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*REVIEW*

# Factors affecting osteogenesis and chondrogenic differentiation of mesenchymal stem cells in osteoarthritis

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## Abstract

Osteoarthritis (OA) is a common degenerative joint disease that often involves progressive cartilage degeneration and bone destruction of subchondral bone. At present, clinical treatment is mainly for pain relief, and there are no effective methods to delay the progression of the disease. When this disease progresses to the advanced stage, the only treatment option for most patients is total knee replacement surgery, which causes patients great pain and anxiety. As a type of stem cell, mesenchymal stem cells (MSCs) have multidirectional differentiation potential. The osteogenic differentiation and chondrogenic differentiation of MSCs can play vital roles in the treatment of OA, as they can relieve pain in patients and improve joint function. The differentiation direction of MSCs is accurately controlled by a variety of signaling pathways, so there are many factors that can affect the differentiation direction of MSCs by acting on these signaling pathways. When MSCs are applied to OA treatment, the microenvironment of the joints, injected drugs, scaffold materials, source of MSCs and other factors exert specific impacts on the differentiation direction of MSCs. This review aims to summarize the mechanisms by which these factors influence MSC differentiation to produce better curative effects when MSCs are applied clinically in the future.

**Key Words:** Osteoarthritis; Mesenchymal stem cells; Differentiation; Hypoxia; Dexamethasone; Cell therapy

**Core Tip:** Several reviews have summarized the current status of mesenchymal stem cells (MSCs) in the treatment of osteoarthritis (OA). These studies usually focus on the paracrine function of MSCs. However, the differentiation function of MSCs also plays an important role in the treatment of diseases. This is the first review to report the factors that may affect the differentiation direction of MSCs in the treatment of OA and aims to provide guidance for more accurate regulation when MSC therapy is applied in the future.

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## INTRODUCTION

Osteoarthritis (OA) is one of the most common degenerative joint diseases, and its incidence increases with age[1]. With the rapid growth of the aging population, the prevalence of OA is increasing[2]. At present, there are more than 300 million OA patients worldwide[3]. The major symptoms of OA are pain and joint dysfunction, which seriously affect the quality of life of patients. Intra-articular microenvironment changes occur as OA develops. Due to tissue injury, severe hypoxia occurs in the joint cavity, and the expression level of hypoxia inducible factor 1 alpha increases significantly[4]. Many inflammatory cytokines infiltrate joints with OA, including interleukin-1 and tumour necrosis factor alpha (TNF-α). The expression of transforming growth factor-beta (TGF-β) in cartilage is significantly lower than that in healthy joints, which can lead to metabolic disorders of chondrocytes[5].

OA is an incurable disease at present, and cartilage degeneration and subchondral bone remodeling are considered the main pathogenic mechanisms of OA. There are no drugs that can delay the progression of OA[6]. The goal of clinical treatment is to relieve symptoms such as pain and loss of function[7]. The common treatments for OA include physiotherapy, pain relievers and nonsteroidal anti-inflammatory drug administration, intra-articular glucocorticoid injection and surgery. When OA progresses to the advanced stage, the only treatment option for most patients is total knee replacement surgery, which causes patients great pain and anxiety[8]. Some innovative new treatment options have been proposed, including mesenchymal stem cell (MSC) therapy.

Mesenchymal stem cells are a branch of stem cells, with the stem cell characteristics of self-renewal and differentiation potential[9]. MSCs can repair tissue damage after injury by differentiating into different tissue cells, so they can play an important role in disease treatment. In 1968, Professor Friedenstein[10] first discovered the existence of MSCs in bone marrow and established an adherent method to isolate and culture MSCs *in vitro*. Pittenger *et al*[11] proved for the first time that MSCs have multidirectional differentiation ability. Since then, MSCs have been widely studied and applied to the treatment of clinical diseases. In 2006, the International Society for Cell Therapy (ISCT)[12] established three minimal criteria for defining MSCs unequivocally: (1) The cells must have the ability to adhere to plastic surfaces when cultivated in standard conditions; (2) they must express CD105, CD73, and CD90, but not CD45, CD34, CD14/CD11b, CD79a/CD19, or HLA-D; and (3) they must have the ability to differentiate into at least the following cell types *in vitro*: Osteoblasts, adipocytes, and chondroblasts.

MSCs can be isolated from various tissues, such as bone marrow, adipose tissue, cord blood and placenta. MSCs from different sources have different characteristics[13]. At present, bone marrow MSCs (BMSCs) and adipose MSCs (ADSCs) are the most commonly used. Heo *et al*[14] found that only BMSCs and ADSCs have the ability to differentiate into three lineages, including osteoblasts, adipocytes and chondrocytes, to meet the minimum MSC standard proposed by the ISCT[15]. However, Beeravolu *et al*[16] believe that MSCs from the human umbilical cord and fetal placenta can also differentiate into three lineages.

At present, there are approximately 1519 studies on "mesenchymal stem cells" registered, according to clinicaltrials.gov (April 2023). MSCs have been used as cellular therapy for various degenerative, inflammatory and autoimmune diseases in a large number of clinical trials. These clinical trials include diseases of the musculoskeletal system, respiratory system, blood system and cardiovascular system and have already shown the effectiveness and safety of MSCs. These cells are most commonly used for the treatment of OA in the musculoskeletal system. At present, the pathogenesis of OA is not completely clear. A large number of studies have shown that subchondral bone destruction[17,18] and cartilage degeneration[19-21] participate in pathogenesis. Osteogenesis and chondrogenesis of MSCs play a key role in the treatment of OA.

Lamo-Espinosa *et al*[22] recruited 30 patients with OA and injected MSCs into the experimental group and hyaluronic acid (HA) into the control group. After 12 mo, magnetic resonance imaging (MRI) showed that the experimental group receiving the high dose of MSCs had a greater cartilage thickness, which is an indicator of the regeneration of cartilage in OA patients, than the control group. Tang *et al*

[23] injected MSCs into rabbit models of OA. Nine weeks later, the knee joints of the rabbits were collected and analyzed. They found that when MSCs were injected, the articular cartilage of the rabbit showed characteristics of good reconstruction, such as a regular surface, restored cartilage thickness, nearly normal chondrocyte morphology, and uniformly distributed red Safranin O staining in the articular cartilage. At present, no experiment has been performed on the differentiation of MSCs in isolated subchondral bone tissue. However, many similar studies that applied MSCs to bone defects have been performed and proved the feasibility of osteogenic differentiation of MSCs *in vivo*. For example, in the treatment of femoral head necrosis in the same hypoxic environment, after MSCs are implanted, the expression of bone-related genes is improved, and alkaline phosphatase and type I collagen are increased, which are indicators of bone formation[24]. MSCs are considered promising candidates for bone and cartilage repair and regeneration in OA. But the differentiation of transplanted MSCs is influenced by the microenvironment. Therefore, this article reviews the factors affecting the osteogenesis and chondrogenesis of MSCs (Figure 1).

## MECHANISM OF OSTEOGENIC AND CHONDROGENIC DIFFERENTIATION OF MSCS

The differentiation of MSCs depends on a number of factors, including chemical, physical and biological factors. These factors activate different signaling pathways and transcription factors that regulate MSC differentiation into different cells[25]. The differentiation of MSCs is precisely controlled by various signaling pathways[26]. These signaling pathways activate lineage-specific transcription factors[27].

Chondrogenesis and osteogenesis of MSCs are interrelated processes. There are two ways for MSCs to form bone: Endochondral or intramembranous ossification. In endochondral ossification, MSCs first differentiate into chondrocytes and secrete cartilage matrix, and then they are stimulated by osteoblasts to form bone. In contrast, in intramembranous ossification, MSCs differentiate into osteoblasts directly [28]. Therefore, there are some common signaling pathways and transcription factors involved in the osteogenic differentiation and chondrogenic differentiation of MSCs.

TGF-β signaling, Wnt/β-catenin signaling and Notch signaling are the key pathways involved in chondrogenic differentiation of MSCs. The key cytokines include Sox9, Runx2, TGF-β, FGF and others [29]. Sox9 plays an essential role during chondrogenic differentiation and is considered an early sign of chondrocyte formation. Complete deletion of Sox9 can prevent the formation of cartilage. When it is overexpressed, it significantly inhibits the proliferation of chondrocytes[30]. Sox9 is a regulator of the type II collagen (*ColII*) gene, which is a specific marker of cartilage formation. The expression of *ColII* in chondrocytes has been found to be in direct proportion to the concentration of Sox9[31]. TGF-β can promote the differentiation of MSCs into chondrocytes and inhibit the terminal differentiation of chondrocytes into mast cells[32]. The differentiation of chondrocytes induced by TGF-β is mainly mediated by the Smad signaling pathway[33], which can upregulate the expression of Sox9 transcription factors and promote the synthesis of collagen and proteoglycan.

The main paracrine signaling pathways involved in the osteogenic differentiation of MSCs include bone morphogenetic protein (BMP) signaling, Wnt signaling, and Notch signaling[28,34-36]. The key transcriptional regulatory factors include Runx2, β-catenin, and osterix[27]. Runx2 is indispensable for the osteogenic differentiation of MSCs because it is a common convergence point for many signaling pathways[25,37]. It leads to the differentiation of MSCs into osteoblasts and inhibits the differentiation of adipogenesis and chondrogenesis. Runx2 promotes the differentiation of MSCs into osteoblasts in the early stage and promotes the maturation and mineralization of osteoblasts in the later stage by regulating extracellular matrix proteins, such as ColI and alkaline phosphatase (ALP). When Runx2 is absent, neither periosteal nor endochondral ossification occurs[38]. BMP2 is also an effective osteogenic induction factor that promotes the expression of Runx2, thus promoting the differentiation and maturation of osteoblasts[28]. Osterix is an osteoblast-specific transcription factor that is only expressed in osseous tissue and plays a decisive role in the differentiation of MSCs into osteoblasts[39]. Activation of the Wnt signaling pathway induces osterix expression. Overexpression of osterix in MSCs leads to osteogenic differentiation and an enhanced bone regeneration ability of MSCs[40]. The activity of β-catenin is also regulated by Wnt signaling. β-catenin can facilitate the shift of MSC fate to osteoblasts and enhance endochondral ossification. Its deficiency hinders the osteogenesis of MSCs and promotes the formation of cartilage and fat[41,42] (Figure 2).

## FACTORS AFFECTING THE OSTEOGENIC AND CHONDROGENIC DIFFERENTIATION OF MSCS IN THE MICROENVIRONMENT OF OA

### *Oxygen concentration*

The effect of oxygen concentration on MSCs has been studied for over twenty years (hypoxia promotes murine bone marrow-derived stromal cell migration and tube formation). Although there are still some controversies, a large number of studies have proven that low oxygen tension (hereinafter "hypoxia")

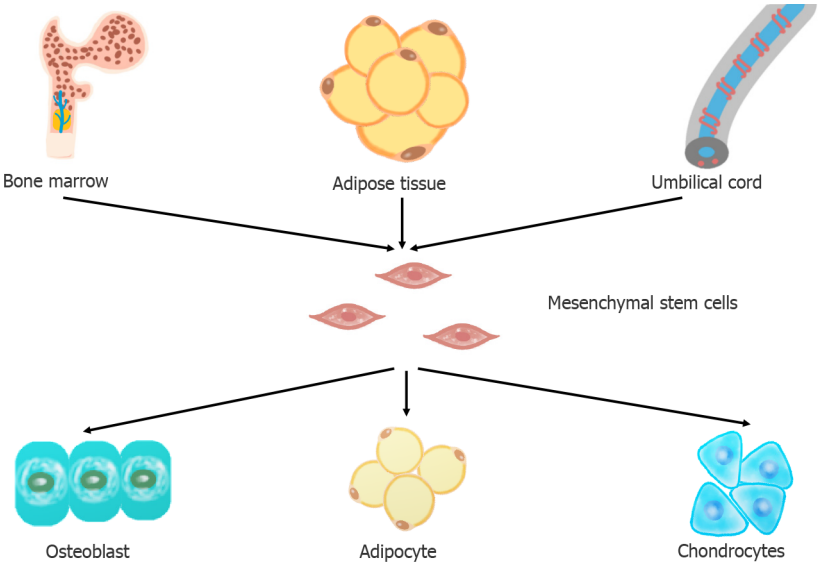


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**Figure 1 Common sources and differentiation potential of mesenchymal stem cells.**

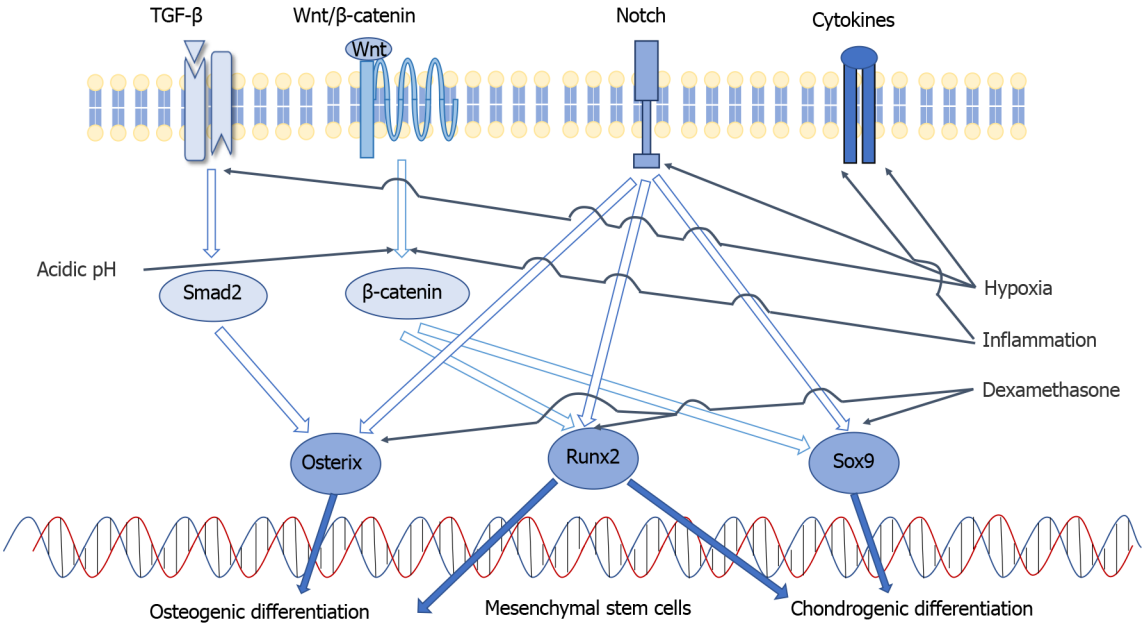


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**Figure 2 Signaling pathways involved in osteogenic and chondrogenic differentiation of mesenchymal stem cells and the mechanism of certain factors.** TGF-β: Transforming growth factor-beta.

exerts a significant impact on the differentiation of MSCs. Hypoxia often occurs in the stem cell microenvironment, which induces beneficial signals, such as upregulation of pluripotency markers, for MSCs to maintain their functions[43]. In the general microenvironment *in vivo*, the oxygen concentration is usually low. For example, the oxygen concentration in healthy bone marrow is only 1.3% to 7.0%[44], and that in articular cartilage is only 2% to 5%[45]. In particular, OA often occurs in a hypoxic environment. Nitric oxide synthase and hypoxia-inducible factor-1 are often upregulated in OA and aggravate the hypoxic environment[46]. Although the oxygen concentration in the microenvironment of MSCs is low, a 21% $O_2$ concentration (hereinafter "normoxia") is routinely used in cell culture.

Ciapetti *et al*[22] isolated and cultured BM-MSCs under 2% $O_2$. They observed a higher tendency of osteogenic differentiation of these cells compared with the cells cultured in standard normoxia. Significant changes in the MSC immunophenotype, such as increased CD73 and CD90 expression, were observed, but CD105 expression was reduced. MSCs cultured under hypoxia have better mineralization, higher mineral density and higher calcium matrix deposition than those cultured under normoxia.

Alizarin red S staining is a convenient method for detecting calcium salt deposition. The positive area observed in hypoxic cultured MSCs was greater than that in cells cultured in normoxia, which means that osteoblast differentiation was enhanced[47,48]. Fennema *et al*[49] found that hypoxic culture increased the levels of osteogenic genes, such as osteopontin, osteocalcin, ALP and ColI[50]. Hypoxia activates the Notch signaling pathway, increases the expression of CBF-1α, and promotes the osteogenic differentiation of MSCs[51,52].

Similarly, hypoxic conditions increased the chondrogenic differentiation efficiency compared to normoxic conditions. Chondrogenic differentiation of MSCs can be quantitatively assessed by Safranin O staining[53,54], and the positive area increases after hypoxic culture. Immunohistochemistry demonstrated that the expression of *ColII* increased[50]. Hypoxia may enhance the chondrogenic differentiation capacity of MSCs by enhancing the expression of chondrogenic genes[55]. This may be manifested as increased mRNA expression of glycosaminoglycans, aggrecan, transcription factor and Sox9[56,57]. The level of cartilage oligomeric matrix protein is higher under hypoxic conditions[53]. These factors play crucial roles in chondrocyte differentiation. Hypoxia affects the overall cellular response through TGF-β, leading to upregulation of cartilage molecular markers, such as *ColII* and Sox9 [58]. However, some studies have shown that hypoxia can enhance chondrogenesis and inhibit osteogenesis of MSCs[59,60]. These differences between studies may be due to differences in culture conditions and sources of MSCs and therefore larger sample sizes and more precise experiments are required to fully elucidate the effect of hypoxia on MSC differentiation.

### Inflammation

OA was once referred to as noninflammatory arthritis, but it is now considered a persistent low-grade inflammatory disease, and many inflammatory cells are involved[61]. Chronic inflammation activates the Wnt/β-catenin pathway, which leads to mitochondrial damage and further impairs the differentiation of MSCs[62]. Interferon-gamma (IFN-γ) and TNF-α are two important inflammatory cytokines involved in OA inflammation[63]. Li *et al*[64] pretreated MSCs with IFN-γ and TNF-α to simulate the inflammatory microenvironment. They found that the inflammatory microenvironment promoted chondrogenic differentiation of MSCs and inhibited their osteogenic differentiation.

### Acidic pH

Inflammation decreases the extracellular pH and makes the OA joint cavity a weakly acidic microenvironment[65]. The pH of joints with OA (6.40 ± 0.08) was obviously lower than that of normal joints (7.01 ± 0.26)[66]. Decreasing pH was shown to inhibit the proliferation and metabolism of MSCs in culture. Furthermore, the activity of alkaline phosphatase was reduced, which means that the osteogenic differentiation of MSCs was decreased[67]. At physiologic pH (8.0), MSCs exhibit the strongest osteogenic differentiation potential[68]. A pH of 8.0 is recommended for a greater therapeutic effect of MSCs in OA.

### Osmolar pressure

The osmolar pressure in the joint cavity of healthy adults is 404 mOsm/L ± 57 mOsm/L, while that in OA patients is 297.0 mOsm/L ± 16.9 mOsm/L. The joint cavity of OA patients is exposed to a hypoosmotic environment[69,70]. At present, there is little research on the effect of osmotic pressure on the osteogenic and chondrogenic differentiation of MSCs. Some studies have demonstrated that hyperosmolarity promotes the chondrogenic differentiation of MSCs and cartilage repair[71-73]. No study on the effect of hypo-osmotic stress has been conducted.

### Cytokines

In contrast to normal bone, subchondral bone in advanced OA is characterized by osteosclerosis, including a higher bone volume fraction, a greater number of trabecular bones in the load-bearing area, and an increase in the thickness of the original trabeculae. This may be due to the overexpression of growth factors in the joints of patients with OA, such as insulin-like growth factor 1 and TGF-β[74]. Both of these cytokines have been shown to promote osteogenic and chondrogenic differentiation of MSCs [75,76]. The local expression of basic fibroblast growth factor (bFGF) in the joints of patients with OA is significantly higher than that in healthy people[77]. bFGF has been proven to be an important growth factor for maintaining the stemness of MSCs[78].

## OTHER COMMON INFLUENCING FACTORS IN THE TREATMENT OF OA

### Glucocorticoids

Dexamethasone is a member of the glucocorticoid class, and it is considered to be the mildest corticosteroid drug used for OA treatment[79]. Intra-articular injection of glucocorticoids is one of the treatment methods for OA[80], and dexamethasone can also be used as an immunosuppressive agent for MSC transplantation. Moreover, dexamethasone is generally considered one of the main components that induces MSCs to differentiate toward osteogenic, adipogenic and chondrogenic lineages[81]. The

osteogenic differentiation of MSCs mainly relies on osteogenic induction medium, which is usually composed of dexamethasone, ascorbic acid and β-sodium glycerophosphate. Dexamethasone induces increased expression of Runx2, osterix, and bone matrix proteins. Furthermore, it can induce osteogenic differentiation by inhibiting Sox9 expression[82]. Ascorbic acid and β-sodium glycerophosphate increase the content of ColI and stimulate the formation of a mineralized matrix[11]. Human MSCs need dexamethasone to produce ALP, a marker used to distinguish osteoblasts in culture[83,84]. The chondrogenic differentiation medium often includes dexamethasone, ascorbic acid and TGF-β3. Dexamethasone enhances the expression of the cartilage-specific gene Sox9[85]. The adipogenic differentiation medium often contains dexamethasone, ascorbic acid, 3-isobutyl-1-methylxanthine, insulin and other components[86]. Although the detailed mechanism of differentiation induced by dexamethasone is currently unknown, dexamethasone clearly affects the direction of MSC differentiation [87].

Doi *et al*[88] found that dexamethasone had certain effects on the osteogenic differentiation of MSCs. The effect of dexamethasone on inducing MSCs to differentiate into osteoblasts depends on the dosage and exposure time of the drugs[89]. It has been reported that short-term use of low-dose ($10^{-8}$, $10^{-7}$ mol/L) dexamethasone can stimulate the osteogenesis of MSCs and significantly increase the formation of mineralized nodules and the expression of osteogenic markers (BSPII and Runx-2) in cells[90,91]. It has also been reported that high concentrations of dexamethasone ($10^{-6}$ mol/L) can inhibit the osteogenic differentiation of MSCs and induce them to differentiate into adipocytes. A high dose can reduce the osteogenic differentiation-related surface phenotype, as indicated, for example, by decreased surface expression of CD73. The higher concentration of dexamethasone resulted in enhanced lipid droplet formation and higher expression of lipid-forming markers (PPAR-γ and CEBP-α) in cells. In addition, a high concentration of dexamethasone exacerbates apoptosis of MSCs, inhibits MSC proliferation, and promotes senescence of MSCs[83]. A concentration of dexamethasone up to $10^{-6}$ mol/L imposes toxic effects on MSCs[89,92]. When the concentration of dexamethasone was lower than $10^{-8}$ mol/L, no differentiation of osteoblasts was detected[93,94]. Therefore, $10^{-7}$ mol/L is considered the most appropriate concentration for inducing MSCs to differentiate into bone[91].

Similarly, dexamethasone can also promote chondrogenic differentiation of MSCs[93]. Tangtrongsup *et al*[95] found that chondrogenic differentiation was suppressed in dexamethasone-free cultures. It can increase the proteoglycan content and collagen type II intracellular content. Dexamethasone may not function as a specific chondrogenic factor to directly promote cartilage differentiation, rather, it may promote it by inducing cells to upregulate cartilage factors, such as Runx2 and Noggin[96]. Its influence is mainly dependent on the context[97].

In addition to the dosage, the duration of dexamethasone treatment also affected the differentiation of MSCs. Dexamethasone is commonly used in bone trauma to relieve edema and pain, but long-term use may lead to osteoporosis through bone loss and bone marrow lipogenesis. Some studies suggest that long-term exposure of MSCs to dexamethasone may negatively impact their differentiation[91]. Others found that a lack of dexamethasone inhibits the differentiation of MSCs, so continuous delivery *in vivo* should be given priority[95]. Moreover, Song *et al*[98] found that within 4 wk, as exposure time increased, stimulation of osteogenic differentiation by dexamethasone strengthened, and calcium deposition increased. According to some authors, the sensitivity of MSCs to dexamethasone depends on the stage of cell maturation. Dexamethasone mainly acts on early stem cells, so it should be applied in the early stage[84]. It has also been suggested that early exposure to dexamethasone has little effect on MSC differentiation, and thus, continuous exposure for at least one week is required[89]. At present, there is little research on the effect of the duration of dexamethasone exposure on MSC differentiation, and more accurate experiments are needed to verify this hypothesis. As a glucocorticoid, dexamethasone is not suitable for systematic use to regenerate local tissue defects due to possible negative effects on healthy tissues and organs. Therefore, the application of local controlled release devices of dexamethasone in MSC therapy is reasonable.

### Scaffolds

MSCs can be injected directly into the damaged site or differentiate into target cells together with the tissue engineering scaffold. Many tissue engineering experiments have proven that biological scaffolds can enhance the osteogenic and chondrogenic differentiation of MSCs. HA is often used to form a stable 3D environment for MSC chondrogenesis *in vitro*, which allows for better provision of oxygen and nutrients to MSCs. HA can promote the osteogenic process of endochondral ossification of MSCs[99]. Three-dimensional nanofibrous scaffolds, such as poly-((D,L)-lactide-ε-caprolactone)dimethacrylate scaffolds and poly(-caprolactone) nanofibrous scaffolds, have been shown to enhance chondrogenic differentiation of MSCs[100,101]. The combination of MSCs with biomaterials can improve the differentiation ability of MSCs. These studies have demonstrated that better efficacy can be achieved by injection of scaffolds loaded with MSCs.

### Sources of MSCs

The source of MSCs also significantly impact their differentiation. By reviewing clinical trials, we found that bone marrow-derived MSCs (BM-MSCs), adipose tissue-derived MSCs (AD-MSCs) and umbilical cord-derived MSCs (UC-MSCs) are mainly used in OA research. MSCs from different sources have

different characteristics and differentiation potentials[102].

BM-MSCs offer the advantages of strong differentiation ability, mild implantation reaction and strong expansion ability *in vitro*. However, BM-MSCs need to be obtained from the patient's bone marrow, and bone marrow collection is a painful and invasive process. The number of BM-MSCs derived *in vivo* is quite low and requires *in vitro* amplification. Moreover, the differentiation potential and proliferative capacity of BM-MSCs decrease with the age of the donor[103]. Adipose tissue was first identified as an alternative source of MSCs in 2001[104,105]. AD-MSCs offer the advantage that they can be obtained in large quantities in a simple, minimally invasive manner. They can be extracted from excess adipose tissue that is discarded as waste during liposuction, avoiding immunogenicity and ethical concerns. The quantity and quality of MSCs from adipose tissues were significantly higher than those of other tissues [106]. Some studies have suggested that the differentiation potential of AD-MSCs depends on the source of adipose tissue[107]. MSCs from visceral adipose tissues have greater osteogenic differentiation capacity[108,109]. UC-MSCs exhibit superior clonogenic, proliferation and migration capacities[43,110]. They can secrete relevant chondrogenic factors[111,112]. Furthermore, UC-MSCs are less mature, which makes them a better choice for allogeneic therapy[113]. Wharton's jelly (WJ) is the most frequently used source of umbilical cord tissue[114]. WJ-MSCs are relatively novel for cell and tissue engineering therapy and are considered promising candidates for the development of cell-based therapies[113,115].

Many studies have shown that BM-MSCs have higher osteogenic and chondrogenic differentiation potential[116,117]. They exhibit a relatively high incidence of bone and cartilage formation[50], and they can generate more mature bone tissue and more compact cartilage pellets[118]. BM-MSCs express high levels of CD90, which means that they are more suitable for bone repair and regeneration[119].

AD-MSCs are more inclined to differentiate into adipocytes, and their potential for osteogenic differentiation and chondrogenic differentiation is relatively low[107]. Some studies hypothesize that the chondrogenic potential of MSCs derived from adipose tissue is higher than that of MSCs derived from UC sources[120]. However, other studies have suggested that AD-MSCs and UC-MSCs show similar chondrogenic potential[110].

Although BM-MSCs have stronger differentiation ability, AD-MSCs and UB-MSCs perform better for pain relief and functional improvement in OA[121]. AD-MSCs are considered the most effective MSCs in relieving pain, while UC-MSCs are considered the most effective MSCs in improving function in OA patients[122]. Therefore, AD-MSCs and UC-MSCs showed better anti-arthritis efficacy than BM-MSCs [123].

## CONCLUSION

In this review, we summarize the common factors that affect the differentiation of MSCs in the OA microenvironment. MSCs can differentiate into different lineages, and these processes are precisely regulated by signaling pathways. Many factors can affect the differentiation direction of MSCs by acting on these signaling pathways. The multidirectional differentiation potential and tunability of MSCs make them a promising treatment for OA and other diseases. A large number of studies have confirmed their safety and effectiveness.

At present, a large number of studies focus on the paracrine effect of MSCs. However, the differentiation function of MSCs can also play an important role in disease treatment. Chemical, physical and biological factors can affect the differentiation of MSCs. Therefore, there are many conditions that can affect the efficacy of MSCs. To control the differentiation of MSCs more precisely to improve their efficacy in the treatment of diseases, it is necessary to understand how various influencing factors work. However, there are few studies on the factors that affect the differentiation direction of MSCs, and we are still at a preliminary stage in understanding how these factors determine the fate of MSCs. More research is needed on the differentiation of MSCs, which is of great value for developing novel therapies for diseases and applying MSCs to clinical practice.

## FOOTNOTES

**Author contributions:** Yi P wrote the paper; Hai J reviewed the literature; Zuo HD designed the outline and coordinated the writing of the paper; and all authors have read and approved the final manuscript.

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