentiate into

*Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA.
†Division of Foot and Ankle Surgery, Hospital for Special Surgery, New York, NY.
‡Department of Clinical Sciences, Cornell University School of Veterinary Medicine, Cornell University, Ithaca, NY.
Address reprint requests to MaCalus V. Hogan, MD, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA 15232. E-mail: hoganmv@upmc.edu

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a limited number of cell types, EMCs have limitless capacity for self-renewal and can easily be directed to differentiate into all cell types in the body. However, the process of embryonic preparation results in termination of the embryo and remains the subject of ethical debates.[1] These ongoing ethical and political considerations have greatly halted the development of therapeutic cell-based medical therapies. Currently, the evidence shows that EM-derived stem cells are simply early progenitor cells free of any reprogramming.[5] They have been programmed to form hepatocytes, bone marrow cells, and endothelial cells in vitro. Theoretically, they can easily be differentiated into chondrocyte formation as well as other cell lineages but this is under early investigation.[6,7] The plasticity or multilineage potential of EMCs and their self-renewal capacity also raises concerns regarding the tumorgenicity of these stem cells.[7] Further studies are needed to help investigate the therapeutic potential of EMCs in cartilage regeneration.

Bone Marrow–Derived Stem Cells

Mesenchymal stem cells (MSCs) are adult-derived stem cells with multipotent and high proliferation capacity. Bone marrow presents the most widely researched and commonly used pluripotent cell lineage in cartilage repair.[1] Concentrated bone marrow aspirate (cBMA) is becoming a widely used biological adjunct in a variety of orthopaedic pathologies including cartilage repair. The inherent advantage of bone marrow aspirate is that it provides a source of MSCs and growth factors that can be obtained at the time of operation in a 1-step procedure from the iliac crest, among other locations. The concentration of MSCs signifies only a small percentage of the total nucleated cells found in the aspirate, with approximately 0.001%-0.01% of mononuclear cells found to be MSCs after density gradient centrifugation.[8,9]

Bone marrow aspirate also contains hematopoietic stem cells, which have the potential to differentiate into platelets providing cBMA with the added benefit of introducing a mileau of anabolic and anticatabolic growth factors that are contained in the platelet α-granules.[8] The growth factors secreted are believed to be involved in facilitating chondrogenesis and upregulating production of articular cartilage ECM.[10,11] The use of cBMA has been investigated as an adjunct to microfracture in a preclinical large animal model. To date, unlike ESCs, MSCs have not been shown to have unrestricted regrowth potential and are believed to have less plasticity, making them an ideal option for cartilage restoration techniques.[1,2] The stimulation of MSCs is the foundation of microfracture, which introduces bone marrow and multipotent MSCs directly into the chondral defect.[12,13]

Bone marrow, blood, cytokines, and growth factors are all introduced via drilling, leading to fibrin clot formation. The ensuing cytokine-mediated inflammatory and growth factor response together promotes tissue healing within the defect. The infill within the substance of the defect is typically fibrocartilaginous repair tissue. It has been shown that this newly formed scar tissue is primarily composed of type-I collagen and inherently differs in mechanical and biological properties from hyaline cartilage.[1,2]

The role of mesenchymal stromal cells in the cartilage healing process is at the foundation of the potential benefits of bone marrow aspirate concentrate delivery as an adjunct in the treatment of OCLs. The delivery of concentrated MSCs in addition to microfracture for OCL is under increased investigation in the veterinary arena. In an equine model, McIlwraith et al[14] treated knee lesions with microfracture alone vs microfracture in combination with bone marrow–derived MSC (BMSCs) injection at 1 month following the index procedure. Analysis at 1 year demonstrated improved repair tissue quality as well as increased aggrecan content in the BMSCs group. Fortier et al compared microfracture alone with microfracture and bone marrow aspirate concentrate for the treatment of full-thickness defects of the lateral trochlear ridge in horses. Histologic results at 8 months demonstrated increased proteoglycan and glycosaminoglycan content as well as greater type-II collagen content in the microfracture plus bone marrow aspirate concentrate group.[15]

Several studies have evaluated the application of BMSCs in the treatment of talar OCLs in the clinical setting. One case series reported improved functional outcomes in 72 patients at 2 years following osteochondral autograft transplantation and bone marrow aspirate concentrate delivery.[16] In their prospective clinical study, Giannini et al[17] evaluated the use of a 1-step arthroscopic technique that entailed the delivery of concentrated bone marrow–derived cells on either collagen or hyaluronic acid (HA) membrane scaffolds for talar lesions in 48 patients with a minimum of 2-year follow-up. They reported improved American Orthopaedic Foot and Ankle Society (AOFAS) scores and varying degrees of cartilage remodeling. They concluded that this technique was a viable alternative to microfracture alone for talar OCLs. This same group looked at their 4-year outcomes using the same 1-step technique. AOFAS scores remained significantly improved than they were preoperatively, though a decline was noted at both the 36- and 48-month time points. Magnetic resonance imaging T2-mapping analysis showed regenerative tissue similar to hyaline cartilage.[18] A recent cohort study compared clinical outcomes of MSC injection and microfracture with microfracture alone in the treatment of talar OCL in patients older than 50 years. The average follow-up for the study was 21.8 months, with the office demonstrating statistically significant improvement in functional outcome scores in the MSC injection and microfracture treatment group.[19]

Adipose-Derived Stem Cells

In vitro studies have also evaluated the chondrogenic potential of adipose stem cells.[1] These studies have found that cartilage with high total collagen but lower levels of type-II collagen can be produced from this cell lineage. Although less chondrogenic than BMSCs, fat cells are an abundant source of stem cells for the production of chondrocytes.[20,21] In vitro studies suggests that with the right mechanoinductive and biological cues in the future, adipose tissues may provide renewable supply of stem