Articular Cartilage Repair: Basic Science

Articular Cartilage Injury

Damage to articular cartilage is common and results from either traumatic injury, such as those experienced during sports activities, or degenerative changes, such as those occurring in joints with osteoarthritis (OA) or osteochondritis dissecans (OCD). When left untreated, damage to articular cartilage tends to progress, eventually resulting in severe joint pain and/or impaired joint function. Careful consideration should be given to the age-effects and immunologic properties of various cartilage treatment modalities.

Current Cartilage Repair Treatment Modalities

Current clinical treatments to repair articular cartilage include debridement, bone marrow stimulation, osteochondral allograft and autograft (OATS/Mosaicplasty) transplantation, and autologous chondrocyte implantation.

Typical cartilage repair alternatives:

- Debridement: removing damaged cartilage tissue from the defect area, which may provide temporary pain relief but does not result in cartilage tissue repair;
- Marrow stimulation (Microfracture/drilling/abrasion): bleeding the subchondral bone to stimulate the formation of fibrous repair tissue, which does not provide long-lasting repair. The repair tissue is fibrous in nature, and this treatment modality is more applicable to small chondral defects of younger patients than large defects of older patients;
- Autologous Osteochondral Transplantation (OATS/Mosaicplasty): transplanting a single or multiple osteochondral plug(s) from the low-weight-bearing donor site(s) of the patient’s joint to the high-weight-bearing recipient site(s). This is limited to treating small to medium (up to 2.5 cm²) defects and has associated donor site morbidity;
- Autologous Chondrocyte Implantation (ACI): transplanting in vitro-expanded chondrocytes, isolated from a cartilage biopsy from the 1st stage of the procedure, to the defect site in the 2nd stage of the procedure. This technique has several limitations, including: (a) the need for multiple operations (2-stages with about 30% of cases requiring a 3rd stage to shave down hypertrophic overgrowth of the periosteal flap that is sutured over the defect during the cell transplantation); hypertrophic overgrowth has previously been reported to be as high as 63%; (b) high cost ($20k+ just for the cell expansion), (c) sub-optimal quality of the implanted cells (de-differentiated fibroblastic cells) and the resulting repair tissue; and (d) unproven clinical advantages over Microfracture and Mosaicplasty;
- Allogenic Osteochondral Transplantation: transplanting osteochondral plugs taken from fresh cadaveric donor joints to repair cartilage defects of a recipient’s joint. This technique has been successfully used in repairing chondral and osteochondral defects even with large defect sizes. However, donor tissue availability limits its usage to about 2,000 cases annually in US. Further, failure of osteochondral allografts has been associated with osseous collapse and poor integration cartilage-to-cartilage.

Age Effects of Immature vs. Adult Cartilage

Unfortunately, once damaged, adult articular cartilage rarely heals spontaneously, as shown in an adult rabbit laceration study (Figure 1). However, immature articular cartilage can heal spontaneously (Figure 2).

Figure 1. Superficial cartilage laceration (8-weeks post-op; adult rabbit)

Figure 2. Superficial cartilage laceration (3-weeks post-op; fetal lamb)
Several reasons could account for the different biologic responses of mature and immature articular cartilage to injury:

- Immature articular cartilage tissue has a significantly higher cell density than mature articular cartilage (Figure 3).

- Immature chondrocytes have superior capabilities of producing extracellular matrix than mature chondrocytes as measured by the rate of production of sulfated glycosaminoglycan (s-GAG). The GAG content defines cushioning properties of articular cartilage.

- Immature chondrocytes show significantly greater mRNA levels for Type II and Type IX collagen (Figure 5).

Risk Associated with Immunological Rejection and Disease Transmission

While osteochondral allograft transplantation is a clinically proven efficacious cartilage repair procedure, immuno-rejection and disease transmission could pose risks to recipients. Fortunately, a significant amount of scientific data accumulated over the past decades addresses these concerns.

Immunology

- Articular cartilage has been shown to be immune privileged, partly due to the lack of vasculature and the dense extracellular matrix of this tissue.

- Clinical experiences of more than three decades of fresh osteochondral allograft transplantation indicate that immune suppressants are not required for these procedures. While elevated levels of relevant antibodies were detected in the serum samples of these recipients, there have been no reports of immunological rejection of these transplanted allografts with the exception of occasional lack of incorporation of the bony portion of the transplants. The weak immune response is reported to arise from marrow elements retained within the osseous component of the osteochondral transplant. No immunological response to the cartilage component of osteochondral allografts has been reported.

- In vitro mixed lymphocyte-chondrocyte reaction (MLLR) allo-reactivity assays have shown that chondrocytes do not elicit an allo-response, as shown by the lack of proliferation of human peripheral blood lymphocytes co-cultured with allogenic human chondrocytes. This was deemed to be due to the fact that chondrocytes lack the expression of specific co-stimulatory molecules (e.g. CD80 and CD86) required for allo-reactivity. Additionally, chondrocytes were found to express cell surface proteins that suppress lymphocytes proliferation.

Disease Transmission

In order to reduce the risk of disease transmission, the FDA has set out stringent requirements in “Donor Eligibility,” 21 CFR Part 1271 subpart C and “Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).” While the risk of disease transmission is a concern for musculoskeletal allograft transplantation, the rate of occurrence is extremely low. Extensive health and lifestyle screening of donors and family members is conducted. Additionally, specimens from each donor must be tested for evidence of, at a minimum, the following communicable disease agents:

- Human immunodeficiency virus, type 1 and 2
- Hepatitis B virus
- Hepatitis C virus
- Treponema pallidium
If the donor is also donating viable, leukocyte-rich cells or tissue, they must also be tested for the T-lymphotropic virus and cytomegalovirus (CMV).

Summary

Articular cartilage injury, left untreated, tends to progress and result in severe joint pain and/or loss of function.

Effect of Age on Chondrocyte Function

• Mature articular cartilage has limited capacity for spontaneous repair.
• Young articular cartilage has a higher chondrocyte density than adult cartilage.
• Young chondrocytes produce more matrix S-GAG, which defines the cushioning properties of the tissue.
• Young chondrocytes show 2-orders of magnitude higher levels of Type II and Type IX collagen mRNA than adult chondrocytes.
• Immature articular cartilage has a greater capacity for spontaneous repair than adult cartilage.

Immunology

• Articular cartilage lacks vascularity and is immune privileged.
• Articular chondrocytes actively suppress allogenic lymphocyte proliferation and can be transplanted without fear of rejection.

Disease Transmission

• Donated tissues procured by FDA registered establishments are screened and tested in accordance with FDA requirements for transplantable human tissue.

References


