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Stem cell-based repair and regeneration of articular cartilage

Abstract

Articular cartilage is a highly specialized tissue, that when critically injured has an extremely limited capacity for regeneration. Accordingly, a clinically acceptable treatment option without risks and recurrence is currently unavailable. Inadequately treated destructive and degenerative cartilage injuries will often develop into progressive joint degeneration or osteoarthritis. Conventional surgical treatments frequently produce fibrocartilage, which cannot support the original cartilage function and deteriorates rapidly, while other conservative therapies only offer symptomatic relief. Here, we review the current tissue engineering technology for cartilage repair and describe our efforts to develop advanced cell-based engineered constructs to replace structural and biological functions, and to facilitate the regeneration of new cartilage. To overcome the limited source of available autologous chondrocytes provide only a limited population for growth and repair, hence the utility of adult bone marrow derived mesenchymal stem cells (MSCs) have been actively investigated. Biocompatible and biodegradable scaffolds, including poly-ε-caprolactone, poly-L-lactic acid, alginate, and collagen type I, have also been evaluated for their physical maneuverability, compatibility, and structural support of mesenchymal stem cells integrated into host cartilage tissue. The combination of MSCs with biomaterial scaffolds produced hyaline cartilage-like tissue with smooth articular surfaces, biochemical compositions most like that of native cartilage, and with stronger mechanical properties. As bone marrow derived MSCs are typically extracted by rather invasive means, recent studies suggest that adipose-derived stromal cells may provide similar therapeutic benefits with isolation methods that are less invasive. Based on a growing body of evidence, future strategies should clarify the role of MSCs and perhaps consider the use of adipose-derived MSCs combined with a durable and physiologically compatible biological scaffold.

Keywords: articular cartilage, regeneration, stem cells, adipose, scaffold

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Abbreviations: MSC, mesenchymal stem cell; ECM, extracellular matrix or matrices; BMP, bone morphogenic protein; IGF, insulin-like growth factor; SVF, stromal vascular fraction; ASC, adipose-derived stromal cell; PGA, polyglycolic acid; PLA, poly-l-lactic acid; PLGA, poly-dl-lactic-co-glycolic acid; PCL, poly-ε-caprolactone; MPa, megapascals; MPC, multipotent progenitor cell; µm, micrometer

Introduction

Articular cartilage disease, trauma and conventional therapy

Articular cartilage is a complex, avascular, multilayered biological composite material found at the surface ends of long bones, comprised of chondrocytes that facilitate in the synthesis and organization of extracellular matrices (ECM).[1] The functional capacity of articular cartilage as a load-bearing tissue is therefore dependent upon the maintenance and integrity of ECM structure.[1] When articular cartilage becomes injured, especially in full-thickness cartilage defects, repair and regeneration is limited due to its characteristically low cellular and avascular nature.[2,3] Consequently, progression to joint disease and degeneration, such as osteoarthritis, typically occurs. In 2005, osteoarthritis was one of the leading causes of adult disability in the United States, and over 50million Americans are projected to be affected by the year 2020.[4] Treatment strategies for impaired articular cartilage remain a major challenge to this day.

Early therapies included arthroscopic drilling and abrasion of the articular surface to penetrate the vascularized subchondral bone, resulting in fenestrations. Such fenestrations promote migration of mesenchymal stem cells (MSC) from the bone marrow space and infiltration to the site of injury for differentiation and repair.[5,6] Unfortunately, this type of surgical intervention also results in the formation of fibrous cartilage that often rapidly deteriorates due to irregularities and poor organization, eventually leading to mechanical failure.[7,8] Furthermore, reports indicate that arthroscopic lavage or debridement provide no additional benefits to physical and medical therapies for osteoarthritis treatment of the knee.[9,10] Other surgical interventions, including total joint replacement, while more invasive, remain one of the primary treatment options offered today for extensive lesions.[11] With total joint replacement, the articulating surface of a deteriorated knee is replaced with metal and/or plastic prostheses, thus completely restoring the load bearing functions of the knee and alleviating osteoarthritic pain. However, total joint replacements have inherent risks, such as the formation of blood clots, infection, and implant failure, as well as implanted prostheses having finite life expectancies.

Since conventional therapies fail to provide complete restoration

and/or continued function of the damaged articular cartilage in knee joints, there is a clear need for alternative therapeutic modalities for articular cartilage injuries. In recent years, the tissue engineering and regenerative medicine community has been exploring the development of biocompatible cartilage substitutes. Cartilage constructs generated by the combination of cells and biomaterials stimulated by growth factors possess characteristics closer to natural articular cartilage as opposed to artificial implants. Implanted cells could directly replace the physical and biological functions of chondrocytes within articular cartilage and indirectly guide the recipient's neighboring cells to support integration by the secretion of trophic signals. Through the use of stem cells, tissue engineering may be enable derivation of functional chondrocytes that express mature markers of differentiation and are functional in a three-dimensional architecture, recapitulating the nuances of the *in-vivo* counterparts physiologically and anatomically.[12,13]

Additionally, the use of biodegradable scaffolds can provide biologically compatible, three-dimensional structural support for implanted cells to expand and generate extracellular matrices, while eliminating the possibility of adverse reactions and/or rejections in recipients.

Autologous chondrocyte implantation

In 1994, Brittberg et al.[14] introduced the utility of autologous cultured chondrocytes to repair cartilage defects in the femorotibial articular surface of the knee joint by demonstrating considerable restoration of knee function in several patients 3 years following transplantation.[14] Other studies, however, found that remodeled tissue after chondrocyte transplantation displayed fibrous and fibrocartilaginous features that are typically associated with inferior mechanical properties and durability.[15–17] Some groups have found chondrocytes frequently dedifferentiated during in vitro expansion, and subsequently lost its chondrocytic phenotype and re-differentiation potential.[18–21] Additionally, chondrocyte implantation was found less effective in the elderly population, the demographic most seriously affected by osteoarthritis due to age-related impairment of normal proliferative capacity and ECM synthesis.[22,23] Furthermore, procurement of autologous articular chondrocytes for culture from otherwise healthy tissue runs the risk of donor site morbidity as well as adverse effects to the surrounding healthy tissue.[24]

Discussion

Adult mesenchymal stem cells

Mesenchymal stem cell (MSC) populations were first identified within the stromal compartment of bone marrow and were later discovered to have clonal expansion properties and differentiation potential.[25] MSCs are now speculated to be present in virtually all post-natal organs and tissues.[25] Tissue damage found in progressive, degenerative, joint diseases is suspected to be associated with the depletion or functional alteration of MSCs.[26] MSCs can be readily isolated from bone marrow and other mature adult tissues of mesenchymal origin, expanded in vitro while maintaining their multipotency, and induced to differentiate into the chondrogenic lineage.[11,27–31] Furthermore, MSCs can be expanded to large scale populations *ex vivo*, making them an attractive cell reserve for autologous cell therapies.[32] The selection of chondroprogenitor cells can also be enhanced by conditioning the culture medium with selective growth factors, such as fibroblast growth factor 2 and transforming growth factor β.[33] The chondrogenic differentiation of MSCs is characterized by the upregulated expression of cartilage-specific transcription factors and proteins specifically involved in ECM production (e.g., SOX9 and aggrecan) as well as an organized network of cartilage-specific collagen type II fibers.[1] When MSCs are stimulated to transform into the chondrogenic phenotype, unlike autologous chondrocytes, they are relatively fragile and care must be performed to prevent chondrocyte hypertrophy and ossification, or damage to the repaired tissue.[2]

Studies have shown that MSCs can also be genetically modified to express and secrete therapeutically beneficial factors within the lesion, which allows for cartilage regeneration while inhibiting apoptosis, osteogenic differentiation, and inflammation.[34,35] Gene-induced chondrogenesis *in vivo* was reported by Gelse et al.[36] in which bone morphogenetic protein (BMP)-2 and insulin-like growth factor (IGF)-1 secreted by modified MSCs facilitated the restoration of the articular surface of partial thickness cartilage lesions induced in rats.[36]

Adipose-derived stromal cells and the stromal vascular fraction

MSCs can be found residing in a number of adult tissues, including but not limited to the brain, synovium, and umbilical cord. However, the most abundant and accessible source of adult stem cells is adipose tissue.[37–39] In addition to their inherent capacity to differentiate into a number of tissue types (e.g., chondrogenic, adipogenic, osteogenic), they can be harvested from patients in abundance using simple, minimally invasive, and relatively inexpensive procedures, that do not require additional culturing. The stromal vascular fraction (SVF), which houses a large population of adipose-derived stromal cells (ASCs) that can be readily expanded and programmed for cell specialization, can be easily isolated from lipoaspirated adipose tissue by chemical and mechanical means.[25,40]

The chondrogenic differentiation capacity of ASCs has been previously demonstrated in mice[41] and rabbits.[42] Recently allogeneic ASCs directly injected into the knee joints of osteoarthritic animals showed a substantial improvement in cartilage degeneration as well as immune tolerance in recipients.[43,44]

Scaffolds for MSC application

Introduction of MSCs, which are often culture-expanded due to their scarcity upon harvest, may be implanted via direct injection into the joint space as previously described, in a matrix, or onto a supportive foundation, like a scaffold. Although direct intra-articular injection may be the simplest method of cell administration, the injected cells are likely to interact with the entire internal surface of the joint and may not target the site of injury. Furthermore, conventional cell culture provides unnatural conditions with only 2-dimensional space for growing cells, leading to the development of physiologically compromised cells.[45] Cells in the body, however, are surrounded by native ECM, other cells, bathed in blood plasma or interstitial fluid, and in continuous communication with the dynamic network of proteins *in vivo*. Culturing cells that differentiate and maintain in vivo cell behavior is not possible by conventional flat surface methods, and will require a 3-dimensional microenvironment with the presence of ECM.[46] Material properties, such as pore size, porosity, biocompatibility, and degradation profile, will likely affect cartilage construct formation and sustainability, and therefore should be considered during scaffold development.[47,48] Scaffolds provide many advantages: (1) is a physically maneuverable construct that has sufficient shape memory for short- to medium-term spatial

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and mechanical support for the defect site; (2) is a substrate that is conducive to cell attachment and migration and allows appropriate ECM assembly and retention of the seeded cells; (3) a favorable microenvironment for chondrogenic differentiation; and (4) maintains compatibility and integration with the host cartilaginous tissue. To date, several synthetic polymers and native biomaterials have been examined to determine the optimal scaffold material for cartilage constructs.

Synthetic scaffolds for MSC application

Synthetic scaffolds offer the selective advantage of design configuration, where fiber diameter, pore size, and degradation rate can be adapted for efficiency. Furthermore, it can be easily reproduced and produced in large quantities. Critical parameters for tissue engineering scaffolds include biocompatibility, biodegradability, optimal mechanical strength, and the ability to regulate appropriate cellular activities.[48] Many commonly investigated synthetic scaffolds in cartilage repair are fabricated using α-hydroxy polyesters, including polyglycolic acid (PGA), poly-L-lactic acid (PLA), the copolymer poly-DL-lactic-co-glycolic acid (PLGA), and poly-ε-caprolactone (PCL).[49–53] While *in vivo*, eventually the scaffold will degrade, in turn providing more space to allow seeded cells to proliferate and deposit newly synthesized ECM.[48] Few studies have evaluated ASC seeding onto artificial scaffolds, however, these studies demonstrate rapid cell attachment, proliferation, and chondrogenic induction can be indeed be achieved.[54,55]

Native extracellular matrices are made of many fibrillar macromolecules, principally collagen, that exhibit an organized nanostructured material milieu for the cells. For this reason, about a decade ago, the electrospinning technology of material science to produce nanofibers of biodegradable polymers was introduced for cell-based tissue engineering applications.[56,57] It was shown that nanofibrous scaffolds do indeed support the proliferation and multi-lineage differentiation of bone marrow-derived MSCs, successfully producing three-dimensional tissue architecture similar to that of bone, cartilage, and adipose.[56] In addition, findings also demonstrated that the size of the nanofibers is critical in maintaining the proliferation and differentiation potential of MSCs.[58] Data showed that the nanofibrous scaffolds in the form of woven mats had a porosity of 90% and the majority of the pore diameters ranged from 25 to 100μm. Their tensile moduli were up to 150MPa, and they yielded strains of up to 7.5%, suggesting they may be physically manipulated and capable of accommodating sutures.[59]

Natural material scaffold for MSC application

Hyaluronan, fibrin, chitosan, alginate, and collagen type I are a few examples of native biomaterials that have been examined as potential candidate scaffolds for cartilage regeneration.[60,61] These native biomaterials offer the selective advantage of providing a more physiological microenvironment. Fibrin, a major component of blood clots, has been examined as a vehicle for the delivery of chondrocytes to articular cartilage defects.[60,62–64] Although some surface improvements were histologically observed, fibrin's mechanical properties were inadequate, and did not support the in growth of host cells.[60] Cross-linked hyaluronan was also a strong potential candidate for cartilage scaffolds since hyaluronan is a major component of cartilage. However, studies found that hyaluronan induced chondrolysis despite its native origin, and the repaired cartilage using hyaluronan scaffolds were frequently thinner in comparison.[65,66]

Collagen type I is the most abundant ECM macromolecule in the body. Purified bovine collagen type I is routinely used clinically, most commonly for skin, orthopedic, and dental applications. Unfortunately, the collagen matrix can be metabolized by cells in vivo via the digestive action of endogenous collagenase, and elicits a moderate, if any, inflammatory reaction. Therefore, investigators have developed a more robust option of collagen hydrogels, which offer comparable material properties to collagen and a three-dimensional surrounding similar to that in hyaline cartilage.[35] Collagen gels are malleable and can be easily molded into any defect shape found in specific cartilage injuries. Compared to mesh or fleece, in which cell seeding is often limited to the superficial regions of the scaffold material, cell seeding in a gelatin-based hydrogel permits uniform three-dimensional distribution of cells, therefore promoting homogeneous ECM deposition by chondrogenic cells.

Recently, groups have been evaluating adipose-derived extracellular matrices as a potential biocompatible scaffold for tissue regeneration. Before adipose-derived ECM can be utilized as a biocompatible scaffold, it is important to completely decellularize the fibers and remove any excess lipids and particulate.[67] Studies evaluating scaffolds for tissue engineering have additionally shown the importance of maintaining high porosity with fibers loosely associated with one another to allow for the mass transport of cell nutrients, cell migration, and cell attachment.[68,69] Once the potential scaffold has been successfully decellularized, the scaffold can be recellularized to allow for the fabrication of tissue types. One study evaluating the potential of a human chondrogenic cell line seeded onto acellular adipose-derived ECM demonstrated successful adhesion, infiltration, and proliferation, while the scaffold maintained porosity and mechanical durability.[70] Our group is also currently investigating the optimal isolation procedure to achieve uniform, porous, decellularized adipose-derived ECM, as well as seeding and differentiation potential of ASCs onto the acellular scaffold.

Animal studies evaluating MSC-seeded cartilage constructs

We have recently tested the efficacy of MSC-seeded electrospun nanofibrous constructs to repair articular cartilage defects in a lapine model.[71] Constructs seeded with MSCs derived from lapine femoral bone marrow were initially cultured in chondrogenic, serum-free medium static culture for three days and then in a rotary wall vessel bioreactor for an additional 21days. The cellular constructs were then implanted into the medial femoral condyle defects created by biopsy punches. After 28days, empty defects with no implants were filled with clots, which resulted in fibrous tissue with little to no organization. A cellular control constructs maintained a rough surface morphology. In contrast, the cellular constructs limited clotting and resulted in a smooth, glossy, opaque plug that integrated with the defect edges and showed neocartilage formation. The nanofibrous poly-L-lactic acid scaffolds were able to support cell survival and integration with the native cartilage.

Supraphysiological impact on the articular joint surface is known to lead to degeneration of the articular cartilage and initiation of osteoarthritis. Biopsy punches, which are frequently used to generate cartilage defects in various animal models, are not the optimal representation of trauma or disease progression in the articular cartilage. To experimentally mimic this physiological sequence of the actual disease process, we have designed a spring-loaded impactor to deliver 100-2000N of force with interchangeable impact orientations.

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By delivering well-controlled supraphysiological impacts of 326±47.3MPa on the articular joint surface intra-operatively, immediately resulting in a fissured articular surface, we could develop a consistent, reproducible small animal model to study the onset and early development of post-traumatic osteoarthritis in mature rabbits. After 3months, we observed focal osteoarthritic degeneration at the point of impact.

We also tested the feasibility of MSC-seeded biodegradable, nanofibrous poly-ε-caprolactone scaffolds for articular cartilage repair in pigs.[51] Defects of 7mm in diameter were created in miniature swine, and scaffolds were seeded with either allogeneic chondrocytes or xenogeneic human MSCs. Six months after implantation, MSC-seeded constructs showed the most complete repair as compared to the control constructs seeded with no cells or allogeneic chondrocytes. MSC-seeded constructs regenerated hyaline-like tissue and restored a smooth cartilage surface reminiscent of native tissues as well as demonstrating the highest equilibrium compressive stress, while chondrocyte-seeded constructs produced mostly fibrocartilage-like tissue with a discontinuous superficial cartilage contour. The acellular constructs showed incomplete repair containing fibrocartilage or fibrous tissue and lowest tensile strength. No evidence of immune reaction against allogeneic chondrocytes and xenogeneic MSCs were observed, which may be attributed to immunosuppressive and immune privileged properties of MSCs.[72] These results lend further support to the utility of allo- or xenograft transplantation of MSCs for treatment of articular cartilage degeneration and/or defects.

In another recent study, culture-expanded MSCs from bone marrow were delivered in a collagen type I hydrogel into a 7mm diameter articular cartilage defect in the trochlea of the miniature swine.[51] Cartilaginous ECM was seen in the construct 6months post-implantation with good attachment to the surrounding host cartilage. Studies evaluating the chondrogenic potential of MSCs isolated from various tissues demonstrated successful in vivo chondrogenesis of ASCs delivered via collagen hydrogels in rabbits, however, was inferior to bone marrow and synovium MSCs.[42] Our group is currently working on improving chondrogenic capability of ASCs for cartilage repair. These findings also lend support to the feasibility and utility of collagen type I as a delivery vehicle of adult MSCs for repair of articular cartilage defects.

Conclusion

The studies described herein, showcase the potential utility of adult MSCs as an alternative to autologous chondrocytes and conventional therapies, as well as reinforce the utility of scaffolds to present a valuable foundation for seeded to cells to attach, grow, and differentiate. While adult stem cells, particularly those derived from bone marrow, are capable of guided chondrogenic differentiation, they are limited in number as primary isolates, and therefore must be expanded *ex vivo*. The majority of current tissue engineering and regenerative medicine-based approaches have utilized pre-engineered cartilage constructs formed with *in-vitro* expanded allogeneic or autologous cells. Expansion of cells may require weeks to months in an off-site processing facility, often in a two-dimensional stagnant culture, and with the use of mitogenic growth factors. Such facilities must operate in compliance with good manufacturing practices, and the costs associated with such regulatory and safety oversights are unavoidably high, adding an economic barrier to clinical viability.[73] Additionally, the most commonly used procedure to obtain adult MSCs is through bone marrow aspiration, a relatively invasive and painful procedure with a limited yield of cells due to the restrictions in the quantity of aspirate which can be obtained.

An alternative to the lengthy process of manufacturing cartilage constructs off-site is a point-of-care approach,[74] in which cell isolation, construct formation, and transplantation are performed during the same operation. Due to the necessity of in-vitro expansion of the cells, many of adult MSCs, including bone marrow MSCs, are not adequate for point-of-care therapy. As previously mentioned, an alternative source of cells that circumvents the limitations of bone marrow MSCs, are ASCs. Several studies have demonstrated that ASCs are capable of differentiating into a number of connective tissue types, including osteogenic, chondrogenic, and adipogenic lineages,[40] and are also capable of secreting growth factors and cytokines that are therapeutically beneficial.[37] The potential utilization of ASCs has wide-ranging implications for osteoarthritis management and the need for continuous treatments.

Multipotent progenitor cells (MPCs) in traumatized human muscle have also generated a growing interest.[75–77] These cells have the ability to differentiate into multiple cell lineages and can be readily isolated from debrided muscle during acute definitive care of war-traumatized muscle injuries, and be present in high abundance than in non-traumatized muscle. Whether these MPCs result from the expansion of endogenous cells and/or are recruited from non-muscle sources is unknown. But, because of their autologous nature and derivation from otherwise discarded debrided tissues, these MPCs should also be considered as a convenient cell source for skeletal tissue regenerative applications.

Lastly, it must be pointed out that the studies described here only evaluated defects equivalent to focal cartilage defects in the clinical setting. Despite the promising features of MSCs and their potential to reverse some of the pathologies of osteoarthritis, the fact that degenerative cartilage defects arising from an underlying disease process are distinct from focal cartilage lesions due to acute injury or osteochondrosis dissecans, and should be taken into consideration for interpretation. Specifically, acute cartilage injury and osteochondrosis dissecans often take place in an otherwise healthy joint in which the patient may be young, and the focal defect will likely require a localized treatment. Whereas in osteoarthritis, the patient is likely to be elderly and require treatment to the entire articulating surface of the inflamed joint. Consequently, repair of the local lesion may only provide symptomatic relief and delay the progression of symptoms. Improvement is unlikely to be long-term unless the underlying disease is also effectively treated.[14] It is, therefore, imperative to thoroughly evaluate current focal injury treatment modalities, so they can be scaled up and applied to larger articular cartilage defects found in osteoarthritis. Understanding the underlying disease mechanism is also crucial to develop a comprehensive and effective treatment for traumatic and degenerative articular cartilage injuries.

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Conflict of interest

The author declares no conflict of interest.

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