Mesenchymal stem cells: ideal seeds for treating diseases

Guanwen Gao1,2 · Chenyang Fan3 · Weiquan Li2 · Runzhang Liang2 · Chuzhong Wei2 · Xiaojie Chen2 · Yue Yang2 · Yueyuan Zhong2 · Yingqi Shao2 · Yi Kong2 · Zesong Li4,5 · Xiao Zhu1,2,4

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Abstract
Mesenchymal stem cells (MSCs), a kind of multipotent stem cells with self-renewal ability and multi-differentiation ability, have become the “practical stem cells” for the treatment of diseases. MSCs have immunomodulatory properties and can be used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and Crohn’s disease. MSCs also can be used in cancer and aging. At present, many clinical experiments are using MSCs. MSCs can reduce the occurrence of inflammation and apoptosis of tissue cells, and promote the proliferation of endogenous tissue and organ cells, so as to achieve the effect of repairing tissue and organs. MSCs presumably also play an important role in Corona Virus Disease 2019 (COVID-19) infection.

Keywords Mesenchymal stem cells · Autoimmune diseases · Aging · Inflammation · Cancer · COVID-19

Abbreviations
AA Alginate
ARDS Acute respiratory distress syndrome
BM-MSCs Bone marrow mesenchymal stem cells
BMP-2 Bone morphogenetic protein 2
CBX4 Chromobox protein homologue 4
CRISPR Clustered Regularly Interspaced Short Palindromic Repeats
Cas9 CRISPR-associated protein-9 nuclease
Col Collagen
COPD Chronic obstructive pulmonary disease
COVID-19 Corona Virus Disease 2019
CRC Colorectal cancer
CXCR7 C-X-C chemokine receptor type 7
CXCL12 C-X-C motif chemokine ligand 12
DGC8 DiGeorge syndrome critical region gene 8
DEX Dexamethasone
ELISA Enzyme-linked immunosorbent assay
FOXO1 Forkhead box D1
FOXO3 Forkhead box O3
FOXO1 Forkhead box P1
GVHD Graft-versus-host disease
hADMSCs Human adipose-derived mesenchymal stem cells
HP1 Heterochromatin protein 1
IFNα Interferon alpha
IGF-2 Insulin-like growth factor 2
IL-1β Interleukin-1beta
IFN-γ Interferon gamma
iMSCs Induced Mesenchymal Stem Cells
iPSCs Induced pluripotent stem cells
IP-10 Interferon gamma-induced protein 10 kDa
IRS-1 Insulin receptor substrate 1
KAP1 KRAB-association protein 1

Guanwen Gao and Chenyang Fan have contributed equally to this work.

* Zesong Li
lzssc@email.szu.edu.cn

* Xiao Zhu
bioxzhu@yahoo.com

1 School of Laboratory Medicine, The First Affiliated Hospital, Bengbu Medical College, Bengbu, China
2 Clinical Research Center, The First Dongguan Affiliated Hospital of Guangdong Medical University, Dongguan, China
3 Department of Clinical Medicine, Medicine and Technology School of Zunyi Medical University, Zunyi, China
4 Guangdong Provincial Key Laboratory of Systems Biology and Synthetic Biology for Urogenital Tumors, Department of Urology, Shenzhen Second People’s Hospital (Shenzhen Institute of Translational Medicine), The First Affiliated Hospital of Shenzhen University, Shenzhen, China
5 Shenzhen Key Laboratory of Genitourinary Tumor, Department of Urology, Shenzhen Second People’s Hospital (Shenzhen Institute of Translational Medicine), The First Affiliated Hospital of Shenzhen University, Shenzhen, China
Introduction

When mesenchymal stem cells (MSCs) were isolated and cultured at an early stage, they were found to be fibroblast-like in shape and were called fibroblast colony-forming units or bone marrow stromal fibroblasts [1]. A large number of studies have shown that MSCs secrete a variety of nutrient factors or growth factors while promoting the survival of a variety of cells through paracrine effects [2]. However, MSCs lack specific surface markers, are multipotent adult stem cells, exist in a variety of tissues, and are targeted to tumors [3, 4]. Although there are many reports about the application of MSCs in the clinic, so far, many clinical studies have not enough evidence to prove that they are effective treatment methods. Therefore, it is particularly important to explore the progress of the clinical application of MSCs in depth.

MSCs can differentiate into a variety of tissue cells derived from mesoderm and neuroectoderm, such as osteoblasts, chondrocytes, adipocytes, tenocytes, smooth muscle cells, bone marrow stromal cells, fibroblasts and a variety of vascular endothelial cells, and even neurons and glial cells of the nervous system [5–7]. Moreover, proteins secreted by MSCs have anti-microbial, anti-fibrotic, and regenerative effects, and have effects on cell proliferation, differentiation, immune regulation, angiogenesis, wound healing, and tissue regeneration [8–10]. Therefore, MSCs have become the “practical stem cells” for the treatment of multiple systemic diseases [11]. Moreover, MSCs have a unique function of secreting cytokines. The active proteins secreted by MSCs have played an important role in tissue healing. For example, they can construct collateral circulation, alleviate ischemic symptoms, inhibit inflammation, regulate immunity, maintain the local microenvironment homeostasis of ulcer wounds, and, most importantly, activate and recruit autologous stem cells for repair [12–14].

To make MSCs better applied in the clinic, the culture and differentiation are particularly important. Studies have found that Poly-L-Lysine can provide a good microenvironment for the culture of MSCs while enhancing the function and dryness of MSCs [15]. Moreover, the Ca/siRNA titanium surface coating can effectively control the differentiation of MSCs, which is also a new method to control MSC differentiation and tissue regeneration [16] (Fig. 1).
Applications of MSCs in diabetes mellitus

Insufficient insulin secretion due to dysfunction of islet beta cells is one of the common features of type 1 and type 2 diabetes, and many patients need lifelong insulin therapy. Studies have shown that a single injection of autologous bone marrow MSCs can protect and maintain the residual function of pancreatic beta cells, but nonetheless, MSCs cannot replace hypoglycemic drugs [17] (Table 2). Therefore, more research is required. Recently, researchers have found the existence of stem cells in the islets of adult mice, which provides theoretical and technical support for the cultivation of functional islet organoids. It is promising to treat diabetes by transplanting functional islet organoids in the future [18]. Researchers have also conducted relevant studies on damaging islets. Studies have shown that the dedifferentiation of islet beta cells is an important mechanism of impaired islet function and may also be an adaptive expression of beta cells in the diabetic state. It is exciting that MSCs can reverse the dedifferentiation of human islets in type 2 diabetes and repair the morbid islets. This study provides a fresh and strong evidence for the treatment of diabetes with MSCs. Specific practice is to reverse the dedifferentiation of β cells by co-culture of MSCs with type 2 diabetic islets. The inflammatory rescue signal released by type 2 diabetic islets with high inflammation level stimulates MSCs to exert their repair function, reduces the level of islet inflammation, reverses the dedifferentiation of β cells, and thus improves islet function. Molecular mechanism studies have shown that hyperinflammatory type 2 diabetic islets secrete interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), and stimulate MSC to secrete interleukin-1 receptor antagonist (IL-1Ra), and IL-1Ra inhibits islet inflammation, thereby reversing the dedifferentiation of β cells, and thus improves islet function. Through this dialog response mechanism, MSCs can adjust the level of inflammation in the islets to a physiological range according to the need of the damaged islets and achieve a precise repair effect [19, 20] (Table 2). In the treatment of diabetes-induced ulcers, the main ways of stem cell transplantation are intravascular injection and local injection. However, in both approaches, stem cells are difficult to migrate to diabetic wounds, so there are problems such as low transplantation efficiency and short-cell action time. Recently, some researchers have used polymer gel to transport MSCs to ulcer wounds, because the polymer gel has a certain anti-reactive oxygen radical effect and can reduce the apoptosis of stem cells when co-transplanted, so it has become a new choice for scientists. At the same time, the study showed that the polymer gel could significantly reduce the inflammatory response mediated by the TNF-α factor, stimulate the formation of human skin fibroblasts and the proliferation of microvascular endothelial cells, thereby improving the efficiency of tissue repair and significantly shortening the healing time of diabetic ulcers. The efficiency of MSCs in the treatment of diabetic foot ulcers also depends on the use of polymer gels [21].

Applications of MSCs in autoimmune diseases

Since MSCs were reported to have immunosuppressive functions in 1998, their application prospects in the treatment of autoimmune diseases have been attracting great attention [22]. MSCs were first demonstrated to modulate immunosuppression in vitro and in vivo in 2002 [23]. MSCs have a strong impact on both innate and adaptive immune responses. The prevailing view is that MSCs are strong inhibitors of the immune system [24]. They inhibit the activation and proliferation of T and B lymphocytes and may also affect the maturation of dendritic cells [25]. MSCs affect the function of most immune effector cells through direct contact with immune cells and local microenvironment factors. It has been found that the immunomodulatory effects of MSCs are mainly mediated by cytokines secreted by MSCs. However, recently, apoptosis and metabolic inactivation of MSC have been shown to have immunomodulatory potential, and regulatory T cells and monocytes play an important role [26] (Table 2). Recent studies have focused on the regulation of T-cell-mediated immune response, because interferon gamma (IFN-γ) and TNF-α produced by T cells can endow mesenchymal stem cells with immunosuppressive function, which is enhanced by cytokines (such as IL-17) stimulation [27]. Recently, the immunosuppressive effects of MSCs have been studied in different directions. Studies have shown that MSCs under hypoxic conditions, through insulin-like growth factor 2 (IGF-2), confer metabolic bias on oxidative phosphorylation of macrophages during maturation, induce the formation of anti-inflammatory macrophages and promote Treg differentiation, thereby effectively inhibiting autoimmune diseases. Analysis of macrophages revealed that IGF-2 did not affect the transition of mature macrophages to macrophages with anti-inflammatory function, but acted on the process of differentiation and maturation of monocytes to macrophages, making macrophages under the regulation of IGF-2 have sustained immunosuppressive capacity. This finding provides new strategies and effective molecules for the treatment of autoimmune diseases [28]. There are also studies, showing that placental MSCs can significantly improve the survival of patients with graft-versus-host disease (GVHD) [29]. Moreover, because MSCs have multiple immunomodulatory effects [30], some researchers have applied them to
the treatment of systemic lupus erythematosus. Current clinical data show that MSC transplantation can significantly improve the symptoms and alleviate the condition of patients with lupus erythematosus, so MSCs have important value in the treatment of systemic lupus erythematosus [31]. In summary, MSCs have great value and significance in the treatment of autoimmune diseases, and it is believed that in the near future, through further research, they will make a great contribution to the treatment of autoimmune diseases in humans.

Application of MSCs in COVID-19

The Corona Virus Disease 2019 (COVID-19) has swept the world, and more and more people are infected with the virus. Therefore, the treatment of patients has become the direction of many scientists. COVID-19 is characterized by pneumonia, lymphopenia, lymphocyte depletion, and cytokine storm [32]. At present, MSC therapy is one of the key research objects [33, 34] (Table 2). Remestemcel-L is an allogeneic MSC-derived from MSCs isolated from unrelated donor bone marrow and prepared by culture and expansion. Remestemcel-L, administered by intravenous infusion, has an immunomodulatory effect by down-regulating the production of proinflammatory cytokines, increasing the production of anti-inflammatory cytokines, and recruiting naturally occurring anti-inflammatory cells into relevant tissues to combat the inflammatory process associated with a variety of diseases. In this outbreak, diseases with potentially fatal inflammation caused by cytokine storms are the leading causes of death in patients with COVID-19. A similar course of cytokine storm can be observed in acute GVHD [35–37]. Therefore, remestemcel-L has potential applications in the treatment of COVID-19 acute respiratory distress syndrome (ARDS). And the researchers conducted a randomized, placebo-controlled study of 60 patients with chronic obstructive pulmonary disease (COPD). The analysis showed that remestemcel-L significantly improved respiratory function in patients with similarly elevated inflammatory biomarkers, which were also observed in COVID-19 ARDS patients (Table 1). These results provide a theoretical basis for evaluating remestemcel-L in the treatment of COVID-19 ARDS patients. However, a phase III clinical trial of remestemcel-L for the treatment of COVID-19 ARDS failed to meet the goal of 30 days mortality reduction. The trial included 300 patients and the goal was to reduce mortality by 43% over 30 days. On the other hand, some researchers have also confirmed that MSCs have a significant effect on the treatment of patients infected with COVID-19 [38]. Studies have shown that plasma cytokine levels in severe COVID-19 patients are significantly increased, suggesting that cytokine storm plays an important role in the lethal process of COVID-19 [39–41]. Therefore, some researchers have proposed a new idea that the use of mature MSC transplantation technology can rapidly and significantly improve the prognosis of severe and critical patients, effectively avoid the cytokine storm, without obvious side effects. Moreover, the safety and reliability of this method have been tested by clinical practice, which provides new hope for reducing the mortality rate of severe and critical patients with new coronary artery disease [42]. In addition, viral-induced acute respiratory distress syndrome is also one of the important causes of death. Recent studies have found that MSCs have great potential in the treatment of acute respiratory distress syndrome through immune regulation, proliferation, differentiation and repair, and anti-microbial effects [34, 43]. A prospective, double-blind, multicenter, randomized trial was conducted, and the results showed that a single dose of MSCs was safe for moderate-to-severe ARDS, but its effect needed to be evaluated in larger clinical trials, and the survival rate of MSCs still needed to be improved [44, 45].

However, the above treatment of the disease cannot solve the problem at the root cause. The most fundamental is how to successfully prevent COVID-19 infection. Therefore, the global pandemic of the current epidemic makes it particularly urgent to develop vaccines [46]. Some researchers have tried to use new stem cell vaccines. In this study, the researchers used the characteristics of heterologous transfusion of MSCs and immune regulation function to over-express the structural protein of COVID-19, so that MSCs become a micro-factory with continuous production of viral proteins, to achieve the effect of mimicking viral infection. After subcutaneous and intramuscular injection in mice, the antibody against new coronavirus can be detected successfully by enzyme-linked immunosorbent assay (ELISA) analysis in serum after only 20 days. At the same time, multiple modifications of various COVID-19 structural proteins can be carried out on MSCs to achieve a cocktail effect and greatly improve the success rate of stem cell vaccines. Moreover, this has confirmed the efficiency and safety of stem cell vaccines from a new perspective, provided a new perspective for the development of vaccines, and has important significance for the development of vaccines for many pathogens without vaccines. Moreover, currently, most pathogens have no effective antibodies, which suggest the limitations of the five existing vaccine platforms. The successful establishment of the stem cell vaccine, the sixth vaccine platform, can point out a new direction for future vaccine research and development [47] (Table 2). With the extensive development of research, the immune regulatory properties, anti-inflammatory properties, and the characteristics of repairing damaged tissues of MSCs are expected to play an important role in this antiviral campaign.
### Table 1  Clinical trials of mesenchymal stem cell therapy

| Types of mesenchymal stem cells | Disease                              | Sample                                                                                       | Operation                                                                                       | Consequence                                                                                                   | References                   |
|---------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------|
| Placental mesenchymal stem cells | Graft-versus-host disease            | Eighty-four patients who received allogeneic hematopoietic stem cell transplantation          | Forty-four of them were also injected with placental mesenchymal stem cells                    | The 1-year survival rate was 67 percent, significantly higher than the average for other treatment regimens in the hospital | Baygan et al. [29]          |
| Placental mesenchymal stem cells | knee arthritis                       | Twenty patients with knee arthritis                                                         | Randomly divided into two groups, one group was injected with placental mesenchymal stem cells as the experimental group, and the other group was injected with normal saline as the control group | Patients in the treatment group showed significant improvement at 8 weeks, and improvements were also observed at 24 weeks after the injection | Khalifeh Soltani et al. [56] |
| Fat mesenchymal stem cells      | Osteoarthritis                       | Eighteen patients with knee osteoarthritis                                                   | Fat mesenchymal stem cells were injected into the knee, including three dose-increasing queues: low dose group, medium dose group and high dose group | After 6 months, WOMAC score decreased and KSS functional score significantly improved                           | Jo et al. [57]              |
| Allogeneic mesenchymal stem cells| Chronic obstructive pulmonary disease| Sixty patients with chronic obstructive pulmonary disease                                    | Remestemcel-l was administered intravenously in a randomized, placebo-controlled study        | Significantly improved respiratory function                                                             | Taghavi-Farahabadi et al. [34] |
| Autologous mesenchymal stem cells| An anal fistula caused by Crohn’s disease | Twelve patients with Crohn’s disease cause anal fistula                                       | The patients’ own MSCS were cultured and amplified in vitro, and then the bioabsorbable materials were used as carriers to fill the fistula of the patients regularly | The anal fistula of ten patients was completely closed, and the anal fistula of two patients improved       | Dietz et al. [59]           |
| Placental mesenchymal stem cells| Hemorrhagic cystitis                 | Eighty-four patients who received allogeneic hematopoietic stem cell transplantation          | Forty-four of them were also injected with placental mesenchymal stem cells                    | One-year survival was as high as 90%                                                                     | Baygan et al. [29]          |
Applications of MSCs in inflammation

MSCs have immune regulatory functions and strong paracrine effects in the inflammatory environment, which can be used to treat inflammatory diseases, and their role remains to be further developed [48, 49]. A large number of studies have shown that MSCs can regulate inflammation and promote tissue regeneration in a variety of ways, so as to alleviate or even treat a variety of inflammatory diseases, such as inflammatory bowel disease [50] and arthritis [51]. However, the effects of MSCs are not immutable but strictly regulated by the type and level of inflammatory cytokines. In inflammatory diseases, inflammation changes frequently. The dynamic changes in the function and composition of immune cells and immune molecules in the inflammatory microenvironment can affect the application of MSCs in inflammation [52]. Some inflammatory factors have been found to endow MSCs with immunosuppressive function [53]. Moreover, the diversity of inflammatory factors and the dynamic changes of their levels determine the plasticity of the immune regulatory capacity of MSCs [54]. For example, IL-17 regulates the immunosuppressive function of MSC and enhances the immunosuppressive effect of MSC by down-regulating mRNA degradation factors, forming inflammatory factors [55]. Recently, scientists have found that an anti-inflammatory factor (CD200) is highly expressed in placental MSCs, inhibiting the production of proinflammatory factors but also increasing the formation of anti-inflammatory response factors and immune regulatory factors, thus playing a role in the treatment of diseases [43]. In addition, studies have shown that placental mesenchymal stem cells are safe and effective in the treatment of knee arthritis. Researchers randomly divided 20 patients with knee arthritis into two groups: one group was injected with placental MSCs as the experimental group, and the other group was injected with saline as the control group. The
results showed that patients in the experimental group had a significant improvement at 8 weeks, and the improvement was also observed at 24 weeks after injection [56]. Placental MSCs can also significantly improve the survival rate of patients with hemorrhagic cystitis. Among 84 patients who received allogeneic hematopoietic stem cell transplantation, 44 of them received placental MSCs at the same time. The results showed that the 1-year survival rate of hemorrhagic cystitis patients treated with placental MSCs was as high as 90% [29] (Table 1).

MSCs not only play a significant role in knee arthritis but also play an important role in osteoarthritis (OA), Crohn’s disease, and other places. For example, researchers have injected autologous fat MSC into the local joint cavity to treat OA (Phase I-II clinical trial). The results show that this can reduce the local inflammatory reaction of joints, reduce pain, improve knee function, and promote the regeneration of articular cartilage. After 6 months, the Western Ontario and McMaster Universities (WOMAC) score decreased and the Knee Society Score (KSS) knee score and KSS function score improved significantly [57]. Researchers have also found that autologous MSCs can be used to treat anal fistulas caused by Crohn’s disease with the help of bio-resorbative materials, while most patients with Crohn’s disease who receive allogeneic bone marrow mesenchymal stem cells (BM-MSCs) for anal fistulas have not seen recurrence 4 years later [58]. The researchers screened 12 patients with anal fistula caused by Crohn’s disease. After the patient’s own MSCs were cultured and expanded in vitro, they were filled into the patient’s anal fistula and fistula regularly with bioreversible materials as carriers for treatment. Six months later, anal fistulas were completely closed in 10 patients, improved in 2 patients, and no serious complications related to MSC therapy occurred. Therefore, MSCs are safe and effective in curing anal fistula caused by refractory Crohn’s disease [59] (Table 1).

Applications of MSCs in bone formation

MSCs are of great significance in bone-related diseases, bone tissue engineering and regenerative medicine [60, 61]. Scientists have found that many factors can promote the osteogenic differentiation of MSCs. For example, nanomembranes composed of collagen (Col) and sodium alginate (AA) show relatively high stiffness, and MSCs coated with Col/AA nanomembranes have higher osteogenic differentiation efficiency compared with other nanomembranes-coated MSCs. It was found that Col/AA nanofilm coating utilized extracellular signal-related kinase and p38 mitogen-activated protein kinase (p38MAPK) signals to activate transcriptional co-activators of PDZ-binding motifs to stimulate osteogenesis [62]. Moreover, the transcriptional co-activator of the PDZ-binding motif (TAZ) plays an important role in the osteogenesis of BM-MSCs and strongly activates the expression of osteogenic differentiation markers. Studies have shown that insulin receptor substrate 1 (IRS-1) gene modification increases TAZ expression through phosphatidylinositol 3 kinase-protein kinase B (PI3K-PKA) signaling and promotes the osteogenic differentiation pathway of rat BM-MSCs [63]. For BM-MSCs, it is a great challenge to maintain the nature of their regenerative applications in culture. However, researchers have found that a culture environment mimicking the bone marrow can be established to regulate the activity of BM-MSCs. In this study, researchers extracted soluble factors from human bone marrow and used them for tissue regeneration culture of bone marrow stromal cells. It has been found that Lipocalin-2 and prolactin are key factors in the bone marrow and are involved in regulating the activity of BM-MSC. Treatment of cells with Lipocalin-2 and prolactin delayed cell senescence in BM-MSCs and triggered cell osteogenesis and cartilage formation. Furthermore, further studies showed that BM-MSCs pretreated with Lipocalin-2 and prolactin could also enhance the repair of skull defects in mice. These all demonstrate that appropriate methods can be used to elicit BM-MSC properties in vitro to improve cell-based tissue regeneration in vivo [64].

Recently, researchers have made many discoveries about adipose-derived MSCs. For example, the reduction of endogenous Smad4 and Jak1 can inhibit the osteogenic differentiation of human adipose stem cells, while the expression of Smad4 and Jak1 is inhibited by MiR-125a-3p. It is suggested that MiR-125a-3p can negatively regulate osteoblast differentiation of human adipose-derived MSCs by targeting Smad4 and Jak1 [65]. To enhance the osteogenic potential of human adipose-derived mesenchymal stem cells (hADMSCs), novel multifunctional nano-scaffold chitosan (CTs) functionalized super-magnetic halloysite nanotubes (M-HNTs) were synthesized and decorated with calcium phosphate 2-D nanosheets (CaP) (called M-HNTs-CTs-CaP). It was found that M-HNTs-CTs-CaP had a strong osteogenic ability of hADMSCs and could be used as a highly applicable next-generation nano-scaffold for bone tissue engineering applications [66]. Speaking of nanoscaffolds, researchers have also fabricated ideal zein/poly L-lactic acid (PLLA) nanofibers by coaxial electrospinning and loaded them with bone morphogenetic protein 2 (BMP-2) and dexamethasone (DEX) for dual-controlled release for bone tissue engineering applications. In vitro osteogenesis studies showed that drug-loaded nanofiber scaffolds induced osteogenic differentiation. In addition, the dual-controlled release of BMP-2 and DEX enhanced the osteogenic differentiation of MSCs caused by synergistic effects. Therefore, zein/PLLA nanofiber scaffolds loaded with BMP-2 and DEX...
have great potential in bone tissue engineering applications [67].

**Applications of MSCs in cancer**

MSCs are one of the important components of the tumor microenvironment [68, 69]. Therefore, much research on cancer is about MSCs. Mesenchymal cells contribute to regulating the microenvironment of stem cells and malignant cells. The primary changes in the hematopoietic microenvironment can lead to secondary tumor diseases. MSC dysfunction may induce leukemia [70]. Some studies have found that acute myeloid leukemia injures the osteogenic differentiation process of MSCs and down-regulates the regulatory molecules required for the hematopoietic process. It reveals that cancer cells regulate specific stromal cells and impair normal tissue function to promote the carcinogenesis process [71–73]. Other studies have found that cancer cells can use MSCs to assist themselves in metastasis, because MSCs are attracted to the vicinity of the tumor by cancer cells during the process of cancer cell metastasis and promote tumor development and metastasis [74–80]. For example, MSCs can promote breast cancer metastasis, but their ability depends on the response to transforming growth factor beta (TGFβ) signals. Among the tumor-associated inflammatory factors, TGFβ is considered to be a key determinant of malignancy [81]. Researchers found that TGFβ could significantly inhibit C-X-C motif chemokine ligand 12 (CXCL12) secreted by MSCs, and over-expression of CXCL12 in MSCs could eliminate the tumor-promoting metastasis ability of MSCs [82]. This study revealed that MSCs originally bound to tumor cells evolved into MSCs that promoted tumor metastasis under the regulation of TGFβ. Moreover, by analyzing the sample information of breast cancer patients, we found that a high level of C-X-C chemokine receptor type 7 (CXCR7) expression and a low level of CXCL12 expression are typical characteristics of breast cancer, and are closely related to the survival rate of breast cancer patients. This study not only reveals a new mechanism of the interaction between TGFβ and MSCs in determining tumor cell metastasis but also provides a new marker molecule for the molecular diagnosis of breast cancer patients. Some cytokines have regulatory effects on breast cancer stem cells. For example, IL8 activates the self-renewal and regeneration ability of cancer stem cells through the IL8-CXCR1 pathway. BM-MSCs can secrete more cytokines such as IL8 and IL6 under the induction of IL6, and migrate from bone marrow to the site of breast carcinoma in situ. And to promote the self-renewal of cancer stem cells and the growth of in situ cancer, leading to further deterioration of cancer [83].

In terms of treatment, tumor-targeted drug delivery has the potential to improve therapeutic efficacy and reduce the non-specific toxicity of anti-cancer drugs [84–87]. BM-MSCs have been shown to migrate specifically to inflammatory sites, including tumors, and are expected to serve as tumor-specific carriers to deliver antineoplastic drugs. Therefore, some scientists use MSCs as the carriers of anti-tumor drugs to achieve effective tumor treatment [88] (Table 2). Interferon alpha (IFNα) has been used clinically to treat various types of tumors; however, because of its short half-life, significant therapeutic effects require high doses, which often lead to serious side effects. Therefore, researchers have successfully constructed MSCs that can continuously secrete IFNα, which can exert long-lasting anti-tumor effects and eliminate side effects associated with high clinical doses of recombinant IFNα. Moreover, MSC-IFNα can effectively inhibit the proliferation of B16 melanoma cells and promote melanoma cell apoptosis, and its anti-tumor mechanism is related to natural killer cells and CD8 + T cells. This study shows that MSCs are an ideal tumor-targeting therapy and drug sustained release carrier, which provides an innovative strategy for the clinical treatment of tumors [89]. In addition, interferon gamma-induced protein 10 kDa (IP-10) is a potent chemoattractant that enhances anti-tumor activity and mediates tumor regression through multiple mechanisms. In the mouse model of melanoma lung metastasis, hADMSCs expressing IP-10 can inhibit the growth of tumor cells and significantly prolong survival time. This suggests that hADMSCs expressing IP-10 can reduce the growth and metastasis of melanoma by targeting metastatic tumor sites. This also may be a novel and effective strategy for the treatment of melanoma [90].

And in colorectal cancer (CRC), radiotherapy is well known for remain one of the cornerstones for improving the prognosis of patients with CRC. Radiotherapy of CRC not only helps destroy cancer cells but also remodels the tumor microenvironment by enhancing the tumor specificity of BM-MSCs from the peripheral circulation. Some researchers found that BM-MSC showed anti-tumor effects by secreting certain cytokines (TNF-α, IFN-γ) when irradiated with low doses of ultraviolet and X-ray. The above cytokines inhibit the proliferation and induce apoptosis of CRC cells. All these indicate that BM-MSC can potentially promote the role of radiotherapy in CRC [91].

Gene-directed enzyme prodrug therapy (GDEPT) or suicide gene therapy is another novel treatment for cancer. MSC is used as a gene carrier to transfer suicide gene into tumor cells, which is based on the characteristics of MSCs secreting exosomes and tending to tumor tissue. In the presence of the prodrug, MSCs chemotactic into the tumor site activate the prodrug to its cytotoxic metabolites. The cytotoxic metabolites kill the adjacent tumor cells to achieve the anti-tumor effect. At the same time, the targeted administration
reduce the toxic and side effects of anti-tumor drugs [92, 93] (Table 2).

Angiogenesis is a common and important physiological or pathological behavior during the growth of solid tumors [94, 95]. MSCs can secrete a variety of proangiogenic factors. Some animal experiments have proved that MSCs promote the growth of breast cancer cells [96], ovarian cancer cells [97], melanoma cells [98], and gastric cancer cells [99]. MSCs promote the growth of tumors. It is speculated that MSCs secrete growth factors to promote the growth of tumor cells, promote the angiogenesis of tumor tissue, and participate in the construction of tumor stem cell microenvironment [100, 101]. Therefore, whether MSC can be used in the treatment of tumors is full of great controversy in theory. It needs rigorous scientific research with large clinical samples.

Application of MSCs in angiogenesis

The formation of blood vessels is fundamental to development, and the deregulation of blood vessels leads to severe diseases [102–104]. MSCs participate in the links of angiogenesis, including the proliferation of endothelial cells in the early stage and the maturation of blood vessels in the late stage. MSCs improve blood supply by releasing angiopoietin and vascular endothelial growth factors to increase angiogenesis in damaged areas [105]. MSCs transplantation has made great progress in the treatment of ischemic heart disease [106]. At present, the mechanism of MSCs in the treatment of myocardial infarction is not that MSCs migrate to the injured myocardium differentiate into cardiomyocytes but secrete cytokines [107, 108] (Table 2). The main reason why ischemic diseases are difficult to recover completely is that the stimulation intensity of angiogenesis is not enough, and the lack of appropriate angiogenesis leads to insufficient blood supply. The emergence of MSC has brought hope to the treatment of diseases with insufficient blood supply such as atherosclerosis [109] and stroke [110].

The anti-aging effect of MSCs

Aging is a major problem facing mankind, and the pursuit of immortality is an eternal topic [111–114]. After more studies mesenchymal stem cells have been found to play a great role in combating aging. Cell senescence and stem cell depletion, as important markers of aging, are important factors driving the occurrence and development of senile diseases [115–119]. The study found that many symptoms of senile patients with the debilitating syndrome were improved without adverse reactions after the reinfusion of young MSCs. The safety and efficacy of MSCs have been demonstrated, and it is also possible to keep the elderly old [120, 121]. As a result, more and more scientists are committed to applying MSCs to anti-aging. Researchers found that zinc-finger proteins with Kruppel associated box (KRAB) and SCAN domain 3 (ZKSCAN3) showed downregulated expression in human premature aging MSCs, replicative senescent MSCs, and primary MSCs isolated from the elderly individuals, suggesting a potential link between ZKSCAN3 and senescence regulation. Furthermore, human embryonic stem cells and MSCs with the targeted knockout of ZKSCAN3 were successfully obtained for the first time using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein-9 nuclease (Cas9)-mediated gene editing technology and stem cell directed induced differentiation technology. ZKSCAN3 was found to delay human stem cell senescence in an autophagy-independent manner. Thus, revealing a new function and mechanism of ZKSCAN3 as an epigenetic regulator to regulate human stem cell homeostasis and inhibit its senescence. This discovery expands people's understanding of the new functions of the zinc-finger protein family, deepens the understanding of the epigenetic mechanism of aging, and provides clues and ideas for delaying stem cell aging and preventing aging-related diseases [122]. At the same time, studies have also found that Yes-associated protein (YAP), the main effector of Hippo signaling, is a single protein factor that can maintain the young state of human MSCs. Researchers have also used CRISPR/Cas9-mediated gene editing to obtain YAP-specific knockout human embryonic stem cells and human MSCs [123] (Table 2). The researchers found that human MSCs lacking YAP exhibited a severe accelerated aging phenotype. Overexpression of YAP in YAP-deficient human MSCs can effectively reverse the accelerated senescence phenotype of cells, suggesting that YAP plays a key role in maintaining the youthful state of human adult stem cells and may play a role of "de-senescence" (Fig. 2). Meanwhile, human induced pluripotent stem cell (iPSC)-derived MSCs (iMSCs) has proven to be a useful clinically relevant source of MSCs, and iMSCs can obtain gene markers for revitalization regardless of donor age and cell source. These genes are expressed in pluripotent stem cells but not in parental MSCs. Moreover, iPSCs can obtain a secreted proteome similar to that of primary MSCs, which highlights their ability to conduct through paracrine signaling pathways. These suggest that human induced pluripotent stem cell-derived MSCs from older organisms may be able to "rejuvenate" [124].

Moreover, the aging of MSCs is considered to be one of the important triggers for the pathogenesis of OA [125]. YAP cooperates with the TEA domain transcription factor (TEAD) to activate the expression of Forkhead box D1 (FOXD1), a geo-protective protein [126]. The key role of the YAP-FOXD1 "young pathway" in human stem cell
de-aging and OA treatment was established. It confirms the feasibility of treating OA by introducing the “rejuvenation” factor of stem cells into the gene and provides a new solution for the intervention of aging-related diseases such as OA, with potential clinical transformation value [127]. Researchers have also found that chromobox protein homologue 4 (CBX4), a component of polycomb inhibitory complex 1 (PRC1), plays an important role in maintaining cell identity and organ development through gene silencing. First, CBX4 protein showed down-regulated expression in human premature aging MSCs, replicative aging MSCs, and primary MSCs isolated from elderly individuals, so the researchers cloned the gene coding sequence of CBX4 into the expression vector of lentivirus and introduced it into the aging human MSCs and found that these stem cells became more “young” and restored the rapid growth characteristics (Fig. 2). Researchers pointed out that this may be because CBX4 maintains nucleolar rDNA heterochromatin homeostasis by interacting with nucleolus and heterochromatin proteins, ensures proper transcription of rRNA, prevents protein over translation, and thus maintains the young state of cells [128]. This study reveals the key role of CBX4 in counteracting cellular senescence by maintaining nucleolar homeostasis and provides a potential therapeutic target for senescence-related diseases. Researchers have also reported that the DiGeorge syndrome critical region gene 8 (DGCR8), a key factor of the miRNA synthesis pathway, inhibits the senescence of human MSCs by stabilizing heterochromatin, providing a new potential intervention target for delaying organ senescence and preventing aging-related diseases. In this study, DGCR8-deficient human MSCs were also obtained by CRISPR/Cas9-mediated gene editing and stem cell directed differentiation. Further studies revealed that DGCR8 could form a complex with nuclear membrane protein Lamin B1 and heterochromatin proteins KRAB-association protein 1 (KAP1) and heterochromatin protein 1 (HP1) to participate in maintaining the stability of heterochromatin structure, thus maintaining the young state of human mesenchymal stem cells. At the same time, gene therapy based on DGCR8 over-expression can effectively inhibit the aging of mouse joint tissue, promote the regeneration of articular cartilage, and alleviate the pathological phenotype of injurious OA and senescent OA. This reveals a new approach for gene therapy of OA targeting DGCR8

Fig. 2 MSCs targeting ZKSCAN3, YAP, and DGCR8 genes were obtained by CRISPR/Cas9-mediated gene editing technology. Then, gene therapy was used to introduce these “stem cell anti-aging factors” to treat osteoarthritis, and studies have proved its feasibility. To treat osteoporosis, researchers have used a third-generation adenovirus vector (helper-dependent adenovirus vector). The two single nucleotides in exon three of the FOXO3 gene in human embryonic stem cells were replaced by gene editing technology, thus inhibiting the phosphorylation and degradation of FOXO3 protein in cells, promoting the aggregation of FOXO3 in the nucleus, and activating the expression of downstream target genes. It can effectively delay cell senescence, resist external stress, and enhance cardiovascular homeostasis.
replacement therapy (Fig. 2). This is another innovative discovery in the field of OA gene therapy following stem cell “young factor” CBX4 and “young pathway” YAP-FOXO1. These findings all prove the feasibility of introducing the “stem cell senescence factor” into gene therapy for OA and have potential clinical application value (Fig. 2). Recent studies have also indicated that exosomes (or similar particles) derived from MSCs may suppress OA development. This provides a new idea for the clinical treatment of OA [130] (Table 2).

Finally, studies have consistently shown that Forkhead box O (FOXO) transcription factors are important determinants of aging and longevity. And mammals have four FOXO genes: FOXO1, FOXO3, FOXO4, and FOXO6. Studies have shown that in BMSCs, the expression level of Forkhead box P1 (FOXO1) decreases with age, in contrast to the expression level of p16(INK4a), a marker of aging. Conditional depletion of FOXP1 in bone marrow MSCs leads to premature aging features, including increased bone marrow obesity, decreased bone mass, and impaired MSC. This suggests that FOXO1 may be a promising molecular target for delaying the senescence of MSCs and treating human osteoporosis [131] (Fig. 2). Forkhead box O3 (FOXO3) is closely related to delaying cell senescence, resisting external stress, and enhancing cardiovascular homeostasis [132]. Activation of FOXO3 can resist the malignant transformation of cells by inducing expression of tumor suppressor genes. The researchers eventually replaced two single nucleotides in exon 3 of the FOXO3 gene in human embryonic stem cells by gene editing using a third-generation adenovirus vector, helper-dependent adenovirus vector. Thus, it can inhibit the phosphorylation and degradation of FOXO3 protein in cells, promote the aggregation of FOXO3 in the nucleus, and then activate the expression of downstream target genes [133]. By comparing with wild-type cells, FOXO3-activated vascular cells exhibited delayed senescence and increased resistance to oxidative damage. This study provides insights into the mechanism of FOXO3-mediated vascular protection and suggests that FOXO3 activation may provide a method to generate more effective and safe biomaterials for cell replacement therapy (Fig. 2).

**Perspectives of MSCs in the treatment of clinical diseases**

MSCs are more and more widely used in clinical practice. In addition to the above-mentioned aspects, there are also the following aspects. For example, in future wound repair and plastic reconstruction, MSCs exist in normal skin and play a key role in wound healing. Exogenous implanted MSCs can promote the regenerative healing of injured skin. Exosomes, an effective component of MSCs, have attracted more and more attention in the field of wound healing and skin regeneration as a new and potential therapeutic method, and have put forward new prospects and expectations for future wound repair and plastic reconstruction [134–136]. Among them, exosomal microRNAs derived from MSCs can be used in cancer therapy, gene therapy, drug delivery, regenerative medicine, and some other biomedical applications. There are some limitations in the application of MSC, including the controversial use in the presence of tumor. MSC-derived exosomes have been suggested as possible cell-free substitutes for intact MSCs. If this view is proved, it will provide unlimited possibilities for the treatment of diseases in the future [137] (Table 2). In recent years, with the emergence of regenerative medicine, more and more studies on MSCs in the treatment of premature ovarian failure (POF), more and more studies have shown that MSCs have great clinical potential in the treatment of POF, but the relevant mechanisms need to be further elucidated [138–142] (Table 2). In terms of organ transplantation, studies have found that immune tolerance can be induced by the infusion of autologous BM-MSCs without taking immunosuppressive agents. This provides evidence for MSCs to solve the problem of transplant rejection in humans. It is believed that MSCs will be widely used in clinical organ transplantation through further research [143] (Table 2).

**The controversial clinical treatment of MSCs**

The definition of MSCs is not clear, and the lack of uniform molecular markers has led to the use of different molecular markers of MSCs in different laboratories. Moreover, MSCs contain too many cell types and have been associated with unproven medical applications, so it has been suggested to rename them as “multipotent mesenchymal stromal cells” [144, 145]. It has also been suggested to classify cells based on their surface proteins and to name them “medicinal signaling cells” because of their ability to transform into other cell types in vitro and to come to the site of injury [146–148]. Some MSCs are promising tools for tissue engineering and regenerative medicine; however, the cellular source of bone regeneration remains controversial [149]. Meanwhile, CRC radiotherapy for colorectal cancer can not only help kill cancer cells [150], but also rebuild the tumor microenvironment by enhancing the tumor specificity of BM-MSC [151–154]. However, the role played by in situ mesenchymal stem cells and recruited stem cells under radiotherapy conditions has not been fully elucidated. The influence of BM-MSC cells on tumor progression under non-radiotherapy conditions is still controversial: on one hand, BM-MSC can regulate immune cell function, leading to reduced immune sensitivity, leading to increased risk of tumor recurrence; on the other hand, it can also secrete a variety of cytokines, which have anti-cancer effects [155–157].
Conclusion

MSCs have good application prospects, and they have no or low immunogenicity, no MHC restriction, can induce host immune tolerance, reduce transplant rejection, and can be applied in tissue engineering, tissue and organ transplantation, gene therapy, immunotherapy, and so on in the future. And MSCs presumably also play a great role in COVID-19. It is believed that after further research by scientists, MSCs can play a significant role in the complex diseases facing human beings at present.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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