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Immunology and cartilage regeneration

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Abstract The intrinsic regenerative capacity of avascular cartilage is limited. Cartilage injuries result in chronic, non-healing lesions requiring surgical management. Frequently, these surgical techniques make use of allogeneic cells and tissues. This review discusses the immune status of these materials. Cartilage allografts, often used in orthopedic and plastic surgeries, have rarely provoked a significant immune response. In whole cartilage transplants, the dense matrix produced by chondrocytes inhibits lymphocyte migration, preventing immune detection rendering them "antigen sequestered." It is unclear whether isolated chondrocytes are immune-privileged; chondrocytes express immune inhibitory B7 molecules, indicating that they have some ability to modulate immune reactions. Allogeneic cartilage grafts often involve a bony portion often retaining immunogenic cells and proteins—to facilitate good surgical attachment and concern that this may enhance inflammation and immune rejection. However, studies of failed cartilage grafts have not found immune responses to be a contributing factor. Meniscus allografts, which also retain a bony portion, raise similar concerns as cartilage allografts. Despite this, the plugs improved patient outcomes, indicating that the immunological effects were not clinically significant. Finally, allogeneic mesenchymal stromal cells (MSCs) also are being investigated as a treatment for cartilage damage. MSCs have been demonstrated to have unique immunomodulatory properties including their ability to reduce immune cell infiltration and to modulate inflammation. In summary, the immunogenic properties of cartilage vary with the type of allograft used: Cartilage allografts demonstrate active immune-suppressive mechanisms as evidenced by lack of allograft rejection, while MSC allografts appear to be safe for transplantation.

Keywords Osteochondral · Cartilage · Allograft · Chondrocyte · Transplantation

Introduction

Articular cartilage is the connective tissue found at the ends of diarthrodial joints to allow low-friction, pain-free movement. It is composed of a dense extracellular matrix (ECM) that contains collagen type II and aggrecan, a high molecular weight proteoglycan [1]. The specialized cells, chondrocytes, comprise only a small percentage (approximately 10 %) of the total tissue volume and are the only cell type found within the tissue. It is highly organized with several zones from the articular surface down to the underlying subchondral bone. Collagen fibers are oriented tangential to the surface in the uppermost superficial zone to resist shear gliding forces at the surface, becoming larger and changing orientation as they progress down into the deeper zones to resist compressive loading [2]. Cartilage is avascular, aneural, and alymphatic, relying on diffusion to provide both cell nutrition and waste removal; this process is facilitated by the mechanical forces applied to the tissue by activities of daily living [3]. These unique

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characteristics have implications for how the tissue responds to injury and ultimately for its immunology.

Cartilage tissue has no inherent regenerative capabilities due to its lack of vascularity and its relatively low cellularity [4]. It cannot detect injury and does not go through the normal phases of repair—necrosis and inflammation—that vascularized tissues exhibit. The density of the ECM inhibits cellular infiltration of macrophages and lymphocytes. This aspect of cartilage biology often results in chronic, non-healing lesions that can cause significant pain and loss of function in the patient. Analgesics and anti-inflammatory medications can provide some relief for mild lesions, but more severe cases involving articular cartilage and meniscus often require surgical management. Surgical management technique for cartilage damage has clustered around three concepts: (1) stimulating or assisting the patient's own body to regenerate cartilage via microfracture, autologous chondrocyte implantation (ACI), and matrix-assisted autologous chondrocyte implantation; (2) autologous cartilage transfer; and (3) allogeneic cartilage or cell transplantation.

The focus of this review is on the last concept—the use of allogeneic material to replace or rebuild cartilage tissue, as autologous cell or tissue transplantation has no inherent immune risk. The transplantation of allogeneic cells or cartilage tissue, whether alone or attached to subchondral bone (osteochondral transplantation), has been studied in pre-clinical and clinical studies. Allografts represent the most advantageous strategy as there is a limited amount of autologous tissue available for resurfacing procedures, especially for large defects. In most solid-organ transplants, the patient and donor are carefully selected and matched based on ABO blood type, Rh status, and human leukocyte antigen (HLA) status. Even with this preparation, these patients usually must be maintained on powerful immunosuppressive medications indefinitely to prevent immune rejection. This presents a new set of risks and possible adverse effects for the patient and physician to manage. As cartilage pathology is usually not life-threatening, the time and expense of donor matching and the significant risks of immunosuppression often outweigh the potential benefits of such interventions.

Cartilage tissue, however, does not evoke the same immune response as solid organs. In fact, cartilage has long been viewed as an "immunoprivileged" tissue [5]. The robust, dense ECM has been theorized to prevent immune cells and factors from recognizing chondrocyte antigens [6]. The ability of lymphocytes and macrophages to infiltrate intact cartilage ECM is severely limited such that the chondrocytes are essentially "antigen sequestered." This concept, combined with a general lack of immune response in patients receiving transplants of this tissue, provided the basis and justification for allogeneic cartilage transplantation. However, the development of more sophisticated laboratory techniques has enabled a more detailed assessment of cartilage immunogenicity. Furthermore, allogeneic mesenchymal stromal cells (MSCs) are now being investigated and delivered to promote cartilage repair. This review will summarize the current understanding of the immune status of allogeneic cartilage, chondrocytes, and MSCs for use in cartilage repair procedures.

Cartilage and chondrocytes

Cartilage allografts were used in plastic surgery as early as 1936, when several groups utilized allogeneic cartilage from the rib or auricle to reconstruct the nose and ear. These groups did not report immune rejection as a complicating factor, suggesting that these tissues had a privileged immune status [7]. Chesterman and Smith first addressed this topic in 1968, when they investigated allogeneic articular chondrocytes and intact cartilage transplantation in rabbits in order to evaluate different methods of processing and freezing these samples. They reported that their histological analysis did not show any evidence of immune reaction or rejection, such as lymphocytic infiltration, in any sample type tested at any of the time points evaluated. They raised the question of whether chondrocytes were non-antigenic or if the isolated cells had produced enough matrix upon transplantation to protect them from immune recognition and response [8]. Our own work (NP) has shown that even isolated chondrocytes rapidly attempt to reconstitute their territorial matrix, the specialized matrix immediately adjacent to the cell surface, which would effectively mask the cell surface markers from engaging in immune recognition.

In 1974, Langer and Gross investigated this concern, evaluating the immunogenicity of cartilage and chondrocytes. Using the lymphocyte migration test and ^{51}Cr cytotoxicity test, they evaluated the cellular and humoral immune response, respectively, in different forms of donor cartilage in rats. Cartilage shavings, isolated chondrocytes, and whole, intact articular cartilage from one rat strain were implanted into rats of another strain as allografts. Intact articular cartilage produced neither cell-mediated nor humoral responses. In contrast, isolated chondrocytes produced both cellular and humoral responses, and cartilage shavings produced a cellular but not a humoral response. The authors concluded that isolated allogeneic chondrocytes were immunogenic and that the ECM must have protected the intact cartilage. They hypothesized that some chondrocytes were exposed in the shavings, resulting in the cellular immune response [5].

Since then, a consensus has been reached that whole cartilage tissue avoids immune response due to its dense

Table 1 Evidence of isolated chondrocyte immune status

References	Study type	Species	Study method	Immune status	Results
Chesterman et al. [8]	Homologous transplant of articular cartilage and isolated chondrocytes	Rabbit	In vivo	Privileged	Tested several methods of preserving chondrocytes and cartilage. None produced immune reaction. Isolated cells transplanted into cancellous bone.
Langer et al. [5]	Immunogenicity	Rat	In vivo	Immunogenic	subQ transplantation, 1 per week × 3 weeks.
Ksiazek et al. [37]	Studies on bone formation	Mice	In vivo	Immunogenic	Isolated epiphyseal cells into muscle. Some combinations (mismatched gender, histocompatibility) caused significant immune reaction, some did not.
Jobanputra et al. [33]	Cellular response human chondrocyte	Human	In vitro	Privileged	Chondrocytes do not stimulate PBMC, even with MHC I and II.
Romaniuk et al. [34]	Chondrocyte rejection	Rat	In vivo	Immunogenic	Isolated cells injected into muscle. Macrophage, NK cells infiltrate.
Adkisson et al. [9, 35]	Juvenile chondrocyte	Human neo to goat	In vitro after in vivo	Privileged	Human chondrocytes do not stimulate goat T cells either before or after implantation.
Adkisson et al. [9, 35]	Immune evasion of chondrocytes	Human, juvenile and adult	In vitro	Privileged	Chondrocytes do not activate T cells and inhibit already activated T cells.
Acosta et al. [36]	Pig intervertebral disk (IVD)	Pig	In vivo	Privileged	Not specifically studied, but pig juvenile chondrocytes were injected into pig IVD and "no inflammatory response was observed."
Huey et al. [4]	Chondrocyte immunogenicity	Bovine, rabbit	In vitro	Privileged	No PBMC reaction.
Niemietz et al. [6]	Chondrocyte mini-pig	Human cells to pig joints	In vivo	Immunogenic xenograft	Cells transplanted in gels, inflammatory response, with macrophage infiltrate.

matrix, which essentially molecularly obstructs cells from penetrating it. Cartilage ECM is composed of type II collagen which has been highly conserved phylogenetically, perhaps providing an additional layer of immune privilege. However, the premise of isolated chondrocyte immune privilege remains contested, as many groups, using different species and different experimental designs, have supported or refuted this theory (Table 1). A recent study by Adkisson et al. [9] reported particularly strong evidence of immune privilege. In vitro analysis of human juvenile and adult chondrocytes demonstrated that these isolated chondrocytes not only failed to activate T cells, but also were able to inhibit activated T cell proliferation. Juvenile chondrocytes were shown to lack the costimulatory molecule B7-1 (CD80), but even adult chondrocytes that expressed B7-1 demonstrated immunosuppressive capabilities. Other factors were investigated to explain the finding of immune inhibition. Immune inhibitory B7 molecules such as B7-DC, B7-H2, and B7-H4 were shown to be expressed on both juvenile and adult chondrocytes. Additionally, chondromodulin-I (ChM-I), a transmembrane protein that is involved in chondrocyte growth and has recognized immunosuppressive capabilities, was expressed by both populations. Finally, indoleamine 2, 3-dioxygenase (IDO), an oxygenase stimulated by cytokines which likely has a function in the induction of immune tolerance, was expressed by both juvenile and adult chondrocytes when stimulated with IFN-γ. When this enzyme was experimentally inhibited, immune suppression was partially impaired at some concentrations. These data suggest that chondrocytes have some role in immune suppression independent of the ECM.

Articular osteochondral tissue

Clinically, the use of allogeneic cartilage has frequently involved the presence of a bony portion for enhanced fixation in large or traumatic defects. This bony portion is recognized as containing cells and proteins that are highly immunogenic [10]. These grafts can be fresh-frozen or cryopreserved, which reduces the cellular component, reducing the risk of disease transmission or immune response [11]. The grafts can also be fresh, which

optimizes cell viability but carries a risk of disease transmission and immune response. Despite the increased potential for immunogenicity of these grafts over cartilage-only grafts, immune response is frequently not discussed, or it is only briefly mentioned in the literature evaluating procedures involving these grafts.

In the 1970–1980s, when osteochondral transplantation was on the rise, Oakeshott et al. evaluated 18 failed fresh osteochondral grafts via clinical history, radiographically, and histological examination. Three failure trends were noticed during this evaluation: continued progression of underlying disease, such as osteoarthritis; abnormal biomechanical alignment; and anatomical mismatch between graft and defect [12]. Some chronic inflammation was noted in several severely degraded grafts, but there was no indication of immune rejection such as lymphocytic infiltration. A similar 2005 study of 60 fresh osteochondral grafts with a minimum of 5-year follow-up noted 12 graft failures caused by fragmentation, osteoarthritis, or deep infection [13]. Immune response was not discussed as a possibility or a potential cause of failure. In 2011, another study looked retrospectively at osteochondral grafts used in the treatment of lesions of the talus [14]. Of the 38 patients, four graft failures were noted. Immune rejection was not proposed as a cause; however, no histological evaluation was done and other imaging was not performed on every case. The authors do mention the potential for immune response, but they claim that its significance in these procedures is not known.

Lack of discussion of the immunological risks as well as earlier work by Sirlin et al. [15] on these grafts prompted Hunt et al. [16] to examine anti-HLA antibody formation in 67 patients that received fresh osteochondral grafts. Anti-HLA antibodies were discovered in 34 patients, and this was shown to have a statistically significant correlation with grafts that were larger in size. Although graft survival was lower in the antibody positive group (79 vs 64 %), this was not statistically significant. The authors used this data to suggest that immune response may play a role in graft survival but could not make more definitive recommendations due to the study size. Current treatment has evolved to utilizing "shell allografts" which are osteochondral allografts that have been prepared to remove a large portion of the cancellous bone essentially leaving the subchondral plate as the only bony component. This approach allows secure surgical fixation of the graft while minimizing potential immunogenicity.

Meniscus allograft

The meniscus plays an important role as a biomechanical stabilizer in the knee joint. It is a fibrocartilaginous, concave structure located between the femur and tibia. It is often damaged in a number of commonly occurring traumatic knee injuries and is a challenge to repair. Like osteochondral articular cartilage grafts, meniscus allografts usually involve bone plugs for fixation. The history and discussion of immunological concerns have been similar for both interventions. After the meniscus allograft procedure had been performed for several years, Hamlet et al. [17] provided a case report of acute rejection of a meniscal allograft. A young athlete with a history of traumatic meniscus injury followed by meniscectomy had undergone cryopreserved meniscus allograft transplant. Following this procedure, the patient presented with persistent, sterile effusions. Ultimately, the graft was determined to be a failure and was resected at 10 weeks postoperatively. Histologically, the authors describe dense lymphocyte and plasma cell infiltration in the superficial layer of the meniscus. HLA typing was not done on the cadaver donor, but the authors felt this was a case of acute immune rejection and called for caution and further study. Building on this, Rodeo et al. reported histological findings of 28 post-transplant biopsies of meniscus allografts, either with or without bone plugs. Immunohistochemical staining revealed mild B and T lymphocyte infiltration in some specimens. While histological grading of tissue quality was statistically significantly better in grafts without bone plugs, clinical outcomes were better with bone plugs. Similarly, the presence of immune cells in the biopsy specimen did not affect clinical outcome. The authors suggest that a low-level immune response may modulate healing, incorporation, and revascularization of the graft, but recognize that the clinical effect is not apparent.

In 2004, Graf et al. [18] reported the long-term follow-up of nine patients that had undergone meniscal allograft transplantation. The authors report excluding one of the patients due to low-grade infection. Similar to the case reported by Hamlet, the patient had persistent effusions in which no organism could be identified. However, whereas the Hamlet case revealed lymphocytic infiltration, this case involved only neutrophilic infiltration. A review by Rijk in the same year echoed the conclusions of Rodeo et al. that, while there was evidence of immune responses in some patients, the clinical effect was not known and there was no evidence of rejection [19]. A meta-analysis by Elattar et al. [20] also acknowledges these previous reports but states that a link to clinical failure has not been shown and, given the efficacy data, concludes that meniscus allograft is a safe and reliable procedure. Finally, a large consecutive case series in 2014 that evaluated meniscus allograft transplantations did not discuss immune concerns, suggesting that immune reactions in this procedure do not affect clinical outcomes [21].

Mesenchymal stromal cells (MSCs)

An active area of research in musculoskeletal repair and tissue engineering is the use of MSCs. Although the definition of what constitutes a MSC is debated, all MSCs are perivascular-derived multipotent cells that have the capability of differentiating into several cell types of mesodermal lineage, including osteocytes, chondrocytes, and adipocytes, among others [22, 23], and thus represent a source of cells that can be employed in tissue engineering repair strategies. MSC's are found in several adult tissues and can be detected in recipients for an extended period of time, indicating a lack of immune system recognition and clearance. Interestingly, allogeneic MSCs have been shown to suppress natural killer (NK) cells, neutrophils, macrophages, and lymphocytes, and they are being actively studied for their potential role in the treatment of systemic inflammatory conditions [23]. Other confirmatory studies using co-cultures of human MSC's with purified subpopulations of immune cells demonstrated the altered cytokine profile of dendritic cells (DC's), naïve and effector T cells (T Helper 1 [T_H1] and T_H2), and NK cells to induce a more anti-inflammatory or tolerant phenotype [24]. MSC's caused DC's type 1 to decrease tumor necrosis factor alpha secretion and mature DC-2 to increase interleukin-10 (IL-10) secretion, while T_H1 cells were induced to decrease interferon gamma secretion and T_H2 cells were induced to increase secretion of IL-4. Mechanistically, MSC's produced elevated levels of prostaglandin E2, while inhibitors of PGE2 mitigated MSC immune modulation [24]. Additional studies have provided further confirmatory support for the use of MSC's to prevent immune complications related to tissue transplantation and to the theory that MSC's are universal suppressors of immune reactivity [25]. Preclinical studies of MSC administration in the treatment of sepsis and acute respiratory response syndrome (ARDS) have been promising and suggest a paracrine-mediated modulation of damaging inflammation [26, 27]. Furthermore, numerous clinical trials investigating allogeneic MSC infusion to treat these conditions have shown this therapy to be both safe and therapeutic [22]. However, the initial theories that MSC were immune-privileged have been modified, as they do elicit some immune response [22].

The concept of using allogeneic cells as the basis for cartilage regeneration and repair is attractive as well. If immune issues do not hinder the progression of this therapy, untethering the cell source from the patient could provide a large, efficiently processed, consistent cell source that allows a level of scalability—making it feasible for industry to invest in MSCs as a therapy [28, 29].

The use of autologous MSCs in cartilage repair has been well studied [30]. While the use of allogeneic cells for this purpose is new, two randomized control trials have shown promise. In 2014, Vangsness et al. [31] examined the effects of intra-articular injections of allogeneic MSCs in patients undergoing partial meniscectomy. The groups receiving MSC injection showed an increase in meniscus volume on MRI and a decrease in pain over a cell-free control group. In 2015, Vega et al. also delivered allogeneic MSCs via intra-articular injection in patients with chronic osteoarthritis of the knee. Improvements in pain, disability, and quality of life were noted in the MSC-treated group. Additionally, improvements were seen in cartilage quality on MRI [32]. The success of these two studies is a welcome development in the treatment of cartilage defects and the study of MSCs in the treatment of disease. However, the authors rightly caution that the full effects of MSC augmentation need to be carefully studied, including any immune reactions.

Conclusion

Frank immunological rejection of cartilage tissue—alone or associated with bone—does not occur in clinical settings. However, some studies have shown a subtle immune response in some patients. Further characterization of this response would be beneficial to the field; however, it does not correlate with the clinical success of these procedures and is not a barrier to the continued use of allogeneic cartilage in this setting. Continued study and characterization of the immune properties of isolated chondrocytes, which have a history of varied conclusions, will assist in the development of new techniques and tissue-engineered solutions to the treatment of cartilage lesions. In summary, there exist immune-suppressive mechanisms which contribute to the observed absence cartilage allograft rejection as supported by numerous studies. Additionally, the continued development of allogeneic MSCs as a therapeutic tool in a myriad of disease states has the potential to cause a paradigm shift in the treatment of inflammatory conditions.

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