

Review Article

Mesenchymal stem cells in osteoarthritis therapy: a review

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Abstract: Osteoarthritis (OA) is a chronic joint disease that generally occurs worldwide with pain and disability. The progression is slow, and it is mostly diagnosed midlife and often disturbs the knees, hips, feet, hands, and spine. Sex, age, obesity, occupation, and hereditary factors are risk factors that increase the opportunity for OA. Physical examinations involving X-rays and MRI, joint fluid analysis and blood tests are common tools for the diagnosis of OA. Interventions including exercise, manual therapy, lifestyle modification, and medication can help relieve pain and maintain mobility in the affected joints, yet none of the therapies enables the promotion of regeneration of degenerated tissues. Mesenchymal stem cells (MSCs) are a promising source for the treatment of OA due to their multipotency for differentiation into chondrocytes and their ability to modulate the immune system. Herein, we review the pathogenesis and treatment of OA and address the current status of MSCs as a novel potential therapeutic agent in OA treatment.

Keywords: Mesenchymal stem cell, cell regeneration, osteoarthritis, immune system

Introduction

Osteoarthritis (OA) is a common chronic disease and accounts for major physical pain and disability in older adults. It is assumed to be the fourth leading cause of disability in the world in 2020 [1]. OA consistently influences the knees, hips, hands, feet, and spine [2]. 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 [3-5]. The particular syndromes of OA encompass chronic pain, stiffness, mobility restriction, and joint tenderness [6]. A number of risk factors such as female sex, age, obesity, genetic factors, and Oxidative stress increase the chances of developing OA [7]. 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 [1].

The structural variations in OA include articular cartilage, subchondral bone, ligaments, synovi-

um, and periarticular muscles. The articular cartilage defect is the most obvious syndrome of OA, which is caused by degeneration of the extracellular matrix [8, 9]. People diagnosed with OA suffer physical weakness, mental pressure and impaired quality of daily life [10]. Currently, both nonpharmacological methods and pharmacological methods are applied to treat OA. Nonpharmacological methods, including self-management, regular exercise, and weight control, are highly recommended and are regarded as first-line treatments for OA [11, 12]. Pharmacological methods recommended in the guidelines are paracetamol and NSAIDs, which are often used when nonpharmacological methods are not able to relieve pain and reduce disability. Patients with hip and knee OA who do not respond to topical analgesics are recommended to take intra-articular corticosteroids [11]. Duloxetine is a serotonin and norepinephrine reuptake inhibitor, which is recommended in some guidelines to reduce the severe pain of OA [13]. New treatments, such as nerve growth factor (NGF) antibodies, have

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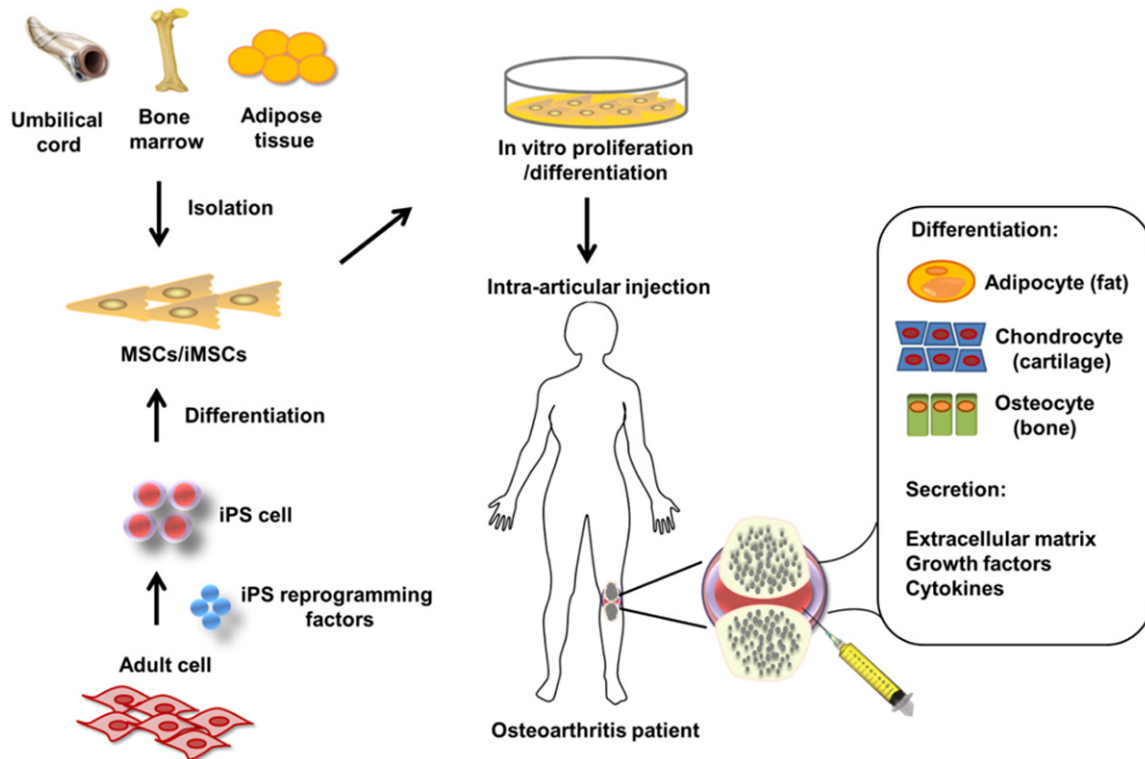


Figure 1. Schematic picture of mesenchymal stem cell applications in the treatment of osteoarthritis. The MSCs can be isolated from bone marrow adipose tissue and umbilical cord or induced from iPS cells. Intra-articular injection of MSCs is followed by in vitro proliferation or differentiation. Patients with OA are treated through bone regeneration and cartilage repair.

been evaluated and have shown positive results in reducing pain in patients with hip and knee OA [14]. Surgical options such as joint replacement surgery, knee osteotomy, and knee joint distraction are either recommended for patients with late-stage OA or young and energetic patients with moderate radiographic severity in OA [15-17]. However, the above treatments are designed to reduce pain and improve the mobility of joints instead of promoting the regeneration of damaged articular cartilage. The regenerative treatments are intended to repair and replace the injured cells and tissues with new ones. As a regenerative cell therapy of OA, mesenchymal stem cells (MSCs) have the potential of self-renewal and differentiation into cartilage and the capability of immune modulation. A number of preclinical and clinical studies have confirmed the potential for MSCs as a novel therapeutic strategy for the treatment of OA. In this review, we provide an extensive review of the pathogenesis and treatment of OA and emphasize the therapeutic features of bone marrow MSCs (BM-MSCs), adi-

pose tissue-derived MSCs (AD-MSCs), and umbilical cord-derived MSCs (UC-MSCs) in OA treatment (Figure 1).

Pathogenesis

OA is not an inactive degenerative disease; on the contrary, it is a dynamic disease caused by the imbalance between restoration and destruction of joints [18]. The pathogenesis of OA is complicated and can be described from different perspectives. We will address the pathogenesis of OA through environmental, inflammatory and metabolic aspects.

OA has become more prevalent in recent decades, and the increase in environmental changes is the main cause. Obesity, metabolic syndrome, dietary changes, and physical inactivity are four major environmental factors in OA pathogenesis [19]. Obesity is recognized as a dominant risk factor, especially for knee OA, because of the excess weight loading pressure on weight-bearing joints [20, 21]. The abnormal

loading of cartilage primarily causes damage to the cartilage matrix of collagen fibrils and proteoglycans and then triggers chondrocyte surface mechanoreceptors, which further trigger the MAPK or NF- κ B intracellular signaling pathway and the production of proinflammatory and catabolic mediators [22, 23]. There is evidence that adipose tissue produces and releases cytokines such as IL-1, IL-6, IL-8, IFN γ , TNF and leptin during bearing, which have been proven to play a role in promoting inflammation and initiating OA [24, 25].

Metabolic syndrome is a cluster of cardiometabolic factors, such as central adiposity, dyslipidemia, impaired fasting glucose levels and hypertension, which follow obesity and are closely associated with cardiovascular disease and type 2 diabetes [26]. Evidence shows that type 2 diabetes can change the structure of the extracellular matrix, and the enrichment of advanced glycation end products can trigger the signal to chondrocytes to finally cause the degradation of cartilage matrix [27].

The obvious change in diets in recent decades has resulted in an increased intake of oxidant foods and proinflammatory omega-6 fatty acids [28]. Although the direct contribution of dietary changes to OA is still controversial, the evidence indicates that a higher fiber intake reduces knee pain in patients with OA [29].

Physical inactivity is another main risk factor for OA, by which people lose the ability to maintain normal joint capacity [30]. Disuse experiments in animals demonstrate a decrease in cartilage layers and cartilage proteoglycan and injury of subchondral bone in joint tissues [31, 32].

In OA, we can see alterations in cellular metabolism, including an increase in the production of antianabolic, procatabolic and proinflammatory factors [33]. The source of energy metabolism in chondrocytes in OA converts from oxidative phosphorylation to anaerobic glycolysis [34, 35]. The alterations in mitochondrial structure and dynamics in chondrocytes lead to mitochondrial metabolism impairment and oxidative damage by enrichment of ROS [36]. Damage to mitochondria reduces AMPK activity, downregulates SIRT1 and decreases PGC1 α expression, which is a master regulator of mitochondrial biosynthesis [37]. The synovium is inflamed in the early and late stages of OA, and

it produces cytokines, ROS, NO, prostaglandin E2 and neuropeptides that alter cellular metabolism and disturb the balance between cartilage matrix degradation and restoration [38, 39]. By understanding the cellular metabolism molecules that are altered in the progression of OA in more detail, we can more precisely enable the design of OA targeting therapy.

Inflammation plays an important role in the destruction of cartilage, and proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α are essential in the pathogenesis and progression of OA [40]. IL-1 β is elevated in the development of OA, induces the release of MMPs and inhibits the expression of ECM components in OA cartilage in which IL-6 synergistically increases inflammation [41, 42]. TNF- α is upregulated in OA in joint tissues and synovial fluid, which suppresses the expression of proteoglycan and ECM components in chondrocytes and stimulates the expression of proinflammatory and procatabolic mediators such as MMP-1, IL-6, MCP-1, and NO [43-46].

Several signaling pathways have been proven to play a key role in the destruction of cartilage. It has been identified that the Notch signaling pathway is activated and that the signaling components are upregulated in humans and a mouse model of OA [47, 48]. However, activation of Notch was proven to help prevent articular cartilage destruction in another study [49]. HIF-2 acts as a central catabolic regulator by stimulating key mediators such as MMPs, ADAMTS4, NOS2, and PTGS2 in the cartilage destruction of OA [50]. The NF- κ B signaling pathway is activated in the development of OA, which induces MMPs and ADAMTSs and inhibits type II collagen and aggrecan expression [51]. Subchondral bone is another tissue affected by catabolic mediators in the progression of OA. Several signaling pathways have been identified to contribute to this progression, including Wnt, TGF- β /BMP, and MAPK signaling, among which Wnt/ β -catenin signaling is a key regulator of bone remodeling. β -Catenin is overexpressed in patients with knee OA. Wnt/ β -catenin signaling in articular chondrocytes in adult mice is activated in the development of OA [52, 53].

Treatment of osteoarthritis

The principal aims for OA treatment are reducing pain, slowing the progression of joint

destruction and maintaining and even improving mobility function [54]. Numerous nonpharmacological and pharmacological therapies are currently applied to relieve pain and maintain the function of joint tissues in the treatment of OA. In addition to traditional medication, a number of novel therapeutic strategies are being examined and developed. In addition, combinational therapies are commonly used in OA treatment to maximize the effects beyond what a single application can reach [55].

Nonpharmacological therapy

Nonpharmacological strategies are recognized as first-line treatments for OA and should be considered first before pharmacological interventions and surgical options [56]. Self-management, regular exercise, strength training, and weight control are highly recommended to reduce pain and improve the mobility function of joints [57]. Combinational management of exercise and weight control has been demonstrated to reduce knee OA syndrome in patients with excess weight and obesity [58, 59].

Pharmacological therapy

Pharmacological strategies are often applied when nonpharmacologic interventions are not able to relieve pain and reduce disability. Traditional medicine, such as NSAIDs, is constantly applied in OA treatment. NSAIDs suppress Cox-1 and Cox-2 activity in the periphery by decreasing prostaglandin synthesis and reducing pain [60]. However, NSAIDs are associated with an increased risk of gastrointestinal disorders and cardiovascular diseases [61]. Acetaminophen is a first-line therapy used to treat moderate OA pain. Acetaminophen reduces Cox-1 and Cox-2 activity in the periphery, suppresses serotonergic neuronal and L-arginine/NO pathways and stimulates the cannabinoid system in the central antinociception process [62]. However, the use of acetaminophen is limited because of its limited efficacy and severe toxicity [63, 64]. Duloxetine is a serotonin-norepinephrine reuptake inhibitor approved by the FDA to relieve pain and improve function in patients with knee OA [65]. Capsaicin is a natural compound obtained from chilies and is also a local analgesic [66]. Both duloxetine and capsaicin are effective adjunct treatments to other treatments [67]. Glucosamine and chondroitin are extracted from animals, and their combination is effective in

reducing joint swelling and pain, increasing flexibility and improving function by stimulating proteoglycan synthesis in articular cartilage [68]. Intra-articular steroids only show effectiveness in short-term trials up to 2 weeks but not in long-term trials [69]. 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 [70]. Platelet-rich plasma (PRP) was used in tissue repair and showed pain alleviation and functional improvement that were sustained for 6 months [71].

In addition to traditional medication, a number of biological therapeutic agents are being explored and evaluated for OA treatment. Tanezumab and fasinumab are well-studied anti-NGF antibodies for knee and hip OA treatment, and evidence shows their preponderance in efficacy compared to placebo [72]. Several antibodies against other targets, such as the anti-TNF antibody adalimumab and the anti-IL-6 antibody tocilizumab, are being tested to reduce pain in OA. Several small molecules targeting GPCRs and ion channels are also under investigation [73].

However, the above treatments are designed for pain relief and functional improvement instead of regeneration of damaged articular cartilage or inflammation alleviation. In recent years, new therapeutic strategies for OA treatment have been intended to regenerate joint tissues and manage inflammation. Cell- or stem cell-based therapy has been developed as a new approach in regenerative medication. Autologous chondrocyte implantation (ACI) is an FDA-approved cell therapy for OA treatment. However, the unexpected dedifferentiation and joint invasiveness during harvest limited the application, and long-term trials are needed to confirm the efficacy [74, 75]. Mesenchymal stem cells (MSCs) capable of releasing the restrictions of ACI have been broadly explored as novel therapeutic agents in the treatment of OA. Hereinafter, we highlight the therapeutic features and recent progress of MSCs in OA treatment.

Mesenchymal stem cell-based therapy for osteoarthritis

As multipotent cells extensively distributed in the bone marrow, periosteum, trabecular bone,

MSC for osteoarthritis treatment

Table 1. Characteristics of different types of stem cells

MSCs source	Advantages	Disadvantages
Bone marrow	Easy accessibility High multilineage differentiation Relatively adequate clinical trials	Relatively low cell growth rate
Adipose tissue	Easy accessibility Greater number of colonies formation Superior immunomodulatory capacity	Reduced differentiation capability Inadequacy in clinical trials
Umbilical cord blood stem cells	Longer culture times Higher proliferation capacity Higher anti-inflammatory effects	Relatively few colonies formation Relatively low yield Inadequacy in clinical trials

fat pad tissue, synovial membrane, and several other tissues, MSCs have great potential in promoting the regeneration of chondrocytes and differentiation into cartilage [76]. MSCs were first isolated from bone marrow and later from other tissues, such as adipose tissue, placenta, umbilical cord, cord blood, dental pulp, and amniotic fluid [76]. Among the tissues, bone marrow and adipose tissue are major sources for therapeutic MSCs. MSCs from different tissues are capable of differentiating into cartilage [77].

Different sources of MSCs feature different characteristics and have their own advantages and disadvantages. With respect to the MSC content in the tissue, the umbilical cord (UC-MSCs) has the highest, followed by the amniotic fluid and fat [78]. With respect to MSC proliferative capacity, umbilical cord and amniotic-derived MSCs have definite advantages, followed by fat and bone marrow (BM-MSCs). In terms of immunomodulatory capacity, umbilical cord, amnion, and adipose tissue-derived MSCs (AD-MSCs) have superior immune regulation over bone marrow MSCs, while placental MSCs have the lowest immunomodulatory capacity. When compared to cytokine secretion profiles, umbilical cord MSCs secrete more cell growth factor than bone marrow MSCs [77]. The advantages and disadvantages of different sources of stem cells are summarized in **Table 1**.

The desirable characteristics of MSCs as cell-based therapeutic agents are their ability to stimulate cartilage formation, vascularization, anti-inflammation, and immunoregulation [79]. A great number of studies have evaluated the potential of MSCs in cartilage tissue regeneration both in vitro and in animal models [80].

Studies have not been restricted to animal models in recent years. 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. The data are summarized in **Table 2**.

BM-MSCs for osteoarthritis therapy

BM-MSCs are the most widely used source of therapeutic MSCs because of their simple accessibility, fast cell proliferation, long-term sustainment of differentiation capacity and reduced immunological exclusion [91]. The first clinical study of BM-MSC transplantation for articular cartilage defect treatment was conducted almost 20 years ago. The trial recruited 24 patients with knee OA who underwent a high tibial osteotomy, and half of them received autologous BM-MSC transplantation with the other half as 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 score was better in the cell-transplanted group than in the cell-free control group, suggesting the suitability of BM-MSC transplantation for OA treatment [81]. Another 2-year follow-up autologous BM-MSC transplantation clinical trial was conducted in 56 patients with unicompartmental knee OA who underwent high tibial osteotomy and microfracture. The cell-recipient group received better Tegner, Lysholm, International Knee Documentation Committee (IKDC) and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores, indicating the effectiveness of autologous BM-MSC transplantation for OA treatment [82]. In another trial, 55 patients who underwent a partial medial meniscectomy were recruited and received

MSC for osteoarthritis treatment

Table 2. Clinical studies of MSCs for osteoporosis treatment

Cell types	Study design	Outcomes	References
BM-MSCs	Autologous culture-expanded BM-MSCs with collagen gel embedded were transplanted into OA knee with articular cartilage defect in the medial femoral condyle	White soft tissue formation, better arthroscopic and histological grading score	[81]
BM-MSCs	Intra-articular injection of cultured autologous BM-MSCs with hyaluronic in varus knees with cartilage defects underwent HTO and microfracture	Better Tegner, Lysholm, IKDC, and MOCART scores	[82]
BM-MSCs	Intra-articular injection of 50×10^6 or 150×10^6 allogeneic BM-MSCs into OA knees 7-10 days after the meniscectomy	No ectopic tissue formation, no serious adverse effects, increased meniscal volume, reduction in pain	[83]
BM-MSCs	Intra-articular injection of hyaluronic acid together with 10×10^6 or 100×10^6 cultured autologous BM-MSCs into OA knees	No adverse effects, improved VAS WOMAC scores in both low and high doses	[84]
AD-MSCs	Intra-articular injection of autologous AD-MSCs with dose escalation: low dose (2×10^6 cells), medium dose (10×10^6), and high dose (50×10^6) to patients with symptomatic and severe knee OA	No serious adverse events, improved WOMAC pain and function subscores	[85]
AD-MSCs	Patients with symptomatic knee cartilage defects were Intra-articular injected of AD-MSCs with fibrin glue and MFX treatment	Better signal intensity for repair tissue, improved KOOS pain and symptom subscores, no significant differences in daily activity, sports and recreation and quality of life	[86]
AD-MSCs	Intra-articular injection of autologous AD-MSCs into OA knees	No serious adverse events, improved WOMAC score, no significant change of cartilage defect	[87]
UC-MSCs	Intra-articular injection of $2-3 \times 10^7$ UC-MSCs once a month for 2 times into OA knee	Pain and swelling incidences after injection, no recurrence of knee pain during follow up, better Lysholm, WOMAC, and SF-36 scale scores	[88]
UC-MSCs	Intra-articular injection of $5-7 \times 10^7$ UC-MSCs once into OA knee	No difference in biochemical parameters, pain reduction, recovered daily activities	[89]
UCB-MSCs	Implantation of UCB-MSCs mixture in the drill holes of cartilage defect site of OA knee Patients with varus or valgus deformity greater than 5 degrees were treated simultaneously with osteotomy	Improved IKDC, WOMAC, and VAS score and mean OAS	[90]

two different doses of allogeneic BM-MSCs in the treatment groups. After 2 years of follow-up, no clinically adverse effects were identified, and the cell-recipient group had increased meniscal volume and a significant reduction in pain based on visual analog scale (VAS) evaluation [83]. A phase I/II multicenter randomized clinical trial demonstrated the long-term effect of two different doses of BM-MSC transplantation versus HA in 30 patients with knee OA. After 4 years of follow-up, the cell-recipient group, especially the high-dose group, received better VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, indicating the therapeutic potential of BM-MSCs in long-term clinical and functional improvement in knee OA [84]. Another 5-year long-term trial of autologous BM-MSC transplantation in 4 patients with moderate to severe knee OA showed similar results. All parameters, such as the walking time, stair climbing, gelling pain, patella crepitus, flexion contracture, and VAS, were improved 6 months after treatment, and they were still better at baseline after 5 years, although gradual decline occurred [92].

AD-MSCs for osteoarthritis therapy

AD-MSCs are another attractive cell source of therapeutic MSCs because of their greater proliferation and differentiation potential than BM-MSCs [93]. Several clinical trials in recent years have demonstrated the effectiveness of AD-MSCs in therapeutic use. In a phase I dose-escalation trial, 18 patients with symptomatic and severe knee OA were transplanted with autologous AD-MSCs in three doses: low dose (2×10^6 cells), medium dose (10×10^6 cells), and high dose (50×10^6 cells). Six-month follow-up showed no clinically adverse effects, and patients treated with low-dose AD-MSCs experienced significant pain relief and functional improvement [85]. This study indicated the safety, tolerance and initial effectiveness of AD-MSCs in knee OA treatment; however, larger, more rigorous long-term trials are needed for further evaluation. Another clinical trial was conducted to evaluate the efficacy of AD-MSCs with microfracture treatment versus microfracture alone in 80 patients aged 18 to 50 years with moderate to severe knee OA. After 24 months of follow-up, the AD-MSC-treated group showed better signal intensity for tissue repair

and KOOS pain and symptom subscores but no significant differences in other subscores, such as daily living activity, sports and recreation and quality of life, indicating the potential of AD-MSCs in tissue repair and pain relief [86]. Recently, a phase IIb randomized, placebo-controlled clinical trial of AD-MSCs for the treatment of knee OA was conducted in 24 patients. Six months of follow-up provided safety, increased WOMAC score, improvement in function and reduction of pain in the AD-MSC-treated group, suggesting the potential of AD-MSCs in therapeutic use [87].

UC-MSCs for osteoarthritis therapy

UC-MSCs have recently been recognized as another source for stem cell therapy because of their advantages of a higher proliferation capacity, active differentiation ability, and superior immunomodulatory capacity compared with BM-MSCs [77, 94]. A number of clinical trials have been conducted for consideration of UC-MSCs in the treatment of OA. A safety and efficacy study of UC-MSC transplantation with follow-up for 6 months was conducted in 36 patients with moderate or severe knee OA. The results showed that the cell treatment group provided better Lysholm, WOMAC and SF-36 scale scores than the control group. The cell treatment group demonstrated higher incidences of pain and swelling than the control group after injection, but no recurrence of knee pain was identified during follow-up, indicating the therapeutic potential of UC-MSCs in joint improvement [88]. Similar results were obtained from another clinical trial in which 3 patients with knee OA received $5-7 \times 10^7$ UC-MSCs by intra-articular injection. After a 3-month follow-up, the 3 patients showed pain relief and recovery of daily activities ability with no biochemical change observed pre- and post-treatment [89]. Recently, a clinical trial of human umbilical cord blood-derived mesenchymal stem cell (hUCB-MSC) application was conducted in patients with knee OA with full-thickness cartilage defects. A review of 64 patients who underwent second-look arthroscopic surgery 1 year after treatment of hUCB-MSCs showed that IKDC, WOMAC, VAS score and Oswestry Arthroscopy Score (OAS) were improved compared with baseline, indicating the potential of hUCB-MSCs as a therapeutic

option for pain relief and functional improvement in OA treatment [90].

To date, several clinical trials have proven the safety and potential efficacy of BM-MSCs, AD-MSCs, and UC-MSCs in the treatment of OA. However, we must admit that some of the trials were conducted with limited samples, without rigorous controls and with relatively short-term follow-ups. Clinical trials with larger samples, more rigorous controls, more careful handling, and long-term follow-ups are needed for further evaluations. Although it has not been highlighted in this review, other considerations should be taken into account to enhance the efficacy in clinical trials. For example, the cell density, the time and location for MSC transplantation, and pretreatment of MSCs by inflammatory cytokines should be carefully evaluated in both preclinical and clinical studies.

Pretreatment of MSCs by a low-level laser to improve therapeutic efficacy

Low-level laser therapy (LLLT) is a therapy that applies low-level lasers or light-emitting diodes (LEDs) to manage cell functions and has been widely acknowledged as a regenerative medical tool in tissue regeneration, improvement in wound healing, reduction in pain, and recovery of functional diseases [95, 96]. Although the molecular mechanism of LLLT in accelerating tissue regeneration is not yet clear, its ability to promote cell proliferation in diverse cell types, such as endothelial cells [97], fibroblasts [98], osteoblast-like cells [99], and mesenchymal stem cells [100, 101], has been confirmed. There is evidence that accelerated cell proliferation is associated with increased synthesis of growth factors, NO, ROS, ATP, RNA and DNA after irradiation [102].

Although MSCs can be obtained from many sources as mentioned before and different sources of MSCs feature distinct characteristics, one of the common properties of MSCs is the relatively low yield and decreased proliferative capability in vitro. This property will inevitably hamper the progress of MSCs to preclinical and clinical trials and practical use. Recent progress has demonstrated the role of LLLT in promoting the cell growth, proliferation and differentiation of MSCs, and the in vivo and in vitro effects of different protocols of LLLT on MSCs are summarized in **Table 3**.

The effects of LLLT on MSCs demonstrated the potential of LLLT as a useful tool in the promotion of cell proliferation and differentiation of MSCs, leading to wound healing, osteogenesis and cell function improvement. The results can be influenced by protocols with different parameters, such as the light spectrum, wavelength, power and energy density, cell types and cell numbers used in the experiments. In future studies, the parameters of LLLT and MSCs should be evaluated more carefully, and more in vitro and in vivo studies should be carried out in MSCs from different cell types.

Conclusions

OA is becoming increasingly popular in modern society. Environmental factors and metabolic and inflammatory factors are highlighted in the pathogenesis of OA. Both nonpharmacological and pharmacological strategies are reviewed in the treatment of OA. The main goals of traditional medication and biological agents in OA treatment are relief of pain and slowing down or halting of the progress of OA. Stem cell-based therapy is of great interest in regenerative medicine because of its potential in the regeneration of new cartilage and strong immunoregulatory capacity. Positive results in preclinical and clinical trials have demonstrated that MSC-based agents are a promising strategy in the treatment of OA. However, the limitations and risks of MSC-based therapy should be realized and treated carefully. First, we have an inadequate understanding of MSCs regarding their physiological properties and cellular functions in vitro and in vivo, including the mechanisms of immune modulation and the role of key mediators in differentiation. Second, the therapeutic efficacy of MSCs in preclinical and clinical studies is influenced by many factors, such as the cell culture conditions, the cell density, the time and location for MSC transplantation and the pretreatment of MSCs by LLLT or inflammatory cytokines. These factors should be elucidated more cautiously in future studies to maximize the potential and minimize the adverse effects of MSCs in OA treatment. Third, since 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, the risks regarding the tumorigenesis potential and serious unwanted immunoregulatory responses in

MSC for osteoarthritis treatment

Table 3. In vivo and in vitro effects of different protocols of low-level laser therapy on mesenchymal stem cells

Cell types	In vitro/ in vivo	Wavelength (nm)	Power density (W/cm ²), energy density (J/cm ²)	Results	References
BM-MSCs	In vivo	804	10 mW/cm ² 1 J/cm ²	Reduced infarct size and ventricular dilatation, increased c-kit+ cells in the infarcted area	[103]
BM-MSCs	In vitro	630	5, 15 mW/cm ² 2, 4 J/cm ²	Enhanced growth of MSCs, increased colony-forming unit fibroblasts	[104]
BM-MSCs	In vitro	1064	0.25 W/cm ² 2, 4, 8, 16 J/cm ²	Promotion of BM-MSCs proliferation and osteogenesis at densities of 2 and 4 J/cm ²	[105]
BM-MSCs	In vitro	810	2, 3, 4, 6 J/cm ²	Enhanced differentiation of BM-MSCs into neuron and osteoblast in the range of 2-6 J/cm ² , increased BM-MSCs proliferation (except for 6 J/cm ²)	[106]
AD-MSCs	In vivo	632.8	17.0 mW 1.2 J/cm ²	Enhanced wound healing, regeneration of skin appendages, enhanced survival of AD-MSCs, increased secretion of growth factors	[107]
AD-MSCs	In vitro	636	5 J/cm ²	No induction of differentiation over 72 h, increased cell viability, and proliferation	[108]
AD-MSCs	In vitro	636	5 J/cm ²	Increased viability and proliferation of AD-MSCs when cultured with EGF	[109]
UC-MSCs	In vitro	635, 808	20 mW/cm ² 12 J/cm ²	Higher proliferation rate in the 635 nm, no induction of cell proliferation at 808 nm, increased CAT, tGPx, and SOD activity, improved UC-MSCs function and increased antioxidant activity	[110]
UC-MSCs	In vitro	620	2 J/cm ²	Higher proliferation rate, higher osteogenic differentiation	[111]
DP-MSCs	In vitro	660	30 mW 0.5, 1 J/cm ²	Increased cell proliferation at 1 J/cm ² , no significant changes in cell viability	[112]

BM-MSCs: bone marrow mesenchymal stem cells; AD-MSCs: adipose tissue-derived mesenchymal stem cells; UC-MSCs: umbilical cord mesenchymal stem cells; DP-MSCs: dental pulp mesenchymal stem cells.

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preclinical and clinical trials should be further considered.

Despite the current limitations and risks, cell therapy, especially MSC-based therapy, is becoming an encouraging approach to regenerative medicine in the treatment of OA. The positive effects of pretreatment with LLLT on MSCs indicate that the combination of MSC-based therapy with other treatments might achieve better efficacy in regenerative medicine.

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Disclosure of conflict of interest

None.

Abbreviations

OA, Osteoarthritis; MSCs, Mesenchymal stem cells; NGF, nerve growth factor; BM-MSCs, bone marrow MSCs; AD-MSCs, adipose tissue derived MSCs; UC-MSCs, umbilical cord derived MSCs; hUCB-MSCs, human umbilical cord blood-derived mesenchymal stem cells; OAS, Oswestry Arthroscopy Score; LLLT, Low-level laser therapy; LEDs, light-emitting diodes.

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