Mol Biol Rep (2012) 39:5683–5689
DOI 10.1007/s11033-011-1376-z

Mesenchymal stem cell-based treatment for cartilage defects in osteoarthritis

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Received: 18 July 2011 / Accepted: 13 December 2011 / Published online: 20 December 2011

Abstract Osteoarthritis (OA) is a common disorder and the restoration of the diseased articular cartilage in patients with OA is still a challenge for researchers and clinicians. Currently, a variety of experimental strategies have investigated whether mesenchymal stem cells (MSCs) instead of chondrocytes can be used for the regeneration and maintenance of articular cartilage in OA. MSCs can modulate the immune response of individuals and positively influence the microenvironment of the stem cells already present in the diseased tissue. Through direct cell–cell interaction or the secretion of various factors, MSCs can initiate endogenous regenerative activities in the OA joint. Targeted gene-modified MSC-based therapy might further enhance the cartilage regeneration in OA. Conventionally, delivery of MSCs was attained by graft of engineered constructs derived from cell-seeded scaffolds. However, intra-articular MSCs transplantation without scaffolds is a more attractive option for OA treatment. This article briefly summarizes the current knowledge about MSC-based therapy for prevention or treatment of OA, discussing the direct intra-articular injection of MSCs for the treatment of OA in animal models and in clinical applications, as well as potential future strategies for OA treatment.

Keywords Osteoarthritis · Mesenchymal stem cells · Cartilage defects · Intra-articular injection

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Introduction

Osteoarthritis (OA) is a chronic degenerative process characterised by progressive cartilage deterioration, subchondral bone remodelling, loss of joint space, marginal osteophytosis, and loss of joint function [1]. Current interventions for OA primarily aim to alleviate symptoms, reduce pain, and control inflammation with nonsteroidal anti-inflammatory drugs [2–4], steroids [5], or hyaluronic acid (HA) [6], which have little impact on the progressive degeneration of joint tissues [7].

Surgical treatments for cartilage repair in OA, such as osteochondral graft transplantation (mosaicplasty) and microfracture, relieve pain temporarily but are unsatisfactory in the long term and eventually fail [8]. In addition, tissue engineering efforts such as autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) offer potential long-term solutions for the biological repair or regeneration of degenerated joint tissues. However, a major limitation of ACI or MACI is the inability to treat large cartilage defects [9], thus excluding patients with OA. Moreover, due to the concerns associated with donor site morbidity and the de-differentiation and limited lifespan of chondrocytes, novel cartilage repair strategies are in need.

The availability of large quantities of mesenchymal stem cells (MSCs) and their multilineage differentiation, especially their chondrogenic differentiation property, have made MSCs the most hopeful candidate progenitor cell source for cartilage tissue engineering. MSCs are multipotent stem cells that have shown the ability to migrate and engraft onto multiple musculoskeletal tissues, especially sites of injury, and undergo site-specific differentiation [10]. This article concentrates on the MSC-based approach to the prevention or treatment of OA, discussing the direct

intra-articular injection of MSCs for the treatment of OA in animal models and in clinical applications, as well as potential future strategies for OA treatment.

Mesenchymal stem cells

Mesenchymal stem cells are multipotent stem cells that can differentiate into various tissues of mesenchymal origin, such as bone, cartilage, fat, muscle, marrow stroma, tendon, ligament, and other connective tissues [11]. MSCs can be isolated from different kinds of tissues, such as bone marrow [11], adipose tissue [12], umbilical cord blood [13], placenta [14], synovium [15], periosteum [16], and muscle [17]. However, a variable number of nucleated cells can be obtained per volume or weight of tissue. The frequency of MSCs in the whole bone marrow of skeletally mature adults ranges from 1 in 50, 000 to 1 in 100, 000 cells, which corresponds to a yield of a few hundred MSCs/millilitre of marrow. Fraser et al. [18] have reported that the frequency of MSCs in adipose tissue is in the order of 1 in 100 cells, about 500-fold more than that found in bone marrow, which suggests that adipose tissue is also a good source of MSCs. However, there are differences in the capacity of MSCs from different sources. One study has compared the chondrogenesis of human MSCs derived from bone marrow, periosteum, synovium, skeletal muscle, and adipose tissue; the results showed that synovium-derived MSCs exhibited the highest capacity for chondrogenesis, followed by bone marrow- and periosteum-derived MSCs [19]. Kern et al. [20] compared the morphology, expansion ability, and differentiation potential of MSCs derived from bone marrow, umbilical cord blood, and adipose tissue. All three sources exhibited most characteristics of MSCs. However, MSCs from cord blood were unable to differentiate into adipocytes and had lower isolation efficiency. MSCs from bone marrow and adipose tissue were readily isolated and expanded, and adipose tissue contained the highest frequency of MSCs [20].

Isolation methods, culture surface, medium, and seeding density, as well as treatment with various growth factors, influence the expansion, differentiation, and immunogenic properties of MSCs [21]. Donor age and disease stage can also influence the proliferation and differentiation of MSCs. It has been reported that the proliferative and chondrogenic capacities of MSCs obtained from patients with OA are reduced compared with those from healthy individuals [22]. However, previous studies have demonstrated that sufficient numbers of MSCs with adequate chondrogenic differentiation potential can be isolated from patients with OA, irrespective of their age or the aetiology of their disease [23, 24]. Dudics et al. [25] also have shown that MSCs from OA patients possess chondrogenic potential similar to that of MSCs from healthy donors. Moreover, OA is associated with progressive and often severe inflammation. MSCs not only have the ability to contribute structurally to tissue repair, but also possess potent immunomodulatory and anti-inflammatory effects [10, 26]. It is well established that MSCs secrete a broad spectrum of bioactive molecules with immunoregulatory [27, 28] and/or regenerative activities [29]. Through direct cell–cell interaction or the secretion of various factors, MSCs can exert a great effect on local tissue repair by modulating the local environment and activating endogenous progenitor cells [30]. Taken together, these properties make MSCs promising candidates for cell therapy in OA diseases. The application of MSCs isolated from different tissues in the treatment of OA is discussed below.

Mesenchymal stem cell-based treatment of cartilage defects in animal models of osteoarthritis

The maintenance or restoration of a fully functional joint with biomechanically stable articular cartilage remains the goal of therapeutic or regenerative strategies in OA. Much early work focused on the repair of articular cartilage and subchondral bone in animal models, which usually required technically demanding procedures with MSC-loaded scaffolds and/or growth factors. The use of MSCs allows cartilage and bone to be repaired simultaneously, and results in better remodelling and integration with the host surface zone [31]. In general, MSCs combined with three-dimensional scaffolds and/or growth factors were implanted into cartilage defects in animal studies by means of open arthrotomy [32–34], which is more invasive and can increase the risk of joint infection [35].

Therefore, a simpler, scaffold-free approach in which MSCs are delivered as a suspension by direct intra-articular injection has been attempted widely for cartilage repair, as an alternative to the much more invasive methods currently available. Lee et al. [35] intra-articularly injected bone marrow-derived MSCs suspended in HA for the treatment of cartilage defects in the medial femoral condyle of an adult minipig. At 6 and 12 weeks postoperatively, the MSC-treated groups showed improved cartilage healing histologically and morphologically, compared with the HA alone or saline groups [35]. OA in the knees can often be caused by meniscal injury or defect. The repair of massive meniscal defects remains challenging due to a lack of cell kinetics for the menisci precursors in the knee joint. Horie et al. [36] investigated the efficiency of meniscal regeneration in rat massive meniscal defects using intra-articular synovium-derived MSCs. The results demonstrated that synovium-derived MSCs adhered to the lesion, differentiated into meniscal cells directly, and promoted meniscal regeneration without mobilisation to distant organs [36].

Recent efforts have focused on the use of the direct intra-articular injection of MSCs as a therapy for OA. A crucial requirement for MSC-based therapy for OA is the delivery of MSCs to the defect site. Previous studies have shown that intra-articularly injected MCSs can mobilise into injured tissues and participate directly in tissue repair, and also have beneficial paracrine effects that can induce a host repair response to replace the injured tissue [29, 37].

In animal models, OA is induced primarily by surgical procedures such as anterior cruciate ligament transection (ACLT) [38], ACLT combined with complete medial meniscectomy [39], or chemical adjuvants [40–44]. Surgically induced OA models may be more clinically relevant than chemically induced models because the biochemical and pathological changes are identical to those seen in human OA [45]. In general, animals received single MSC injections on day 14 after surgery [39, 46]. Animal experiments using MSCs derived from different tissues in therapies for the prevention and treatment of OA have shown encouraging results; articular cartilage degeneration, osteophytic remodelling, and subchondral sclerosis were reduced and progressive destruction was retarded in MSC-treated joints [39, 47]. Murphy et al. [39] injected autologous bone marrow-derived MSCs in a dilute HA solution directly into the knee joints of goats, in which OA had been induced by total medial meniscectomy and resection of the anterior cruciate ligament. Joints exposed to MSCs showed evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Articular cartilage degeneration, osteophytic remodelling, and subchondral sclerosis were also reduced in the treated joints [39]. In a horse model, Frisbie et al. [46] observed a greater improvement with the intra-articular injection of bone marrow-derived MSCs for the treatment of OA induced arthroscopically in the middle carpal joint. Surgically induced OA in animal models was established 14 days after surgery [39, 46], which may be considered the period of early OA. Single MSC injections have also shown exciting results in advanced or late OA. Toghraie et al. [47] delivered a single dose of 1 million infra-patellar fat pad-derived MSCs suspended in 1 ml medium to OA knees by direct intra-articular injection at 12 weeks after ACLT operation in a rabbit model. At 20 weeks after surgery, rabbits that received MSCs showed good cartilage quality and lower degrees of cartilage degeneration, osteophyte formation, and subchondral sclerosis compared with the control group. The results showed that the direct intra-articular injection of MSCs reduced the development of advanced OA lesions in a rabbit model [47]. Even in a mouse model of human rheumatoid arthritis induced by collagen, a single injection of bone marrow-derived MSCs prevented the occurrence of severe, irreversible damage to bone and cartilage [48].

Black et al. [49] reported the results of the first randomised, blinded, placebo-controlled trial examining the effectiveness of stem cell therapy in dogs with chronic OA of the hip. Dogs treated with adipose-derived stem cell therapy had significantly improved scores for lameness and combined scores for lameness, pain, and range of motion compared with control dogs [49]. Black et al. [50] subsequently evaluated the effectiveness of adipose tissue-derived MSC therapy in dogs with chronic OA of the humeroradial (elbow) joints. Statistically significant improvement in lameness, pain on manipulation, range of motion, and functional disability outcome measures was demonstrated at 180 days after receiving stem cell treatment [50].

The exact mechanisms by which implanted MSCs retard the progression of OA are not known. However, it is clear that the implanted MSCs engraft into the defect site and are involved in tissue repair. In addition, MSCs can exert a great effect on local tissue repair by modulating the local environment and activating of endogenous progenitor cells [30].

Clinical studies of mesenchymal stem cell-based treatment of cartilage defects in osteoarthritis

The results of animal models investigating the MSC-based treatment of OA induced after an acute traumatic event (e.g. ACLT) have been encouraging. However, compared with OA in humans, the pathology may develop rapidly in the ACLT model. Human OA progression is slow and may occur over a period of 15–30 years [51]. Therefore, the changes in animal models may not be generalisable to the slowly progressive damage of human OA. MSCs may be useful for the resurfacing of eburnated joints in patients with OA [52]. However, the MSC-based treatment of human OA is still at the early stage and its effects will be further investigated.

Wakitani et al. [53] reported on the first study of the use of transplanted bone marrow-derived MSCs seeded with collagen type I hydrogels to repair cartilage defects in human knees with OA. Twenty-four patients with knee OA and articular cartilage defects in the medial femoral condyle were treated with MSC-loaded collagen gels covered with autologous periosteum. Forty-two weeks after transplantation, the defects were covered with white soft tissue, and some hyaline cartilage-like tissue was observed. The arthroscopic and histological grading scores were better in the cell-transplanted group than in the cell-free control group [53].

Generally, cartilage lesions in OA are large, unconfined, and affect more than one location; opposed (or 'kissing') lesions are common. The direct intra-articular injection of

MSCs for OA treatment is a minimally invasive alternative to open arthrotomy. In a 46-year-old man, the intra-articular injection of autologous bone marrow-derived MSCs to treat knee OA showed good results after 6 months [54]; pain measured on a visual analogue scale (VAS) and the range of motion improved. Magnetic resonance imaging (MRI) showed a significant growth of articular cartilage and the regeneration of the meniscus [54]. Davatchi et al. [55] assessed four patients aged 54, 55, 57, and 65 years with moderate to severe knee OA who received intra-articular injections of autologous bone marrow-derived MSCs ($8–9 \times 10^6$). After 6 months, walking time and pain scores improved in three patients. All patients showed improvement in the number of stairs they could climb and pain on VAS [55].

These clinical results are reassuring. However, Noth et al. [56] has suggested that the direct intra-articular injection of MSCs might be effective only in the early stages of OA, when the defect is restricted to the cartilage layer. Later-stage OA often involves the bony component of the joint, and the presence of scaffolds suitable for the regeneration of subchondral bone is also an important factor. However, kissing lesions are common in knees with OA due to joint articulation, and the implanted matrix is readily and rapidly worn down [56]. The direct intra-articular injection of MSCs might have an advantage over the conventional method of seeding MSCs into a scaffold. Future studies will determine whether such direct intra-articular MSC injection will be suitable for repairing large areas of eroded cartilage, as occurs in advanced OA.

Gene-modified mesenchymal stem cells for cartilage repair in osteoarthritis

Because MSCs can be receptive to transduction with various viral vectors, the limitations of current MSC-based therapies for advanced or late OA might be overcome by the adaptation of MSC-based gene-transfer technologies [57]. MSCs should be transfected with genes that encode proteins that might reverse some of the major pathologies of OA [9, 58]. Genetically modified MSCs can be delivered to joints as a cell suspension to counteract the inflammatory and matrix-degradation processes. Following the delivery of genetically modified MSC suspensions, the transduced MSCs can release therapeutic proteins that interact with the site of injured cartilage tissue [56]. In addition, MSCs still can exert a tremendous effect on local tissue repair by modulating the local environment and activating endogenous progenitor cells [30].

Few reports have examined the possibility of intra-articular injection of gene-modified MSCs for cartilage repair in affected joints. The following three studies are most relevant. Murphy et al. [39] demonstrated the retardation of cartilage destruction in a sheep model of OA following the transplantation of retrovirally modified bone marrow-derived MSCs. However, the transfected gene was not the target therapeutic gene, but rather was used to trace the implanted MSCs [39]. Hu et al. [59] showed that the injection of bone marrow-derived MSCs transfected to express Bcl-xL enhanced the regeneration of cartilage defects in rabbits. Bcl-xL is an anti-apoptotic protein that can prevent cell death and improve the implantation efficiency of MSCs [59]. Matsumoto et al. [60] reported that the intra-articular injection of murine muscle-derived MSCs expressing bone morphogenetic protein (BMP)-4 in combination with MSCs expressing the vascular endothelial growth factor antagonist, soluble Flt-1 (sFlt-1), improved the quality and persistence of regenerated articular cartilage in an immunodeficient rat model of OA. Moreover, encouraging results have been obtained by applying differentiated cells transduced to produce therapeutic factors (e.g. transforming growth factor (TGF)-β, interleukin-1 receptor antagonist) in patients affected by cartilage disorders [61, 62]. However, the clinical application of genetically modified MSCs has not yet begun and much further work is needed. Before clinical application, the safety of genetically modified MSCs must be guaranteed.

Problems in mesenchymal stem cell application

Mesenchymal stem cells hold great promise as therapeutic agents in regenerative medicine. However, the complication rate and the problems of MSC-based therapy have received much attention. Between 2005 and 2009, patients with diseases of the peripheral joints ($n = 213$) or intervertebral discs ($n = 13$) were treated with direct injections of autologous bone marrow-derived MSCs [63]. High-field MRI tracking and general surveillance detected no neoplastic complication at any stem cell reimplantation site, demonstrating the safety of MSCs [63]. However, many problems remain in the application of MSCs. First, the required cellular dose for OA therapy should be clarified. Agung et al. [37] reported that the intra-articular injection of 10^7 MSCs generated free bodies of scar tissue in the rat knee. In addition, future studies are necessary to determine whether one injection will be sufficient to reach the desired result within a given time period. Second, the function and potency of MSCs are variable, and the best subtype of MSCs for OA therapy should be determined. Third, it remains uncertain whether the implanted MSCs survive or integrate into the newly formed tissue. Thus, the ability to monitor the in vivo behaviour of implanted MSCs in host tissue and to understand the fate of the MSCs is very important for the development of successful cell therapies.

An effective, non-invasive, and nontoxic technique for cell tracking is required. Fourth, further investigations are required to determine whether MSCs should be induced to chondrogenesis and then implanted in vivo. In a sheep model of OA, bone marrow-derived MSCs were cultured for 3 weeks in medium containing 5 ng/ml TGF-β3 + 50 ng/ml insulin-like growth factor-1, and then injected intra-articularly into the OA knee joint [64]. Knee joints treated with autologous MSCs cultured in chondrogenic medium showed improved articular cartilage regeneration [64]. Lastly, the choice of OA patients is important. Patients who are treated earlier by the intra-articular injection of MSCs and who are in better clinical condition achieve better outcomes.

Novel therapeutics for the later stages of osteoarthritis

Koelling and Miosge [30] found that repaired tissue from human articular cartilage during the late stage of OA has a unique progenitor cell population, termed chondrogenic progenitor cells (CPCs). CPCs exhibit a multipotent differentiation capacity, especially toward the chondrogenic lineage [30], and provide a potential starting point for the development of cell-based therapy for OA [65]. CPCs are already active as a physiological response to biological stimuli in the diseased tissue that they are supposed to repair, and might be more effective than cells derived from a totally different source (e.g. bone marrow) and implanted from outside [65]. However, there are several key limitations of CPC-based therapy. First, the chondrogenic potential of CPCs differs among patients. Second, it remains unclear whether the chondrogenic potential of CPCs can be sustained for a long time and whether they can produce an extracellular matrix that supports a more cartilage-like repair tissue. Likewise, the in vivo behaviour and fate of implanted CPCs must be monitored. Thus, numerous scientific questions remain to be addressed before the clinical application of CPC therapy for OA.

Conclusions

The potential use of MSCs in direct injection therapy for OA has generated much enthusiasm, due to their trophic anti-inflammatory and immunosuppressive properties. Many clinical and animal studies have produced exciting data suggesting the prospect of the widespread clinical application of MSC-based therapy. However, many problems must be resolved and much further work is required before the clinical application of the direct intra-articular injection of MSCs. We believe that MSCs offer great potential in relieving the disease burden of degenerative joint diseases through direct intra-articular injection. Moreover, it is crucial to increase our understanding of the mechanisms by which MSCs affect the progression of OA or contribute to the pathogenesis of the disease, to enable the development of innovative therapeutic options. Gene therapies offer some promise, particularly in the modulation of inflammatory mediators associated with OA. Genetically modified MSCs can be delivered to joints as a cell suspension to counteract synergistically the inflammatory and matrix-degradation processes, which might have great potential in the treatment of advanced OA. Recently, CPCs isolated from late-stage OA specimens have shown good chondrogenic differentiation capacity [30], and seem to be a possible new cell source for the treatment of late OA [65]. However, much research is needed before the clinical application of CPC-based therapy for OA.

Acknowledgments The project was supported by the Science Technology Program of Zhejiang Province (2008C13025) and the Natural Science Foundation of China (81071259)

Conflicts of interest All authors have no conflicts of interest.

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