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Novel Bioregenerative Options for Chondrocyte Restoration in Osteoarthritis

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ABSTRACT

Cartilage diseases refer to an umbrella of joint disorders, joint injuries and cartilage tumors that are largely characterized by degenerative chondrocyte changes in joints. Osteoarthritis (OA) is the most common form of chronic cartilage diseases, affecting 250 million people and is the fourth leading cause of disability worldwide. The widely used pharmacological treatments for OA have shown limited benefits, and further studies are required. Stem cells have been proposed as regenerative cell therapy for OA to repair and replace the injured cells and tissues with new ones, due to their potential for self-renewal and differentiation into cartilage-forming chondrocytes and immune-modulating capabilities. A number of preclinical and clinical studies have confirmed the potential for mesenchymal stem cells as a novel therapeutic strategy for the treatment of OA. In this review, we look at the promising evidence for stem cell use in OA treatment.

Keywords

Chondrocyte, Cartilage diseases, Joint degeneration, Stem cell, Orthopedics.

Introduction

Cartilage diseases refer to an umbrella of joint disorders, joint injuries and cartilage tumors largely characterized by degenerative changes in joints. This group includes injuries of articular cartilage (e.g., sport trauma, professional diseases or mechanical stress), osteoarthritis, vertebral herniation, accidental or chondrodysplasia (acquired because of toxic substances or radioactive influence), relapsing polychondritis, cartilage tumors (benign, such as chondroma, and malignant, such as chondrosarcoma). The global burden of cartilage diseases is great and its incidence is rising.

Osteoarthritis (OA) is the most common form of chronic cartilage diseases; affecting hundreds of millions of people worldwide [1]. OA is assumed the fourth leading cause of disability in the world [2]. OA influences the knees, hips, hands, feet, and spine. The knee is the most frequently affected site and accounts for almost 85% of the burden of OA worldwide, followed by the hand and hip. A number of risk factors such as female sex, age, obesity, genetic factors, and oxidative stress increase the chances of developing OA. It is growing more prevalent today because of the combined factors of aging, obesity and the increasing numbers of damaged joints, and an estimated 250 million people are affected by this syndrome [3].

Hyaline cartilages, fibrocartilages and elastic cartilages play multiple roles in the human body, including bearing loads in particular joints and intervertebral discs, providing joint lubrication and forming the long bones during development and growth. The structure and organization of the cartilage's extracellular matrix (ECM) are the primary determinants of normal function. Most diseases involving cartilage led to dramatic changes in the chondrocytes ECM, which can cause the main symptoms of the disease, govern disease progression (e.g., in osteoarthritis) or occur as collateral damage in pathological processes occurring in other nearby tissues [4]. Until recently, it was accepted that cartilage diseases were primarily a disorder of reactive subchondral changes to cartilage. However, there is now some evidence that they might be primarily a subchondral problem with secondary changes in the articular cartilage, and that early subchondral changes include redistribution of blood supply with marrow hypertension, oedema and probably micronecrosis [5]. The challenges associated with cartilage diseases include poor understanding of its etiology and pathogenesis, delayed diagnoses due to the neural nature of the tissue and drug delivery issues due to the avascular nature of adult cartilages.

Current approaches to osteoarthritis

OA is a dynamic disease caused by the imbalance between restoration and destruction of cartilage tissue [6]. The anatomical changes that occur with OA involve the chondrocytes forming the articular cartilage, subchondral bone, ligaments, synovium, and periarticular muscles. The articular cartilage defect is the most obvious syndrome of OA, and is caused by degeneration of the ECM [7]. Currently, both non-pharmacological methods and pharmacological methods are applied to treat OA. Non-pharmacological methods, including self-management, regular exercise, and weight control, are highly recommended and are regarded as first-line treatments for OA. Pharmacological methods recommended in the guidelines are paracetamol and NSAIDs [8]. Patients with OA who do not respond to topical analgesics are recommended to take intra-articular corticosteroids [9]. Surgical options such as joint replacement surgery, knee osteotomy, and knee joint distraction are recommended for either patients with late-stage OA or young and physically active patients with moderate severity in OA [10]. Such medical approaches are designed to reduce pain and improve the mobility of joints instead of repairing damaged articular cartilage. Intra-articular steroids only show effectiveness in short-term trials up to 2 weeks but not in long-term trials [11]. The widely used pharmacological treatments for OA have shown limited benefits, and further studies are required.

Bio regenerative treatments are intended to repair and replace the injured cells and tissues with new ones. Existing regenerative approaches however, are currently limited. Exogenous hyaluronic acid (HA) is a natural joint fluid that can stimulate the synthesis of endogenous HA and proteoglycans in chondrocytes, therefore suppressing cartilage destruction and promoting regeneration. Platelet-rich plasma (PRP) was used in tissue repair and showed pain alleviation and functional improvement that were sustained for 6 months [12]. Promising new bio regenerative technologies offer exciting therapeutic options for OA patients.

Mesenchymal stem cells (MSCs) as a bioregenerative technology for OA

Stem cells (SCs) have been proposed as a bioregenerative cell therapy for OA, due to their potential for self-renewal and differentiation into cartilage and immune modulating capabilities [13]. A number of preclinical and clinical studies have confirmed the potential for mesenchymal SCs (MSCs) as a novel therapeutic strategy for the treatment of OA [14]. Multipotent SCs are distributed extensively in the bone marrow, trabecular bone, fat pad tissue, synovial membrane, and several other tissues. MSCs were first isolated from bone marrow and later from adipose tissue, placenta, umbilical cord / cord blood, dental pulp, and amniotic fluid. MSCs have shown great potential in promoting the regeneration of chondrocytes and their further differentiation into cartilage [15]. A systematic review of 61 studies of OA and stem cell therapy in humans done by Jevotovsky et al. [16] concluded that MSC therapy has a positive effect on OA patients. However, it identified that there is limited high quality evidence available and that long-term follow-up is lacking. It also noted that the studies showed a lack of consistency, including a diversity of MSC preparations.

Saghahazrati et al. [17] showed that different tissue sources of MSCs demonstrate different characteristics that confer advantages and disadvantages for therapeutic usage, including proliferative capacity, immunomodulatory capacity and cytokine secretion profiles. Amniotic-derived MSCs have the advantageous proliferative capacity, followed by MSCs from fat and bone marrow (BM-MSCs). Umbilical cord, amnion, and adipose tissue derived MSCs (AD-MSCs) have superior immunomodulatory capacity, including immune regulation, compared to bone marrow MSCs and placental MSCs have the lowest immunomodulatory capacity. In terms of cytokine secretion profiles, umbilical cord MSCs secrete more cell growth factors than bone marrow MSCs.

A number of studies have evaluated the potential of MSCs in cartilage tissue regeneration both *in vitro* and in animal models. A number of clinical trials have demonstrated the potential efficacy of MSCs derived from bone marrow, adipose tissue, and umbilical cord blood in the treatment of OA.

Bone marrow derived MSCs

Wakitani et al. conducted the first clinical study of bone marrow derived MSC (BM-MSCs) transplantation for articular cartilage treatment in 2002 [18]. The trial recruited 24 patients with knee OA who underwent a high tibial osteotomy. Half of the cohort received autologous BM-MSC transplantation and the other half were matched controls. After 42 weeks of transplantation, metachromasia was observed in almost all areas of the sampled tissue, and hyaline cartilage-like tissue was partially observed. The arthroscopic and histological grading scores were better in the cell-transplanted group than in the cell-free control group, suggesting the suitability of BM-MSC transplantation for OA treatment. Vangsness et al. [19] studied 55 patients who underwent a partial medial meniscectomy and received two different doses of allogeneic BM-MSCs treatments. The intra-articular injection was performed using 50×10^6 or 150×10^6 allogeneic BM-MSCs in patients with OA into their knees 7-10 days after the meniscectomy. After 2 years of follow-up, no clinically adverse effects were identified. The authors concluded that there was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human MSCs. These results support the study of human MSCs for knee-tissue regeneration in treating OA.

Soon after, a multicenter randomized clinical trial demonstrated the long-term therapeutic effect of intraarticularly injected HA together with two different doses of autologous BM-MSC (10×10^6 or 100×10^6) transplantation versus HA alone in 30 patients with knee OA [20]. After 4 years of follow-up, the cell-recipient group, especially the high-dose group of the single-dose injection of BM-MSCs showed long-term clinical and functional improvement in knee OA.

In summary, BM-MSCs are characterized by their simple accessibility, fast cell proliferation, long-term sustainment of differentiation capacity and reduced immunological exclusion. Therefore, they are the most widely used source of therapeutic MSCs for OA.

Adipose derived MSCs (AD-MSCs)

With the greater proliferation and differentiation potential than BM-MSCs, AD-MSCs are an attractive cell source of therapeutic MSCs. The effectiveness of AD-MSCs therapeutic use in OA has been demonstrated in several studies. A bicentric, uncontrolled, open phase I clinical trial was conducted in France and Germany [21] with regulatory agency approval for AD-MSCs expansion procedure in both countries. From April 2012 to December 2013, 18 consecutive patients with symptomatic and severe knee OA were treated with a single intra-articular injection of autologous AD-MSCs. The study design consisted of three consecutive cohorts of six patients each with the following dose escalation: low dose (2×10^6 cells), medium dose (10×10^6), and high dose (50×10^6). The primary outcome parameter was safety, evaluated by recording adverse events throughout the trial, and the secondary parameters were pain and function subscales of the Western Ontario and McMaster Universities Arthritis Index [22]. After 6 months of follow-up, the procedure was found to be safe, and no serious adverse events were reported. Interestingly, the study showed that patients treated with low-dose AD-MSCs experienced significant improvements in pain levels and function compared to that at baseline. These data suggest that intra-articular injection of AD-MSCs is a safe therapeutic alternative to treat severe knee OA patients.

A few years later, Lee et al. [23] conducted a study to evaluate the efficacy of AD-MSCs with micro fracture treatment versus micro fracture alone in 80 patients aged 18 to 50 years with moderate to severe knee OA. After 24 months of follow-up, the autologous AD-MSC-treated group showed better signal intensity for tissue repair and Knee injury and Osteoarthritis Outcome Score pain and symptom sub-scores. However, results showed no significant differences in other sub-scores, such as daily living activity, sports and recreation and quality of life, demonstrating the potential of AD-MSCs in tissue repair and possibly pain relief in addition.

In 2021, Caforio and Nobile published the results of the study to evaluate the safety and efficacy of the intra-articular administration of autologous purified adipose tissue to treat knee OA following arthroscopy. Thirty patients with radiological evidence of knee OA were recruited. Small liposuction and arthroscopic lavage and debridement were performed at the same surgical time. The harvested fat was processed intraoperatively to purify the adipose tissue injected into the knee. Results showed that pain, as measured with visual analogue scale (VAS), significantly decreased, showing a 53% reduction after 1 month and an 83% reduction after a year. Functional recovery showed an improvement of 47% at 1-month post-treatment and 84% after 1 year. No adverse effects were observed. This study suggested that intra-articular administration of the cells derived from adipose tissue associated with arthroscopic lavage and debridement is a safe and effective strategy in improving the symptoms of knee osteoarthritis in up to 1 year of follow-up.

Umbilical cord derived MSCs (UC-MSCs)

Another source for stem cell therapy is UC-MSCs because of their proliferation ability and immunomodulatory capacity. A number of clinical trials have been conducted using UC-MSCs in the treatment of OA.

Studying the safety of the SCs for the treatment of OA, Iturriaga et al. [24] reviewed the preclinical and clinical trials performed in recent years in order to take a glance at the potential benefits that such therapies could deliver to the patients. They concluded that SCs had proven their potential and safety for OA treatment. Wang et al. [25] conducted a safety and efficacy study of UC-MSC transplantation on 36 patients with moderate or severe knee OA with a 6-month follow-up. Results showed a significant improvement in joint function and quality of life after 1 month and a sustained treatment effect for 6 months. This study suggests that intra-articular injection of human UC-MSCs is effective, at least temporarily, for treating degenerative knee OA.

A few years later, Wu et al. [26] induced cartilage wear in the knees of age-, weight-, and sex-matched miniature pigs to generate an animal model of OA and transplanted 1.5 mL of a UC-MSCs (5×10^6 cells) and HA hydrogel composite into the chondral-injured area in the right knee of each pig. The left knee was used as a control. After 12 weeks of transplantation, the degree of cartilage repair was determined by macroscopic and microscopic observation. The cartilage wear in the treatment group was significantly reversed compared to that in the control group. Macroscopically, at 12 weeks after transplantation, the articular surface in the transplanted knee was relatively smooth, with the same coloration as the surrounding normal cartilage. The histological score of the knee joint after treatment by the International Society of Cartilage Repair was higher than that of the control group.

Matas et al. [27] evaluated the safety and efficacy of single or multiple intra-articular injections of UC-MSCs in the treatment of OA in humans. Twenty-nine patients with knee OA were randomly sampled at baseline and 6 months, and injected with single dose (20×10^6) UC-MSCs at baseline or repeated UC-MSCs doses at baseline and 6 months ($20 \times 10^6 \times 2$). At the 12-month follow-up, no adverse reactions such as death, neoplasia, or infection were observed. The pain and function of the patients injected with UC-MSCs significantly improved. According to their data, only MSC-treated patients showed significant improvements in pain and function from baseline, as opposed to the HA-treated patients. At 12 months, patients in the MSC group experienced 86% pain reduction and 89% disability reduction ($p = 0.001$), unlike 38% and 50% in the control HA group, respectively. The clinical score was significantly higher than that of the control group. There was no statistical difference in imaging results. This study suggests that multiple injections of UC-MSCs show a good safety profile in the treatment of OA, with clinical efficacy in the treatment of long-term pain caused by OA.

In conclusion, several clinical trials have demonstrated the safety and potential efficacy of BM-MSCs, AD-MSCs, and UC-MSCs in the treatment of OA. The study of OA, particularly the use of stem cell therapy in joint disease research has attracted considerable attention. Precise studies have been carried out on the function and characteristics of MSCs and their application in cartilage regeneration to treat OA. According to reports from basic research and clinical trials, it is safe and effective to use MSCs to treat OA [28].

Organ-specific stem cells for OA

SCs are principally characterized by their ability to self-renew and differentiate along multiple lineages. Embryonic SCs are termed pluripotent because of their ability to progress along the endodermal, mesodermal, and ectodermal lineages. Adult SCs are usually referred to as multipotent, because of their more limited lineage differentiation abilities. During development, it is generally assumed that the potency of SCs becomes more restricted, and that some SCs can exist in certain tissues as quiescent progenitor cells. Numerous studies have shown that these tissue-specific SCs are present and that they are likely involved in the maintenance of tissue homeostasis.

Articular cartilage is a physiologically non-self-renewing avascular tissue, consisting of a single cell type, the chondrocyte. Jiang et al. [29] showed that cartilage-derived stem/progenitor cells (CSPCs) have been observed in human, equine and bovine articular cartilage. The endogenous population of SCs in articular cartilage serves as reparative cells. However, the lack of a perichondrium and vasculature in articular cartilage also probably contributes to the non-reparative nature of this tissue. Nonetheless, recent studies have identified, isolated and characterized a population of SCs from articular cartilage.

In early OA, the basic goal of therapeutic strategies is to preserve tissue structure and function. Cartilage SCs enhance joint resurfacing which recruits cells producing lubricin to generate a new surface layer, thus replacing degenerated tissue. In addition, cartilage SCs enhance extracellular matrix (ECM) production, which promotes tissue homeostasis. Signaling molecules such as transforming growth factor β and bone morphogenic proteins are clearly effective in enhancing chondrocyte re-differentiation and ECM production, as shown by Koelling et al. [30] in studies on isolated CSPCs *in vitro*. Targeting CSPCs to enhance the intrinsic chondroprotective ability of these cells through inhibition of matrix-degrading enzymes induces the production of anti-inflammatory cytokines such as an IL-1 receptor antagonist [31].

The physiological repair mechanisms of diseased hyaline cartilage tissues are sparse and overridden by matrix destruction, thereby resulting in less functional fibro cartilaginous, collagen type I-rich scar tissue. In 2009, Koelling et al. found evidence that migratory cells derived from the repair tissue of late-stage OA possess a high chondrogenic potential and have progenitor cell characteristics [32]. These cells might possibly migrate through breaks in the tidemark. Authors isolated a stem cell population from human osteoarthritic tissue and demonstrated that these cells possess a multipotent differentiation capacity, especially towards the chondrogenic lineage and that they are highly migratory. Because these cells show heterogeneity in these properties and because of their migratory potential, scientists preferred to call them chondrogenic progenitor cells (CPCs). CPCs have sustained expression of markers of relevance to SCs, such as CD29 and CD73. This speaks to the profound role of ECM components on CPC and underlines the importance of the ECM in stem cell biology. The chondrogenic potential of CPC was dramatically enhanced via aggrecan and collagen type II expression of chondrocytes. The authors concluded that these progenitor cells seem to be a possible starting-point for the development of a cell-based therapy for OA.

In later stages of OA, the loss of cartilage ECM and the accompanying tissue structural changes result in the formation of channels from the synovium to the subchondral bone, enabling cell passage between these tissues. The migratory ability of CSPCs is known. If uncontrolled cell migration is a consequence of or accelerates tissue disruption in later-stage OA, blocking cell migration might delay degeneration. On the other hand, if the travelling cells function in tissue rebuilding, cell migration should be promoted. As end-stage, OA is characterized by cartilage loss

and thickening of the subchondral bone, adapting the altered tissue structure to facilitate joint movement is of critical importance, in addition to pain management. Interestingly, in some clinical cases, a very thin, protective, cartilage-like layer can be found on the surface of the abnormal subchondral bone. Although the mechanisms responsible for this neocartilage formation in the joint environment of such late-stage OA are unknown, the involvement of CSPCs is highly probable and could be a target for OA therapy.

In 2012, Seol et al. performed a study to assess their hypothesis that the migrating cell population included chondrogenic progenitor cells that are drawn to injured cartilage by alarmins [33]. Osteochondral explants obtained from mature cattle were injured by blunt impact or scratching, resulting in localized chondrocyte death. Injured sites were serially imaged by confocal microscopy, and migrating cells were evaluated for chondrogenic progenitor characteristics. Chemotaxis assays were used to measure the responses to chemokines, injury-conditioned medium, dead cell debris, and high mobility group box chromosomal protein 1 (HMGB-1). It was shown that migrating cells were highly clonogenic and multipotent and expressed markers associated with chondrogenic progenitor cells. Compared with chondrocytes, these cells overexpressed genes involved in proliferation and migration and under expressed cartilage matrix genes. They were more active than chondrocytes in chemotaxis assays and responded to cell lysates, conditioned medium, and HMGB-1. Glycyrrhizin, a chelator of HMGB-1 and a blocking antibody to the receptor for advanced glycation products (RAGE), inhibited responses to cell debris, conditioned medium, and reduced the numbers of migrating cells on injured explants. Authors concluded that injuries that caused chondrocyte death stimulated the emergence and homing of chondrogenic progenitor cells, in part via HMGB-1 release and RAGE-mediated chemotaxis. Their repopulation of the matrix could promote the repair of chondral damage that might otherwise contribute to progressive cartilage loss.

Chondrogenic progenitor cells are regarded as being biologically primed for chondrogenesis. They are not entirely lineage restricted, and, as such, they exhibit enough plasticity to differentiate along osteogenic and adipogenic lineages. According to Jayasuriya et al. [34,35], the local tissue SC niche is a critical feature that can dictate which path to maturation these cells will ultimately take. Similarly, when seeking to utilize SCs in cell-based therapy for cartilage repair/regeneration, it is essential to consider the effects of the local tissue microenvironment into which these SCs are introduced. From a tissue-engineering perspective, there are two important factors to consider in this regard. First, a viable source of SCs/progenitor cells that offer a biological repertoire that complements the desired path of differentiation is required. Second, one must consider how to provide the best SC niche for these cells to mature. There is a great need to develop strategies that can be used in conjunction with SCs to promote the most desirable repair response. Such strategies include anything that will favorably alter the local SC niche, including the use of recombinant growth factors, implementation of artificial/biological scaffolds and even the use of small interfering RNAs to attenuate further damage.

Stem cell-derived peptides / exosomes for OA

Given the important role of SCs in maintaining cartilage homeostasis and the reparative potential of SCs in cartilage repair, researchers have developed the use of natural extracellular matrix proteins, scaf-folding, and combined growth factors for SC attachment, growth, and regulation of cell differentiation. Extracellular vesicles (EVs), including exosomes, have also been applied as novel therapeutic options for OA in pre-clinical and clinical studies [36,37].

Decellularized ECMs (dECMs) are used for cartilage repair because they have little to no cytotoxicity and contain many of the natural structural components that modulate cell attachment, growth, and differentiation [38]. The dECM can be used as a scaffold that closely mimics the natural tissue matrix in which cells can reside and function. The successful use of the dECM for promoting cartilage repair embodies the importance of preserving the local tissue microenvironment for improving cellular function, as demonstrated by Zhao et al. [39] study using 3D bioprinting techniques, for their potential roles in effective cartilage healing.

Using a canine model, Yang et al. [40] confirmed that decellularized osteochondral scaffolds can successfully induce primary canine BM-MSCs to produce repair tissue with a stiffness (70.77% of normal cartilage) and glycosaminoglycan content (74.95% of normal cartilage) comparable to that of native cartilage. Osteochondral constructs were fabricated *in vitro* using chondrogenically-induced BM-MSCs and a biphasic scaffold, then assessed by SEM for cell attachment. Osteochondral defects of 4.2 mm diameter × 6 mm depth were created in canine femoral condyles and treated with a construct of the biphasic scaffold/chondrogenically-induced BM-MSCs or with a cell-free scaffold (control group). The repaired defects were evaluated for gross morphology and by histological, biochemical, biomechanical and micro-CT analyses at 3 and 6-months post-implantation. Results showed that the osteochondral defects of the experimental group demonstrated more repair than those of the control group. Macroscopic and histologic grading scores of the experimental group were consistently higher than those of the control group, and the scores for the experimental group at 6 months were significantly higher than those at 3 months. Micro-CT analysis of the subchondral bone showed that mature trabecular bone regularly formed at 3 and 6 months, with no significant difference between the experimental and control groups. The authors concluded that the ECM-derived, integrated, biphasic scaffold showed potential for the repair of large, high-load-bearing osteochondral defects.

Studies in small animal models of OA showed that stem cell derived EVs attenuated OA disease progression *in vitro* and *in vivo* by displaying similar biological functions as SCs. Mao et al. [41] investigated the molecular mechanism of exosomal miR-92a-3p and WNT5A in chondrogenesis and cartilage degeneration. Exosomal miR-92a-3p expression was assessed *in vitro* in a human MSC model of chondrogenesis and in normal and OA primary human chondrocytes (PHCs). MSCs and PHCs were treated with exosomes derived from MSC-miR-92a-3p (MSC-miR-92a-3p-

Exos) or its antisense inhibitor (MSC-anti-miR-92a-3p-Exos) respectively. It was shown that exosomal miR-92a-3p expression was elevated in the MSC chondrogenic exosome, while it was significantly reduced in the OA chondrocyte-secreted exosome compared with normal cartilage. Treatment with MSC-miR-92a-3p-Exos promoted cartilage proliferation and matrix gene expression in MSCs and PHCs respectively. In contrast, treatment with MSC-anti-miR-92a-3p-Exos repressed chondrogenic differentiation and reduced cartilage matrix synthesis by enhancing the expression of WNT5A. These results suggest that exosomal miR-92a-3p regulates cartilage development and homeostasis.

Another study by Cosenza et al. [42] evaluated the effect of microvesicles/microparticles (MPs) or exosomes (Exos) on OA-like murine chondrocytes in murine models. MPs and Exos were isolated from bone marrow murine BM-MSCs. In OA-like chondrocytes, BM-MSC-derived MPs and Exos were shown to reinduce the expression of chondrocyte markers (type II collagen and aggrecan) while inhibiting catabolic (MMP-13, ADAMTS5) and inflammatory (iNOS) markers. Exos and MPs were also shown to protect chondrocytes from apoptosis and inhibit macrophage activation. In the study, Exos or MPs were injected into the collagenase-induced OA model *in vivo* and histomorphometric analyses of joints were performed. Results showed that BM-MSCs, MPs and Exos equally protected mice from joint damage. The authors concluded that MPs and Exos exerted similar chondroprotective and anti-inflammatory functions *in vitro* and protected mice from developing OA *in vivo*, suggesting that either Exos or MPs reproduced the main therapeutic effect of BM-MSCs.

To explore the mechanism and effects of pre-cartilaginous SCs engraftment-inducing tissue repair in a knee OA rat model, Fan et al. [43] conducted a study using Sprague Dawley rats by partial removal of the medial meniscus of the right knees. PSCs were engrafted by injecting pre-cartilaginous SCs into the right knee cavities of the mice. At 4 and 8 weeks, OA rats demonstrated significantly higher IL-1β, TNF-α, and IL-6 levels than normal rats ($p < 0.05$), whereas pre-cartilaginous SCs treatment prominently attenuated IL-1β upregulation ($p < 0.05$). In OA rats, the number of chondrocytes dramatically decreased over time in OA rats, with an ensuing disruption of chondrocytes organization and cell layers. Pre-cartilaginous SCs alleviated the deterioration of cartilage, as evidenced by the relatively smooth articular surface, distinct tidemark and clear cell layers. The study suggests that pre-cartilaginous SCs treatment downregulated the expression of inflammatory cytokines, thereby alleviating OA in the knee of rats.

In summary, specific matrix molecules can be used to regulate cell behavior. All of these features contribute to future consideration of cartilage tissue repair strategies, as they hold promise for helping to provide an optimal microenvironment to promote chondrogenesis, while simultaneously inhibiting chondrocyte hypertrophy and terminal differentiation. Many questions remain for scientists to resolve before the widespread use of SCs in clinical practice; such as the treatment mechanism, the best cell source, the most appropriate processing method, the most effective dose and delivery procedure, and their efficacy. In this sense, long-term follow-up and larger randomized controlled trials utilizing standardized and established outcome scores are mandatory to make objective conclusions.

Conclusions

Joint degenerative chondrocyte disorders are becoming an increasing burden as their incidence is rising worldwide. Osteoarthritis, the most common joint disease, is driven by both mechanical and inflammatory factors. Both nonpharmacological and pharmacological strategies are the initial strategies in OA treatment. The main goals of traditional medication and biological agents in OA treatment are pain relief and slowing down or halting the progression of OA. Surgical correction is the next step to treat OA. Stem cell-based bioregenerative therapy is gaining interest worldwide because of its potential for the regeneration of new chondrocytes, cartilage and strong immunoregulatory capacity. MSCs are multipotent cells with a high capability of cell proliferation and differentiation and both autologous and allogeneic MSCs have been applied in several studies. Positive results in preclinical and clinical trials have demonstrated that mesenchymal and tissue-specific stem cell-based agents are a promising bioregenerative strategy in the treatment of OA. Cell therapy, especially cartilage stem cell-based therapy, is becoming an encouraging approach to regenerative medicine in the treatment of OA. The promising effects of cartilage stem cell therapy indicate that, in combination with other treatments, might achieve better regenerative efficacy for degenerative joint disorders.

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