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Chondrogenic Progenitor Cells and Articular Cartilage Repair

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Abstract

Treatment of articular cartilage injury is challenging due in part to the paucity of potential repair cells within articular cartilage. While chondrocytes can be expanded in culture and returned to the site of injury, autologous applications require removal of healthy articular cartilage - a limited resource. Additional sources of chondrogenic progenitor cells that may be suitable for articular cartilage repair include Mesenchymal Stem Cells (MSCs) isolated from more abundant tissues such as bone marrow, synovium, infrapatellar fat pad, subcutaneous fat, periosteum, perichondrium, and muscle.

Introduction

Articular cartilage has a unique functional architecture that permits movement and load transmission with exceptionally low coefficients of friction. Traumatic and degenerative lesions to articular cartilage heal poorly due in part to the relative paucity of resident repair cells and the absence of a blood supply for recruitment of cells and bioactive factors necessary for repair [1]. While partial thickness chondral lesions do not heal [2], full thickness lesions that penetrate the subchondral bone access the blood supply resulting in an influx of repair cells which contribute to the formation of fibrous or fibrocartilaginous repair tissues. However, the resulting repair tissue lacks the structural, biochemical, and biomechanical properties of age-matched normal articular cartilage [3,4].

While chondral lesions are often left untreated, due to both limited treatment options as well as a seemingly non-progressive course, there is now evidence that even small lesions may lead to osteoarthritis (OA). Some reports reveal that a high proportion of articular cartilage lesions result in clinical symptoms or radiological changes when observed for more than 10 years [4,5]. For this reason, there is strong interest in whether early treatment of cartilage lesions can prevent or delay the onset of osteoarthritis.

Current treatment techniques include microfracture, chondrocyte implantation, and osteochondral grafting. Microfracture, in which small perforations are made through the subchondral plate to facilitate entry of repair cells from the underlying bone marrow, is simple and commonly performed. The influx of mesenchymal stem cells (MSCs) and blood clot into the defect produces type I and II collage and proteoglycans, but the reparative cells fail to organize a healthy layered structure. The resulting fibrocartilage shows a variable architecture that is biochemically and biomechanically different from healthy articular cartilage [3].

Symptomatic chondral lesions can be also treated with structurally normal articular cartilage through transplantation of osteochondral grafts. A shortage of available tissue limits the use of both osteochondral allografts and autografts. Autograft tissue is in such short supply that it is an option only for relatively small lesions. Additional limitations include the potential for donor site morbidity and difficulty healing between osteochondral grafts when multiple smaller diameter plugs are used to fill a larger defect. For large defects, allograft tissue is available but expensive and carries risks of disease transmission as well as loss of viable donor cells during storage [6].

Consequently, there has been longstanding interest in improving articular cartilage repair through the implantation of chondrocyte progenitor cells into symptomatic chondral defects. Chondrocytes function to restore the extracellular matrix [7], and thus have potential in recreating a type II collagen dominant hyaline repair cartilage to restore the joint surface. During embryogenesis, articular cartilage forms through the condensation of MSCs, which then undergo differentiation to chondrocytes. The articular cartilage formed has an abundance of type II collagen and proteoglycans, which serve to protect the ends of bones and articulate movement. Chondrocytes make up a small component of the tissue, with chondrocytes embedded within the matrix at a low density. Homeostatic matrix turnover is coordinated by the chondrocytes through tightly regulated anabolic and catabolic processes and involves growth factors, cytokines, and matrix degrading enzymes [8].

Autologous Chondrocyte Implantation (ACI) aims to provide complete hyaline repair tissues for articular cartilage repair. In this technique, normal articular cartilage is harvested arthroscopically from a non-weight-bearing area, the cells are expanded *in vitro*, and then the chondrocytes are applied on the damaged area during a second knee surgery [9]. Although good results have been reported with ACI [10,11], the quantity of harvested chondrocytes from non-weight bearing areas of cartilage is limited. Consequently, the chondrocytes harvested from small biopsies must be culture expanded where dedifferentiation occurs. Dedifferentiated cells exhibit a reduction of collagen II, IX, XI and aggrecan production and an increase of collagen I and III that are typical of unhealthy cartilage or fibrocartilaginous tissues [12].

Given the challenges of current treatment modalities for cartilage repair, there is intense interest in stem cell mediated therapies. A chondrocyte progenitor cell is any cell that may transform into a chondrocyte. Stem cells, the term often used interchangeable with progenitor cells, can be described by their potency. Pluripotent stem cells can differentiate into cells derived from any of the three germ layers. Multipotent stem cells can give rise to cells from multiple, but a limited number, of lineages; i.e., can produce only cells of a closely related family of cells [8]. Mesenchymal stem cells (MSCs), an example of multipotent stem cells, can differentiate into a number of tissues, including bone, adipose tissue, and cartilage. This review will focus on a number of MSCs locations that are potential sources of chondrogenic cells.

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Chondrocytes and their Ability for Repair

Previously it had been thought that chondrocytes have no ability to self-repair. This poor capacity for self-repair of articular cartilage has been explained by cell senescence and the lack of chondroprogenitor cells [2,13]. However, it has recently been demonstrated that human articular chondrocytes cultured *in vitro* display phenotypic plasticity with chondrogenic, adipogenic and osteogenic potential [14-16].

The surface of mature articular cartilage contains chondrocytes as well as collagen fibrils that run parallel to the joint surface. This surface layer serves a unique role, as it maintains the mechanical response of articular cartilage to load. The superficial surface is the first layer to degrade due to shear forces. This has brought about a specific interest in regeneration of the surface zone layer of cartilage [17-20]. Hayes et al. [19], was able to isolate progenitor cells from the surface zone of 7-day-old bovine calf articular cartilage. Karlsson et al. [13], then studied the origin of these progenitor cells. Using BrdU injections to label progenitor cells, the authors demonstrated two important findings in 3-month old Monodelphis domestica (opossum) [13]. First, there are slow-cycling cells in the surface zone of the articular cartilage. Second, a stem cell niche was noted in the perichondrial groove of Ranvier, an area near the physis of the joint. The authors suggest that the cells in the perichondrial groove of Ranvier may function as a reservoir of MSCs. Further, it is also possible that these cells can migrate to the surface of the articular cartilage [13].

Specialized cells with chondrogenic progenitor properties have also been identified by another group [21]. The cells, termed "Side Population" (SP) cells, are based on a characteristic pattern by flow cytometry analysis to discriminate SP cells based on the differential efflux of Hoechst 33342 dye by a multi-drug-like transporter [21,22]. Hattori et al. [21], isolated SP cells from the superficial zone articular cartilage, and then demonstrated the presence of progenitor cells that can differentiate towards superficial articular chondrocytes.

Despite these new studies that show chondrogenic potential with articular cartilage, injury to the cartilage, ranging from focal cartilage defects to tricompartmental osteoarthritis, still show little innate ability for repair. Further, cartilage injury disrupts the surface layer of cartilage, where progenitor cells are found. Therefore, other sources of chondrocyte progenitor cells may be useful in treatment of these injuries.

Other Potential Sources of Chondrocyte Progenitor Cells

Most studies involving chondrocyte progenitor cells focus on new techniques for cartilage repair. The goal has been to find easily accessible stem cells that, under optimized conditions, can differentiate into chondrocytes that function to restore the articular cartilage surface.

Bone marrow

The best characterised populations of MSCs are those originating from bone marrow. Under appropriate culture conditions, bone marrow derived MSCs have been shown to selectively form adipocytes, osteoblasts, fibroblasts, and chondrocytes *in vitro* [4,23,24]. Multiple studies have shown that bone marrow derived MSCs differentiate into cells with chondrogenic progenitor cell properties, and some even show their superiority over other stem cell sources, such as adipose tissue derived MSCs [25] and fetal lung and placental-derived MSCs [26].

Bone marrow derived MSCs have been used *in vivo*. Wakitani et al. [27], implanted bone marrow derived stem cells embedded into a collagen gel into full-thickness osteochondral defects in the medial femoral condyles of rabbits and showed that there lesions were histologically superior according to the total histologic grading, and mechanically stiffer and less compliant compared to empty defects.

Further, this technique has been used in multiple human studies. Patients with medial unicompartmental knee osteoarthritis underwent high tibial osteotomy and bone marrow MSC transplantation [28]. Bone marrow MSCs were aspirated from the iliac crest, expanded *in vitro*, embedded within a collagen scaffold, and then transferred into the defect and covered with autologous periosteum. Post-operatively, compared to cell-free controls, the lesions were arthroscopically and histologically superior based upon quantitative scoring of the reparative tissue, although there were differences in clinical outcome. In a similar study [29], this technique was used in two patients who presented with knee pain due to cartilage defects. Two years after surgery, the authors concluded that autologous bone marrow MSC transplantation was an effective approach for promoting the repair of articular cartilage defects. However, the authors note that upon arthroscopic follow-up, the defects had been repaired with fibrocartilage. In 2007, the authors used bone marrow MSC transplantation to repair lesions of the patellofemoral joint, noting improved patient outcomes but also reporting fibrocartilaginous tissue at the defect site [30]. Similarly, Kuroda et al. [31], used bone marrow MSCs for repair of a full thickness cartilage defect of the medial femoral condyle. The authors' again aspirated bone marrow from the iliac crest, expanded the cells *in vitro*, embedded the cells within a collagen scaffold, and then transferred this scaffold into the defect. The patient reported return to previous level of activity without pain, and unlike the previous two studies that showed unhealthy tissue, histology showed hyaline-like cartilage tissue within the defect.

Using a variation of the technique, Haleem et al. [32], culture expanded autologous bone marrow MSCs, intra-operatively placed them on platelet rich fibrin glue, and then positioned the construct into full-thickness cartilage defects of femoral condyles and covered them with an autologous periosteal flap. Clinically, all patients had significant improvement, and 12 month post-operative MRI revealed complete defect fill and complete surface congruity with native cartilage, whereas that of 2 patients showed incomplete congruity.

Wakitani et al. [33], subsequently evaluated the safety of all patients that had undergone bone marrow MSCs transplants, and reported no infections or tumor growths. Bone marrow derived MSCs have other advantages. Unlike microfracture, which delivers a limited source of MSCs to the defect area, bone marrow derived MSCs can be expanded *in vitro*.

Additionally, as opposed to ACI, the use of bone marrow MSCs does not require more than one surgery. However, given that the bone marrow may not be the optimal source of MSCs due to the painful and risk-containing sampling procedure, isolation of stem cells from other sources would bring an attractive alternative. Over the past several years, other sources of MSCs with chondrogenic potential have been identified.

Synovial cells

Synovial cells are reported to have good capacity for differentiating into cartilage [4,34]. In 2001, De Bari et al. [35], isolated MSCs from the synovial membrane of human knees. Under the appropriate culture conditions, the authors were able to induce the differentiation of synovial membrane-derived cells to chondrocytes, osteocytes, and adipocytes. Since this initial development, the chondrogenic potential

of MSCs in the synovial membrane have been explored in multiple studies. Yoshimura et al. [36], showed superior chondrogenic potential in *in vitro* pellet culture in rat MSCs taken from synovial membrane compared to that taken from bone marrow, periosteum, adipose tissue, and muscle tissue [36]. The same group also compared the chondrogenic potential of human MSCs derived from bone marrow, synovium, periosteum, adipose tissue, and skeletal muscle of patients undergoing anterior cruciate ligament reconstruction. Synovium-derived cells had the greatest ability for chondrogenesis [34,37]. To further distinguish an optimal source of chondrogenic progenitor cells, the group compared cells derived from fibrous synovium, adipose synovium (also known as the infrapatellar fat pad), and subcutaneous fat. The authors showed comparable chondrogenic potential in the fibrous synovium- and adipose synovium-derived cells, and higher chondrogenic potential in both compared to subcutaneous fat [38].

These ideas were carried on to an *in vivo* model by Koga et al. [39]. The authors transplanted MSCs derived from bone marrow, synovial membrane, adipose tissue, or muscle tissue, mixed in a collagen gel and covered with a periosteal patch, into rabbit cartilage defects. After four weeks, rabbits transplanted with BM and synovial membrane had superior cartilage matrix within the defect.

Tissue from the synovial membrane can be harvested from the knee during arthroscopy with minimal complications. Synovial tissue has high self-regenerative capability, as show by its ability to fully heal after synovectomy in animals [40,41].

Adipose tissue

Adipose-derived stromal cells have been studied more recently. They are more readily available than bone marrow derived stem cells, which involves aspiration of bone marrow cells in a procedure that has risks and complications. Under specific and controlled culture conditions, adult human adipose tissue can be induced to express the phenotypic characteristics of chondrocytes, osteoblasts, adipocytes, or neurons [42-45].

While the tissue described as fat, apidose, or lipoaspirate can often be lumped together for simplicity, adipose tissue obtained from subcutaneous fat and Infrapatellar Fat Pad (IFP) differ. The IFP is a heterogeneous and fibrous structure, and histologic studies show that much of the fat pad is dense collagenous tissue [46]. However, the IFP contains the cell surface markers used to identify MSCs, although they are not identical to those of subcutaneous fat or bone marrow derived stromal cells. This may be a reflection of the significant numbers of fibroblasts since it can be described as dense connective tissue. As such, some authors [38] refer to the IFP as adipose synovium. Overall, it is important to consider that although subcutaneous fat and IFP may be described synonomously, the two tissues may have different properties and produce differences in chondrogenesis.

Infrapatellar fat pad

There are many advantages of IFP as the source of MSCs. In humans, obtaining IFP tissue may be more feasiable in certain patients. IFP resection is well tolerated in patients undergoing total knee arthroplasty, as the fat pad is easy to resect and is no longer necessary following replacement. Additionally, patients with chronic fat pad impingement and fibrosis (Hoffa's disease) undergo complete resection of the IFP as treatment for their disease process. Despite the ease of access to the IFP, both of these patient populations may have unhealthy cells given the chronicity of their disease. In young, active patients, resection of the fat pad is invasive. An important part of the surgical technique is to maintain the anterior capsular layer. Partial resection is often completed during arthroscopy to enhance visualization, and thus this option may be feasible in patients already undergoing surgery [47]. In fact, in patients with osteochondral defects, diagnostic or therapeutic arthroscopy may be the ideal time to obtain tissue since there is minimal additional morbidity associated with obtaining this tissue. Further, it may be possible to perform a biopsy of the IFP in order to obtain mesenchymal stem cells to treat young patients.

In addition to ease of access and lower donor site morbidity, especially compared to bone marrow aspiration and liposuction, some suggest that IFP offers greater potential due to its larger tissue mass. Therefore, it may be used without the need for tissue culture expansion. Also, the tissue is more consistent than synovial tissue, which can become inflamed or fibrotic in certain disease states.

The fat pad as a source of MSCs may also be especially important in patients with advanced OA, as English et al. [48], has shown that stem cells isolated from the fat pad of patients with OA have good chondrogenesis while these same patients have poor chondrogenesis from harvested OA cartilage. Khan et al. [49], additionally showed that MSCs from the IFP do have chondrogenic potential, and this is increased at a lower oxygen tension (5% oxygen).

In vivo studies have used adipose derived MSCs from the IFP in prevention of OA. Toghraie et al. [50], obtained MSCs for the IFP of rabbits and expanded the cells *in vitro*. The expanded MSCs were later injected into the knee joints of the rabbits 12 weeks after anterior cruciate ligament transection. Rabbits receiving MSCs showed lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis than control group at 20 week after surgery. Further, the quality of cartilage was significantly better in MSC-treated group compared with control group after 20 weeks, leading the authors to conclude that IFP derived MSCs could be the promising cell sources for the treatment of OA.

In addition to the chondrogenic potential of adipose derived MSCs harvested from the IFP, Lee et al. [51], showed that Superficial Zone Protein (SZP) is expressed by IFP obtained from bovine knees. Superficial zone protein is known to be produced by chondrocytes and synovial cells, and acts as a lubricant within the joint. The discovery of SZP expression by IFP provides further potential for IFP as a source of MSCs, since it may be able to stimulate the superficial zone of articular cartilage.

Subcutaneous fat

In addition to adipose tissue obtained from IFP, MSCs can also be isolated for subcutaneous fat. Liposuction is readily performed, and an isolation procedure for the isolation of MSCs from adipose tissue has been described [52-54]. Human liposuction aspirates contain multipotential cells, often known as processed lipoaspirate cells [47].

While adipose derived stem cells, either from IFP or subcutaneous fat, are an easily accessible and plentiful cell source, how to better promote chondrogenesis is warranted. Some authors have shown that fat derived MSCs are equal to bone marrow derived MSCs [55]. Others have demonstrated that the two populations are difficult to compare due to unique responses to growth factor chondrogenic induction [45] or higher initial cell numbers with adipose derived MSCs that may distort results [56]. Overall, however, most studies have shown that fat derived MSCs have inferior chondrogenic potential in comparison to bone marrow derived MSCs [25] [57-60].

Periosteum

Periosteum has been studied as a source of chondrogenic progenitor

cells for nearly two decades. As described above, Wakitani et al. [27], collected both periosteal and bone marrow-derived cells from rabbits, cultured the cells *in vitro*, and then used the cultured cells embedded in a collagen gel to fill full thickness osteochondral defects of the medial femoral condyle. The authors concluded that hyaline-like cartilage developed in the defects filled with either periosteum or bone marrow, with no differences between the two cell sources.

Further work to characterize periosteum-derived stem cells has been developed by O'Driscoll's group. They describe the cambium layer (the inner layer) of the periosteum as the location of chondrogenic precursor cells [61]. In an additional study, similar to other sources of MSCs, the group showed that chondrogenic potential decreases with age [62]. In an effort to maximize chonogenic potential, Fukumoto et al. [63], showed that the addition of IGF-1 and TGF-β1 can help regulate the differentiation of periosteal MSCs during chondrogenesis [63].

Perichondrium

Perichondrium has also been explored as a source of chondrogenic precursors. Doenchis et al. [64], characterized the chondrocytic phenotype of perichondrium-derived cells, noting that exogenous TGF-β1 upregulates the expression of type II collagen *in vitro*. Chu et al. [65], evaluated osteochondral repair after implantation of an allogenic perichondrium cell polylactic acid composite graft into full thickness defects of the medial femoral condyle in rabbits. While none of the specimens returned to normal at one year, hyaline like tissue was dominant at one year, and compressive properties were similar to untreated controls.

The chondrodgenic potential of MSCs from periosteum/perichondrium, bone marrow, and fat was evaluated by Park et al. [66]. Using MSCs isolated from adult rats, the authors showed periosteum/perichondrium and bone marrow derived MSCs to be superior to fat derived MSCs both *in vitro* and *in vivo*, with impressive upregulation of type II collagen mRNA, high levels of type II and IX collagen in the *in vitro* work.

Muscle

Adachi et al. [67], looked at implantation of muscle derived MSCs or chondrocytes embedded in collagen gels into full thickness articular cartilage defects of the trochlea of rabbits. *In vitro*, following 4 weeks of culture, the muscle derived MSC group had a siginificantly higher number of cells. *In vivo*, at 4, 12, and 24 weeks post-operative, the muscle derived MSC and chondrocyte groups were similar and superior to the gel control group. Following this study, the same group also demonstrated that sex influences chondrogenic differentiation and cartilage regeneration potential, with male muscle derived MSCs superior over female [68]. To understand muscle derived MSCs further, Li et al. [69], isolated both fascia derived cells from the gluteus maximus muscle fascia and muscle derived cells from the muscle body of rats. Both populations alone had chondrogenic potential, and mixed pellets of the populations indicated that the chondrogenic potential decreased with the increased ratio of myogenic cells to fascia derived cells, suggesting that non-myogenic cells residing in the fascia of skeletal muscle have a strong chondrogenic potential and may represent a novel donor cell source for cartilage regeneration and repair.

Embryonic stem cells

In addition to the multiple sources of adult MSCs described above, Embryonic Stem Cells (ESCs) are an additional source of stem cells. Unlike multipotent MSCs, ESCs are pluripotent and can potentially provide an unlimited supply of cells. However, this also means that undifferentiated ECSs are tumorigenic. Therefore, *in vitro* work to direct differentiation and expansion of ESCs is very important, including precision regarding growth factors, signaling, additives, small molecules, and media conditions [70].

A myriad of studies have used *in vivo* models of ESCs applied using hydrogels or polymer scaffolds. Wakitani et al. [71] transplanted ESCs into articular cartilage defects in immunosuppressed rats, with the ESCs producing cartilage which resulted in repair of the defects at 8 weeks after the transplantation without formation of any teratomas. Hwang et al. [72] treated rat osteochondral defects with chondrogenically committed human ESC derived MSCs. At 8 weeks post-operative, the authors described normal cartilage architecture. Similarly, Toh et al. [73], filled rat osteochondral defects with human ESC derived chondrogenic cell-engineered cartilage and noted regenerated osteochondral tissue resembled closely that of age-matched unoperated native control. Overall, these studies suggest the potential of ESCs in the treatment of articular cartilage defects, although there is much work ahead before this cartilage regeneration can be employed.

Conclusions

Chondrogenic potential *in vitro* and *in vivo* treatment options

The *in vitro* chondrogenic potential of MSCs is well established. Pittenger et al. [42], demonstrated the chondrogenic potential of MSCs during pellet culture, and numerous other methods have since been described, from culture in alginate and agarose gels [8,74] as well as tissue engineering biomaterials that promote chondrogenesis. Culture media, substrate, cell density [75], growth factors, oxygen tension [8,44,76,77] and methods for improved cell selection require optimization to support consistent chondrocyte differentiation and improved cartilage repair. Using well described *in vitro* laboratory techniques of Ficoll gradient followed by monolayer culture to assist in isolating MSCs, both large animal [78,79] and human [32] studies show potential for improved cartilage repair through the addition of cultured MSCs. However, the major barriers toward improving cartilage repair clinically in humans remains the extreme low numbers of pluripotential progenitor cells within minimally manipulated mesenchymal cell preparations as well as the difficulty in assessing clinical outcomes following cartilage repair procedures. The *in vitro* and preclinical promise of stem cell and chondrogenic progenitor cell therapies to promote chondrogenesis will need to be tempered against these barriers to clinical translation in future research and development of new treatment options for symptomatic chondral defects.

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