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Review

Revolutionizing osteoarthritis treatment: How mesenchymal stem cells hold the key

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ABSTRACT

Osteoarthritis (OA) is a multifaceted disease characterized by imbalances in extracellular matrix metabolism, chondrocyte and synoviocyte senescence, as well as inflammatory responses mediated by macrophages. Although there have been notable advancements in pharmacological and surgical interventions, achieving complete remission of OA remains a formidable challenge, oftentimes accompanied by significant side effects. Mesenchymal stem cells (MSCs) have emerged as a promising avenue for OA treatment, given their ability to differentiate into chondrocytes and facilitate cartilage repair, thereby mitigating the impact of an inflammatory microenvironment induced by macrophages. This comprehensive review aims to provide a concise overview of the diverse roles played by MSCs in the treatment of OA, while elucidating the underlying mechanisms behind these contributions. Specifically, the roles include: (a) Promotion of chondrocyte and synoviocyte regeneration; (b) Inhibition of extracellular matrix degradation; (c) Attenuating the macrophage-induced inflammatory microenvironment; (d) Alleviation of pain. Understanding the multifaceted roles played by MSCs in OA treatment is paramount for developing novel therapeutic strategies. By harnessing the regenerative potential and immunomodulatory properties of MSCs, it may be possible to devise more effective and safer approaches for managing OA. Further research and clinical studies are warranted to optimize the utilization of MSCs and realize their full potential in the field of OA therapeutics.

1. Introduction

Osteoarthritis (OA) is a degenerative joint disease causing stiffness, pain, cartilage defects, and osteophyte hyperplasia [1]. The development of OA is mainly due to chondrocyte senescence and excessive extracellular matrix metabolism in cartilage. Current drug treatments, such as non-steroidal steroids, are limited to providing temporary relief from painful symptoms, without effectively halting the progression of the underlying condition [2]. Surgical treatment, such as total joint replacement, can result not only in heavy economic burdens for patients

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but also in serious sequelae. As a result, it is crucial to investigate an effective remedy for OA.

Articular cartilage only covers the surface of mature bones in joints. It has a unique development process that results in the absence of blood and lymphatic vessels, and the extracellular matrix makes up 95% of articular cartilage [3]. Due to this, articular chondrocytes are always in a low-oxygen environment and are unable to absorb nutrients efficiently [4]. According to the different mechanical forces, chondrocytes can be divided into three parts: 1) surface cartilage, 2) middle cartilage, and 3) deep cartilage. There are some differences in the secretion of lubricants and other factors among the three kinds of cells. Still, they all maintain the balance of synthesis and metabolism of cartilage extracellular matrix in a low turnover way [5]. Articular chondrocytes account for only 5% of articular cartilage and are very stable, meaning they do not divide frequently. Too low quantities and a unique living environment make the extracellular matrix challenging to repair once degraded [6]. In joints, the immune response relies heavily on macrophages as no lymphatic vessels are present in the joint cavity. One of the main reasons for the continuous progression of osteoarthritis is its mediated non-specific immunity [7].

Mesenchymal stem cells (MSCs) are a type of pluripotent stem cells that possess self-renewal solid abilities and have the potential to differentiate in multiple directions [8]. Currently, there are three major types of extensive research being conducted: Bone marrow mesenchymal stem cells (BMSCs), adipose-derived mesenchymal stem cells (ADMSCs), and umbilical cord mesenchymal stem cells (UCMSCs) [9]. Multiple studies have demonstrated that mesenchymal stem cells are a promising treatment option for osteoarthritis [10,11]. They can potentially reduce inflammation, suppress the expression of inflammatory factors and enhance the production of anti-inflammatory factors [12]. This article aims to review the role of MSCs in treating OA from different perspectives. These include: (a) Promotion of chondrocyte and synoviocyte regeneration: MSCs have been shown to stimulate the regeneration of damaged chondrocytes and synoviocytes, thereby restoring the integrity and functionality of the affected tissues. (b) Inhibition of extracellular matrix degradation: By modulating the activity of matrix metalloproteinases and other detrimental enzymes, MSCs can impede the degradation of the extracellular matrix, which is a key driver of OA progression. (c) Attenuating the macrophage-induced inflammatory microenvironment: MSCs suppress the polarization of macrophages towards the pro-inflammatory M1 phenotype and promote their transition to the anti-inflammatory M2 phenotype. (d) Alleviation of pain: MSCs have been found to alleviate pain associated with OA through their secretion of analgesic factors, thereby improving the quality of life for patients (Fig. 1).

2. MSCs promotes chondrocyte and synoviocyte regeneration

Cellular senescence is a major characteristic of aging and contributes to many diseases, such as the progression of OA [13]. Senescent cells release numerous pro-inflammatory factors, such as IL-1 and TNF family members, through paracrine signaling [14]. Moreover, mitochondrial dysfunction leads to the accumulation of excessive ROS in and around the microenvironment, creating an inflammatory and oxidative stress milieu that perpetuates a negative feedback loop [15,16]. In addition, senescent cells are unable to perform their normal biological functions. For instance, chondrocyte senescence significantly decreases extracellular matrix synthesis and secretion, which cannot compensate for its excessive degradation, leading to cartilage structure destruction and loss of biomechanical function [17]. The extracellular cartilage matrix provides the joint with resistance to shear stress and elasticity [18]. More importantly, synovial cells also secrete lubricating fluids that play a crucial role [19,20].

2.1. MSCs inhibit the senescence of chondrocytes

Various evidence shows that the aging of chondrocytes is closely related to osteoarthritis, which also occurs with age. Patients with osteoarthritis often show signs of chondrocyte aging, which is attributed to either replicative aging or stress-induced premature aging [21]. These aging mechanisms involve chondrocyte aging due to telomere shortening and apoptosis via p53/p21 and p38 MAPK/PI3K/Akt pathways [21]. MSCs have been identified as having a significant potential for delaying the aging process of tissues and organs. Col-X, a marker associated with cartilage calcification, chondrocytes hypertrophy [22,23] and age-related OA [24], has also been found to be up-regulated in monosodium iodoacetate (MIA)-induced OA [25]. However, it has been demonstrated that treatment with UCMSCs can effectively reduce the

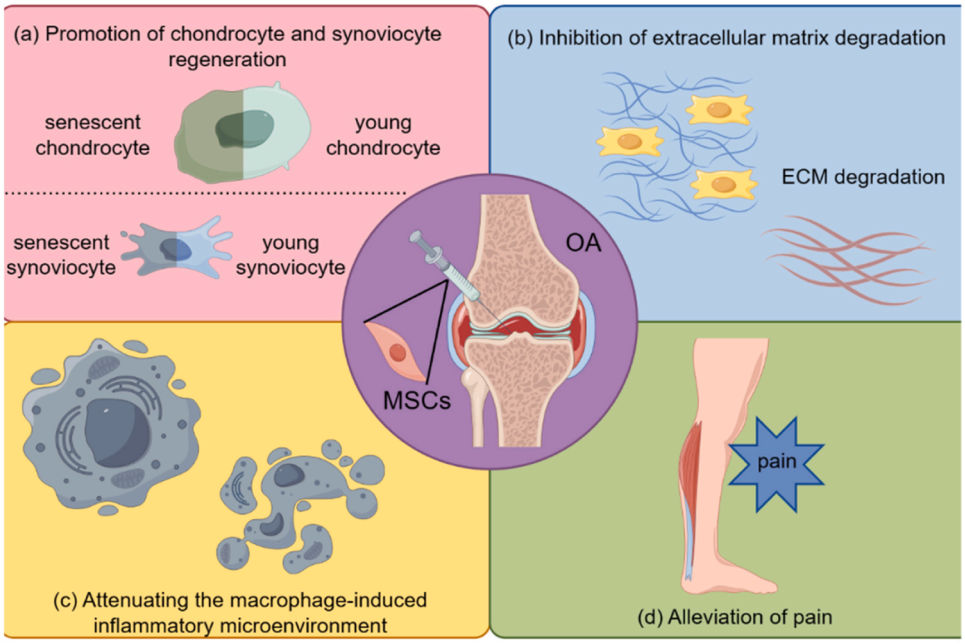

Fig. 1. Mesenchymal stem cells in treating osteoarthritis by (a) Promotion of chondrocyte and synoviocyte regeneration; (b) Inhibition of extracellular matrix degradation; (c) Attenuating the macrophage-induced inflammatory microenvironment; and (d) Alleviation of pain. By Figdraw.

expression of Col-X to normal levels. This reduction in Col-X expression suggests that UCMSCs treatment has the potential to alleviate the catabolic state of chondrocytes [25]. BCL-2, a known regulator of apoptosis, plays a crucial role in inhibiting programmed cell death [26]. Also, studies have shown that BCL-2 is involved in the regulation of senescence-associated cell cycle arrest and has been implicated in the control of the senescent secretome [27]. Following treatment with MIA, chondrocytes typically experience increased apoptosis [25]. However, co-culture of chondrocytes with UCMSCs has been shown to effectively promote the expression of BCL-2 [28]. This up-regulation of BCL-2 subsequently leads to the inhibition of chondrocyte apoptosis [28], suggesting that UCMSCs treatment can exert a protective effect on chondrocytes in anti-senescence. In another study conducted by Lv et al., it was proposed for the first time that MSCs can potentially achieve this by promoting mitochondrial autophagy, thereby regulating the homeostasis of cell metabolism [29]. In addition, studies on cartilage have proved that MSCs can stimulate chondrocytes to produce collagen and other matrix molecules by secreting growth factors such as cytokines TGF-β, IGF-1, and SDF-1, promote the synthesis of cartilage matrix, and then affect the aging process of chondrocytes [30–32]. In addition to secreting growth factors, MSCs can effectively reduce the inflammatory response of cartilage tissue by releasing anti-inflammatory factors and antioxidant substances, such as IL-10, to protect chondrocytes from oxidative damage and delay the aging process [33]. In addition, extracellular vesicles (EVs), such as exosomes derived from MSCs, have been found to have a beneficial therapeutic effect on OA. Studies have shown that TGF-β1–induced BMSC-derived exosomes effectively inhibit the progression of osteoarthritis in OA model mice [23]. Isolated EVs from the higher ratio of chondrocytes co-cultured with MSCs exhibit superior chondrogenic potential for OA treatment [34].

2.2. MSCs delay the senescence of synovial cells

Synovium is a membrane that lines the articular cavity and produces synovial fluid, which lubricates and nourishes articular cartilage [35]. As we age, synovial cells undergo cell aging, resulting in irreversible growth stagnation and accelerating the progression of chronic inflammation and age-related joint diseases such as OA [13]. The typical senescence-associated secretory phenotype (SASP) of synovial cells involves the release of proinflammatory cytokines and chemokines [13]. Research has shown that MSCs can affect the senescence of synovial cells and have multifaceted interactions with them. Osteoarthritis synovial fibroblasts presented downregulated pro-inflammatory and pro-catabolic genes on exposure to MSCs in the short term [36]. More importantly, UCMSCs produce bioactive molecules that function in different species and modify inflammation and matrix turnover genes, including MMP-1, MMP-3, MMP-13, TIMP1, and IL1-β in synoviocytes [37]. In total, MSCs can delay synovial cell senescence by inhibiting the pro-inflammatory environment through their anti-inflammatory effects.

2.3. The MSCs differentiate into chondrocytes

MSCs have demonstrated their capacity for differentiation into chondrocytes for many years. In addition to the differentiation potential, MSCs can also produce many nutritional factors, including growth factors, cytokines, and chemokines through the paracrine pathway, which can stimulate MSCs to differentiate into cartilage [38]. Different sources of MSCs may show different differentiation potential and mechanisms, especially when generated into different scaffolds or biomaterials [39–41]. The differentiation of MSCs into chondrocytes involves several signaling pathways, particularly in certain circumstances. As indicated by Uzieliene et al., TGF-β and BMP-2 are functional in MSC condensation, proliferation, differentiation, and maturation, while FGF-2 is important in MSC condensation and proliferation (Fig. 2) [42]. TGF-β families can promote the expression of cartilage matrix-related genes Collagen II and Aggrecan by activating the Smad2/3 signaling pathway [43,44]. During the expansion phase of fat pad-derived MSCs, activation of Wnt signaling promotes proliferation, reduces senescence, and improves stemness. Conversely, during the differentiation phases of MSCs, inhibiting Wnt signaling generates cartilage that resembles hyaline and has minimal hypertrophy when done *in vitro* [45]. Bone marrow is also one of the commonly used sources of MSCs. Compared with ADMSCs, BMSCs often show some different characteristics in cartilage differentiation. Transfection of the IHH gene into BMSCs effectively promotes cartilage formation while inhibiting osteogenesis and cartilage aging [46]. In addition, miRNA has also been found to regulate the cartilage differentiation of MSCs by targeting the expression of critical genes. Indeed, it has been observed that certain miRNAs can exert a suppressive effect on the chondrogenesis of MSCs by targeting key factors involved

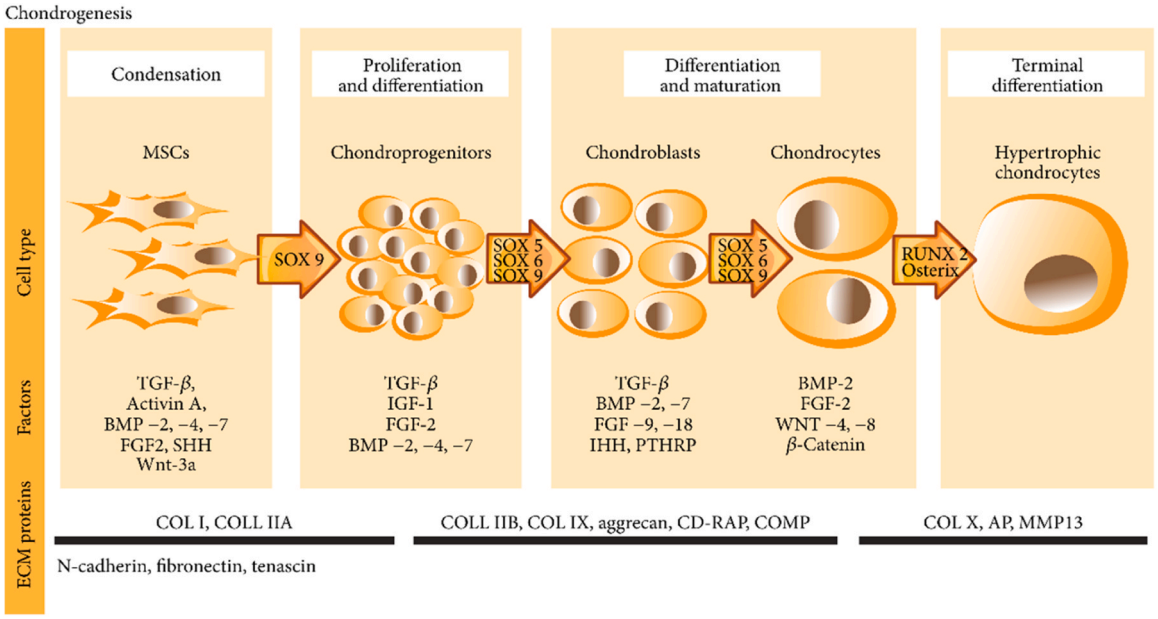

Fig. 2. The differentiation of MSCs into chondrocytes involves several signaling pathways, particularly in certain circumstances. Adapted with permission from ref [42]. Copyright © 2018 I. by the authors. Licensee Hindawi. CC-BY-4.0.

in this process, such as SOX9 (miR-145 and miR-495), BMPR2 (miR-143–3p and miR-125b), FOXO3A (miR-29a), LEF-1 (miR-449a), HDAC4 (miR-29b), SMAD4 (miR-483), RXRα (miR-574–3p), TRPS1 (miR-221), Mdm2 (miR-221), WNT (miR-26b) and FGF2 (miR-23c). Conversely, there are miRNAs that have been found to enhance the chondrogenesis of MSCs by downregulating the expression of negative regulators of chondrogenesis, such as CDK6 (miR-320c), HDAC2/8 (miR-95–5p), RALA (miR-140–5p), FZD6 (miR-140–5p), FUT-1 (miR-149–5p), GALNTL1(miR-140–5p), DLL4 (miR-30a), HDAC3 (miR-193b-3p), SMAD7 (miR-526b-3p and miR-590–5p), KLF10 (miR-892b), Daam-1 (miR-355–5p), ROCK1 (miR-355–5p), DKK1 (miR-355–5p) and ADAMTS5 (miR-132–3p). The intricate interplay between these miRNAs and their target genes underscores the complex regulatory network governing the chondrogenic differentiation of MSCs (Fig. 3) [47]. It has been observed from the aforementioned evidence that MSCs possess a significant potential for effective differentiation into chondrocytes. However, the process of cartilage differentiation in MSCs can be influenced by various factors such as the cell source, signaling pathways, and regulatory factors. Ongoing research endeavors are focused on developing efficient differentiation techniques and identifying suitable materials for this purpose [40]. With these advancements, MSC therapy will be able to evolve into a practical treatment for OA patients.

3. MSCs can inhibit the degradation of extracellular matrix of cartilage

Cartilage extracellular matrix (ECM) constitutes 95% of the total articular cartilage, and its primary components are proteoglycan, collagen, water, minerals, and fibrin, which confer strong biomechanical properties to articular cartilage [48]. Proteoglycan enhances the osmotic pressure of the cartilage extracellular matrix, endowing articular cartilage with elasticity and compressive ability [49]. Collagen is aligned parallel to the joint surface, enabling articular cartilage to resist shear stress [50]. Despite chondrocytes itself only repair the extracellular matrix at a low turnover rate, the presence of an inflammatory and oxidative stress microenvironment leads to continuous excessive degradation of chondrocyte extracellular matrix, far exceeding the degree of chondrocyte repair. Therefore, delaying the degradation of cartilage extracellular matrix and promoting its repair are crucial for treating OA.

The imbalance between anabolism and catabolism of articular chondrocytes results in excessive degradation of functional ECM, releasing a large number of matrix degrading enzymes, including MMP13 and ADAMTS-4 and –5 [51]. MMPs are zinc-dependent endogenous proteases that play multiple roles in tissue remodeling of

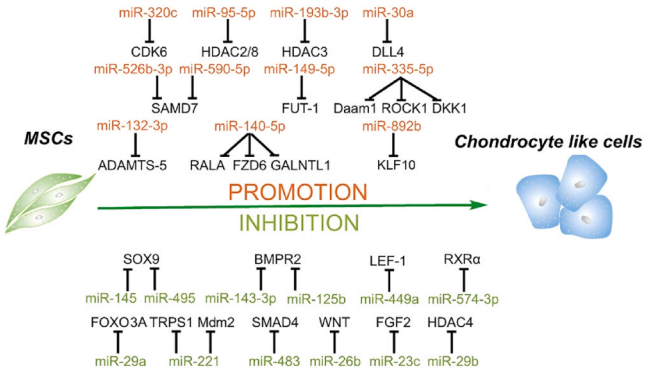

Fig. 3. Functions of miRNA in MSCs differentiation into chondrocytes. The miRNAs labeled in red have been identified to actively promote chondrogenesis, while those labeled in green have been found to inhibit this process. Adapted with permission from ref [47]. Copyright © 2021 by the authors. Licensee Frontiers Media S.A. CC-BY-4.0.

ECM and degradation of various proteins [52]. There has been a long-standing debate over which of the two classical aggrecanases, ADAMTS4 or ADAMTS5, is responsible for the development of OA pathology [53]. Compared to ADAMTS4, ADAMTS5 show more functions in both normal and osteoarthritic cartilage [54]. ADAMTS5 is a member of the zinc endopeptidase family and plays a crucial role in many biological processes, such as procollagen processing, ECM remodeling, inflammation, cell migration, and angiogenesis [55]. When ADAMTS5 and MMP13 are overexpressed in chondrocytes, it leads to excessive degradation of cartilage ECM, which is often the key factor in degenerative joint diseases [56]. Therefore, inhibiting the release of ADAMTS5 and MMP13 in cells has become a breakthrough in the treatment of OA. In a study by Tong et al., OA rat models were induced by monosodium iodoacetate (MIA), and UCMSCs was locally injected into the knee joint of OA rats [25]. The results showed that repeated injection of UCMSCs significantly improved the cartilage injury in OA rat models, and the expression levels of ADAMTS5 and MMP13 in the chondrocytes of the whole cartilage layer were also significantly down-regulated [25]. Even the existing ADAMTS5 and MMP13 in the articular cavity and cartilage layer were significantly metabolically removed, excessive degradation of ECM in chondrocytes causes the joint to lose its original biomechanical properties, leading to the aggravation of OA [56]. MSCs can effectively inhibit the expression of MMPs and ADAMTS family and efficiently remove matrix-degrading enzymes accumulated in the articular cavity, which is essential and extremely important for effective treatment of OA [57].

4. MSCs attenuate the effect of macrophage-induced inflammatory microenvironment

Macrophages are the most abundant immune cells in the joint cavity, and they have been confirmed to be the primary innate immune cells that mediate initial inflammation in the pathological process of OA [58]. From an immunological perspective, macrophages can be artificially divided into two phenotypes: pro-inflammatory (M1) and anti-inflammatory (M2) [59]. When intra-articular chondrocytes and synovial cells produce damage-associated molecular patterns (DAMPs) due to increased apoptosis or necrosis, it causes macrophages to polarize towards M1 [60]. Polarized M1 type macrophages secrete a large number of inflammatory factors, which lead to overactivation of the inflammatory signal pathway in healthy chondrocytes, promote the overexpression of matrix metalloproteinases, and further deepen osteoarthritis. On the other hand, when macrophages polarize towards M2 type, they secrete a large number of anti-inflammatory factors, which connect chondrocytes and macrophages to form a positive feedback circuit that reduces inflammation. These anti-inflammatory factors not only protect healthy chondrocytes but also inhibit the expression of matrix metalloproteinases in chondrocytes and promote collagen synthesis and aggregate polysaccharide production, thus delaying the progression of osteoarthritis [61]. MSCs exert immunosuppressive effects by converting pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages via MSC-macrophage interaction, efferocytosis, mitochondrial transfer, soluble mediators, and exosomes (Fig. 4) [62].

5. MSCs can relieve the pain caused by OA

OA can lead to chronic widespread pain and low stress pain thresholds, which may be associated with obesity and leptin levels [63]. However, it is undeniable that this kind of pain not only brings inconvenience to patients' actions but also mental burden. Chronic pain for a long time can lead to mental disorders such as comorbid depression, and long-term inconvenience may also lead to adverse psychology such as anxiety. Chronic pain caused by OA can also occur after total joint replacement or hip replacement, which is a great burden on patients and society. Chronic pain has always been known as an interdisciplinary problem, which is inextricably linked with neurological diseases [64].

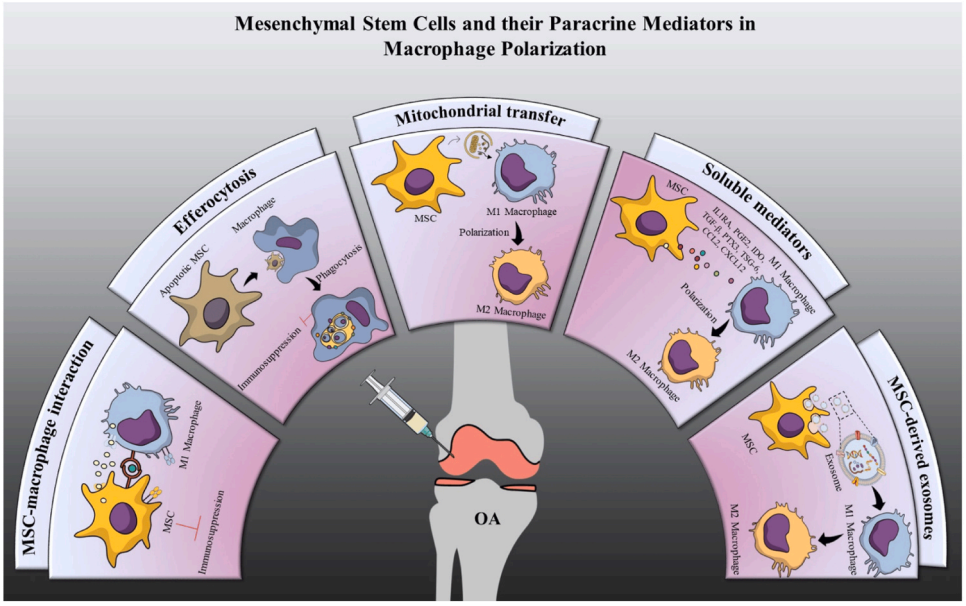

Fig. 4. MSCs exert immunosuppressive effects by converting pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. Adapted with permission from ref [62]. Copyright © 2022 by the authors. Licensee MDPI, Basel, Switzerland. CC-BY-4.0.

Therefore, it is very important to reduce the pain of patients with OA whether in medicine, psychology or sociology.

There are no nerves and blood vessels in articular cartilage, so cartilage cannot directly produce OA pain. However, when OA occurs, tissues around the joint, including synovium, ligaments, and subchondral bone, are highly innervated by rich sensory and sympathetic nerves, which often contribute to nociceptive pain [65]. With the extensive research on MSCs in multiple sources, there is a growing optimism regarding their potential applications in the treatment of OA. However, a crucial aspect that requires attention is whether MSCs possess the capacity to alleviate the pain associated with this debilitating condition. A South Korea phase III clinical trial through the injection of autologous fat-derived MSCs into 261 patients with Kellgren-Lawrence grade Three OA for one month showed that all patients in the clinical group had improved OA symptoms, and the degree of pain relief was statistically different from that of the control group [66]. In addition, a meta-analysis suggests that ADMSCs exhibit the greatest efficacy in alleviating pain associated with knee OA [67]. The peripheral mechanism of chronic pain in patients with OA is relatively complex, which may be quite different from other diseases with chronic pain, such as spinal cord injury, but it can at least provide a feasible and effective way to delay chronic pain in other diseases [68]. NGF is both a neurotrophic factor and a pro-inflammatory cytokine that can induce the growth of sensory and sympathetic nerves and mediate pain signal transduction, leading to nervous system sensitization [69]. NGF upregulates the expression of neurotransmitters such as CGRP and brain-derived neurotrophic factor (BDNF), which cause central pain sensitivity [69]. NGF can be produced by non-nerve cells such as macrophages, mast cells, synoviocytes, and neutrophils in joint tissues of patients with OA [69]. CGRP is a neuropeptide expressed in the peripheral nervous system and central nervous system, which is most abundant in nociceptive neurons. CGRP, as a sensory neuropeptide, can dilate blood vessels, affect peripheral pain sensitization and inflammation, and play a key role in neurogenic inflammation and pain production [70]. He et al. treated OA model with exosomes derived from BMSCs, which could effectively slow down the upregulation of CGRP and iNOS in nerve tissue and significantly improve pain perception [71]. Similar to iNOS, indoleamine 2, 3-Dioxygenase (IDO) is an immunomodulator and sustained activity is enhanced pain sensitivity [72]. Indeed, the modulation effects of MSCs on iNOS and IDO expression can vary depending on the species. In mouse, rat, rabbit, and hamster, MSCs have been shown to modulate iNOS expression, whereas in monkey, pig, and human, MSCs mediate IDO expression [73]. These species-specific differences in the modulation of iNOS and IDO expression by MSCs highlight the importance of considering the specific characteristics of MSCs from different species when developing therapeutic strategies for pain management in OA. Further research is necessary to fully understand the underlying mechanisms and potential therapeutic implications of these species-dependent modulation effects. Therefore, MSCs can secrete various factors, such as neurotrophic factors and cytokines, which can modulate pain signaling pathways. These factors can inhibit the transmission of pain signals and reduce pain perception in OA.

6. Clinical application of MSCs for OA therapy and perspectives

Up to now, many clinical trials have been applied in MSC-based OA therapy. More importantly, most applications are focus on knee OA, but the volumes of MSCs are various and the most source of them are bone marrow or fat. However, there are still challenges and unresolved issues in this field, such as optimizing MSC sources, standardizing isolation and culture protocols, and clarifying dosage and administration regimens. Additionally, considering the complexity of joint aging and multiple factors that contribute to its progression, further research is needed to evaluate the safety and effectiveness of long-term MSC interventions.

With the advancement of tissue engineering technology, many researchers have started using biomaterials or biomolecules combined with stem cells to treat OA. Compared to MSCs alone, biomaterials coupled with drugs and seed cells offer targeted therapy, more accurate promotion of cartilage repair, reduced inflammation, and improved therapeutic efficacy [40]. Scaffolds made from synthetic polymer materials and natural biomaterials provide the necessary microenvironment and structure for regeneration [41]. For example, hydrogels, particularly microgels, have gained attention for their biocompatibility, biodegradability, and bioactivity, which is similar to the natural ECM. The integration of MSCs with hydrogels offers several advantages in the context of OA treatment. Hydrogels provide a 3D microenvironment that mimics the native ECM, facilitating cell adhesion, proliferation, and differentiation. Moreover, hydrogels possess tunable mechanical properties and porosity, allowing for the regulation of cell behavior and nutrient diffusion [74,75]. In recent years, various strategies have been

employed to enhance the functionality of MSC-loaded hydrogels in OA therapy. For instance, genetic engineering and 3D bioprinting techniques have been utilized to overexpress specific genes in MSCs, promoting their chondrogenic differentiation and secretion of trophic factors [76,77]. Additionally, the incorporation of nanoparticles within hydrogels can provide sustained release of therapeutic agents, such as anti-inflammatory drugs or growth factors, improving the therapeutic potential of MSCs [76]. For example, TGF-β3 and KGN have a synergistic effect in promoting chondrogenesis of rabbit MSCs, and can effectively repair cartilage defects by regenerating hyaline cartilage [78]. Jiang et al. developed a biodegradable nano-carrier system (MNP) loaded with KGN to target cartilage via BMSCs in articular matrix, improving joint structure and enhancing cartilage differentiation [79]. Thus, the combination of MSCs with natural or synthetic hydrogels represents a promising approach for enhancing their functionality in OA therapy. The tunable properties of hydrogels and the ability to incorporate bioactive molecules or nanoparticles offer opportunities for optimizing the microenvironment and improving the regeneration potential of MSCs. Further research and development in this field hold great promise for the future treatment of OA.

7. Conclusion

In conclusion, osteoarthritis (OA) remains a complex disease with limited treatment options and significant side effects. However, the emergence of mesenchymal stem cells (MSCs) as a potential therapeutic approach has provided new hope for managing OA. This review has highlighted the diverse roles that MSCs play in treating OA and the underlying mechanisms behind their therapeutic effects. The ability of MSCs to promote the regeneration of chondrocytes and synoviocytes, inhibit extracellular matrix degradation, attenuate the macrophage-induced inflammatory microenvironment, as well as alleviate pain, showcases their potential as a comprehensive treatment strategy for OA. By addressing multiple aspects of OA pathogenesis, MSCs offer a promising avenue for achieving improved clinical outcomes and enhancing the quality of life for patients. However, further research is needed to optimize the use of MSCs in OA therapy. This includes exploring optimal dosing regimens, understanding the interactions between MSCs and the OA microenvironment, and identifying specific mechanisms that drive MSC-mediated tissue regeneration and immunomodulation. Moreover, long-term studies are necessary to assess the durability and safety of MSC-based therapies. Overall, MSCs represent a promising frontier in the field of OA treatment, holding the potential to revolutionize how we approach and manage this debilitating disease. Continued investigation and clinical trials are essential to fully unlock the therapeutic power of MSCs and pave the way for more effective and personalized treatment strategies for OA patients.

Ethical approval

Not applicable.

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CRediT authorship contribution statement

Yang Jiao: Resources. **Weihong Xing:** Resources. **Ziheng Tian:** Validation. **Tongmeng Jiang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Juan Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Ruijiao Tian:** Writing – original draft, Investigation. **Shibo Su:** Writing – original draft, Investigation. **Yang Yu:** Writing – original draft, Investigation. **Siqiang Liang:** Software, Investigation. **Chuqing Ma:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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