

Research Progress of Stem Cells in The Treatment of Osteoarthritis

Qian yun Li^{1*} and Jianhui Xiao¹

¹Zunyi Medical University, China

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*Corresponding author: Jian Hui Xiao, Zunyi Medical University, China; E-mail: jianhuixiao@zmc.edu.cn

Abstract

Osteoarthritis is a common disease of the musculoskeletal system that endangers the health of the elderly. It is manifested by the progressive degradation and loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and synovial inflammation. There is no cure for joint dysfunction and joint deformity. With the development of tissue engineering and regenerative medicine technology, the multi-directional differentiation potential of stem cells is used to induce their differentiation into chondrocytes, so that they have cartilage repair function, improve the damaged cartilage and improve the quality of life of patients. Treatment brings new hope. This article summarizes the latest findings in pre-clinical and clinical studies using stem cells to treat osteoarthritis in the past five years, and provides references for stem cells from various sources to treat osteoarthritis.

Key words: stem cells; cartilage differentiation; osteoarthritis; exosomes; small molecules.

Osteoarthritis (OA) is currently the most common chronic degenerative joint disease in the world, characterized by progressive cartilage degradation and loss, osteophyte formation, subchondral bone reconstruction, synovial inflammation, meniscus injury, cells Osteoarthritis is seriously affected by the degradation of the outer matrix and the reduction of chondrocytes. Common risk factors include aging, obesity, genetic and systemic inflammation [1-3]. With the development of social aging, the prevalence of OA is increasing year by year, and it will become the fourth leading cause of disability by 2020[4]. The most common affected areas of OA are knees, hips, hands, ankles and neck weight-bearing joints. During the activity, joint swelling, pain, morning stiffness, dysfunction, and even complete loss of joint function will eventually result in disability. Seriously affect the patient's quality of life. It is now clear that articular cartilage is hyaline cartilage, a type of connective tissue that lubricates joints, reduces joint friction, cushions shocks, and transfers loads. It plays an important role in cartilage joint activity. The main mechanism is the imbalance between catabolism and anabolism [5]. Because cartilage tissue lacks the nutritional support of blood vessels, nerves, and lymph fluids and chondrocytes are terminally differentiated cells, their proliferation ability is extremely weak, and it is difficult to regenerate after destruction [6]. Therefore, early detection, early diagnosis, and early treatment have become

extremely challenging new goals.

At present, commonly used OA treatment methods mainly include drug treatment and surgical treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are commonly used in drug treatment, but their effects are limited to controlling pain. Long-term use will cause gastrointestinal bleeding and cardiovascular adverse reactions [7]. With the development of technology, people have tried to use surgery for treatment. Common surgical treatment methods include autologous chondrocyte transplantation (ACI), joint lavage and debridement, joint replacement, micro fracture technology, and more recently Nano fracture technology. Although these treatments can have a certain effect on the repair of cartilage damage, in most cases, the regenerated tissue does not have the same biochemical and biomechanical properties as natural cartilage tissue, and cannot withstand the continuous pressure exerted on it. Eventually, it leads to fibrocartilage formation and cartilage degradation. These treatments also have some side effects, such as loss of dedifferentiation phenotype during cell expansion, pain and deformity, thrombosis, and inevitable secondary surgery. Therefore, although these treatments have expanded the treatment of articular cartilage injury to a certain extent, the side effects they produce are still inevitable. In recent years, with the development of tissue engineering and regenerative medicine and the unremitting efforts of researchers, stem cell-based treatment has become a new hope for cartilage repair [8-9].

Stem cells are a type of cells with the potential for self-renewal and multi-directional differentiation. They have the functions of inhibiting natural killer cells, macrophages, dendritic cells and anti-inflammatory. Stem cells are known as "universal cells" in the medical community. According to different sources, it can be divided into: adult stem cells (ASCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), etc. This article reviews the latest findings of different types of stem cells in the pre-clinical and clinical studies of OA in the past five years, and provides strategies for the treatment of osteoarthritis. Although embryonic stem cells are a good source of chondrocytes, the use of adult stem cells, especially various MSCs and iPSCs, as cartilage regeneration and OA repair cells has been introduced due to ethical issues and carcinogenicity that limit their use.

Stem Cells from Different Sources to Repair Osteoarthritis

Adult Stem Cells Repair Osteoarthritis

One Marrow Mesenchymal Stem Cells

Bone marrow derived MSCs (BM-MSCs) are non-hematopoietic stem cells isolated from bone marrow. They have the advantages of sufficient source, convenient material extraction, strong regeneration ability and multi-directional differentiation potential. Bone marrow mesenchymal stem cells are an ideal seed cell in cartilage tissue engineering. By adding dexamethasone, ascorbic acid and transforming growth factor (transforming growth factor- β , TGF- β) can induce BM-MSCs to differentiate into chondrocytes. The mechanism of BM-MSCs treatment of OA has previously been believed to adhere to the surface of damaged tissue to differentiate into damaged tissue cells to achieve repair of damaged tissue, and recent studies have shown that mainly by regulating the secretion of T cells, natural killer cells and dendritic cells, decreasing the pro-inflammatory factors TNF- α , interferon- γ , and increasing the levels of the anti-inflammatory factors interleukin-4 and interleukin-10 allows cartilage repair. Pittenger first isolated MSCs from the bone marrow and demonstrated their multi-directional differentiation potential [10]. Subsequently, Wakitani transplanted BM-MSCs, and a type of hyaline cartilage-like tissue was observed 42 weeks later. Arthroscopy and histological grading scores showed the potential of BM-MSCs in cartilage repair [11]. Recent studies have shown that paracrine can produce therapeutic effects. BMSCs-derived exosomes have a complete membrane structure and can be loaded with proteins, nucleic acids, lipids and other substances. Zhang research showed that the injection of exosomes derived from BM-MSCs into the rat model of temporomandibular arthritis significantly improved the damage of rat cartilage tissue, and found that it mainly inhibits the occurrence of inflammation, restores the homeostasis of the matrix, and increases the proliferation capacity of chondrocytes by promoting CD73-mediated AKT and ERK signaling pathways[12]. Cosenza established a model II collagenase-induced mouse OA model, and injected BMSCs-derived cell vesicles and exosomes into the joints of mice to alleviate the damage of articular cartilage in mice and exert cartilage protection and anti-inflammatory functions. It shows that exosomes can inhibit the expression of MMP-13 and ADAMTS-5 to promote cartilage matrix, and play an anti-inflammatory and anti-apoptotic role [13-14]. Studies have shown that co-culture of BMSCs with chondrocytes can promote BMSCs to chondrocyte proliferation, differentiation and synthesis of extracellular matrix. When the ratio of chondrocytes to BMSCs is 25% -50%, it can play the best induction effect, so co-culture is an effective method to induce differentiation. In addition, the reasonable addition of some small molecule compounds can help BMSCs differentiate into chondrocytes. Recent studies have shown that a novel non-protein heterocyclic small molecule compound Kartogenin (KGN) can promote the differentiation of MSCs into chondrocytes, and at the same time inhibit the degradation of extracellular matrix to exert cartilage protection[15-16], Its main mechanism is: KGN's ligand envelope protein filamin A

(FLNA) can bind to actin to regulate the cytoskeletal structure, destroy its binding to the core binding factor β subunit (CBF β), Rearrangement of the cytoskeleton can induce cartilage differentiation[17]. Lubricin is a viscous glycoprotein secreted by chondrocytes. When it is lacking, it will accelerate joint cartilage damage. Some studies have found that KGN and TGF- β 1, BMP-7 cytokines have a synergistic effect to increase the content of Lubricin. Recent studies have shown that co-culture of KGN with BMSCs and chondrocytes into rat cartilage injury model can significantly increase the ability of cartilage repair. In addition to the small molecule KGN, Wang research shows that the combination of icariin and growth differentiation factor-5 (GDF-5) can promote the chondrogenic differentiation of BMSCs, by detecting the expression of proteoglycan staining and cartilage differentiation marker genes Aggrecan and type II collagen. But icariin mainly reduces the level of TGF- β 1, down-regulates the expression level of Wnt / β -catenin signaling pathway inhibitor DKK2, increases the activity of Wnt / β -catenin signaling pathway, corrects the formation of subchondral bone mineralization and It plays a protective role in OA subchondral bone[18]. Although the clinical trials of using small molecule compounds to promote the differentiation of BMSCs into cartilage have not been carried out, the dosage, method of use and adverse reactions are not yet clear, but the use of small molecules provides a new idea for the treatment of OA in the future. Recent studies have found that TGF- β 1 mainly plays a role in cartilage differentiation by regulating the ERK / JNK signaling pathway[19]. Through the above research, it was found that BMSCs have a positive effect on the treatment of osteoarthritis, however, BMSCs will reduce the proliferation and differentiation ability with age. Bone marrow aspiration technique can only isolate a small amount of BMSCs, accounting for 0.001% -0.002 % [20-21].

Adipose mesenchymal stem cells

Adipose-derived mesenchymal stem cells (ADMSCs) have the advantages of easy material selection, abundant sources, less damage, weaker immune rejection, and faster proliferation in vitro. ADMSCs can induce differentiation and formation Chondrocytes through the addition of bone morphogenetic protein (BMP-6), fibroblast growth factor (FGF), and transforming growth factor- β (TGF- β) in vitro [22]. Studies have shown that paracrine or cytokines can make ADMSCs cartilage forming ability similar to BMSCs [23]. The treatment mechanism of ADMSCs for OA is mainly through the secretion of interleukin 10, interleukin 1RA (interleukin 1 receptor antagonist), indolamine 2,3-dioxygenase (IDO) and other anti-inflammatory factors to promote chondrocyte proliferation and inhibit cartilage Inhibition of chondrocyte inflammation, apoptosis, hypertrophy, fibrosis and other methods to inhibit the destruction of cartilage tissue.

Frisbie first injected autologous ADSCs into the articular cavity to treat OA in horses, and no adverse reactions occurred but did not improve the OA situation [24]. Subsequent research found that the paracrine effect of fat sources can regulate T cell proliferation, reduce inflammation, and promote angiogenesis,

especially exosomes have a positive effect on OA repair [25]. The Tof10-Vian study found that the addition of ADSCs-derived exosome medium to the interleukin-1 β (IL-1 β) -mediated cartilage injury model not only down-regulated the aging-related β -galactosidase activity, but also reduced inflammation. It is proved that exosomes derived from ADSCs have a therapeutic effect on damaged chondrocyte metabolism [26]. Studies have shown that ADSCs combined with stents or vehicle suspensions can be used to treat OA. Anggraini Barlian research shows that by planting ADSCs on silk fibroin scaffolds and using ascorbic acid (LAA) and platelet-rich plasma (PRP) as bioactive factors, ADSCs can be promoted to differentiate into chondrocytes [27]. The Yamasaki study found that by establishing a pig femoral cartilage cartilage defect model, using 3D printing technology at 3 and 6 months, histological scores, CT, and MRI showed good effect of cartilage after implantation [28]. Kuroda showed that intra-articular injection of ADSCs and hyaluronic acid (HA) suspension into rabbit OA can significantly inhibit cartilage degeneration [29]. The Zhou study showed that by establishing a rat knee OA model, real-time fluorescence quantitative amplification of genes and Western blotting were used to detect the expression of cartilage-related genes and proteins, and to assess the level of chondrocyte apoptosis, demonstrating that ADSCs can reduce the symptoms of OA in rats and mainly through autophagy to reduce the release of pro-inflammatory factors and inhibit cartilage apoptosis [30]. The study found that transfecting genes related to the differentiation of stem cells into cartilage into ADSCs can improve the ability to differentiate into cartilage cells. The Lee study found that after 8 weeks of treatment with fibrin and ADSCs transfected with SOX-5, SOX-6, and SOX-9 genes in the OA joint cavity of rats, the symptoms of cartilage injury in rats were significantly improved [31]. In addition, there are reports that the addition of natural drugs and their derivatives can promote cartilage formation. Hyunjin Lee research shows that adding 1 μ g / ml quercetin can promote cartilage formation [32]. Another study showed that the addition of compound H-89 sulfonamide derivatives can increase the expression of GAG in hADSCs, promote the differentiation of hASCs into chondrocytes, and increase the phosphorylation level of extracellular regulatory protein kinase (ERK). It shows that H89 can promote cartilage formation by activating the ERK pathway [33]. Adipose tissue accounts for 1% -7% of the mononuclear cell population, and contains 500 times more MSCs than the same volume of bone marrow [34]. Studies have found that the proliferation potential of ADSCs is hardly affected by the age and gender of patients, but the number of ADSCs is negatively correlated with body mass index (BMI) [35-36].

Synovial Mesenchymal Stem Cells

The synovium is composed of A and B cells. A cell are macrophage-like cells and B cells are fibroblast-like cells. Synovium-derived mesenchymal stem cells (SMSCs) derived from B cells are closely related to cartilage differentiation. SMSCs are adult stem cells with rich sources of high proliferative activity, strong regeneration ability, and good cartilage-forming ability. In vitro addition of transforming growth factor- β (TGF- β), bone morphogenetic protein-2 (BMP-2), and fibroblast growth factor

(FGF) can induce SMSCs to differentiate into chondrocytes. Studies have shown that SMSCs can maintain similar growth kinetic characteristics after being expanded for more than 10 generations [37]. And the number of ADSCs cells obtained under the same conditions is 500 times that of BMSCs [38]. This high amplification capacity may be related to the transferase at the end of the telomere [39]. Interestingly, synovium and articular cartilage are developed from common mesenchymal precursor cells, so synovial mesenchymal stem cells may be an ideal source for repairing articular cartilage damage. For the first time, De Bari isolated SMSCs with multi-directional differentiation potential from the synovium near the knee joint and pointed out that it has the potential to treat OA [40]. Recent studies have shown that the administration of exosomes from rat synovial MSCs into the joint can partially prevent cartilage damage in injured rats. Tao research shows that exosomes released by SMSCs can increase the proliferation of chondrocytes through the Wnt5a / b-YAP signaling pathway in vitro, while inhibiting SOX9 gene expression and inhibiting cartilage matrix synthesis [41]. Co-culture of chondrocytes and synovial stem cells can promote cartilage formation. Tae Woo Kim uses different ratios of human chondrocytes and synovial-derived stem cells to co-culture. When the ratio is 1: 1, it can inhibit cartilage dedifferentiation and increase the expression of GAG, type II collagen and SOX9. The optimal ratio of cultivation is 25% to 50% [42]. Xing Hu research proved that SMSCs and chondrocytes were mixed and cultured in chitosan / type I collagen composite scaffold material, and transplanted into the body can form cartilage-like tissues, which is beneficial to the repair of knee joint cartilage. Studies have shown that low-glucose culture during the differentiation stage of SMSCs can increase the cartilage-forming ability of SMSCs. The mechanism of action is that glucose can regulate the TGF- β and PKC signaling pathways during the differentiation stage to affect cartilage-forming ability. The establishment of animal models to study the effectiveness of synovial mesenchymal stem cells to repair OA. Mak research showed that cartilage injury was significantly repaired after injection of SMSCs progenitor cells in the mouse joint injury model for 4 weeks [43]. Zhao feng Jia can detect hyaline cartilage after injecting SMSCs in a rabbit knee cartilage defect model [44]. At present, the use of small molecules to repair cartilage damage has attracted more and more attention. TD-198946 can increase the expression of cartilage marker type II collagen in a dose-dependent manner to play a role in cartilage repair. The gene chip technology researched the mechanism and targets found that the expressions of RUNX1, SOX5, SOX6 and other genes related to cartilage differentiation were up-regulated, indicating TD-198946 can play the role of OA treatment by regulating RUNX1. Chijimatsu research shows that the small molecule compound TD-198946 can promote hSMSCs cartilage differentiation and cartilage tissue formation. When the concentration is greater than 1 nm, the expression of GAG, SOX9 and type II collagen increases [45]. Studies have reported that the ability of SMSCs to differentiate into chondrocytes is 100 times that of bone marrow cells [46 -47].

Induced pluripotent stem cells repair osteoarthritis

Induced pluripotent stem cells (iPSCs) are derived from human or animal cells. After introducing multiple specific related transcription factors or chemicals into mature somatic cells through gene transfection technology, they are reprogrammed to have pluripotency. iPSCs have the characteristics of strong self-renewal capacity, tissue regeneration potential and multi-directional differentiation potential, and there is no immune rejection and ethical issues. Researchers use a variety of different gene combinations to reprogram cells from different sources into iPSCs. With the in-depth study of iPSCs and the continuous improvement of preparation methods, the efficiency of iPSCs has been significantly improved. Compared with stem cells from other sources, iPSCs have the following advantages:

Wide source and can be obtained by reprogramming from various mature somatic cells;

The preparation process is more controllable;

Because it is taken from mature somatic cells, immune rejection is avoided. At present, there is no effective method for widely accepting differentiated cartilage from iPSC, so most of them use iPSC for three methods:

use normal bone marrow MSC in vitro cartilage growth factor to induce MSC-like iPSC and differentiate these cells into cartilage Cells;

Co-culture of chondrocytes or other trophoblast cells derived from iPSCs-derived MSCs and primary cells;

Culture embryoid bodies (EB) from iPSCs, and then differentiate mesoderm in EB into chondrocytes by growth factor treatment.

Induced pluripotent stem cells were originally obtained by Japanese scientists using viral vectors to reprogram the transcription factors Oct4, Sox9, Klf4, and c-Myc into somatic cells [48]. Koyama uses a multi-step culture method to differentiate human iPSC cells into chondrocytes. About 70% of iPSCs cells express type II collagen and aggrecan. iPSCs-MSCs can be passaged for more than 40 generations and maintain the self-renewal capacity of MSCs. Recent studies have shown that exosomes derived from iPSCs have a positive effect on the treatment of OA and can promote cartilage proliferation and migration [49]. Zhu research showed that exosomes secreted by iPSCs showed better chondrocyte proliferation in vitro compared with SMSCs, and iPSCs had stronger cartilage protection in the mouse knee OA model [50]. At present, studies have shown that the use of different biomaterial scaffolds can enhance the cartilage formation of iPSCs. Kazutoshi Hontani and other studies have shown that the use of ultra-purified sodium alginate gel (UPAL gel) and three-dimensional culture of mouse iPSCs can upregulate the cartilage formation markers SOX9, COL2 α And GAG expression effectively promotes iPSCs to differentiate into chondrocytes [51]. Hossein Mahboudi research shows that the use of nanofiber-based polyether sulfone (PES) scaffolds can also

increase the differentiation of human iPSCs into cartilage [52-53]. Liu showed that PCL / gelatin scaffolds as nanofiber scaffolds enhance the cartilage formation of iPSCs in vitro and in vivo. The above results indicate that a reasonable scaffold can effectively promote the differentiation of iPSCs into cartilage. Yan Xia Zhu research showed that by transplanting human iPSCs into a rat OA model induced by monosodium iodoacetate (MIA), the gene and protein expression of Col2 α , GAG and Sox9 were significantly increased after 2 weeks. After 15 weeks of transplantation, CT showed improved chondrocyte plate integrity [54]. The above research results show that iPSCs provide a new strategy for cartilage formation.

Clinical study of stem cells in the treatment of osteoarthritis

The use of stem cells to treat damaged tissues is hailed as a breakthrough in the medical world in the 21st century and provides exciting results for the treatment of chronic degenerative diseases. Based on the above stem cells used in the treatment of OA, researchers in different countries have conducted clinical evaluations. As of "April 2019", advanced search was performed on the US clinical trial website (WWW.clinicaltrials.gov) using "stem cells" AND "Osteoarthritis" as search terms, and 113 clinical trials were retrieved, among which completed trials there are 41 items, including 5 sources of BMSCs and 5 sources of ADMSCs. The research in recent years is summarized in Table 1.

The current treatment using stem cells is only maintained in clinical phase I / II trials. So far, only two countries, South Korea and Iran, have completed phase III clinical trials in 2017 and 2013, respectively, and no adverse reactions have occurred. It is proved that the use of stem cell therapy is safe and the clinical effect is good. The stem cells currently used in clinical trials are mainly concentrated on bone marrow, fat and synovium. With the progress of research, the separation of stem cells from trabecular bone, skeletal muscle, and urine has become the focus of research. In summary, using stem cells to treat OA is a promising, safe, effective, and well-tolerated treatment.

Summary and outlook

Osteoarthritis is a common chronic degenerative joint disease at present, with complex causes and weak self-regeneration ability. At present, some scholars believe that the repair degree of articular cartilage injury is related to the degree of injury. When the cartilage injury diameter is 1.0-2.0 mm, repair tissue similar to normal transparent cartilage will be produced. When the damage diameter is more than 3 mm, it is also called articular cartilage defect, and most of them cannot be completely repaired, and are filled by fibrous cartilage regeneration; When the diameter of articular cartilage injury is > 6 mm, the injury can not only be repaired, but also further damage the surrounding bone wall and surrounding articular cartilage, In turn, the cartilage surrounding the injury slips and the articular cartilage collapses, causing osteoarthritis.

Despite the potential advantages of using stem cell therapy to

Table 1: Clinical trials of MSC for the treatment of OA

NC T number	Number of patients	Stem cell type	Average transplanted cell dose (pcs / Kg)	Transplantation Method / Research Type	Cell algebra	OA grade	Follow-up time	Evaluation indicators	evaluation result	references
550524	3	Auto BMSCs	8.5×10 ⁶	Knee injection	1	KL: II-III Class	5 years	6 months, 1 year, 2 years, 5 years after injection: VAS,knee movement range pain score, X-ray	after 12 months the test indicators show a gradual improvement	[55]
1585857	18 (6 people / group)	Autologous adipose mesenchymal stem cell	Low dose: 2 × 10 ⁶ , Medium dose 10 × 10 ⁶ , High dose: 50 × 10 ⁶	Knee injection / I stage	1	KL: III-IV Class	6 months	1 week, 3 months, and 6 months after injection:WOMAC score, VAS score,KOOS score,knee injury, and OA score	Low-dose group for pain and improvement knee function	[56]
2037204	10	Allogeneic bone Marrow mesenchymal stem cells	1.5-2×10 ⁶	Implantation / I / II	3	KL: III-IV Class	24 months	3 months, 6 months, and 12months of injection KOOS score, AS score,WOMACscore, EQSD healthquestionnaire, MRI	After the follow-up, the detection indicators were improved, MRI results showed structural repair,and knee thickness of the knee Joint increased.	[57]
1809769	18	Autologous adipose mesenchymal stem Cells	5×10 ⁷	Intra-articular injection / I / IIa	4	KL: III-IV Class	24 months	24-month injection indicators:WOMAC score, NRS-11score, SF-36 score,MRI	Pain relief,increased knee function, improved rate of improvement	[58]
2118519	53	Autologous bone marrow mesenchymal stem cells	61×10 ⁶	Intra-articular injection /Phase I / II	4	KL: II / III Class	24 months	24 months of injection indicators:KOOS score,MRI, knee injury and OA score	Reduced pain, improved knee function, increased cartilage thickness	[59]
2123368	30	Autologous bone marrow mesenchymal stem cells	10×10 ⁶ 100×10 ⁶	Intra-articular injection / Phase I / II	--	--	12 months	12-month injection indicators: VASscore, WOMAC score, MRI	WOMAC and VAS improved after 12 months of follow-up	[60]

2658344	24	Autologous adipose mesenchymal stem cells	1×10 ⁸	Intra-articular injection / IIb	3	KL: ii-IV Class	6 months	1, 3, and 6-month injection:VAS score,WOMAC score, MRI,KOOS score, X-ray film	pain relieved significantly and cartilage defects weresignificantly improved	[61]
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Table notes:

VAS score; visual simulation score; KOOS score: knee injury and osteoarthritis score scale; WOMAC score: West Lake and McMaster University osteoarthritis index score; MRI: magnetic resonance imaging; KL Grading: Kallgren-Lawrence, the severity of image changes is graded. According to the changes of knee joint space and bone hyperplasia on X-rays, it is divided into 5 grades. Grade 0 is normal and grade 4 is the most serious

treat OA, there are still some outstanding issues:1) Stem cells are mostly sourced from human tissues, which are invasive and prone to infection; 2) Regulate the differentiation of stem cells, promote their stable differentiation into chondrocytes and avoid cartilage hypertrophy and ossification of cartilage; 3) Different materials have different differentiation ability, activity and content, which need to be verified by a section; 4) The optimal number and method of transplantation and the quality of cartilage repair after transplantation. These problems need to be overcome or circumvented in future research. In addition, there are still some shortcomings in the current clinical trials, mainly including: the limited number of cases reported in the clinical trials, the density and method of cell transplantation into the body, the cultivation method of stem cells and the number of transplants are not uniform, and the follow-up time after the trial is insufficient. Therefore, the safety of MSCs transplantation and the existing problems need to be further expanded in the future to expand the sample and other studies to further optimize the treatment of stem cells. We believe that with continuous efforts worldwide, MSCs will be routinely applied in the treatment of osteoarthritis in the near future.

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