*Nanomed Res J 8(2):110-126, Spring 2023*

REVIEW ARTICLE

# Mesenchymal stem/stromal cells and their exosomes as natural nano-particles for arthritis therapy; hype and hope

***Ahmed Hjazi [1*], Shadia Hamoud Alshahrani [2*], Shallal M. Hussein [3], Mohammed Kadhem Abid [4], Beneen M. Hussien [5]***

*[1] Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia*

*[2] Medical Surgical Nursing Department, King Khalid University, Khamis Mushate, Saudi Arabia*

*[3] College of Health and Medical Techniques, Al-Bayan University, Baghdad, Iraq*

*[4] Department of Anesthesia, College of Health & medical Technology, Al-Ayen University, Thi-Qar, Iraq*

*[5] Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq*

**ARTICLE INFO**

***Article History:***
*Received 03 Feb 2023*
*Accepted 24 Apr 2023*
*Published 01 May 2023*

***Keywords:***
*Inflammation*
*Rheumatoid arthritis (RA)*
*Osteoarthritis (OA)*
*Mesenchymal stem/stromal cells (MSCs)*
*Exosomes,*
*Extracellular matrix (ECM)*
*Cartilage*

**ABSTRACT**

In order to reduce cartilage damage and enhance tissue regeneration in a variety of musculoskeletal conditions, particularly rheumatoid arthritis (RA) and osteoarthritis (OA), mesenchymal stem/stromal cells (MSCs)-based treatments have attracted increasing attention. The effects of MSCs are primarily controlled by inhibiting inflammatory reactions and inducing immunomodulation, which is largely accomplished by the secretion of a variety of anti-inflammatory cytokines. These mediators prevent the proliferation and motility of FLS in vivo, which prevents cartilage degeneration. Furthermore, MSCs-derived nanometric exosome therapy can inhibit the activity of matrix metalloproteinases (MMPs), which function as matrix-degrading enzymes, and ultimately results in decreased extracellular matrix (ECM) breakdown. MSCs-derived exosome in fact act as cell-free sources in the context of the regenerative medicine. In addition, administration of MSCs intravenously and systemically to patients with OA and RA has been shown to be safe and effective therapeutically. Here, we have focused on the ability of MSC-based approaches like using MSCs-derived exosome to favor both chondrogenic and chondroprotective influences in arthritis.

**How to cite this article**
*Hjazi A., Hamoud Alshahrani Sh., M. Hussein Sh., Kadhem Abid M., M. Hussien B. Mesenchymal stem/stromal cells and their exosomes as natural nano-particles for arthritis therapy; hype and hope. Nanomed Res J, 2023; 8(2): 110-126. DOI: 10.22034/nmrj.2023.02.001*

## INTRODUCTION

Arthritis as the most common orthopedic disorder is characterized by pain and inflammation in a joint. Cartilage is mainly described as a chief target tissue in both osteoarthritis (OA) as well as rheumatoid arthritis (RA), two well-known and most common sorts of arthritis (1, 2). Articular cartilage, which is positioned on the surface of musculoskeletal joints, can endure complex mechanical impetuses, including pressure and shear force (3). Given that articular cartilage has no blood vessels, it typically obtains essential nutrients through synovial fluid infiltration, hindering cartilage to restore itself upon damage (4, 5). In the absence of an appropriate therapeutic modality, cartilage damage may bring about post-traumatic OA, which is described by joint pain, deformity, and movement diseases (6). These pathological manifestations, in turn, diminish patients' quality of life. Now, microfracture technologies, autologous or allogeneic cartilage

* Corresponding Author Email: *alshahrani.shadia@gmail.com*
*a.hijazi@psau.edu.sa*

transplantation concomitant with autologous chondrocyte implantation are typical treatments to treat arthritis (7, 8). Such therapeutic although can partially compromise cartilage deficits, and prolonged efficacy is not provided. To circumvent this difficulty, various scientists have concentrated on the unique capabilities of mesenchymal stem/stromal cells (MSCs) (9, 10).

The MSCs as unique types of the human multipotent adult stem cells can efficiently be procured from a myriad of human tissue, including bone marrow (BM), adipose tissue (AT), synovial membrane, umbilical cord (UC), etc (11, 12). Thanks to the great competencies of MSCs, such as self-renewal, trans-differentiation in association with immunomodulation, MSC-based therapeutic plans have become an excellent treatment for cartilage recovery as a result of their osteogenic and chondrogenic potential, harvest simplicity, and ease of cultivation in culture (13, 14). Concerning the clinical results, MSCs therapy is safe and feasible with no stern untoward events. Thereby, it has been evinced that MSCs transplantation by intraarticular route or arthroscopic implantation can considerably lessen pain and recover knee activity (15, 16). Notwithstanding, basic and clinical investigation of MSCs and MSCs-derived exosomes to treat articular cartilage lesions have also met various difficulties. Due to the MSCs' heterogeneity, the influences of cultivation circumstances in vitro, and the presence of inflammation in the joint, some injected cells show unstable cell morphology, exhibit reduced viability in vivo, and also experience inefficient chondrogenic differentiation and cartilage matrix generation (17). In fact, the small populations of transplanted MSCs will ultimately be effective, making it difficult to achieve steady and homogeneous cartilage tissue or continued therapeutic influences (18). Thus, using MSCs-derived exosomes have attracted increasing attention. They carry and exchange proteins, lipids, miRNA, or DNA between diverse cell types. These nanometric exosomes also have key roles in various biological processes, such as tumor metastasis and tissue regeneration, and have been regarded as prognostic markers for manifold diseases (19, 20, 21).

Herein, we will deliver an overview based on MSCs therapy and also their exosomes as natural nanoparticles for cartilage regeneration in common types of arthritis, and also will discuss the potent mechanism behind the MSCs- mediated cartilage recovery.

## THE PATHOPHYSIOLOGY OF COMMON ARTHRITIS

*OA*

Based on its etiology, OA is categorized into two main groups: primary (idiopathic or non-traumatic) and secondary (mainly resulting from trauma or mechanical abnormalities) (22). The sternness also is graded regarding the radiographical discoveries by the Kellgren-Lawrence (KL) system suggested in the 1960s. Previously it was supposed that OA was solely a cartilage degenerative disorder, while the latest results have shown that OA has a multi-dimensional aspect, comprising various contributing factors, such as biochemical response, trauma, mechanical forces, dysregulated immunological responses as well as metabolic abnormalities (23). Since cartilage has no vasculature, making it difficult to inspire inflammation or pain by itself, it has been suggested that the pain is largely elicited from alteration in the non-cartilaginous parts of the joint, including joint capsule, subchondral bone, ligaments, synovium, and even peri-articular muscles (24). As the disorder spreads, pathological signs like bone remodeling, formation of the bone spurs (osteophyte), ligamentous laxity, weakening of periarticular muscles as well as synovial effusion can be befallen (25, 26).

There is an ongoing debate about the contribution of inflammation in OA. It is of paramount importance to elucidate whether inflammatory response instigates the OA variations or the inflammation is itself secondary to the OA variation (27). The chronic inflammation comprising the innate immune system is frequently observed in OA. Synovitis, as a hallmark of OA, refers to the infiltration of inflammatory cells into the synovium and is detected in early phase of OA (28). However, it is more common in more developed steps and has tight correlation with OA severity. Notably, the synovial fluid in OA mainly includes several inflammatory molecules like plasma C-reactive protein (CRP), cyclooxygenase-2 (COX-2), prostaglandin-2 (PGE2), inflammatory cytokines, growth factors (e.g., TGFβ), nitric oxide (NO), and complement ingredient. Such mediators in association with matrix metalloproteinases (MMPs) and other hydrolytic enzymes lead to the deterioration of proteoglycan and collagen construction and thereby eases cartilage breakdown (29, 30, 31, 32). Damage-associated molecular patterns (DAMPs)

released upon ECM degeneration enables a further cascade of inflammatory reactions, potentiating cartilage destruction. In vivo results have provided clear evidence conferring that macrophages largely contribute to the osteophytes' progress, an indicator of the OA severity. Decreased expression of some growth factors like IGF-1, PDGF, FGF, and also TGF-β in the affected joint also results in more sustained destructive effects of OA (23).

*RA*

The RA, a systemic inflammatory disorder, is mainly described by synovitis along with joint damages. While the RA etiology is unidentified, the potential impacts of the genetic factors are apparent. Of course, genetics is not adequate to explicate the causing of the immune deregulated response (33). The RA hallmark is inflammation predominantly in synovium; with obvious hyperplastic synovial membrane. The existence of autoantibodies known as rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPA) is a common feature of RA (34). An increased frequency of T follicular helper (Tfh) cells related with autoantibodies in RA patients indicates a possible contribution of Tfh cells in RA pathogenesis. Pathological analysis has proven both types of synoviocytes as well inflammatory cells like dendritic cells (DCs), macrophages, B- and T-lymphocytes and plasma cells in affected tissue in OA (35). Although such cells signify the immunological features of RA, most of the RA-associated lesions result from their products, such as cytokines and other mediators. Meanwhile, an improved level of the inflammatory cytokines mainly underlies the prolongation of synovial inflammation (36). Besides, neutrophils' recruitment to the joint is induced by IL-8 and leukotriene B4 and leads to up-regulation of complement activation (37). Pro-inflammatory cytokines, such as IL-1 and TNF-α, target chondrocytes and synovial fibroblasts, and provoke them to secrete proteolytic enzymes (38, 39). Proteolytic enzymes motivate the dissolution of the cartilage matrix, and thereby inspire narrowing of joint spaces.

## MSCS ROLE IN AMELIORATION COMMON ORTHOPEDIC DISEASES

*Chondrogenic differentiation*

Even though endogenous MSCs induce tissue repair, their capacity is inadequate to entirely restore damaged cartilage. It has recently been verified that transplanted MSCs can migrate to the damage zone and then partially differentiate into target cells and substitute injured tissue. Accordingly, exogenous MSC transplantation recently is considered a rapidly evolving therapeutic plan with desired capability for migration, proliferation, and eventually for cartilage regeneration (40). Also, chondrogenic differentiation of MSCs in vitro and transplantation of differentiated chondrocyte alone or association with engineered scaffold is another suggested approach (41). Pellet culture is the most extensively used culture systems for chondrogenesis (42). Pellets including about 2-5 $\times 10^5$ cells are provided for chondrogenic differentiation of MSCs by a basal medium comprising dexamethasone, ascorbate, insulin, transferrin, and selenous acid (43, 44). Moreover, the classic growth factor used for chondrogenesis is TGF-β. Importantly, TGF-β can significantly trigger chondrogenesis and enable the accumulation of proteoglycan and collagen type II once exploited as solitary factors (45). Also, bone morphogenic protein-2 (BMP2) for BM-MSCs (46) and BMP6 for AT-MSCs (47) act as chondrogenesis-inducer factors. BMP2, BMP4, BMP6, and IGF1 typically are described as inducers of chondrogenesis when applied together or in association with TGF-β (48). Apart from soluble mediators, environmental factors like mechanical stimulation (49) and hypoxia (50) have also can modify MSCs' chondrogenesis in vitro. Also, there is some evidence indicating that ex vivo ultrasound could induce chondrogenesis of MSCs in vivo post-administration (51). Importantly, Aung et al. also found that co-culture with primary OA chondrocytes stimulates the chondrogenic differentiation of human MSCs without the presence of growth factors (52). Owing to their finding that primary OA chondrocytes-derived conditioned medium has no similar effect on MSCs, it seems that cell-to-cell contacts played pivotal roles in this regard (52). Besides, another study demonstrated that MSC chondrogenesis was suppressed by OA synovium conditioned medium because of the soluble mediators released by synovial M1 macrophages (53). Various reports have shown that BM-MSCs could shape a cartilage-like tissue in vitro upon exposure with cocktails of such factors. The established tissue can express various biomolecules typical of hyaline cartilage-like type II collagen and aggrecan (54). However, collagen content is mainly lower than 50% compared to native healthy adult cartilage, with

undesirable effects for tensile strength and load-carrying capabilities (54).

*MSCs immunomodulatory and anti-inflammatory competencies*

Thanks to their substantial immunoregulatory capacities, MSCs can dampen dysregulated immunological responses throughout tissue recovery and deliver a proper milieu for cartilage repair and regeneration (Fig. 1) (55). As described, the presence of the various immune cells in association with high levels of pro-inflammatory mediators in the synovium of arthritis patients confers the significance of immunomodulation to treat such disorders (56, 57). MSCs universally regulate immunological response by negative regulation of (M1Mφ), TH1, TH17, DCs, B cells as well as NK cells activation and maturation while promoting TH2 and anti-inflammatory macrophages (M2Mφ) and T regulatory (Treg) cells proliferation through the generation of soluble biomolecules or cell-to-cell contact (58, 59). MSCs inhibit the activation of M1Mφ mainly by the secretion of IL-10 and suppression of the infiltration of antigen-presenting cells (APCs) (60). The expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) is crucial for MSCs to induce immunomodulatory impact on T cells by potentiating the interfaces between MSCs and T cells (60).

A large number of reports have evidenced that MSC-derived secretome largely mediates the paracrine influences of MSCs. The anti-inflammatory impacts of MSCs largely depend on a myriad of soluble mediators, including TGF-β1, PGE2, hepatocyte growth factor (HGF), indoleamine-pyrrole 2, 3-dioxygenase (IDO), NO, COX-2 and IL-10 (58, 59, 61). In damaged tissue, IFN-γ, TNF-α, IL-1α or IL-1β provoke MSCs to generate COX-2, PGE2, and IDO and thus elicit anti-inflammatory effect (58). PGE2 inhibits T-cell growth (62) while IDO impairs immune cells proliferation and function through facilitating tryptophan breakdown (63). MSCs-produced NO also could alleviate immune cell growth through

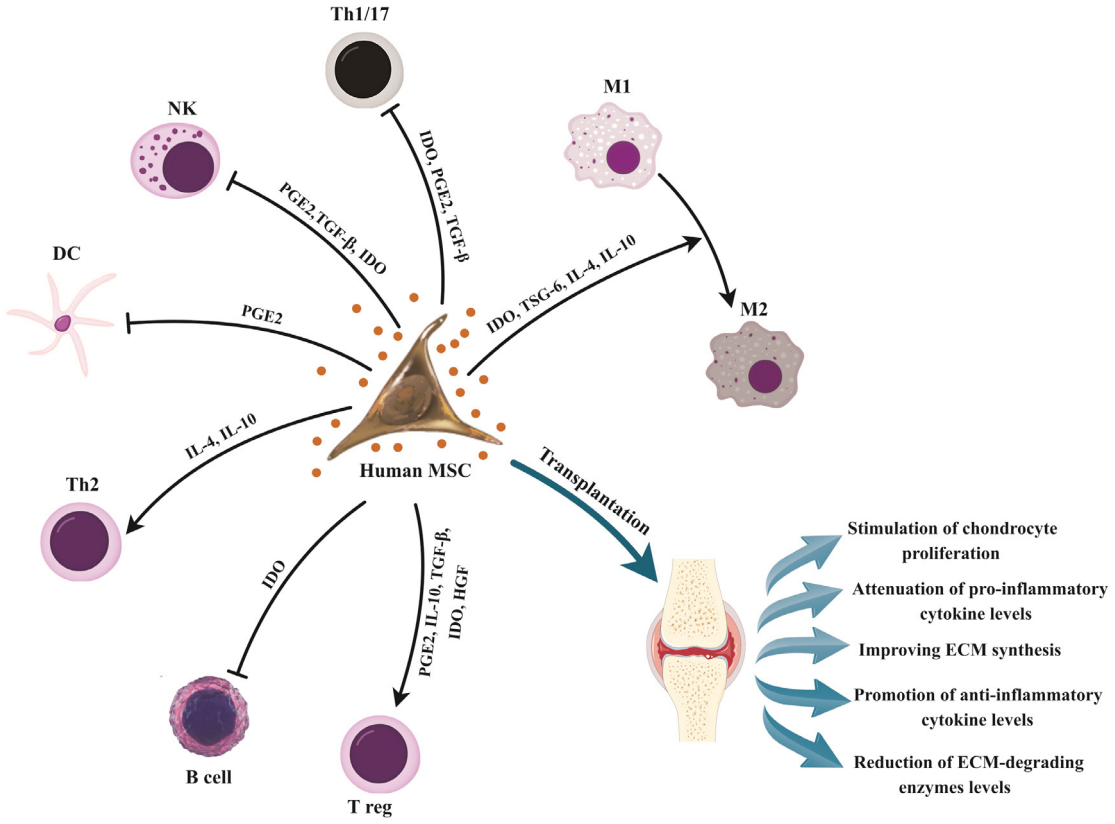


Fig. 1. MSCs-mediated immunomodulation in cartilage disease therapy.

suppression of the STAT5 phosphorylation (64). The NO and NO-derived reactive nitrogen species also can interrelate with several enzymes, ion channels, and also receptors in immune cells, eventually impairing their activation (65).

The MSCs sources (66) and also target tissue (67) can affect the MSCs-mediated impacts on immune cells activity. In this light, the potential of AT-MSCs is more evident than BM-MSCs on the inhibiting the growth of peripheral PBMC and also monocytes differentiation to DCs (68). Also, chorionic plate-derived MSCs (CP-MSCs) are capable of secreting IL-2, IL-4, IL-13, and GM-CSF cytokines at higher levels compared to BM-MSCs and AT-MSCs (69). Besides, BM-MSCs have superiority over placenta-derived MSCs (PD-MSCs) in terms of the suppressing T cell activation, based on Fazekasova et al.'s reports (70). Taken together, there is worldwide consensus about the immunoregulatory impacts of MSCs. Nonetheless, more comprehensive investigations are essential to clarify the in depth biological mechanisms corresponding these influences.

## PRECLINICAL STUDIES IN MSCS BASED APPROACHES RA

*MSCs based therapies*

During last decades, the therapeutic capacity of MSC is being investigated in RA (Table 1). In vitro, BM-MSCs could down-regulate secretion of the inflammatory cytokines, TNF-α, IL-17, IL-6, IL-2, IFN-γ, and IL-9, by T cells isolated from patients suffering from RA (71). In contrast, BM-MSCs could promote the expression of IL-10 and TGF-β by both CD4+ as well as CD8+ T cells, thereby stimulation of the remarkable inhibitory impacts against RA patients-derived T cells. Importantly, BM-MSC-elicited immunoregulation could target naive, effector, and memory T cells (71). Also, MSCs could avert the differentiation of Tfh cell in RA patients largely by secreting IDO (72). Studies in collagen-induced arthritis (CIA) mice model of RA exhibited that MSCs transplantation inhibited arthritis development by the hindrance of both the Tfh cells number as well as action in vivo, thus indirectly affecting both proliferation and differentiation of B cells (72). Meanwhile, ER-stressed MSC showed more prominent inhibitory effects on Tfh cells isolated from RA patients by promoting PGE2 binding with responding receptors on Tfh cells, known as EP1-4 (73).

The MSCs derived from RA patients usually demonstrate the impaired capability to obstruct Th17 cell polarization (74). Further, the interaction of MSCs or fibroblast-like synoviocytes (FLS) isolated from patients with RA with T cells could promote Th17 cells' growth and activation by caspase 1 activation (74). Molecular studies revealed that deubiquitinating enzyme A20, a master regulator of arthritis, was reduced in RA patients' BM-MSCs and consequently led to the IL-6 secretion at higher levels, and thereby impaired balance of Th17/Treg (10). A20 typically attenuates inflammasome-induced arthritis by suppression of macrophage necroptosis and also down-regulated NF-kB pathways (75), thereby the influences of A20 on pro-inflammatory IL-6 generation is a potent target for MSCs transfer in RA adoptive therapy (10). However, human UC-MSCs suppressed the proliferation and induced apoptosis in Th17 cells in CIA mice. In addition, the intervention reduced transcription factors RORγt expression (largely expressed in Th17), improved the expression levels of Foxp3, and amplified the numbers of Tregs in the spleen (76). Also, UC-MSCs therapy reduced IL-17 and enhanced TGF-β expression in the serum. These events, in turn, enabled hindrance of RA progression, and also attenuated synovial hyperplasia in RA rats (76). Also, hUCB-MSCs could affect the polarization of macrophage and also modify the activation process of inflammasome for attenuating RA severity. Meanwhile, Shin et al (2016) found that hUCB-MSCs strikingly diminished the RA severity in CIA mice mainly through targeting macrophage action (77). In vitro, they found that hUCB-MSCs increased M2/M1 phenotype ratio by secretion of COX-2 and TNF-stimulated gene/protein 6 (TSG-6). Consistently, hUCB-MSCs suppressed the stimulation of nucleotide-binding domain and leucine-rich repeat pyrin 3 (NLRP3) inflammasome through a paracrine loop of IL-1β signaling (77). The NLRP3 inflammasome is shown to involve in the IL-1β and IL-18 maturation as well as release. It engages pro-caspase-1 by adapter molecule apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) to establish NLRP3 inflammasome following activation (78). Importantly, the fact that inhibition of NLRP3 results in down-regulation of the generation of TNF and IL-6 in RA joints has conferred the critical role of NLRP3 in RA pathogenesis (78).

Given the eminent role of NF-κB in the expression of inflammatory response genes and

Table 1. Animal studies based on MSCs based therapies for RA treatment

| Model | Source | Results | Reference |
|---|---|---|---|
| **Mice** | BM | Reserve of inflammation by the hindrance of Th17 activation | (138) |
| **Rat** | BM | Down-regulation of RANKL expression, and IL-22 levels, supporting amelioration of bone destruction | (139) |
| **Rat** | UC | Suppression of T lymphocytes growth, downregulation of RORγt expression, inhibition of Th17 activation, and improving Treg cell population | (140) |
| **Mice** | BM | Attenuation of articular tissue inflammation as well as cartilage destruction by targeting IL-9 expression | (141) |
| **Mice** | Synovial | Inhibition of FLS proliferation and migration by down-regulation of MMP14 and VEGF | (90) |
| **Mice** | BM | Down-regulation of COMP, TIMP1, MMP1, IL-1R, TNF-α, MCP-1 levels following combination therapy with IL-4 | (142) |
| **Mice** | BM | Attenuation of TNF-α levels by MSC-conditioned medium | (143) |
| **Mice** | BM | Regeneration of cartilage tissue | (144) |
| **Mice** | UC | Cartilage protection by inhibition of the Th17 cell activation | (145) |
| **Mice** | BM | Inhibition of the NG-κB activation, and thus suppressing inflammation | (146) |
| **Mice** | UC | Attenuation of disease progress by inhibition of the Tfh cells activation by secretion of the IDO | (147) |
| **Mice** | Gingival | Stimulation of T-cell apoptosis via the FasL/Fas pathway | (148) |
| **Mice** | AT | Suppression of RANKL-mediated osteoclastogenesis | (149) |
| **Mice** | ESC-MSC | Inhibition of inflammation by IDO secretion | (150) |

also adjustment of the cell cycle (79, 80), other studies have focused on MSCs' potent effects on NF-κB signaling pathways. Yan and colleagues (2016) found that BM-MSC transplantation could down-regulate the NF-κB axis and attenuate microRNA-548e (miR-548e) levels of CIA mice joints. Molecular analysis revealed that miR-548e acts as an inducer of NF-κB expression due to their competencies to down-regulate IκB expression (81). Besides, TGF-β secreted from BM-MSCs down-regulate miR-548e activity and consequently inhibited the NF-κB signaling axis. Accordingly, MSCs therapy could inhibit NF-κB-mediated inflammatory response in RA (81). In contrast to miR-548e, miR-146a, which is found at measurable levels in MSCs, inhibits FLS proliferation as well as inflammatory responses through the down-regulation of the TLR4/NF-kB axis (82).

Recently, scientists have concentrated on finding novel methods or molecules to potentiate the favored effects of the MSCs therapy in RA (9, 83, 84). For instance, combination therapy with MSC and IL-4 could ameliorate the symptoms of synovitis in CIA mice by down-regulation of TNF-α, MCP-1, COMP, TIMP1, MMP-1, and IL-1R expression in vivo (83). As well, pre-treatment of MSCs with caffeine potentiated MSCs-mediated immunoregulation in RA rats as a result of down-regulation of IFN-γ, IL-6, and IL-1β and simultaneously up-regulation of IDO, TGF-β, and IL-10 expression (84). Pretreated-MSCs also exhibited superiority over naïve MSCs therapy in terms of the amelioration of RA severity. Also, they cause a profound reduction in serum levels of CRP, NO, Myeloperoxidase (MPO), and TNF-α, while enhancing IL-10 levels (84). Yamagata et al. (2019) also found that poly-lactic-co-glycolic acid (PLGA) and soluble IL-6R (sIL-6R) improved articular cartilage repairing with high efficacy (85). They, firstly, pre-treated BM-MSCs with sIL-6R to enhance their chondrogenic differentiation. Thereafter, pre-treated BM-MSCs were seeded on a PLGA sheet to improve their localization. The higher level of aggrecan along with symptoms of knee joint recovery was detected in antigen-induced arthritis (AIA) rats following implantation of PLGA containing BM-MSCs than direct use of BM-MSCs and thereby offering a promising approach to recovery of articular cartilage in RA patients (85). PLGA also could stimulate MSC differentiation into bone and cartilage (86). Also, the encapsulation of IL-1 receptor antagonist (IL-RA) gene-modified MSCs in alginate-poly-L-lysine (APA) microcapsules with the aim to the prolonged delivery of IL-RA has been led to favorable outcomes (87). In vivo, the intervention led to the persistent delivery of IL-1RA up to 4 weeks posy-implantation, and also reduced RA severity (87).

Also, MSCs exposure with extremely-low frequency pulsed electromagnetic field (PEMF) improves their anti-inflammatory action, augment their differentiation to chondrocytes and osteocytes, and finally intensify collagen deposition, making them a more appropriate option for RA therapy (9).

*MSCs secretome*

Several reports and clinical results have evidenced the appreciated effects of MSCs in arthritis, whereas MSCs are capable of undergoing abnormal differentiation and thereby the creation of tumor. Also, aging phenomena fences partially MSCs application. Therefore, the medical application of MSCs secretome, such as extracellular vesicles (EVs), has attracted growing attention (88). Extracellular vesicles (EVs), including exosomes and microvesicles, are more efficient, less toxic, and steadier than the parental MSCs. As well, they divers types of nucleic acids (e.g., miRNAs), proteins, and lipids from MSCs cells to target cells, resulting eventually in the prohibiting chronic inflammatory and immune reactions (89).

Recent reports have indicated that desired events upon transplantation of MSCs-exosomes mainly rely on miRNA transportation by such EVs. The MSC-derived miR-150-5p exosomes was shown to restore joint damage in RA (90). In vitro, the miR-150-5p containing exosomes diminished migration and invasion in RA patient-derived derived FLS. In vivo, exosome therapy diminished hind paw thickness, ameliorated joint destruction by down-regulation of synoviocyte hyperplasia and angiogenesis in CIA mice. The favored effects were most probably caused by down-regulation of MMP-14 and VEGF by MSC-derived miR-150-5p exosomes, leading to suppressed angiogenesis and joint damage (90). Besides, in another study, MSCs were genetically modified to overexpress miR-146, a well-known immune response regulator (91). Exosomes derived from miR-146a-transduced MSC strongly enhanced FOX-P3, TGFβ, and IL-10 gene expression in a rodent model of RA. Results implied that the modification of MSC-derived exosomes by anti-inflammatory miRNA could augment Treg cell frequency and also improve anti-inflammatory cytokines levels, providing a suitable milieu for damaged tissue recovery (91). Moreover, miR-320a enriched exosomes could target activation and migration of RA-FLSs by down-regulation of CXC chemokine ligand 9 (CXCL9). Indeed, miR-320a enriched exosome robustly inhibited RA-FLS in vitro and also decreased arthritis and bone destruction in vivo (92). Thanks to the important role of CXCL9 in RA pathology; higher serum levels of CXCL9 are related to more severe RA, theses consequences signify that manipulation of MSCs can be an innovative potential therapeutic option to treat RA by enhancing miR-320a contents in MSCs-exosomes (92). In addition to miRNAs, Yu et al. (2021) exhibited that MSC-exosome could contribute to the intercellular transport of long non-coding RNA heart and neural crest derivatives expressed 2-antisense RNA 1 (HAND2-AS1) and thereby inhibited RA-FLSs proliferation, motility as well as inflammation by inactivation of NF-κB pathway (93). MSCs could also reduce RA progress by the transferring of IL-1 receptor antagonist (IL-1Ra), and thereby restraining of IL-1 induced inflammatory response (94). IL-1Ra as a member of the IL-1 family can typically make interactions with IL-1 receptors without exerting any intracellular signaling. Thereby, IL-1Ra enriched vesicles could be a rational option for inflammatory disease therapy (95).

## PRECLINICAL STUDIES IN MSCS BASED APPROACHES OA

*MSCs based therapies*

Various reports have evaluated the effects of MSCs therapy in OA preclinical models (Table 2). Fernandez-Pernas and coworkers showed that intravenous and also intra-articular transplantation of human synovial-MSCs into OA monkeys could be safe and effective (96). Likewise, intra-articular transplantation of infrapatellar fat pad derived-MSCs led to a lower grade of cartilage damages, osteophyte establishment, and subchondral sclerosis in OA rabbits (97). The BM-MSCs therapy also in OA rat model significantly enhanced collagen II expressions, promoted cartilage repair, and finally impaired OA development 3-4 weeks post-transplantation (98). MSCs universally exhibit favored influences on OA by provoking the generation of ECM, enhancing chondrocyte proliferation also suppression of inflammatory reaction (99). Another study in a monosodium iodoacetate-induced temporomandibular joint (TMJ) rabbit model of OA displayed that UC-MSCs administration supported regenerative outcome and stimulated immunomodulatory influences by up-regulation of growth factors expression, ECM synthesis, improving anti-inflammatory cytokines levels, and finally via attenuation of

Table 2. Animal studies based on MSCs based therapies for OA treatment

| Model | Source | Results | Reference |
|---|---|---|---|
| **Rat** | AT | Reduction of MMPs and CII degrading enzymes levels | (151) |
| **Rat** | Synovial | Suppression of OA progress miR-140-5p delivery | (152) |
| **Rat** | BM | Reduction of pain, improving the levels of anti-inflammatory cytokine levels, and induction of cartilage repair by TSG-6 delivery | (101) |
| **Mouse** | IPFP | Stimulation of cartilage recovery by suppression of mTOR-autophagy pathway | (111) |
| **Monkey** | Synovial membranes | MSCs efficient migration into OA joint | (96) |
| **Mouse** | NA | Reduction of pain in association with cartilage damage amelioration | (110) |
| **Rat** | Synovial | Promotion of the cartilage repair | (153) |
| **Rabbit** | BM | Stimulation of the cartilage regeneration by hyaluronan-based scaffold carrying BM-MSCs | (154) |
| **Guinea pigs** | Synovial | Stimulation of cartilage repair by hyaluronic acid hyaluronan-based scaffold carrying SMSCs | (155) |
| **Horse** | AT | No significant effect | (156) |
| **Dogs** | AT | Cartilage repair | (99) |
| **Mouse** | Synovial | Reduction of the MMPs and inflammatory cytokines levels following intraarticular injection | (157) |
| **Rat** | BM | Supporting subchondral bone and matrix homeostasis by normalizing the MMP-13 to TIMP-1 ratio | (158) |
| **Mouse** | NA | Reduction of the chondrocytes apoptosis up-regulation of GIT1 expression | (118) |
| **Mouse** | ESC-MSC | Provoking the CII synthesis and reducing the ADAMTS5 | (159) |
| **Rabbit** | UC | Cartilage repair by enhancing the growth factors, ECM synthesis, and anti-inflammatory cytokines levels | (100) |
| **Rabbit** | IPFP | Inhibition of cartilage destruction, osteophyte formation, and subchondral sclerosis | (97) |
| **Horse** | NA | Improving the CII and TGF-β1 levels concomitant with reduction of COX-2 and IL-1β levels in joints | (160) |
| **Sheep** | BM | Improving the aggrecan and CII levels in association with attenuation of MMP-13 expression | (161) |

the levels of pro-inflammatory cytokines, such TNF-α, IL-1β, and IL-6 (100). Thereby, it seems that MSCs not only trigger chondrogenesis but also provoke chondroprotection processes. Consistently, up-regulation of expression of TSG-6, a well-recognized anti-inflammatory and cartilage protective molecules, following MSCs therapy delivered the proof of the concepts that MSCs induce a chondroprotective effect in vivo (101).

Due to the inductive roles of ADAMTS5 in OA progression (102), scientists have focused on finding therapeutic modalities to avert its activity. Expression and activation of ADAMTS5 with robust aggrecan-degrading activity have previously been suggested as a negative factor in OA therapy (103). The suppressive effect of the MSCs on ADMATS5 expression and action has sustained the reasonability of MSCs therapy to treat arthritis. Recently, the study of the effects of the MSCs' intra-articular administration in OA rat models showed that intervention brought about the down-regulation of ADAMTS5 expression in joint cartilage in treated animals (101). MSCs also reduced ADAMTS-5, MMP13, and iNOS expression in human chondrocytes in vitro, based on Xian et al. (2015) reports (104).

In 2018, Barrachina et al. showed that BM-MSCs primed with TNF-α and IFN-γ improved collagen type II and TGF-β1 levels and conversely reduced COX-2 and IL-1β levels in the synovium of transplanted OA animal models (105). Moreover, administration of UC-MSCs loaded with graphene oxide (GO) granular lubricant elicited therapeutic influences by stimulation of anti-inflammatory effect in OA rabbit models (106). UC-MSCs loaded with GO was more effective than UC-MSCs alone in terms of suppression of NO, IL-6, and TNF-α levels, and also improving glycosaminoglycan (GAG), and collagen-II in the articular cavity in transplanted animals (106). These changes, in turn, suppress the inflammatory environment and thus potentiate cartilage repair. In another study, photobiomodulation therapy (PBMT) augmented the bioavailability and chondroprotective effects

of AT-MSCs injected into the knees of rats with OA (107). Moreover, rats receiving PBMT plus AT-MSCs experienced down-regulated expression of the pro-inflammatory cytokine, MMPs, and also attenuated degradation of type II collagen in their cartilage compared with rats receiving AT-MSCs alone (107). Other reports also revealed that implantation of hyaluronan-based scaffold (Hyaff11) seeded with BM-MSCs could support more appreciated outcomes for OA therapy (108). A significant amelioration was achieved in terms of regenerated tissue between scaffolds carrying MSCs and scaffold or MSCs alone in vivo, As well, collagen-based scaffold carrying chondroprogenitor cells derived from human BM-MSCs enabled the formation of cartilage-like tissue with lacuna in OA animal model 4 months post-transplantation, conferring their potential as an effective treatment plan for OA (109).

*MSCs secretome*

The intra-articular administration of MSCs secretome was shown to attenuate pain and avert cartilage damages in OA murine model by various mechanisms (110). Wu et al. found that MSCs-exosome reduced the severity of OA in vivo and also suppressed cell apoptosis, improved matrix generation, and decreased the catabolic factor expression in vitro (111). As well, MSCs-exosome also elevated autophagy levels in chondrocytes through down-regulation of mTOR. Further analysis showed that miR-100-5p composition in such exosomes inhibits the expression of mTOR protein by binding to mTOR 3'UTR and thereby inhibiting of mTOR signaling axis. MSCs-exosome ameliorated OA-related abnormalities through the supporting cartilage homeostasis (111). Also, MSCs derived exosomes could maintain the chondrocyte phenotype upon promotion of the collagen type II synthesis concomitant with ADAMTS5 expression, leading to alleviated cartilage destruction in vivo (112). Owing to the fact that ADAMTS5 is the main aggrecanase complicated in the pathogenesis of OA and also stimulates articular cartilage destruction and matrix degeneration, its inhibition by exosome can be reasonable and effective therapeutic modalities in OA (112). Also, WNT5A is recognized to be contributed to OA pathogenesis. In a recent report, miR-92a-3p enriched MSCs-exosome suppressed WNT5A expression in OA primary human chondrocytes (PHCs) in vitro (113). These exosomes also up-regulated matrix genes expression in PHCs and also improved their proliferation in vitro, and also attenuated cartilage destruction in the OA rodent model (113). This study in association with other reports has outlined the significance of exosomal miRNAs in ameliorating OA-related abnormalities in vivo. Likewise, human BMSC-derived exosomes overexpressing miR-26a-5p alleviated cartilage breakdown in the OA rat model by down-regulation of the expression of prostaglandin-endoperoxide synthase-2 (PTGS2), which is highly expressed in OA patients (114). PTGS2 activation typically underlies the production of PGD2 and subsequently stimulates neutrophil recruitment into the synovium of arthritis patients (115). Thereby, targeting PTGS2 by miR-26a-5p largely could inhibit synovial fibroblasts damages and results eventually in cartilage restoration. Similarly, the anti-inflammatory and chondroprotective impacts of MSC-derived exosomal miR-9-5p on OA by down-regulation of SDC1 expression were shown by and coworkers (116). Previous studies reported that G-protein-coupled receptor kinase interacting protein-1 (GIT1)-elicited mitogenic signals in chondrocytes by transducing ERK1/2 pathway lead to chondrocyte proliferation, and thereby up-regulation of its activation can reduce OA associated damages (117). Interestingly, lncRNA-KLF3-AS1 enriched human MSCs-exosome was found to trigger chondrocyte proliferation by sponging miR-206 to ease GIT1 expression, which in turn, brought about promoting chondrocyte growth and suppressing their apoptosis (118). Silencing of Y box binding protein 1 (YBX1) prevented MSC-exosome-mediated KLF3-AS1 from activating the PI3K/Akt/mTOR pathway in chondrocytes. Chondrocyte autophagy and apoptosis were suppressed by MSC-exosome-mediated KLF3-AS1 through stimulating the PI3K/Akt/mTOR pathway. Our findings show that IL-1-treated chondrocyte autophagy and apoptosis are inhibited by MSC-exosome-mediated KLF3-AS1 via the PI3K/Akt/mTOR signaling pathway. KLF3-AS1 targets YBX1 to engage the PI3K/Akt/mTOR axis and slow the development of osteoarthritis (119).

Currently, Wang et al. (2018) showed that TGF-β1 stimulation improved miR-135b expression in MSC-exosome (120). Thereafter, miR-135b decreased Sp1 expression, leading to induced chondrocyte proliferation and resultant cartilage rapier (120). MSCs pretreatment with kartogenin, an inducing factor of MSCs into

chondrocytes, also could potentiate MSCs-exosome capacity to enable stronger chondral matrix formation and less degradation (121, 122). By inhibiting the WNT-beta-catenin signaling pathway, MSC-derived exosome also reduced OA-induced chondrocyte senescence and synovial fibrosis in both in vivo and in vitro models. The miR-376c-3p in MSCs-exosome was also shown to reduce OA-induced chondrocyte breakdown and synovial fibrosis, according to the in vivo tests. By targeting WNT3 or WNT9a, MiR-376c-3p in exosomes inhibited OA's induction of chondrocyte degeneration and synovial fibrosis. This provided a theoretical foundation for the clinical application of treatment (123).

## CLINICAL TRIALS

*RA*

Promising preclinical results have encouraged researchers to evaluate the safety and efficacy of MSCs application in the clinic. Meanwhile, a phase I open-label trial verified the safety of systemic administration of $5 \times 10^7$ - $1 \times 10^8$ cells of hUCB-MSCs during 4 weeks follow-up (124). Also, the intervention reduced serum erythrocyte sedimentation rate (ESR), 1β, IL-6, IL-8, and TNF-α levels more strongly in $1 \times 10^8$ cells of hUCB-MSCs, justifying their application in RA patients (124). Also, systemic transplantation of autologous BM-MSCs ($1 \times 10^6$ /kg) led to up-regulation of the FOXP3 expression in PBMCs (125). Moreover, reduced levels of IL-10 and TGF-β1 levels indicated the suppressive influences of autologous BM-MSCs on Tregs in refractory RA patients (125). On the other hand, a single systemic administration of autologous BM-MSCs reduces the Th17 percentage in 9 patients with RA (126). The intervention also reduced ESR and visual analog scale (VAS) scores with no effect on CRP and anti-CCP levels. In sum, the clinical signs were considerably ameliorated following administration of the autologous BM-MSCs to RA patients (126). Cervus and Cucumis peptides (Lugua polypeptides, LG) as a traditional Chinese medicine showed synergistic effect with UC-MSCs in RA patients. A study in 119 patients suffering from RA demonstrated that LG could induce UC-MSCs to secret higher levels of anti-inflammatory molecules (127). In addition to the intravenous injection, another trial also exhibited that intra-articular knee implantation of MSCs was safe and well-tolerated (128).

*OA*

Like RA, clinical results have approved the feasibility, safety, modest efficacy of MSCs in knee OA. Meanwhile, Matas et al. showed that UC-MSCs ($20 \times 10^6$) injection had no untoward effect while reducing pain in OA patients (129). It has been suggested that the maximum impacts of hUC-MSCs are obtained after 6 months of transplantation (130). Besides, intra-articular transplantation of autologous AT-MSCs ($1 \times 10^8$) in 18 patients reduced the size of the cartilage defect and also enhanced cartilage volume with thick, hyaline-like cartilage (131). Intervention, in fact, restored function and reduced pain of the knee joint with no unwanted effects, conferring their capacity for OA therapy (131). The intra-articular administration of BM-MSCs also ameliorated OA outcomes, as evidenced by alteration in KOOS and ROM, which are typically used to assess disability and pain (132). As well, it was found that combination therapy with single intra-articular application of autologous BM- MSCs and hyaluronic acid ameliorated functional of knee OA in patients more evidently than direct implantation of BM-MSCs (133). Of course, patients receiving BM-MSCs also experienced amelioration clinically concerning the WOMAC (133). As predicted, reduction of synovial inflammation and cartilage degradation play central roles in BM-MSC-mediated amelioration in the function of knee OA post-transplantation (134). As well, BM-MSCs therapy plus microfracture and medial opening-wedge high tibial osteotomy (HTO) was found that exhibit better therapeutic outcomes in OA patients, as evidenced by promoting both short-term clinical and MOCART outcomes in treated patients (135). Another trial in 60 patients also indicated that injection of BM-MSCs in the subchondral bone of an OA knee has superiority over intra-articular implantation to delay total knee arthroplasty (TKA) (136, 137).

## CONCLUSION AND FUTURE DIRECTION

Many investigations with various animal models of orthopedic diseases, more frequently, OA and RA, have verified the capability of MSCs to exert favored effects in vivo. These effects are most probably elicited by MSCs competence to reduce inflammatory reaction and also stimulate immunomodulation by the release of a myriad of cytokine and other molecules. In fact, the

paracrine action of MSCs is the chief mechanism, which contributes to tissue repair following MSCs implantation. Notwithstanding, the desirable influences MSCs are usually unstable partly as a result of their heterogeneity. Thereby, clarification of the heterogeneity of MSCs in detail and the capacity of various types of MSCs for cartilage recovery can ease choosing better MSCs for cartilage regeneration. The intravenous and intra-articular route is the most commonly used route for MSCs delivery in clinical trials; however, the optimal route, as well as the optimal dose of cell transplantation, is still to be defined. Moreover, the conduction of large-scale studies is urgently required to elucidate the disadvantages of MSCs therapy. For instance, recruitment of neutrophil to knee joints, as shown upon MSCs impanation, was suggested that might harm cartilage regeneration. Then, further experiments are needed to verify the long-term safety of MSCs in addition to their efficacy. Due to that only a few cells survived in the place of transplantation, finding novel approaches to promote their viability post-transplantation is of paramount importance. Also, given that the quality of the human MSC product relies on the isolation and cultivation technique, the optimum isolation and culture method must be determined. Finally, considering risk factors such as immunological response and also infections following transplantation of allogeneic MSCs is necessary.

Moreover, it has been demonstrated that an essential component of MSC-based treatment for arthritis involves trophic substances encapsulated in extracellular vesicles (EVs), particularly exosomes. Exosomes produced from various MSC sources are clearly capable of protecting various joint cell types and rescuing the arthritis phenotype by focusing on numerous biological processes linked to cartilage ECM breakdown. Despite this development, arthritis exosome treatment studies have shown contradictory results depending on the exosome payload, cell source, and clinical status. These encouraging results imply that stem cell therapy may not be necessary and that therapeutic exosomes may be a new treatment option for arthritis patients. In order to reduce arthritis symptoms and possibly repair the damage to joints caused by arthritis, the development of therapeutic exosomes that target the condition promises to get around the limitations of current arthritis medications. Sadly, earlier research was mostly conducted in small animal models and at the preclinical stage. Exosome adoption as a cell-free biological product may be hampered in the future by the absence of extensive arthritis animal models and clinical studies. The development of smart therapeutic exosomes for osteoarthritis clinics will require the creation of inventive methods to modify drug exomes and deliver specific ones.

## DISCLOSURE STATEMENTS

None

## ACKNOWLEDGEMENT

None

## CONFLICT OF INTEREST

None

## FUNDING/SPONSORSHIP

None

## INSTITUTIONAL ETHICAL COMMITTEE APPROVAL (FOR ALL HUMAN STUDIES)

None

## AUTHORS CONTRIBUTION

Ahmed Hjazi: Conceptualization, Methodology, Writing – original draft, Writing – review & editing

Shadia Hamoud Alshahrani: Conceptualization, Methodology, Writing – review & editing

Shallal M. Hussein: Investigation, Methodology, Writing – original draft

Mohammed Kadhem Abid: Investigation, Writing – original draft

Beneen M. Hussien: Investigation, Software, Writing – original draft

## REFERENCES

1. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003;423(6937):356-61. https://doi.org/10.1038/nature01661
2. Glyn-Jones S, Palmer A, Agricola R, Price A, Vincent T, Weinans H, et al. Osteoarthritis. The Lancet. 2015; 386(9991):376-87. https://doi.org/10.1016/S0140-6736(14)60802-3
3. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clinical Orthopaedics and Related Research®. 2004;427:S6-S15. https://doi.org/10.1097/01.blo.0000143938.30681.9d
4. Sinusas K. Osteoarthritis: diagnosis and treatment. American family physician. 2012;85(1):49-56.
5. Latourte A, Kloppenburg M, Richette P. Emerging pharmaceutical therapies for osteoarthritis. Nature Reviews Rheumatology. 2020;16(12):673-88. https://doi.org/10.1038/s41584-020-00518-6
6. Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis,

and treatment options. Medical Clinics. 2020;104(2):293-311. https://doi.org/10.1016/j.mcna.2019.10.007
7. Gregori D, Giacovelli G, Minto C, Barbetta B, Gualtieri F, Azzolina D, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. Jama. 2018;320(24):2564-79. https://doi.org/10.1001/jama.2018.19319
8. Wu Y, Goh EL, Wang D, Ma S. Novel treatments for osteoarthritis: an update. Open access rheumatology: research and reviews. 2018;10:135. https://doi.org/10.2147/OARRR.S176666
9. Ross CL, Ang DC, Almeida-Porada G. Targeting mesenchymal stromal cells/pericytes (MSCs) with pulsed electromagnetic field (PEMF) has the potential to treat rheumatoid arthritis. Frontiers in immunology. 2019;10:266. https://doi.org/10.3389/fimmu.2019.00266
10. Feng Z, Zhai Y, Zheng Z, Yang L, Luo X, Dong X, et al. Loss of A20 in BM-MSCs regulates the Th17/Treg balance in rheumatoid arthritis. Scientific reports. 2018;8(1):1-11. https://doi.org/10.1038/s41598-017-18693-0
11. Marofi F, Hassanzadeh A, Solali S, Vahedi G, Mousavi Ardehaie R, Salarinasab S, et al. Epigenetic mechanisms are behind the regulation of the key genes associated with the osteoblastic differentiation of the mesenchymal stem cells: The role of zoledronic acid on tuning the epigenetic changes. Journal of cellular physiology. 2019;234(9):15108-22. https://doi.org/10.1002/jcp.28152
12. Ahani-Nahayati M, Shariati A, Mahmoodi M, Olegovna Zekiy A, Javidi K, Shamlou S, et al. Stem cell in neurodegenerative disorders; an emerging strategy. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience. 2021. https://doi.org/10.1002/jdn.10101
13. Arrigoni C, D'Arrigo D, Rossella V, Candrian C, Albertini V, Moretti M. Umbilical cord MSCs and their secretome in the therapy of arthritic diseases: a research and industrial perspective. Cells. 2020;9(6):1343. https://doi.org/10.3390/cells9061343
14. Markov A, Thangavelu L, Aravindhan S, Zekiy AO, Jarahian M, Chartrand MS, et al. Mesenchymal stem/stromal cells as a valuable source for the treatment of immune-mediated disorders. Stem cell research & therapy. 2021;12(1):1-30. https://doi.org/10.1186/s13287-021-02265-1
15. Geng Y, Chen J, Alahdal M, Chang C, Duan L, Zhu W, et al. Intra-articular injection of hUC-MSCs expressing miR-140-5p induces cartilage self-repairing in the rat osteoarthritis. Journal of bone and mineral metabolism. 2020;38(3):277-88. https://doi.org/10.1007/s00774-019-01055-3
16. Kim SH, Ha C-W, Park Y-B, Nam E, Lee J-E, Lee H-J. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. Archives of orthopaedic and trauma surgery. 2019;139(7):971-80. https://doi.org/10.1007/s00402-019-03140-8
17. Lv X, Wang L, Zou X, Huang S. Umbilical Cord Mesenchymal Stem Cell Therapy for Regenerative Treatment of Rheumatoid Arthritis: Opportunities and Challenges. Drug design, development and therapy. 2021;15:3927. https://doi.org/10.2147/DDDT.S323107
18. Berthelot J-M, Le Goff B, Maugars Y. Bone marrow mesenchymal stem cells in rheumatoid arthritis, spondyloarthritis, and ankylosing spondylitis: problems rather than solutions? Arthritis research & therapy. 2019;21(1):1-9. https://doi.org/10.1186/s13075-019-2014-8
19. Zadi Heydarabad M, Baharaghdam S, Azimi A, Mohammadi H, Eivazi Ziaei J, Yazdanpanah B, et al. The role of tumor suppressor of resveratrol and prednisolone by downregulation of YKL-40 expression in CCRF-CEM cell line. Journal of Cellular Biochemistry. 2019;120(3):3773-9. https://doi.org/10.1002/jcb.27659
20. Yazdanpanah S, Esmaeili S, Bashash D, Nayeri ND, Farahani ME, Gharehbaghian A. Cytotoxic and apoptogenic activity of Bryonia aspera extract on pre-B acute lymphoblastic leukemia cell lines. International Journal of Hematology-Oncology and Stem Cell Research. 2018;12(3):204.
21. Esfini-Farahani M, Farshdousti-Hagh M, Bashash D, Esmaeili S, Dehghan-Nayeri N, Yazdanpanah S, et al. Analysis of cytotoxic activity and synergistic effect of curcuma longa extract in combination with prednisolone on acute lymphoblastic leukemia cell lines. International Journal of Cancer Management. 2017;10(11). https://doi.org/10.5812/ijcm.14174
22. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019;393(10182):1745-59. https://doi.org/10.1016/S0140-6736(19)30417-9
23. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. Journal of pain research. 2018;11:2189. https://doi.org/10.2147/JPR.S154002
24. Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. Osteoarthritis and Cartilage. 2020;28(3):242-8. https://doi.org/10.1016/j.joca.2020.01.002
25. Ogawa H, Matsumoto K, Akiyama H. Functional assessment of the anterior cruciate ligament in knee osteoarthritis. Journal of Orthopaedics. 2021;23:175-9. https://doi.org/10.1016/j.jor.2020.12.035
26. Hsia AW. Osteophyte Formation in Post-traumatic Osteoarthritis: University of California, Davis; 2019.
27. Chow YY, Chin K-Y. The role of inflammation in the pathogenesis of osteoarthritis. Mediators of inflammation. 2020;2020. https://doi.org/10.1155/2020/8293921
28. Griffin TM, Scanzello CR. Innate inflammation and synovial macrophages in osteoarthritis pathophysiology. Clinical and experimental rheumatology. 2019;37(Suppl 120):57.
29. Jin X, Beguerie JR, Zhang W, Blizzard L, Otahal P, Jones G, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(4):703-10. https://doi.org/10.1136/annrheumdis-2013-204494
30. Kim YK, Yeo MG. Treatment with ultra-dilutions of Arnica montana increases COX-2 expression and PGE2 secretion in mouse chondrocytes. Journal of the Korea Convergence Society. 2019;10(2):331-7.
31. Woodell-May JE, Sommerfeld SD. Role of inflammation and the immune system in the progression of osteoarthritis. Journal of Orthopaedic Research®. 2020;38(2):253-7. https://doi.org/10.1002/jor.24457
32. Van Den Bosch M. Inflammation in osteoarthritis: is it time to dampen the alarm (in) in this debilitating disease? Clinical & Experimental Immunology. 2019;195(2):153-66. https://doi.org/10.1111/cei.13237
33. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. Jama. 2018;320(13):1360-72. https://doi.org/10.1001/jama.2018.13103
34. Xie S, Li S, Chen B, Zhu Q, Xu L, Li F. Serum anti-citrullinated protein antibodies and rheumatoid factor increase the risk of rheumatoid arthritis-related interstitial lung disease: a meta-analysis. Clinical Rheumatology. 2021;40(11):4533-43. https://doi.org/10.1007/s10067-021-05808-2
35. Zhai K-f, Duan H, Chen Y, Khan GJ, Cao W-g, Gao G-z, et al.

Apoptosis effects of imperatorin on synoviocytes in rheumatoid arthritis through mitochondrial/caspase-mediated pathways. Food & function. 2018;9(4):2070-9. https://doi.org/10.1039/C7FO01748K
36. Firestein GS, Yeo M, Zvaifler NJ. Apoptosis in rheumatoid arthritis synovium. The Journal of clinical investigation. 1995;96(3):1631-8. https://doi.org/10.1172/JCI118202
37. Wright HL, Moots RJ, Edwards SW. The multifactorial role of neutrophils in rheumatoid arthritis. Nature Reviews Rheumatology. 2014;10(10):593-601. https://doi.org/10.1038/nrrheum.2014.80
38. Pap T, Van Der Laan WH, Aupperle KR, Gay RE, Verheijen JH, Firestein GS, et al. Modulation of fibroblast-mediated cartilage degradation by articular chondrocytes in rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2000;43(11):2531-6. https://doi.org/10.1002/1529-0131(200011)43:11<2531::AID-ANR21>3.0.CO;2-V
39. Zuo J, Yin Q, Wang Y-W, Li Y, Lu L-M, Xiao Z-G, et al. Inhibition of NF-κB pathway in fibroblast-like synoviocytes by α-mangostin implicated in protective effects on joints in rats suffering from adjuvant-induced arthritis. International immunopharmacology. 2018;56:78-89. https://doi.org/10.1016/j.intimp.2018.01.016
40. Liu Y, Mu R, Wang S, Long L, Liu X, Li R, et al. Therapeutic potential of human umbilical cord mesenchymal stem cells in the treatment of rheumatoid arthritis. Arthritis research & therapy. 2010;12(6):1-13. https://doi.org/10.1186/ar3187
41. O'Sullivan J, D'Arcy S, Barry FP, Murphy J, Coleman CM. Mesenchymal chondroprogenitor cell origin and therapeutic potential. Stem cell research & therapy. 2011;2(1):8. https://doi.org/10.1186/scrt49
42. Fan H, Zhang C, Li J, Bi L, Qin L, Wu H, et al. Gelatin microspheres containing TGF-β3 enhance the chondrogenesis of mesenchymal stem cells in modified pellet culture. Biomacromolecules. 2008;9(3):927-34. https://doi.org/10.1021/bm7013203
43. Grigull NP, Redeker JI, Schmitt B, Saller MM, Schönitzer V, Mayer-Wagner S. Chondrogenic Potential of Pellet Culture Compared to High-Density Culture on a Bacterial Cellulose Hydrogel. International journal of molecular sciences. 2020;21(8):2785. https://doi.org/10.3390/ijms21082785
44. Watts AE, Ackerman-Yost JC, Nixon AJ. A comparison of three-dimensional culture systems to evaluate in vitro chondrogenesis of equine bone marrow-derived mesenchymal stem cells. Tissue engineering Part A. 2013;19(19-20):2275-83. https://doi.org/10.1089/ten.tea.2012.0479
45. Futrega K, Robey PG, Klein TJ, Crawford RW, Doran MR. A single day of TGF-β1 exposure activates chondrogenic and hypertrophic differentiation pathways in bone marrow-derived stromal cells. Communications Biology. 2021;4(1):29. https://doi.org/10.1038/s42003-020-01520-0
46. Schmitt B, Ringe J, Häupl T, Notter M, Manz R, Burmester GR, et al. BMP2 initiates chondrogenic lineage development of adult human mesenchymal stem cells in high-density culture. Differentiation; research in biological diversity. 2003;71(9-10):567-77. https://doi.org/10.1111/j.1432-0436.2003.07109003.x
47. Estes BT, Wu AW, Guilak F. Potent induction of chondrocytic differentiation of human adipose-derived adult stem cells by bone morphogenetic protein 6. Arthritis and rheumatism. 2006;54(4):1222-32. https://doi.org/10.1002/art.21779
48. Boeuf S, Richter W. Chondrogenesis of mesenchymal stem cells: role of tissue source and inducing factors. Stem cell research & therapy. 2010;1(4):31. https://doi.org/10.1186/scrt31
49. Fahy N, Alini M, Stoddart MJ. Mechanical stimulation of mesenchymal stem cells: Implications for cartilage tissue engineering. Journal of Orthopaedic Research®. 2018;36(1):52-63. https://doi.org/10.1002/jor.23670
50. Kanichai M, Ferguson D, Prendergast PJ, Campbell VA. Hypoxia promotes chondrogenesis in rat mesenchymal stem cells: A role for AKT and hypoxia-inducible factor (HIF)-1α. Journal of cellular physiology. 2008;216(3):708-15. https://doi.org/10.1002/jcp.21446
51. Cui JH, Park K, Park SR, Min B-H. Effects of low-intensity ultrasound on chondrogenic differentiation of mesenchymal stem cells embedded in polyglycolic acid: an in vivo study. Tissue engineering. 2006;12(1):75-82. https://doi.org/10.1089/ten.2006.12.75
52. Aung A, Gupta G, Majid G, Varghese S. Osteoarthritic chondrocyte-secreted morphogens induce chondrogenic differentiation of human mesenchymal stem cells. Arthritis & Rheumatism. 2011;63(1):148-58. https://doi.org/10.1002/art.30086
53. Fahy N, De Vries-Van Melle M, Lehmann J, Wei W, Grotenhuis N, Farrell E, et al. Human osteoarthritic synovium impacts chondrogenic differentiation of mesenchymal stem cells via macrophage polarisation state. Osteoarthritis and cartilage. 2014;22(8):1167-75. https://doi.org/10.1016/j.joca.2014.05.021
54. Somoza RA, Welter JF, Correa D, Caplan AI. Chondrogenic differentiation of mesenchymal stem cells: challenges and unfulfilled expectations. Tissue Engineering Part B: Reviews. 2014;20(6):596-608. https://doi.org/10.1089/ten.teb.2013.0771
55. Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J. Mesenchymal stem cells for regenerative medicine. Cells. 2019;8(8):886. https://doi.org/10.3390/cells8080886
56. Sobacchi C, Palagano E, Villa A, Menale C. Soluble factors on stage to direct mesenchymal stem cells fate. Frontiers in bioengineering and biotechnology. 2017;5:32. https://doi.org/10.3389/fbioe.2017.00032
57. Joel MDM, Yuan J, Wang J, Yan Y, Qian H, Zhang X, et al. MSC: immunoregulatory effects, roles on neutrophils and evolving clinical potentials. American journal of translational research. 2019;11(6):3890-904.
58. Gao F, Chiu S, Motan D, Zhang Z, Chen L, Ji H, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. Cell death & disease. 2016;7(1):e2062-e. https://doi.org/10.1038/cddis.2015.327
59. Cheung TS, Galleu A, von Bonin M, Bornhäuser M, Dazzi F. Apoptotic mesenchymal stromal cells induce prostaglandin E2 in monocytes: implications for the monitoring of mesenchymal stromal cell activity. haematologica. 2019;104(10):e438. https://doi.org/10.3324/haematol.2018.214767
60. Zhao X, Zhao Y, Sun X, Xing Y, Wang X, Yang Q. Immunomodulation of MSCs and MSC-derived extracellular vesicles in osteoarthritis. Frontiers in Bioengineering and Biotechnology. 2020;8. https://doi.org/10.3389/fbioe.2020.575057
61. Liu Y, Mu R, Wang S, Long L, Liu X, Li R, et al. Therapeutic potential of human umbilical cord mesenchymal stem cells in the treatment of rheumatoid arthritis. Arthritis research & therapy. 2010;12(6):R210. https://doi.org/10.1186/ar3187
62. Coimbra R, Junger W, Liu F, Loomis W, Hoyt D. Hypertonic/hyperoncotic fluids reverse prostaglandin E2 (PGE2)-induced T-cell suppression. Shock (Augusta, Ga). 1995;4(1):45-9. https://doi.org/10.1097/00024382-199507000-00007
63. Gualdoni GS, Jacobo PV, Sobarzo CM, Pérez CV, Matzkin

ME, Höcht C, et al. Role of indoleamine 2, 3-dioxygenase in testicular immune-privilege. Scientific reports. 2019;9(1):1-14. https://doi.org/10.1038/s41598-019-52192-8
64. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood. 2007;109(1):228-34. https://doi.org/10.1182/blood-2006-02-002246
65. Edwards TM, Rickard NS. New perspectives on the mechanisms through which nitric oxide may affect learning and memory processes. Neuroscience & Biobehavioral Reviews. 2007;31(3):413-25. https://doi.org/10.1016/j.neubiorev.2006.11.001
66. Eljarrah A, Gergues M, Pobiarzyn PW, Sandiford OA, Rameshwar P. Therapeutic Potential of Mesenchymal Stem Cells in Immune-Mediated Diseases. Stem Cells: Springer; 2019. p. 93-108. https://doi.org/10.1007/978-3-030-31206-0_5
67. Kusuma GD, Carthew J, Lim R, Frith JE. Effect of the microenvironment on mesenchymal stem cell paracrine signaling: opportunities to engineer the therapeutic effect. Stem cells and development. 2017;26(9):617-31. https://doi.org/10.1089/scd.2016.0349
68. Cheng HY, Ghetu N, Wallace C, Wei F, Liao S. The impact of mesenchymal stem cell source on proliferation, differentiation, immunomodulation and therapeutic efficacy. J Stem Cell Res Ther. 2014;4(10):1-8.
69. Lee JM, Jung J, Lee H-J, Jeong SJ, Cho KJ, Hwang S-G, et al. Comparison of immunomodulatory effects of placenta mesenchymal stem cells with bone marrow and adipose mesenchymal stem cells. International immunopharmacology. 2012;13(2):219-24. https://doi.org/10.1016/j.intimp.2012.03.024
70. Fazekasova H, Lechler R, Langford K, Lombardi G. Placenta-derived MSCs are partially immunogenic and less immunomodulatory than bone marrow-derived MSCs. Journal of tissue engineering and regenerative medicine. 2011;5(9):684-94. https://doi.org/10.1002/term.362
71. Pedrosa M, Gomes J, Laranjeira P, Duarte C, Pedreiro S, Antunes B, et al. Immunomodulatory effect of human bone marrow-derived mesenchymal stromal/stem cells on peripheral blood T cells from rheumatoid arthritis patients. Journal of tissue engineering and regenerative medicine. 2020;14(1):16-28. https://doi.org/10.1002/term.2958
72. Liu R, Li X, Zhang Z, Zhou M, Sun Y, Su D, et al. Allogeneic mesenchymal stem cells inhibited T follicular helper cell generation in rheumatoid arthritis. Scientific reports. 2015;5(1):1-11. https://doi.org/10.1038/srep12777
73. Wei J, Ouyang X, Tang Y, Li H, Wang B, Ye Y, et al. ER-stressed MSC displayed more effective immunomodulation in RA CD4+ CXCR5+ ICOS+ follicular helper-like T cells through higher PGE2 binding with EP2/EP4. Modern rheumatology. 2020;30(3):509-16. https://doi.org/10.1080/14397595.2019.1651446
74. Sun Y, Deng W, Geng L, Zhang L, Liu R, Chen W, et al. Mesenchymal stem cells from patients with rheumatoid arthritis display impaired function in inhibiting Th17 cells. Journal of immunology research. 2015;2015. https://doi.org/10.1155/2015/284215
75. Polykratis A, Martens A, Eren RO, Shirasaki Y, Yamagishi M, Yamaguchi Y, et al. A20 prevents inflammasome-dependent arthritis by inhibiting macrophage necroptosis through its ZnF7 ubiquitin-binding domain. Nature cell biology. 2019;21(6):731-42. https://doi.org/10.1038/s41556-019-0324-3
76. Ma D, Xu K, Zhang G, Liu Y, Gao J, Tian M, et al. Immunomodulatory effect of human umbilical cord mesenchymal stem cells on T lymphocytes in rheumatoid arthritis. International immunopharmacology. 2019;74:105687. https://doi.org/10.1016/j.intimp.2019.105687
77. Shin T-H, Kim H-S, Kang T-W, Lee B-C, Lee H-Y, Kim Y-J, et al. Human umbilical cord blood-stem cells direct macrophage polarization and block inflammasome activation to alleviate rheumatoid arthritis. Cell death & disease. 2016;7(12):e2524-e. https://doi.org/10.1038/cddis.2016.442
78. Guo C, Fu R, Wang S, Huang Y, Li X, Zhou M, et al. NLRP3 inflammasome activation contributes to the pathogenesis of rheumatoid arthritis. Clinical & Experimental Immunology. 2018;194(2):231-43. https://doi.org/10.1111/cei.13167
79. Baeuerle PA, Baichwal VR. NF-kB as a frequent target for immunosuppressive and anti-inflammatory molecules. Advances in immunology. 1997;65:111-38. https://doi.org/10.1016/S0065-2776(08)60742-7
80. Tak PP, Firestein GS. NF-κB: a key role in inflammatory diseases. The Journal of clinical investigation. 2001;107(1):7-11. https://doi.org/10.1172/JCI11830
81. Yan X, Cen Y, Wang Q. Mesenchymal stem cells alleviate experimental rheumatoid arthritis through microRNA-regulated IκB expression. Scientific reports. 2016;6(1):1-12. https://doi.org/10.1038/srep28915
82. Liu W, Wu Y-H, Zhang L, Xue B, Wang Y, Liu B, et al. MicroRNA-146a suppresses rheumatoid arthritis fibroblast-like synoviocytes proliferation and inflammatory responses by inhibiting the TLR4/NF-kB signaling. Oncotarget. 2018;9(35):23944. https://doi.org/10.18632/oncotarget.24050
83. Haikal SM, Abdeltawab NF, Rashed LA, El-Galil A, Tarek I, Elmalt HA, et al. Combination therapy of mesenchymal stromal cells and interleukin-4 attenuates rheumatoid arthritis in a collagen-induced murine model. Cells. 2019;8(8):823. https://doi.org/10.3390/cells8080823
84. Ghaffary EM, Froushani SMA. Immunomodulatory benefits of mesenchymal stem cells treated with caffeine in adjuvant-induced arthritis. Life sciences. 2020;246:117420. https://doi.org/10.1016/j.lfs.2020.117420
85. Yamagata K, Nakayamada S, Zhang T, Zhang X, Tanaka Y. Soluble IL-6R promotes chondrogenic differentiation of mesenchymal stem cells to enhance the repair of articular cartilage defects using a rat model for rheumatoid arthritis. Clinical and experimental rheumatology. 2019;38(4):670-9. https://doi.org/10.1186/s41232-018-0061-1
86. Sonomoto K, Yamaoka K, Kaneko H, Yamagata K, Sakata K, Zhang X, et al. Spontaneous differentiation of human mesenchymal stem cells on poly-lactic-co-glycolic acid nano-fiber scaffold. PloS one. 2016;11(4):e0153231. https://doi.org/10.1371/journal.pone.0153231
87. Hu J, Li H, Chi G, Yang Z, Zhao Y, Liu W, et al. IL-1RA gene-transfected bone marrow-derived mesenchymal stem cells in APA microcapsules could alleviate rheumatoid arthritis. International journal of clinical and experimental medicine. 2015;8(1):706.
88. Phinney DG, , Pittenger MF. Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. Stem Cells. 2017;35(4):851-8. https://doi.org/10.1002/stem.2575
89. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. Journal of Cell Biology. 2013;200(4):373-83. https://doi.org/10.1083/jcb.201211138
90. Chen Z, Wang H, Xia Y, Yan F, Lu Y. Therapeutic Potential of Mesenchymal Cell-Derived miRNA-150-5p-Expressing Exosomes in Rheumatoid Arthritis Mediated by the Modulation of MMP14 and VEGF. Journal of immunology (Baltimore, Md : 1950). 2018;201(8):2472-82. https://doi.

org/10.4049/jimmunol.1800304
91. Tavasolian F, Hosseini AZ, Soudi S, Naderi M. miRNA-146a Improves Immunomodulatory Effects of MSC-derived Exosomes in Rheumatoid Arthritis. Current gene therapy. 2020;20(4):297-312. https://doi.org/10.2174/1566523220666200916120708
92. Meng Q, Qiu B. Exosomal MicroRNA-320a Derived From Mesenchymal Stem Cells Regulates Rheumatoid Arthritis Fibroblast-Like Synoviocyte Activation by Suppressing CXCL9 Expression. Frontiers in physiology. 2020;11:441. https://doi.org/10.3389/fphys.2020.00441
93. Su Y, Liu Y, Ma C, Guan C, Ma X, Meng S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. Journal of orthopaedic surgery and research. 2021;16(1):116. https://doi.org/10.1186/s13018-021-02248-1
94. Tsujimaru K, Takanashi M, Sudo K, Ishikawa A, Mineo S, Ueda S, et al. Extracellular microvesicles that originated adipose tissue derived mesenchymal stem cells have the potential ability to improve rheumatoid arthritis on mice. Regenerative therapy. 2020;15:305-11. https://doi.org/10.1016/j.reth.2020.08.004
95. Arend WP. The balance between IL-1 and IL-1Ra in disease. Cytokine & growth factor reviews. 2002;13(4-5):323-40. https://doi.org/10.1016/S1359-6101(02)00020-5
96. Fernandez-Pernas P, Rodríguez-Lesende I, de la Fuente A, Mateos J, Fuentes I, De Toro J, et al. CD105+-mesenchymal stem cells migrate into osteoarthritis joint: An animal model. PloS one. 2017;12(11):e0188072. https://doi.org/10.1371/journal.pone.0188072
97. Toghraie FS, Chenari N, Gholipour MA, Faghih Z, Torabinejad S, Dehghani S, et al. Treatment of osteoarthritis with infrapatellar fat pad derived mesenchymal stem cells in Rabbit. The Knee. 2011;18(2):71-5. https://doi.org/10.1016/j.knee.2010.03.001
98. Cui YP, Cao YP, Liu H, Yang X, Meng ZC, Wang R. [Bone marrow mesenchymal stem cells in Sprague-Dawley rat model of osteoarthritis]. Beijing da xue xue bao Yi xue ban = Journal of Peking University Health sciences. 2015;47(2):211-8.
99. Yun S, Ku SK, Kwon YS. Adipose-derived mesenchymal stem cells and platelet-rich plasma synergistically ameliorate the surgical-induced osteoarthritis in Beagle dogs. Journal of orthopaedic surgery and research. 2016;11:9. https://doi.org/10.1186/s13018-016-0342-9
100. Kim H, Yang G, Park J, Choi J, Kang E, Lee BK. Therapeutic effect of mesenchymal stem cells derived from human umbilical cord in rabbit temporomandibular joint model of osteoarthritis. Scientific reports. 2019;9(1):13854. https://doi.org/10.1038/s41598-019-50435-2
101. Ichiseki T, Shimazaki M, Ueda Y, Ueda S, Tsuchiya M, Souma D, et al. Intraarticularly-Injected Mesenchymal Stem Cells Stimulate Anti-Inflammatory Molecules and Inhibit Pain Related Protein and Chondrolytic Enzymes in a Monoiodoacetate-Induced Rat Arthritis Model. International journal of molecular sciences. 2018;19(1). https://doi.org/10.3390/ijms19010203
102. Apte SS. Anti-ADAMTS5 monoclonal antibodies: implications for aggrecanase inhibition in osteoarthritis. The Biochemical journal. 2016;473(1):e1-e4. https://doi.org/10.1042/BJ20151072
103. Glasson SS, Askew R, Sheppard B, Carito B, Blanchet T, Ma H-L, et al. Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis. Nature. 2005;434(7033):644-8. https://doi.org/10.1038/nature03369
104. Xia Q, Zhu S, Wu Y, Wang J, Cai Y, Chen P, et al. Intra-articular transplantation of atsttrin-transduced mesenchymal stem cells ameliorate osteoarthritis development. Stem cells translational medicine. 2015;4(5):523-31. https://doi.org/10.5966/sctm.2014-0200
105. Barrachina L, Remacha AR, Romero A, Vitoria A, Albareda J, Prades M, et al. Assessment of effectiveness and safety of repeat administration of proinflammatory primed allogeneic mesenchymal stem cells in an equine model of chemically induced osteoarthritis. BMC veterinary research. 2018;14(1):1-17. https://doi.org/10.1186/s12917-018-1556-3
106. Wang X-d, Wan X-c, Liu A-f, Li R, Wei Q. Effects of umbilical cord mesenchymal stem cells loaded with graphene oxide granular lubrication on cytokine levels in animal models of knee osteoarthritis. International orthopaedics. 2021;45(2):381-90. https://doi.org/10.1007/s00264-020-04584-z
107. Stancker TG, Vieira SS, Serra AJ, do Nascimento Lima R, dos Santos Feliciano R, Silva JA, et al. Can photobiomodulation associated with implantation of mesenchymal adipose-derived stem cells attenuate the expression of MMPs and decrease degradation of type II collagen in an experimental model of osteoarthritis? Lasers in medical science. 2018;33(5):1073-84. https://doi.org/10.1007/s10103-018-2466-0
108. Grigolo B, Lisignoli G, Desando G, Cavallo C, Marconi E, Tschon M, et al. Osteoarthritis treated with mesenchymal stem cells on hyaluronan-based scaffold in rabbit. Tissue Engineering Part C: Methods. 2009;15(4):647-58. https://doi.org/10.1089/ten.tec.2008.0569
109. Tseng WJ, Huang S-W, Fang C-H, Hsu L-T, Chen C-Y, Shen H-H, et al. Treatment of osteoarthritis with collagen-based scaffold: A porcine animal model with xenograft mesenchymal stem cells. Histology and histopathology. 2018;33(12):1271-86.
110. Khatab S, van Osch GJ, Kops N, Bastiaansen-Jenniskens YM, Bos PK, Verhaar JA, et al. Mesenchymal stem cell secretome reduces pain and prevents cartilage damage in a murine osteoarthritis model. European cells & materials. 2018;36:218-30. https://doi.org/10.22203/eCM.v036a16
111. Wu J, Kuang L, Chen C, Yang J, Zeng WN, Li T, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. Biomaterials. 2019;206:87-100. https://doi.org/10.1016/j.biomaterials.2019.03.022
112. Wang Y, Yu D, Liu Z, Zhou F, Dai J, Wu B, et al. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. Stem cell research & therapy. 2017;8(1):189. https://doi.org/10.1186/s13287-017-0632-0
113. Mao G, Zhang Z, Hu S, Zhang Z, Chang Z, Huang Z, et al. Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A. Stem cell research & therapy. 2018;9(1):247. https://doi.org/10.1186/s13287-018-1004-0
114. Jin Z, Ren J, Qi S. Human bone mesenchymal stem cells-derived exosomes overexpressing microRNA-26a-5p alleviate osteoarthritis via down-regulation of PTGS2. International immunopharmacology. 2020;78:105946. https://doi.org/10.1016/j.intimp.2019.105946
115. Mishima S, Kashiwakura JI, Toyoshima S, Sasaki-Sakamoto T, Sano Y, Nakanishi K, et al. Higher PGD(2) production by

synovial mast cells from rheumatoid arthritis patients compared with osteoarthritis patients via miR-199a-3p/prostaglandin synthetase 2 axis. Scientific reports. 2021;11(1):5738. https://doi.org/10.1038/s41598-021-84963-7
116. Jin Z, Ren J, Qi S. Exosomal miR-9-5p secreted by bone marrow-derived mesenchymal stem cells alleviates osteoarthritis by inhibiting syndecan-1. Cell and tissue research. 2020;381(1):99-114. https://doi.org/10.1007/s00441-020-03193-x
117. Ren K, Tang J, Jiang X, Sun H, Nong L, Shen N, et al. Periodic Mechanical Stress Stimulates GIT1-Dependent Mitogenic Signals in Rat Chondrocytes Through ERK1/2 Activity. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2018;50(3):1015-28. https://doi.org/10.1159/000494513
118. Liu Y, Lin L, Zou R, Wen C, Wang Z, Lin F. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. Cell Cycle. 2018;17(21-22):2411-22. https://doi.org/10.1080/15384101.2018.1526603
119. Wen C, Lin L, Zou R, Lin F, Liu Y. Mesenchymal stem cell-derived exosome mediated long non-coding RNA KLF3-AS1 represses autophagy and apoptosis of chondrocytes in osteoarthritis. Cell Cycle. 2022;21(3):289-303. https://doi.org/10.1080/15384101.2021.2019411
120. Wang R, Xu B, Xu H. TGF-β1 promoted chondrocyte proliferation by regulating Sp1 through MSC-exosomes derived miR-135b. Cell Cycle. 2018;17(24):2756-65. https://doi.org/10.1080/15384101.2018.1556063
121. Liu C, Li Y, Yang Z, Zhou Z, Lou Z, Zhang Q. Kartogenin enhances the therapeutic effect of bone marrow mesenchymal stem cells derived exosomes in cartilage repair. Nanomedicine (London, England). 2020;15(3):273-88. https://doi.org/10.2217/nnm-2019-0208
122. Shao J, Zhu J, Chen Y, Fu Q, Li L, Ding Z, et al. Exosomes from Kartogenin-Pretreated Infrapatellar Fat Pad Mesenchymal Stem Cells Enhance Chondrocyte Anabolism and Articular Cartilage Regeneration. Stem Cells Int. 2021;2021:6624874. https://doi.org/10.1155/2021/6624874
123. Li F, Xu Z, Xie Z, Sun X, Li C, Chen Y, et al. Adipose mesenchymal stem cells-derived exosomes alleviate osteoarthritis by transporting microRNA -376c-3p and targeting the WNT-beta-catenin signaling axis. Apoptosis : an international journal on programmed cell death. 2022.
124. Park EH, Lim HS, Lee S, Roh K, Seo KW, Kang KS, et al. Intravenous Infusion of Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Rheumatoid Arthritis: A Phase Ia Clinical Trial. Stem cells translational medicine. 2018;7(9):636-42. https://doi.org/10.1002/sctm.18-0031
125. Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Mohammadi M. The Sufficient Immunoregulatory Effect of Autologous Bone Marrow-Derived Mesenchymal Stem Cell Transplantation on Regulatory T Cells in Patients with Refractory Rheumatoid Arthritis. Journal of immunology research. 2020;2020:3562753. https://doi.org/10.1155/2020/3562753
126. Ghoryani M, Shariati-Sarabi Z, Tavakkol-Afshari J, Ghasemi A, Poursamimi J, Mohammadi M. Amelioration of clinical symptoms of patients with refractory rheumatoid arthritis following treatment with autologous bone marrow-derived mesenchymal stem cells: A successful clinical trial in Iran. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;109:1834-40. https://doi.org/10.1016/j.biopha.2018.11.056
127. Qi T, Gao H, Dang Y, Huang S, Peng M. Cervus and cucumis peptides combined umbilical cord mesenchymal stem cells therapy for rheumatoid arthritis. Medicine (Baltimore). 2020;99(28):e21222. https://doi.org/10.1097/MD.0000000000021222
128. Shadmanfar S, Labibzadeh N, Emadedin M, Jaroughi N, Azimian V, Mardpour S, et al. Intra-articular knee implantation of autologous bone marrow-derived mesenchymal stromal cells in rheumatoid arthritis patients with knee involvement: Results of a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. Cytotherapy. 2018;20(4):499-506. https://doi.org/10.1016/j.jcyt.2017.12.009
129. Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: Repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. Stem cells translational medicine. 2019;8(3):215-24. https://doi.org/10.1002/sctm.18-0053
130. Dilogo IH, Canintika AF, Hanitya AL, Pawitan JA, Liem IK, Pandelaki J. Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study. European Journal of Orthopaedic Surgery & Traumatology. 2020;30(5):799-807. https://doi.org/10.1007/s00590-020-02630-5
131. Jo CH, Chai JW, Jeong EC, Oh S, Shin JS, Shim H, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a 2-year follow-up study. The American journal of sports medicine. 2017;45(12):2774-83. https://doi.org/10.1177/0363546517716641
132. Bastos R, Mathias M, Andrade R, Amaral RJ, Schott V, Balduino A, et al. Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2020;28(6):1989-99. https://doi.org/10.1007/s00167-019-05732-8
133. Lamo-Espinosa JM, Mora G, Blanco JF, Granero-Moltó F, Núñez-Córdoba JM, López-Elío S, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II). Journal of translational medicine. 2018;16(1):1-5. https://doi.org/10.1186/s12967-018-1591-7
134. Chahal J, Gómez-Aristizábal A, Shestopaloff K, Bhatt S, Chaboureau A, Fazio A, et al. Bone marrow mesenchymal stromal cell treatment in patients with osteoarthritis results in overall improvement in pain and symptoms and reduces synovial inflammation. Stem cells translational medicine. 2019;8(8):746-57. https://doi.org/10.1002/sctm.18-0183
135. Wong KL, Lee KBL, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 Years' follow-up. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2013;29(12):2020-8. https://doi.org/10.1016/j.arthro.2013.09.074
136. Hernigou P, Bouthors C, Bastard C, Lachaniette CHF, Rouard H, Dubory A. Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study. International orthopaedics. 2021;45(2):391-9. https://doi.

org/10.1007/s00264-020-04687-7
137. Hernigou P, Delambre J, Quiennec S, Poignard A. Human bone marrow mesenchymal stem cell injection in subchondral lesions of knee osteoarthritis: a prospective randomized study versus contralateral arthroplasty at a mean fifteen year follow-up. International orthopaedics. 2021;45(2):365-73. https://doi.org/10.1007/s00264-020-04571-4
138. Lee K, Park N, Jung H, Rim YA, Nam Y, Lee J, et al. Mesenchymal stem cells ameliorate experimental arthritis via expression of interleukin-1 receptor antagonist. PloS one. 2018;13(2):e0193086.https://doi.org/10.1371/journal.pone.0193086
139. Li F, Li X, Liu G, Gao C, Li X. Bone Marrow Mesenchymal Stem Cells Decrease the Expression of RANKL in Collagen-Induced Arthritis Rats via Reducing the Levels of IL-22. Journal of immunology research. 2019;2019:8459281. https://doi.org/10.1155/2019/8459281
140. Ma D, Xu K, Zhang G, Liu Y, Gao J, Tian M, et al. Immunomodulatory effect of human umbilical cord mesenchymal stem cells on T lymphocytes in rheumatoid arthritis. International immunopharmacology. 2019;74:105687. https://doi.org/10.1016/j.intimp.2019.105687
141. Abd-Elhalem SS, Haggag NZ, El-Shinnawy NA. Bone marrow mesenchymal stem cells suppress IL-9 in adjuvant-induced arthritis. Autoimmunity. 2018;51(1):25-34. https://doi.org/10.1080/08916934.2018.1428956
142. Haikal SM, Abdeltawab NF, Rashed LA, Abd El-Galil TI, Elmalt HA, Amin MA. Combination Therapy of Mesenchymal Stromal Cells and Interleukin-4 Attenuates Rheumatoid Arthritis in a Collagen-Induced Murine Model. Cells. 2019;8(8):823. https://doi.org/10.3390/cells8080823
143. Nazemian V, Manaheji H, Sharifi AM, Zaringhalam J. Long term treatment by mesenchymal stem cells conditioned medium modulates cellular, molecular and behavioral aspects of adjuvant-induced arthritis. Cellular and molecular biology (Noisy-le-Grand, France). 2018;64(1):19-26. https://doi.org/10.14715/cmb/2018.64.2.5
144. Tseng WJ, Huang SW, Fang CH, Hsu LT, Chen CY, Shen HH, et al. Treatment of osteoarthritis with collagen-based scaffold: A porcine animal model with xenograft mesenchymal stem cells. Histology and histopathology. 2018;33(12):1271-86.
145. Wu CC, Liu FL, Sytwu HK, Tsai CY, Chang DM. CD146+ mesenchymal stem cells display greater therapeutic potential than CD146- cells for treating collagen-induced arthritis in mice. Stem cell research & therapy. 2016;7:23. https://doi.org/10.1186/s13287-016-0285-4
146. Yan X, Cen Y, Wang Q. Mesenchymal stem cells alleviate experimental rheumatoid arthritis through microRNA-regulated IκB expression. Scientific reports. 2016;6:28915. https://doi.org/10.1038/srep28915
147. Liu R, Li X, Zhang Z, Zhou M, Sun Y, Su D, et al. Allogeneic mesenchymal stem cells inhibited T follicular helper cell generation in rheumatoid arthritis. Scientific reports. 2015;5:12777. https://doi.org/10.1038/srep12777
148. Gu Y, Shi S. Transplantation of gingiva-derived mesenchymal stem cells ameliorates collagen-induced arthritis. Arthritis Res Ther. 2016;18(1):262. https://doi.org/10.1186/s13075-016-1160-5
149. Garimella MG, Kour S, Piprode V, Mittal M, Kumar A, Rani L, et al. Adipose-Derived Mesenchymal Stem Cells Prevent Systemic Bone Loss in Collagen-Induced Arthritis. Journal of immunology (Baltimore, Md : 1950). 2015;195(11):5136-48. https://doi.org/10.4049/jimmunol.1500332
150. Gonzalo-Gil E, Pérez-Lorenzo MJ, Galindo M, Díaz de la Guardia R, López-Millán B, Bueno C, et al. Human embryonic stem cell-derived mesenchymal stromal cells ameliorate collagen-induced arthritis by inducing host-derived indoleamine 2,3 dioxygenase. Arthritis Res Ther. 2016;18:77. https://doi.org/10.1186/s13075-016-0979-0
151. Stancker TG, Vieira SS, Serra AJ, do Nascimento Lima R, Dos Santos Feliciano R, Silva JA, Jr., et al. Can photobiomodulation associated with implantation of mesenchymal adipose-derived stem cells attenuate the expression of MMPs and decrease degradation of type II collagen in an experimental model of osteoarthritis? Lasers in medical science. 2018;33(5):1073-84. https://doi.org/10.1007/s10103-018-2466-0
152. Tao S-C, Yuan T, Zhang Y-L, Yin W-J, Guo S-C, Zhang C-Q. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. Theranostics. 2017;7(1):180. https://doi.org/10.7150/thno.17133
153. Neybecker P, Henrionnet C, Pape E, Mainard D, Galois L, Loeuille D, et al. In vitro and in vivo potentialities for cartilage repair from human advanced knee osteoarthritis synovial fluid-derived mesenchymal stem cells. Stem cell research & therapy. 2018;9(1):329. https://doi.org/10.1186/s13287-018-1071-2
154. Grigolo B, Lisignoli G, Desando G, Cavallo C, Marconi E, Tschon M, et al. Osteoarthritis treated with mesenchymal stem cells on hyaluronan-based scaffold in rabbit. Tissue engineering Part C, Methods. 2009;15(4):647-58. https://doi.org/10.1089/ten.tec.2008.0569
155. McGonagle D, Baboolal TG, Jones E. Native joint-resident mesenchymal stem cells for cartilage repair in osteoarthritis. Nature Reviews Rheumatology. 2017;13(12):719-30. https://doi.org/10.1038/nrrheum.2017.182
156. Frisbie DD, Kisiday JD, Kawcak CE, Werpy NM, McIlwraith CW. Evaluation of adipose-derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2009;27(12):1675-80. https://doi.org/10.1002/jor.20933
157. Xia Q, Zhu S, Wu Y, Wang J, Cai Y, Chen P, et al. Intra-articular transplantation of atsttrin-transduced mesenchymal stem cells ameliorate osteoarthritis development. Stem cells translational medicine. 2015;4(5):523-31. https://doi.org/10.5966/sctm.2014-0200
158. Chen W, Sun Y, Gu X, Hao Y, Liu X, Lin J, et al. Conditioned medium of mesenchymal stem cells delays osteoarthritis progression in a rat model by protecting subchondral bone, maintaining matrix homeostasis, and enhancing autophagy. J Tissue Eng Regen Med. 2019;13(9):1618-28. https://doi.org/10.1002/term.2916
159. Wang Y, Yu D, Liu Z, Zhou F, Dai J, Wu B, et al. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. Stem cell research & therapy. 2017;8(1):1-13. https://doi.org/10.1186/s13287-017-0632-0
160. Martel-Pelletier J, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. Seminars in arthritis and rheumatism. 2003;33(3):155-67. https://doi.org/10.1016/S0049-0172(03)00134-3
161. Song F, Tang J, Geng R, Hu H, Zhu C, Cui W, et al. Comparison of the efficacy of bone marrow mononuclear cells and bone mesenchymal stem cells in the treatment of osteoarthritis in a sheep model. International journal of clinical and experimental pathology. 2014;7(4):1415-26.