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Clinical Applications of Mesenchymal Stromal Cells (MSCs) in Orthopedic Diseases

Jiazhao Yang, Shiyuan Fang, Lei Xu, Li Li, Kai Xie, Jinsen Lu, Hao Wang, Xujin Wang and Lixin Kan

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Abstract

Mesenchymal stromal cells (MSCs) have the capacity for self-renewal and multi-lineage differentiation, have many advantages over other cells, and are thought to be one of the most promising cell sources for cell-based treatments. In fact, MSCs have already been widely applied in clinics as a treatment for numerous disorders, including orthopedic diseases, such as bone fracture, articular cartilage injury, osteoarthritis (OA), femoral head necrosis, degenerative disc, meniscus injury, osteogenesis imperfecta (OI), and other systemic bone diseases. With the progressions in R&D, the safety and efficacy of MSC-based treatments in orthopedic diseases have been largely recognized, but many challenges still exist. In this chapter, we intend to briefly update the recent progressions and discuss the potential issues in the target areas. Hopefully, our discussion would be helpful not only for the clinicians and the researchers in the specific disciplines but also for the general audiences.

Keywords: mesenchymal stromal cells (MSCs), orthopedic disease, cell therapy, tissue engineering, regenerative medicine

1. Introduction

Around 1960s, Friedenstein first found that there was a non-hematopoietic stem cell population in the bone marrow that could be differentiated into bone and fibrous tissue [1]; however, this population did not gain broad recognition until Caplan coined the term bone mesenchymal stem cells (MSCs) in 1991 [2]. This umbrella term did raise up the attention of this population, but this term is misleading and very controversial, and many investigators argue against to use this term loosely. As a result, many different terms have been proposed for this or the

similar populations, including mesenchymal stromal cells (MSCs), mesenchymal progenitor cells, multipotent mesenchymal stromal cells, bone marrow stromal cells (BMSCs), bone marrow-derived MSCs, multipotent stromal cells, mesenchymal precursor cells, and skeletal stem cells [3]. Currently, most investigators prefer an alternative term, that is, multipotent mesenchymal stromal cells (MSCs). For this reason, we also use this term throughout this chapter.

Theoretically, self-renewal without significant loss of their characteristics (stemness) and multi-lineage differentiation potential are the two criteria that define MSCs as real stem cells, but in practice, this heterogeneous population proliferates *in vitro* as plastic-adherent cells, as fibroblast-like morphology, forms colonies *in vitro* and can at least differentiate into bone, cartilage and fat cells [4]. In addition, literatures also provided evidence that MSCs can differentiate into multiple other mesenchymal lineages or even non-mesenchymal cell types, including endothelial cells, osteoblasts, chondrocytes, fibroblasts, tenocytes, vascular smooth muscle cells, myoblasts, and neurons [5], though some of these capacities are controversial. The key caveat is that it is unlikely that all cells in the culture meet the above-mentioned two criteria.

MSC-like cells can be obtained from almost all tissues, including the umbilical cord, amniotic fluid, placenta, adipose tissue, joint synovium, synovial fluid, dental pulp, endosteum, and periosteum [6]. Cultured MSCs have been characterized either by using cell surface antigens and/or by examining the cells' differentiation potential. The International Society for Cellular Therapy recommended that cells should fulfill the following criteria to be considered as MSCs: (1) the cells must be plastic adherent when maintained under standard culture conditions; (2) they must express CD73, CD90, and CD105 markers and should not express CD34, CD45, CD14, HLA-DR, CD11b, or CD19; and (3) they should be able to differentiate at least into osteoblasts, chondroblasts, and adipocytes *in vitro* [7]; however, this criteria has obvious problems therefore not been commonly accepted. For this reason, it is still challenging to consistently isolate or purify a well-defined clinical applicable MSC population.

On the other hand, the increasingly aging population has made the degenerative, non-traumatic and traumatic musculoskeletal diseases main socioeconomic issues, and MSCs seem to be a promising solution. In fact, MSCs have been widely used as a treatment for numerous orthopedic diseases, including bone defects, osteoarthritis (OA), femoral head necrosis, degenerative disc, spinal cord injury, knee varus, osteogenesis imperfecta, and other systemic bone diseases [8]. Currently, orthopedic researchers are still focusing on overcoming a variety of challenges so that they can fully realize the clinical therapeutic potential of MSCs, and the long-term goal is to change the main treatment strategy in the field of orthopedics from surgical replacement and reconstruction to bioregeneration and prevention [9].

In this chapter, we will briefly update the main advancements in these areas and discuss the major current and potential future applications pathways.

2. MSCs in nonunion bone fracture

Inadequate healing can lead to nonunion of the fractured bone. Clinically, about 5–10% of all fractures end up in persistent nonunion [10]; therefore, nonunion is one of the most troublesome complications. Since MSCs have the osteogenic differentiation ability, can secrete a

variety of cytokines and promote angiogenesis. It is reasonable to speculate that MSCs could accelerate fracture healing. In fact, there are experimental evidences to support the idea that MSCs treatment indeed promoted healing of nonunion fractures. For example, MSCs has been transplanted to animals to promote bone loss and fracture healing [11, 12]. Also, there are reports of BMSC treatment of bone nonunion caused by a bone defect, osteogenesis and local microenvironment disorders in patients [13–15]. It was reported that, after traumatic injuries, BMSCs could migrate from blood circulation to the lesion site, and then directly differentiate locally, and replace the injured cells. Consistently, the circulating BMSC can be detected in peripheral blood 39 to 101 hrs after fracture [16]. However, other data also suggested that these circulating cells account for only a small portion of cells in the fracture callus under normal circumstances, suggesting that the majority of the cells at the fracture site are migrated from the adjacent tissues [13]; nevertheless, therapeutic amplification of circulating MSCs through their mobilization could also represent a potential therapeutic opportunity in fracture repair [13].

Indirectly, BMSCs promote bone healing mainly through the secretion of bioactive molecules and extracellular membrane vesicles, which induce angiogenesis, regulate inflammation, inhibit apoptosis, and regulate osteogenesis differentiation. Since defective blood supply (ischemia) is an important cause of nonunion of bone, promoting blood vessel formation is beneficial to the healing of the nonunion bone. MSCs are known to secrete angiogenesis-related factors include angiopoietin Ang-1 and Ang-2, vascular endothelial growth factor (VEGF), FGF-2, and hepatocyte growth factor (HGF)-1 [17]. Furthermore, BMSCs have an anti-fibrotic effect and can limit that fibrosis progression of fracture zone and promote the regeneration of bone tissue. This is mainly accomplished by immunoregulating, inhibiting TGF- β mediated differentiation of fibroblasts, inhibiting oxidative stress, and matrix reconstruction [18]. Interestingly, it was also found that HGF, VEGF, and microbubble secreted by BMSCs had an anti-apoptotic effect, which inhibits the apoptosis of transplant cells in the injured area [19, 20].

In addition, other conserved signaling pathways, such as the transformation growth factor (TGF)- β_3 /bone morphogenetic proteins (BMP), Wnt, Hedgehogs, FGF, platelet-derived factor (PDGF), epidermal cell growth factor (EGF), and insulin-like growth factor (IGF), may also indirectly participate in the regulation of BMSCs and promote bone healing processes [21, 22]. Based on these observations, factors such as TGF- β_3 and its analogs, BMP, BMP-2, and BMP-7, have been used clinically to enhance and accelerate the bone repair or regeneration.

Technically, MSCs can be isolated from many different tissues. The iliac crest is the ideal position for bone marrow aspiration. In clinical practice, we indeed found that injection of bone marrow aspirate into the fracture space can promote the healing of fracture and shorten the healing time. For example, in one case with an open tibial fracture, which did not develop callus within the 6 months after surgery, and then we extracted marrow aspirate from the iliac crest and injected it into the fracture space. We found that the fracture healed well 6 months after the transplantation (**Figure 1**). Consistently, bone marrow aspirate injection has been shown to have a potential role in the treatment of aseptic, atrophic nonunions with acceptable alignment and minimal gap, or displacement between fracture fragments [15]. Generally, Tibial nonunion treatment with bone marrow aspirate has been well-documented and found to be successful in 75–90% of reported tibial nonunion case series [23, 24].

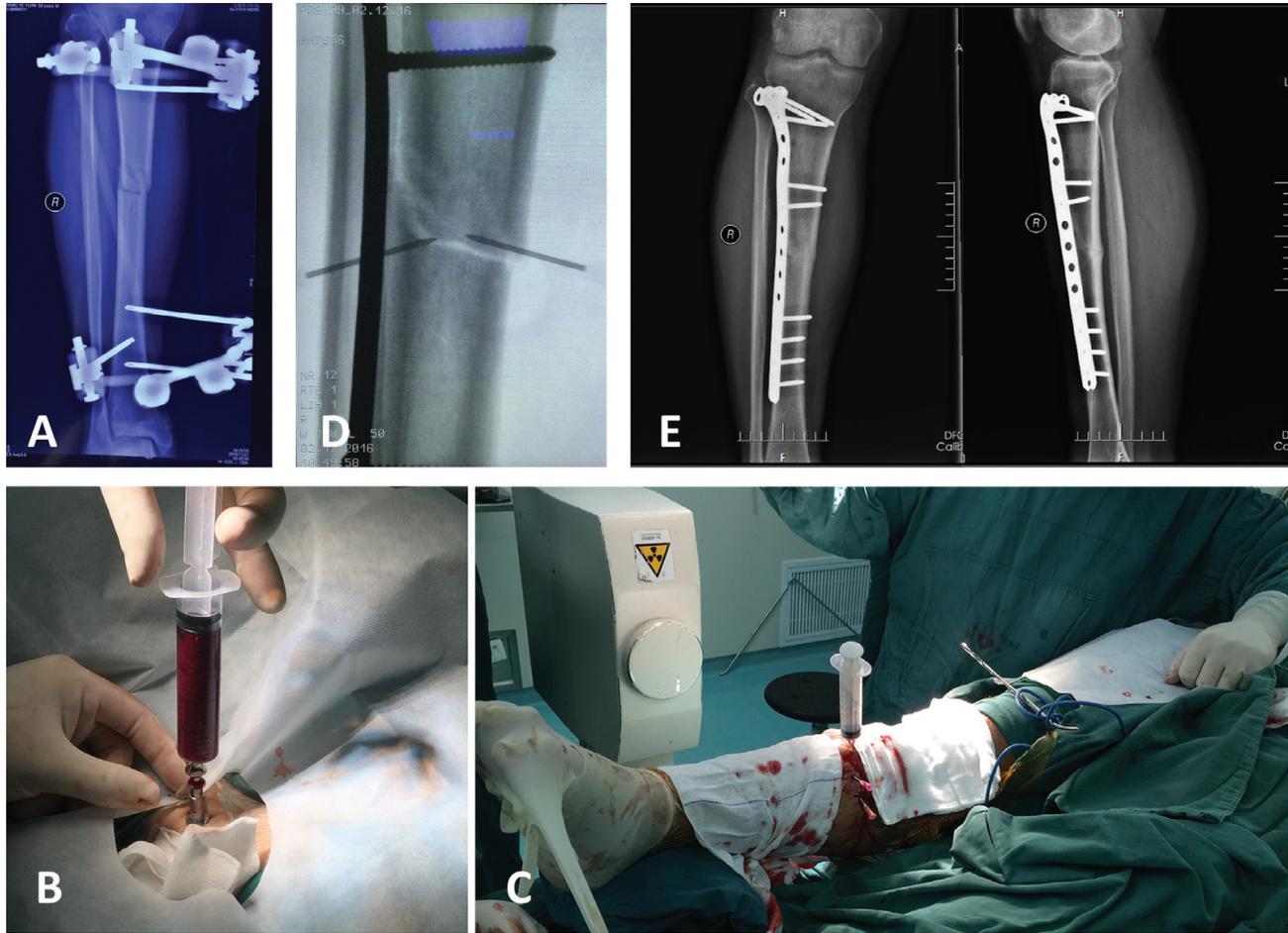


Figure 1. (A) A 32-year-old male underwent external fixation of an open tibial fracture. After surgery, no callus was observed in 6 months. (B, C) he underwent bone marrow aspiration and percutaneous grafting directly into the nonunion site. (D, E) 6 months after the transplantation, frontal and lateral X-ray images indicated the fracture healed well.

Researchers have described the purification and expansion of bone marrow MSCs from mice, rats, rabbits, dogs, and humans, and the ability of these cell populations to form bone when implanted ectopically with hydroxyapatite or an appropriate carrier has been established. To isolate MSCs from blood, mobilization of MSCs to the peripheral circulation with granulocyte colony-stimulating factor (G-CSF) is normally necessary. Data also suggests that the tissue-engineered constructs with MSCs (either genetic modified or not) brings us closer to a clinical application. However, nonunion still occurred in nearly half of the bone defects in a large animal model [25]. In fact, the commonly accepted idea that atrophic nonunion is due to lack of MSCs activities of MSCs might be not accurate. For example, an interesting study found the existence of MSCs (confirmed by their expression profile of CD105, CD73, HLA-DR, CD34, CD45, CD14, and CD19) in the site of atrophic nonunion, at a similar number and viability to those isolated from the iliac crest [26]. In another clinical study, Ismail et al. [14] also reported that iliac crest autograft with or without autologous MSCs (with 5 g/cm³ hydroxyapatite granules, as scaffold carrier) had similar treatment efforts on atrophic nonunion.

3. MSCs in articular cartilage injury

Due to the limited ability of proliferation capacity of chondrocytes, articular cartilage injury often causes progressive degeneration of the joint and OA, which is a serious health and economic problem [27]. The typical current treatment for this disorder is microfracture, which is a surgical technique that was developed 20 years ago. This treatment uses the body's own healing abilities to regenerate the chondral surface. However, the regenerated fibrocartilage often has poor mechanical properties compared with normal cartilage.

Recently, the MSC-based autogenous transplantation treatment was proposed, since the potential of the MSCs to differentiate into chondrocytes has been well-recognized [28]. Compared with allogeneic cells, generally, autogenous cartilage progenitor cells are more effective in the treatment of articular cartilage defect [29]. The emerging typical paradigm to apply MSCs in this disorder is [30]: (1) during the first operation, a cartilage biopsy is taken from areas of damaged cartilage within the ankle or knee; (2) chondrocytes are isolated from the biopsy via enzymatic digestion and cultured in 2D monolayer cultures; (3) monolayer culture-expanded chondrocytes are seeded on a collagen type I-III membrane; and (4) in the second operation, the cartilage lesion is prepared and the collagen membrane is cut to size, placed in the lesion and secured with fibrin glue.

To clarify whether donor MSCs indeed contribute to cartilage regeneration in vivo via a progenitor-mediated mechanism [31], Zwolanek et al. describe a novel cell tracking system based on genetic transgenic donor and corresponding cell marker, and the results showed that MSC could contribute to cartilage regeneration via a progenitor - or nonprogenitor - mediated mechanism [31]. The study by Windt et al. in humans also produced similar results [32]. Further study found that chondrogenesis can be regulated by adjusting the time and concentration of TGF- β [33].

To further improve the efficiency of MSC-based treatment, combining bone marrow-derived MSCs with scaffold have been tried for the reconstruction of cartilage [34]. For example, Sadlik et al. reported that the scaffold-embedded MSC was implanted into the knee to repair cartilage through dry arthroscopy, and the tissue regeneration was successful [27]. In addition, other approaches, such as the stem cells cultured from the subpatellar fat pad of arthritis patients can also be induced to differentiate into chondrocytes, which are very similar to the normal chondrocytes [29]. Koga et al. also found that the transplantation of synovial MSCs (SMSCs) in a rabbit model resulted in a large number of cartilage matrix development, and they also observed that SMSCs differentiated into osteocytes deeper into the defect, but differentiated into chondrocytes on the surface [35].

4. MSCs in meniscus injury

Meniscus injury in the knee joint is probably the most frequent intra-articular damage. The typical treatment is a partial sursectomy, but it can lead to degeneration of articular cartilage, narrow joints, and early osteoarthritis. Intra-articular injection of MSCs could be a simple treatment with little damage since MSCs might promote the regeneration of meniscus. Indeed, it was found that when MSCs were injected directly into the articular cavity, they could migrate to the lesion site, directly participate in the tissue repair, and induce the repair of the host through the collateral secretion, and replace the injured tissue [36]. Murhpy et al. reported the first study of injection of BMSCs in sheep articular cavity [37], and observed the obvious repair of cartilage damage in meniscus injury, 6 and 12 weeks after injection. Whitehouse et al. also reported that undifferentiated MSCs/collagen-scaffold implant could provide a safe way to augment avascular meniscal repair in some patients [38]. Another study investigating the injection of allogenic MSCs in the context of post-subtotal meniscectomy found that there was evidence of meniscal regeneration in the two groups treated with MSCs [39]. However, Hong et al. used arthroscopic surgery to repair the meniscus of the posterior articular cavity with or without BMSCs after meniscus injury [40], and found that the meniscus and tibial plateau were not fully integrated, and the efficacy of MSCs treatment group was not significantly different from that of the control group. They argued that MSCs may differentiate into other tissue cells if they were not effectively induced to differentiate into specific cell types. Therefore, it is still a challenge to induce the cells into the meniscus cartilage phenotype in this context.

5. MSCs in the treatment of osteoarthritis

Osteoarthritis (OA) is a major cause of joint pain and loss of mobility in the elderly, which seriously affects the quality of life and causes huge social and economic burden. Many researchers have conducted a series of clinical studies on BMSCs transplantation to treat OA (**Table 1**), and these studies demonstrated that moderate confidence could be placed on the safety of MSCs therapy for knee OA, but the confidence in efficacy outcomes is low, mainly

References	Location	BMCS ^a	Follow-up time	No. of cases	Pain subscale		Outcomes
					Pre-infusion values	Post-infusion values	
[41]	knee	Auto_ BM_MSC	1 year	12	24 ± 14 ^b	6 ± 6 ^b	pain improvement, higher cartilage quality (MRI)
[42]	knee	Auto_ AT_MSC	6 months	12	56 ± 19 ^b	34 ± 23 ^b	clinical improvements
[43]	knee	Allo_ BM_MSC	1 year	15	46 ± 15 ^b	30 ± 16 ^b	pain improvement, higher cartilage quality (MRI)
[44]	knee	Auto_ BM_MSC	24 weeks	2	4 ^c	0.38 ^c	pain improvement, higher cartilage quality (MRI)
[45]	Hip	Auto_ BM_MSC	3 years	10	34.5 ± 8.2 ^b	19.2 ± 6.1 ^b	pain improvement, improved function

^aAuto_BM_MSC, Autologous Bone Marrow-derived MSCs. Auto_AT_MSC, Autologous Adipose Tissue-derived MSC. Allo_BM_MSC, Allogeneic Bone Marrow-derived MSC.

^bThe WOMAC index (pain subscale) has been used; scale 0–100.

^cThe VAS index (pain subscale) has been used; scale 0–10.

Table 1. Summary of MSCs as the treatment of osteoarthritis.

due to limited clinical case number [46]. Therefore, further high-quality studies for OA with high internal and external validity are still required. In addition, Shi et al. compared the clinical results of platelet-rich plasma (PRP) and MSCs treatments for osteoarthritis of the knee in a systematic review and pointed out MSCs provide more significant disease therapeutic effect [47].

6. MSCs in femoral head necrosis

Avascular necrosis of the femoral head (ANFH) is a serious clinical problem. If untreated, about 80% of ANFH progresses to the collapse of the head within 1–4 years [48]. Numerous clinical methods have been tried, including core decompression (CD), a commonly used method for treating the early stages of ANFH. The presumption is that CD can reduce the intraosseous pressure and also stimulate stem cell regeneration. But the outcome of CD is variable and is still controversial.

With the development of non-biological materials, MSCs and tissue engineering techniques, the treatment of ANFH has been significantly improved recently [49]. For example, it was

reported that the efficacy of MSCs transplantation group was significantly better than that of the pure medullary decompression group [50]. In another study, 100 patients with early-stage ANFH were recruited and randomly assigned to BMMSC treatment or CD treatment only [51], a similar result was observed, that is, this intervention was proved to be safe and more effective in delaying or avoiding FH collapse. In another study of eight patients with bilateral femoral head necrosis, the researchers performed the medullary decompression on one side, while on the other side medullary decompression MSCs transplantation. The Harris hip score (HHS) and VAS score of the MSCs transplantation group were significantly improved, and the results of MRI quantitative analysis showed a significant decrease in necrosis area [52]. Consistently, another study found that the group of MSCs had a significantly superior recovery of the early stages of necrosis [53].

However, there have been reports of unsatisfactory success rates for end-stage osteonecrosis of the femoral head (ONFH), even with MSCs [54]. To improve the outcome, Zhao et al. describe a modified technique using BMSCs associated with porous tantalum rod implantation combined with vascularized iliac grafting for the treatment of end-stage ONFH, and they followed up for 5 years, and these authors found that Harris hip score was improved from 38.74 ± 5.88 points (range 22–50) to 77.23 ± 14.75 points (range 33–95) [55]. It is worthy to mention that, in this procedure, approximately 10 mL of bone marrow from the subtrochanteric region was directly aspirated once the decompression tunnel was established during the surgery, avoiding the need for bone marrow aspiration from the iliac crest.

7. MSCs in intervertebral disc degeneration

Intervertebral disc degenerative is a serious worldwide problem for the aging population. The apoptosis of nucleus pulposus cells could be the main cause of intervertebral disc degeneration, with a variety of manifestations, that is, reduced number of the cells, the changes of the mechanical structure, down-regulated synthesis of matrix components (such as proteoglycan), nucleus pulposus dehydration, and increased metabolic waste [56, 57]. Many treatment options have been proposed, including physical therapy, pain medication, epidural steroid drug injection, disc radiating, myeloid nucleation, intervertebral fusion, and intervertebral disc displacement. However, these therapeutic approaches aim only to relieve the symptoms of disc degeneration, not treat its underlying cause. MSCs transplantation provides a new therapeutic strategy for promoting proteoglycan synthesis, decelerating the course of disc degeneration, and stimulating disc regeneration.

For example, Sobajima et al. reported that BMSCs was injected into the lumbar intervertebral disc of the New Zealand white rabbit, and found that the transplanted BMSCs survived and migrated to the fibrous ring after 24 weeks [58]. Hee et al. confirmed that BMSCs implantation and axial distraction may have a synergistic effect in reversing degenerative disc disease in the rabbit model [59]. Some scholars have discovered that drug stimulation can regulate the differentiation of nucleus pulposus MSCs into nucleus pulposus cell

by promoting expression of hypoxia-inducible factor to repair and reconstruct degenerated intervertebral disc [60].

In a recent study, under fluoroscopic guidance, the BMCs were injected into the nucleus pulposus of 26 patients' with chronic (>6 months) discogenic low back pain [61]. These authors found the evidence of safety and feasibility in the non-surgical treatment of discogenic pain using autologous BMCs with durable pain relief (71% VAS reduction) and Oswestry Disability Index improvements (>64%) through 2 years.

Overall, the BMSCs as a treatment of degenerated intervertebral disc is successful both in an animal model and in clinical studies; however, there are no long-term follow-up results and the number of reports and the number of cases are still relatively low. Another concern is that, at least in theory, BMSCs may cause osteophyte formation in the vertebral isthmus when it is released from the nucleus. Further clinical trials are needed to clarify these concerns.

8. MSCs in osteoporosis

Osteoporosis is a common metabolic bone disease, characterized by loss of bone mass, bone density reduction, and bone structure damage, which leads to increased bone fragility and risks of bone fracture [62]. The exact underlying mechanisms of osteoporosis are still unclear, but a shift of the cell differentiation of MSCs to adipocytes rather than osteoblasts partly contributes to osteoporosis [63]. Furthermore, it was observed that osteoclast activity (bone resorption) was enhanced, while osteoblast function (bone formation) decreased. For this reason, the drugs that inhibit the activity of osteoclasts have been widely used in clinical practice; however, these drugs have many complications, such as mandibular necrosis, reflux esophagitis, and atypical fracture [62, 64]. Recently, it is found that the decrease of BMSC to osteogenic differentiation and the increase of lipid differentiation is an important factor in the pathogenesis of osteoporosis [65, 66], therefore, one of the new ways to inhibit osteoporosis is to promote osteogenesis differentiation of endogenous BMSCs. In the meantime, BMSCs transplantation can also effectively increase bone mass and density, increase bone mechanical strength, correct the imbalance in bone metabolism, and increase bone formation, and is expected to provide a new strategy and method for the treatment of osteoporosis [67].

Scholars have carried out a large number of studies, including signal transduction, gene transcription, and post-transcriptional level, and found that miRNA and epigenetic modifications are probably the main mechanisms for BMSC differentiation [63]. In addition, conserved signal regulation, mechanical stimuli, radiation, and diet also play important roles in regulating the differentiation fate of MSCs. Even though an MSC transplant could, at least in theory, provide a treatment for osteoporosis, the clinical trials of MSCs in osteoporosis have just begun; nevertheless, the animal studies have already found that autograft or allogeneic MSC transplantation can increase the bone mass of animal models of osteoporosis [66, 67]. Since

osteoporosis is a systemic disease, and the hormone levels and cytokines have changed dramatically, it is still unclear whether the simple local MSC transplantation can improve these changes in the long-term. In addition, the bone marrow homing efficiency of MSCs and the long-term survival of MSCs are still uncertain.

9. MSCs in genetic diseases

9.1. Osteogenesis imperfecta (OI)

Osteogenesis imperfecta is a rare congenital bone development disorder characterized by bone fragility, blue sclera, deafness, and joint relaxation. Horwitz et al. reported three cases of OI using allogeneic bone marrow cells [68]. Six months after the implantation, the new bone formation was observed with a reduced frequency of fractures, suggesting that bone marrow cells could be used to treat OI. The further study from the same group with BMSCs transplantation [69], obtained similar results, that is, donor BMSCs survived in 5/6 OI patients' which significantly improved the clinical symptoms of these patients.

9.2. Hypophosphatasia (HPP)

Hypophosphatasia is a rare, heritable, metabolic bone disease due to deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase [70]. The disease is characterized by the disturbance of bone and tooth mineralization and reduced serum ALP activity. Tadokoro et al. used allogeneic MSCs obtained from the patient's father for an 8-month-old patient with hypophosphatasia [71], and they observed improved respiratory condition, and de novo bone derived from both donor and patient cells. Similarly, Cahill et al. reported an 8-month-old girl with worsening and life-threatening infantile HPP improved considerably after marrow cell transplantation [72]. More importantly, 4 months after treatment, radiographs demonstrated improved skeletal mineralization. The authors speculated that donor bone fragments and marrow may provide precursor cells for distribution and engraftment in the skeletal micro-environment in HPP patients to form tissue-nonspecific isoenzyme of alkaline phosphatase-replete osteoblasts that can improve mineralization.

10. Conclusions

BMSCs are easy to obtain, isolated and amplified, which provide a wide application prospect for the treatment of orthopedic diseases. Here, we briefly reviewed the progressions of MSCs in a variety of orthopedic diseases. Many studies have demonstrated the safety and efficacy of autologous bone marrow MSCs transplantation in animal models as well as in human clinical trials. However, there are still some issues to be solved, such as the reference standards of BMSCs, the regulatory mechanism of proliferation and differentiation of BMSCs, the time, route of administration, and dosages of the transplant. With the further BMSCs researches, we believe that these problems will be solved soon.

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Conflict of interest

The authors declare no competing interests.

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