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Review Article

Mesenchymal stem cell–derived extracellular vesicles in joint diseases: Therapeutic effects and underlying mechanisms

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ABSTRACT

Joint diseases greatly impact the daily lives and occupational functioning of patients globally. However, conventional treatments for joint diseases have several limitations, such as unsatisfactory efficacy and side effects, necessitating the exploration of more efficacious therapeutic strategies. Mesenchymal stem cell (MSC)-derived EVs (MSC-EVs) have demonstrated high therapeutic efficacyin tissue repair and regeneration, with low immunogenicity and tumorigenicity. Recent studies have reported that EVs-based therapy has considerable therapeutic

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effects against joint diseases, including osteoarthritis, tendon and ligament injuries, femoral head osteonecrosis, and rheumatoid arthritis. Herein, we review the therapeutic potential of various types of MSC-EVs in the aforementioned joint diseases, summarise the mechanisms underlying specific biological effects of MSC-EVs, and discuss future prospects for basic research on MSC-EV-based therapeutic modalities and their clinical translation. In general, this review provides an in-depth understanding of the therapeutic effects of MSC-EVs in joint diseases, as well as the underlying mechanisms, which may be beneficial to the clinical translation of MSC-EV-based treatment.

The translational potential of this article: MSC-EV-based cell-free therapy can effectively promote regeneration and tissue repair. When used to treat joint diseases, MSC-EVs have demonstrated desirable therapeutic effects in preclinical research. This review may supplement further research on MSC-EV-based treatment of joint diseases and its clinical translation.

Abbreviations

ACAN	Aggrecan
ACECM	Acellular cartilage extracellular matrix
ACL	Anterior cruciate ligament
ACLR	ACL reconstruction
ADMSCs	Adipose-derived MSCs
ADMSC-EXOs	ADMSC-derived exosomes
α-SMA	A-smooth muscle actin
BMP	Bone morphogenetic protein
BMSC-EXOs	BMSC-derived exosomes
CAP	cartilage-affinity peptide
COL2A1	Type II collagen alpha 1
dECM	Decellularized extracellular matrix
ECM	Extracellular matrix
EVs	Extracellular vesicles
GelMA	Gelatin methacrylate
HUVECs	Human umbilical vein endothelial cells
ICA	Icariin
IPFP-MSCs	Infrapatellar fat pad-derived MSCs
IPFP-MSC-EXOs	IPFP-MSC-derived exosomes
KGN	Kartogenin
LIPUS	Low-intensity pulsed ultrasound
lncRNA	Long non-coding RNA
MMPs	Matrix metalloproteinases
MMP13	Matrix metalloproteinase13
MSCs	Mesenchymal stem cells
MSC-EXOs	MSC-derived exosomes
MVBs	Multivesicular bodies
OA	Osteoarthritis
ONFH	Osteonecrosis of the femoral head
p-HA	Photopolymerizable hyaluronic acid
PTH	Parathyroid Hormone
RA	Rheumatoid arthritis
RCCS	Rotary cell culture system
RCT	Rotator cuff tendon
SAH	Sodium alginate hydrogel
Scx	Scleraxis
SLE	Systemic lupus erythematosus
SMSC-EXOs	Synovial mesenchymal stem cell-derived exosomes
SOX9	SRY-box 9
TBH	Tendon-bone healing
TDSCs	Tendon stem cells
TDSC-EXOs	TDSC-derived exosomes
TE	Tropoelastin
TnC	Tenascin C

1. Introduction

Joints are the most fundamental organs executing motor functions, composed of various tissues including articular cartilage, subchondral bone, synovium, joint capsule, ligament and tendon [1]. Multiple factors can contribute to pathological joint damage, resulting in the development of various joint diseases such as osteoarthritis (OA), tendon and ligament injuries, osteonecrosis of the femoral head (ONFH), and rheumatoid arthritis (RA). These joint diseases induce joint swelling, pain and limited movement, considerably worsening the patient's quality of life and leading to large social and economic burdens [2–4]. Conventional treatments for joint disease primarily include conservative treatments and surgical therapy. Conservative treatments, such as physical therapy and pharmacotherapy, are hindered by their inability to reverse joint disease progression, limited efficacy, and their side effects [5–8]. Surgical therapeutic strategies have some limitations, such as surgical trauma, postoperative complications, and economic burden [5,7,9]. Therefore, research on and establishment of superior strategies for joint diseases treatment are highly warranted.

Mesenchymal stem cells (MSCs), which have multidirectional differentiation potential, can be obtained from tissues such as bone marrow, brain, adipose tissue, synovium, umbilical cord, spleen, and pancreas [10–15]. MSCs demonstrate great potential in the treatment of a variety of diseases, such as joint diseases, as well as nerve and heart injuries [16–19]. Recent research shown that MSCs exerted their biological regulatory role through extracellular vesicles (EVs) secretion, including wound healing, cardiac injury repair, nerve repair, kidney injury repair, liver injury repair, and bone regeneration [20–22].

EVs, membranous structures secreted by cells, are characterised by the presence of a lipid bilayer [23]. EVs encapsulate proteins, lipids, nucleic acids, and other biomolecules; these EV contents play a crucial role in intercellular communication, immune regulation, cell proliferation and differentiation, angiogenesis, and tissue repair [24,25]. Diverse cellular origins and microenvironments can induce variations in EVs contents, thus modulating the actions and functions of EVs [26]. EVs can be obtained through different techniques on the basis of their physicochemical characteristics (Table 1) [24,27,28]. On the basis of the differences in their sizes and biogenesis, EVs can be categorised into microvesicles, exosomes, and apoptotic bodies [29]. Among different types of EVs, exosomes are the most extensively studied currently. In the first stage of exosome biogenesis, extracellular components are internalised by MSCs through endocytosis and plasma membrane fusion and then incorporated with organelle-derived components, such as mitochondria and the endoplasmic reticulum, to form early endosomes. These early endosomes gradually mature into late endosomes. The limiting membranes of late endosomes invaginate to generate multivesicular bodies (MVBs). These MVBs subsequently release exosomes through fusion with the plasma membrane (Fig. 1) [6,30]. MSC-derived EVs (MSC-EVs), a promising cell-free therapy for regenerative medicine, are associated with low toxicity and few side effects. In this review, we provide a comprehensive overview of the therapeutic effects and

underlying mechanisms of MSC-EVs, particularly exosomes, in joint diseases including OA, tendon and ligament injuries, ONFH, and RA (see Table 2).

2. MSC-EVs in OA treatment

OA is a chronic degenerative joint disease, with common symptoms including swelling, pain, deformities, and limited mobility. Globally, the estimated number of patients with OA exceeds 240 million [31]. As such, OA greatly worsens the patients' quality of life and leads to a major socioeconomic burden [32,33]. The main pathological features of OA include articular cartilage degeneration, synovial inflammation, and subchondral sclerosis [34,35]. Commonly used OA treatment modalities can be divided into nonsurgical interventions and surgical procedures. The primary objective of OA management involves pain control, functional improvement, and disability reduction [31,36,37].

Articular cartilage, a type of hyaline cartilage, varies in thickness (2–4 mm) and is composed of an extracellular matrix (ECM) and chondrocytes [38]. This ECM is mainly composed of type II collagen and aggrecan (ACAN), which can maintain the stability and structural integrity of cartilage and provide a viable environment for chondrocytes [39,40]. Increased amounts of collagen-degrading enzymes, particularly matrix metalloproteinase 13 (MMP13) and a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 4/5 (ADAMTS4/5), play a role in reducing type II collagen and ACAN levels, eventually resulting in ECM breakdown [40,41]. The chondrocytes are located in the ECM, accounting for only 1%–5% of the articular cartilage content. They are quiescent cells, which can synthesise many ECM-associated proteins, such as collagen, hyaluronic acid, and proteoglycan, under physiological conditions [47]. Several signalling molecules are involved in chondrocyte regulation. For instance, SRY-box (SOX)9 is a main regulatory protein in chondrocytes, playing a major role during chondrogenesis. It can enhance the expression of ECM genes, including type II collagen alpha 1 (COL2A1) and ACAN [44]. The Wnt pathway is essential for maintaining the normal characteristics and proliferation of chondrocytes, and BMP is also involved in the regulation of chondrocyte proliferation and differentiation [45]. mTOR is closely associated with chondrocyte apoptosis [46]. In OA, chondrocytes in the quiescent state undergo hypertrophy. Hypertrophic chondrocytes then secrete matrix metalloproteinases (MMPs), downregulate COL2A1 and SOX9 expression, and mediate ECM degradation. In addition, the hypertrophic chondrocytes finally progress to apoptosis, further reducing cartilage quality [47,48]. Chondrocytes in patients with OA also express senescence-related phenotypes, and the senescent chondrocytes contribute to ECM degradation through MMPs secretion [49]. In the joint cavity of patients with OA, inflammatory chondrocytes release proinflammatory cytokines [e.g. interleukin (IL) 7], which mediate cartilage degradation and cartilage fragment production. In addition, the cartilage fragments can enhance inflammatory chondrocyte activation, leading to increased secretion of proinflammatory cytokines and polarisation of M1 macrophages within the synovial membrane. The proinflammatory cytokines can mediate synovial hypertrophy and inflammation [50,51].

A considerable amount of recent research has focused on tissue regeneration and repair capabilities of MSC-derived exosomes (MSC-EXOs) [5,30,52]. These MSC-EXOs [e.g. bone marrow MSC (BMSC)-derived exosomes (BMSC-EXOs) and adipose MSC (ADMSC)--derived exosomes (ADMSC-EXOs)] can facilitate chondrocyte proliferation, inhibit chondrocyte apoptosis, promote ECM synthesis, and regulate inflammation in OA (Fig. 2) [30,53–56].

2.1. BMSC-EVs in OA treatment

BMSC-EXOs have considerable therapeutic capabilities, enhancing OA-related cartilage damage repair [55,57]. BMSC-EXOs can enhance type II collagen and proteoglycan production and suppress MMP13 and ADAMTS5 expression, thereby facilitating the maintenance of ECM homeostasis [58–60]. The underlying mechanisms may be associated with exosome contents, such as circRNA_0001236 and KLF3-AS1, among which circRNA_0001236 can acts as an miR-3677-3p sponge to regulate the ECM homeostasis [61,62]. In addition, BMSC-EXOs carrying miR-320c can upregulate SOX9 expression in chondrocytes, promote COL2A1 and ACAN synthesis, and alleviate cartilage damage [44,63].

BMSC-EXOs can also facilitate chondrocyte proliferation and migration and suppress chondrocyte senescence and apoptosis in OA [64–66,76]. Dysregulated activation of the NF-κB pathway, a crucial pathogenic factor involved in OA, can mediate chondrocyte hypertrophy and apoptosis or mediate chondrocyte senescence through oxidative stress [67]. BMSC-EXOs carrying miR-326 and miRNA-361-5p can prevent chondrocyte senescence and apoptosis by inhibiting NF-κB pathway activation [64,65]. Typical Wnt pathway activation can be observed in the joint cartilage of patients with OA, and β-catenin overexpression in mature chondrocytes can cause chondrocyte hypertrophy

Table 1
EVs or EXOs isolation methods.

Isolated methods	Principles	Advantages	Disadvantages
Differential ultracentrifugation [217,218]	Based on size	● Gold standard for exosome separation ● Low cost ● Suitable for large-volume samples	● High equipment requirement ● Complex operation ● Potential for exosome destruction
Density gradient ultracentrifugation [219]	Based on density	● High purity ● Allowing separation of exosome subpopulations	● Complex operation ● Low yield
Ultrafiltration [24,219,220]	Based on size	● Low equipment cost ● Good portability	● Medium purity ● Clogging and membrane trapping
Tangential flow filtration [221–223]	Based on size	● High yield ● Little exosome destruction ● Suitable for large-volume samples	● Contamination with exosomes similar in diameter
Size-exclusion chromatography [217,224,209]	Based on size	● High purity ● Little exosome destruction ● High recovery efficiency	● Protein contamination ● High equipment cost ● Time-consuming
Polymer-based precipitation separation [220,226,227]	Based on solubility	● Simple operation ● Low equipment requirement	● Little specificity ● High cost
Immunological separation [209,219,228,229]	Based on antigen–antibody response	● High purity ● Easy to use	● High cost ● Separation of exosomes with targeted proteins only
Microfluidic chip [225]	Based on different principles, including immunoaffinity, size, and density	● Easy to operate ● Small sample volume requirement ● Separation–detection integration	● Complex instrument ● Difficulty in maintaining high yield and purity

and mediate cartilage damage [68]. BMSC-EXOs carrying miRNA-127-3p can inhibit IL-1β-induced chondrocyte apoptosis by inhibiting CDH11-mediated Wnt/β-Catenin pathway activation [66]. In an OA mouse model, miR-92a-3p-overexpressing BMSC-EXOs could promote chondrocyte proliferation and migration, as well as regulate chondrogenesis and ECM homeostasis, through WNT5A down-regulation, thereby enhancing cartilage formation and inhibiting cartilage degradation [54]. Glutamine can engender ATP production—the fundamental energy source for cellular activities—via the tricarboxylic acid cycle. Therefore, glutamine content is somewhat positively correlated with cell activity. BMSC-EXOs can inhibit chondrocyte apoptosis and maintain chondrocyte homeostasis through the regulation of glutamine metabolism [69,70]. Moreover, BMSC-EXOs can increase the expression of the chondrogenic genes COL2A1 and ACAN and reduce the expression of the chondrocyte hypertrophy markers MMP13 and RUNX2 in OA chondrocytes. The underlying mechanisms may be associated with the activation of the lncRNA-KLF3-AS1/miR-206/GIT1 axis by BMSC-EXOs [71]. Furthermore, BMSC-EXOs can reduce the levels of proinflammatory cytokines and concurrently elevate anti-inflammatory cytokines in the synovial fluid of OA joints. Moreover, they can inhibit synovial hyperplasia and ameliorate OA synovitis and osteophyte formation [55,72]. The possible underlying mechanisms are associated with the regulation of proinflammatory cells such as synovial macrophages by BMSC-EXOs [55,73]. BMSC-EXOs can inhibit synovial inflammatory cell recruitment by promoting the transition of proinflammatory (M1) macrophages to anti-inflammatory (M2) macrophages and reducing proinflammatory mediator secretion [55]. M2 macrophage polarisation by BMSC-EXOs may be related to

Table 2
Biological functions and mechanisms of miRNA-carrying MSC-EVs or MSC-EXOs in joint diseases.

Source	miRNAs	Diseases	Biological functions	Mechanisms
	miR-92a-3p [54]	OA	● Promoting chondrocyte proliferation and migration ● Regulating chondrogenesis and ECM homeostasis	● Downregulating WNT5A expression
	miR-326 [64]	OA	● Regulating chondrogenesis and ECM homeostasis	● Targeting HDAC3 and STAT1//NF-κB p65 in chondrocytes
	miRNA-361-5p [65]	OA	● Improving chondrocyte senescence and apoptosis	● Downregulating DDX20 and inactivating the NF-κB pathway
	miRNA-127-3p [66]	OA	● Inhibiting IL-1β-induced chondrocyte apoptosis	● Inhibiting CDH11-mediated Wnt/β-Catenin pathway activation
	miR-320c [44,63]	OA	● Improving cartilage damage	● Upregulating SOX9 expression ● Promoting COL2A1 and ACAN synthesis
	miR-21-5p [154]	Tendon and ligament injuries	● Facilitating fibrocartilage regeneration	● Inhibiting SMAD7 expression
	miR-23a-3p [141]	Tendon and ligament injuries	● Promoting M1 to M2 macrophage polarisation ● Inhibiting local inflammation at the tendon–bone interface	● Inhibiting IRF1 expression and the NF-κB pathway in macrophages
	miR-223 [192]	RA	● Inhibiting proinflammatory cytokine release	● Downregulating NLRP3 expression in macrophages
	miR-6924-5p [156]	Tendon and ligament injuries	● Suppressing osteoclastogenesis ● Inhibiting bone resorption surrounding the bone tunnel ● Ultimately enhancing TBH's mechanical strength	● Downregulating CXCL12 and OCSTAMP expression
	miR-224-3p inhibited [173]	ONFH	● Promoting angiogenesis	● Upregulating FIP200 expression
	miR-122-5p [180]	ONFH	● Promoting osteoblast proliferation	● –
	miR-150-5p [194,195]	RA	● Reversing proangiogenic effects of FLSs ● Inhibiting FLS invasiveness	● Inhibiting MMP14 and VEGF expression in FLSs
	miR-320a [196]	RA	● Inhibiting FLS activation	● Suppressing CXCL9 expression
ADMSCs	miR-140-5p [98]	OA	● Counteracting inhibitory effects of exosomes on ECM secretion	● –
	miR-451-5p [94]	OA	● Improving cartilage matrix synthesis and alleviating Osteoarthritis	● –
	miR-199-3p [93]	OA	● Promoting cartilage repair	● Inhibiting mTOR expression
	miR-376c-3p [90]	OA	● Inhibiting cartilage degradation ● Alleviating synovial fibrosis and synovial hyperplasia	● Inducing target inhibition of WNT3/WNT9a, thereby suppressing WNT-β-catenin pathway activation
	miR-338-3p [89]	OA	● Inhibiting inflammation injury in chondrocytes	● Inhibiting RUNX2 expression
	miR-378 [170]	ONFH	● Enhancing angiogenesis and osteogenesis	● Downregulating Sufu and activating Shh
	miR-146a [190]	RA	● Increasing Treg proportions	● –
IPFP-MSCs	miR-100-5p [92]	OA	● Promoting proliferation and inhibiting apoptosis in chondrocytes to rescue damaged cartilage	● Inhibiting mTOR pathway
SMSCs	miR-320c [97]	OA	● Inhibiting ECM degradation and chondrocyte apoptosis	● Supressing ADAM19-dependent Wnt signal pathway
	miR-212-5p [99]	OA	● Suppressing chondrocyte degeneration and inflammation	● Inhibiting ELF3
TDSCs	miR-145-3p [127]	Tendon and ligament injuries	● Promoting TDSC proliferation, migration, and tenogenic differentiation	● –
UCMSCs	miR-29a-3p [128]	Tendon and ligament injuries	● Increased the expression of tendon markers in TDCSs	● Activating PTEN/mTOR/TGF-β1 pathway
	miR-365a-5p [175]	ONFH	● Promoting osteogenesis	● Activating Hippo pathway
	miR-21-5p [172]	ONFH	● Promoting osteogenesis	● Inhibiting SOX5/EZH2 axis
	miR-451a [197]	RA	● Inhibiting FLS proliferation, migration, and invasion	● Suppressing ATF2 expression
	miR-140-3p [200]	RA	● Inhibiting chondrocyte apoptosis ● Promoting FLS apoptosis ● Inhibiting FLS proliferation	● Downregulating SGK1 expression
Labial gland MSCs	miRNA-125b [202]	RA	● Inhibiting plasma cells	● Suppressing PRDM1 expression
iPSCs	miR-135b [176]	ONFH	● Reducing osteocyte apoptosis	● –

PINK1/Parkin pathway inhibition [74]. In addition, increased expression of long noncoding RNA (lncRNA) TUC339 in BMSCs can improve the ability of BMSC-EXOs to promote M2 macrophage polarisation [75]. The common pathological features of OA include subchondral bone remodelling and sclerosis. BMSC-EXOs can partially maintain the normal structure of trabeculae in OA subchondral bones, promote subchondral bone remodelling, and alleviate OA pain [76,77]. Transforming growth factor (TGF) β1-modified BMSC-EXOs can inhibit uncoupled subchondral bone remodelling and alleviate OA pain by suppressing platelet-derived growth factor-BB secretion and H-type vascular activity in the subchondral bone [78]. Moreover, BMSC-EXOs may alleviate OA pain by inhibiting nerve invasion in the OA subchondral bone [77].

Several studies assessed different approaches to improve the efficacy of BMSC-EXOs in OA treatment. Mechanical stimulation of MSCs through low-intensity pulsed ultrasound, or pretreatment with decellularized ECM, parathyroid hormone (1–34), and kartogenin (KGN), can further enhance the capacity of BMSC-EXOs to exert a more protective effect in OA chondrocyte [60,79–81]. Similarly, pretreatment of BMSCs with TGF-β1 can enhance the capacity of BMSC-EXOs to promote M2 macrophage polarisation, possibly through miR-135b-mediated inhibition of MAPK6 [73]. Chen et al. developed a scaffold composed of 3D-printed cartilage ECM/gelatin methacrylate (GelMA)/exosomes, facilitating the gradual release of BMSC-EXOs at the damaged cartilage and extending the duration of BMSC-EXOs' effects effectively [59]. Zeng et al. designed a mussel-inspired multifunctional hydrogel system that can protect cartilage by enhancing the synergistic effects of MSC-EXOs with icariin (ICA) [82]. A recent study employed a combination of strategies to enhance the therapeutic effects of BMSC-EXOs against OA. First, the researchers loaded BMSC-EXOs with LRRK2-IN-1, a small molecule drug that can alleviate OA efficaciously. Next, these drug-loaded BMSC-EXOs were modified with a cartilage-affinity peptide (CAP) to increase their chondrocyte-targeting ability. Finally, to prevent rapid clearance and degradation at the administration site, these modified BMSC-EXOs were encapsulated within photo-crosslinked spherical hydrogels [83].

2.2. ADMSC-EVs in OA treatment

Adipose tissue can be easily obtained from common clinical procedures such as liposuction, arthroscopy, and plastic surgery. ADMSCs, originating from adipose tissue, play a crucial role in regenerative medicine for damaged cartilage and hold great potential for OA treatment [56,84–87]. In a comparative study on the chondrogenic abilities between different MSC-EV types, ADMSC-EVs demonstrated a stronger capacity for cartilage formation than BMSC-EVs [88]. ADMSC-EXOs can hinder the release of inflammatory substances (e.g. IL-6 and prostaglandin E) and concurrently promote the release of anti-inflammatory substances (e.g. IL-10), thus improving the inflammation state within joint microenvironments [87,89]. In a study on rat models with OA induced by monosodium iodoacetate, ADMSC-EXOs carrying miR-376c-3p not only inhibited cartilage degradation but also alleviated synovial fibrosis and synovial hyperplasia; the underlying mechanism involved the targeted inhibition of WNT3/WNT9a, which consequently suppressed the Wnt/β-catenin pathway [90]. Similarly, the infrapatellar fat pad–derived MSCs (IPFP-MSCs) obtained from patients with OA and healthy individuals (i.e. patients undergoing ligament reconstruction) enhanced cartilage repair, with a chondrogenic potential superior to that of BMSCs or subcutaneous ADMSCs [91]. In an OA mouse model, IPFP-MSC-derived exosomes (IPFP-MSC-EXOs) carrying miR-100-5p activated the mTOR pathway in chondrocytes, promoting proliferation and inhibiting apoptosis, eventually rescuing the damaged cartilage [92]. Another study combined CAP with LAMP2 on the membranes of subcutaneous ADMSC-EXOs for targeted delivery to chondrocytes. These subcutaneous ADMSC-EXOs loaded with miR-199-3p exhibited a substantial effect in promoting cartilage repair in an OA rat model, potentially through inhibition of mTOR expression [93]. Furthermore, pretreating ADMSCs with tropoelastin can increase the yield of ADMSC-EXOs and enhance their capacity to alleviate OA cartilage injury by increasing miR-451-5p levels [94]. In addition, pretreating IPFP-MSCs with KGN can enhance the capacity of IPFP-MSC-EXOs to promote chondrocyte proliferation and facilitate chondrogenic differentiation of in situ MSCs [95].

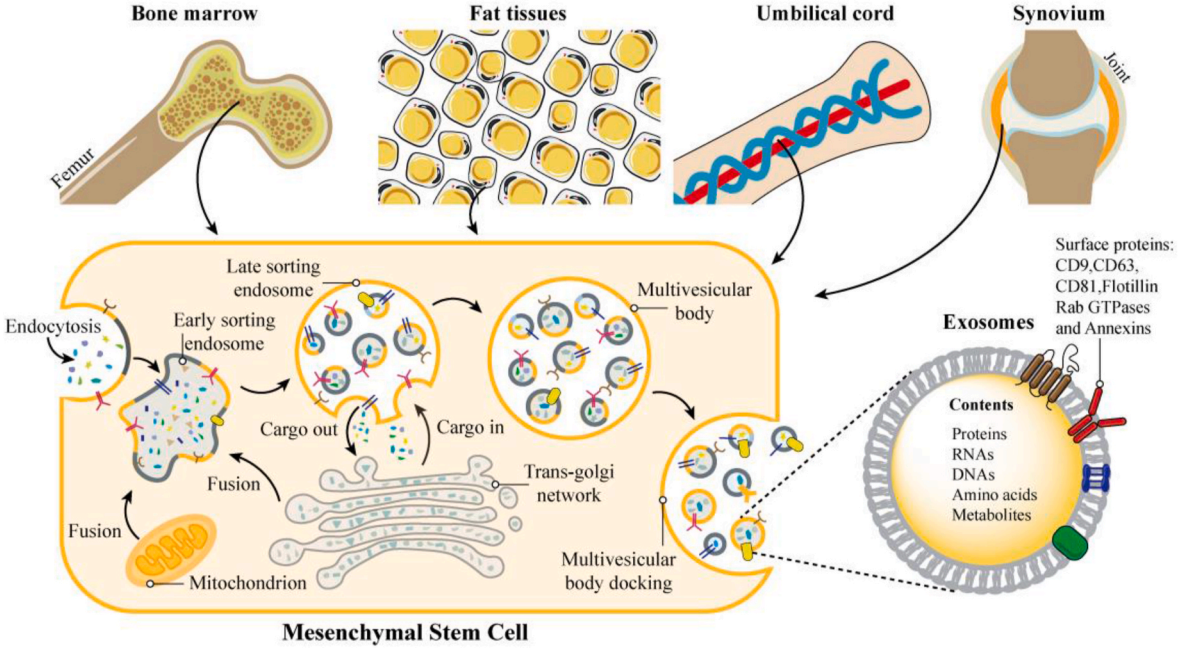

Figure 1. MSCs origin and MSC-EXOs biogenesis. MSCs can be isolated from various sources, such as bone marrow, fat tissue, umbilical cord, and synovium. MSC-EXOs secretion involves multiple stages, such as endocytosis, early and late endosome formation, multivesicular body formation, and exocytosis. MSC-EXOs contents include proteins, RNAs, DNAs, amino acids, and metabolites.

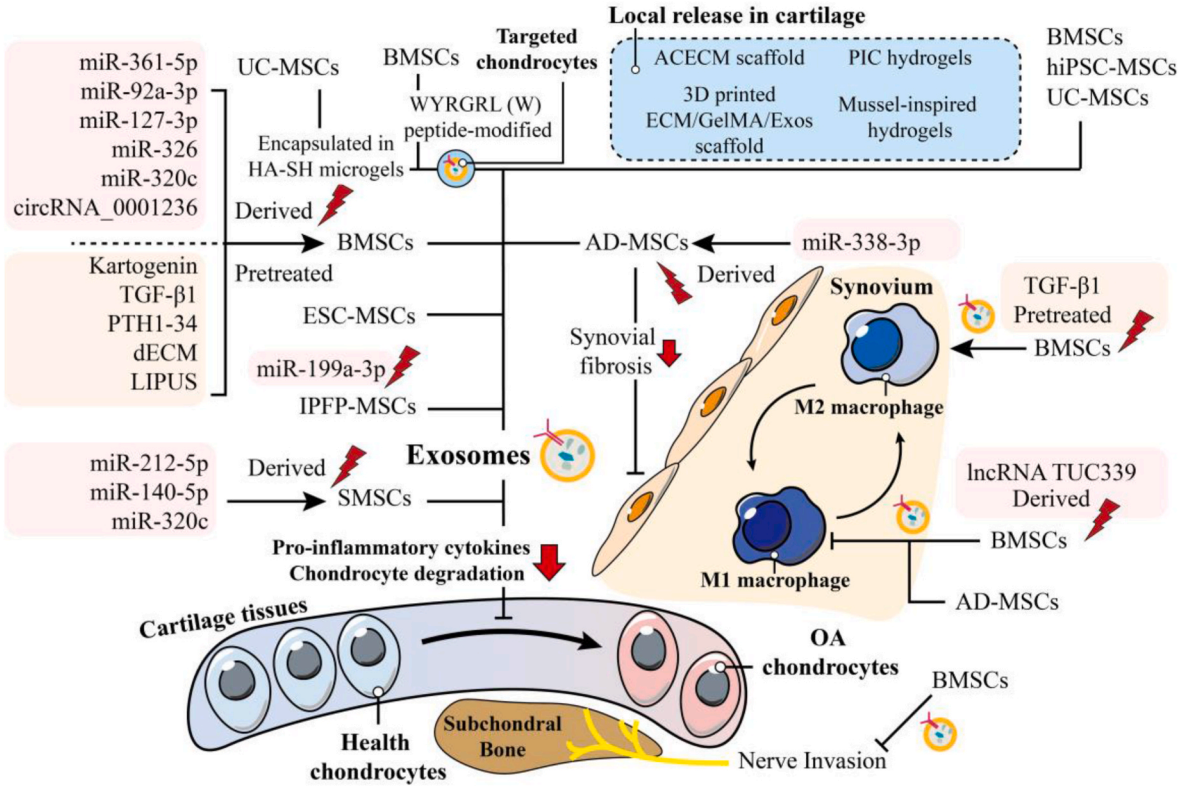

Figure 2. MSC-EXOs in OA treatment. In OA, MSC-EXOs can inhibit chondrocyte degeneration, M1 macrophage polarisation, and synovial fibroblast proliferation and migration. ECM/GelMA/EXOs, ECM–gelatin methacrylate–exosome scaffold; ESCs, embryonic stem cells; HA-SH microgels, thiolated hyaluronic acid microgels; LIPUS, low-intensity pulsed ultrasound; PTH, parathyroid hormone; SMSCs, synovial MSCs.

2.3. Other MSC-EVs in OA treatment

In addition to the aforementioned MSC-EXOs, exosomes derived from other types of MSCs can have some therapeutic potential against OA. Exosomes derived from embryonic stem cells can maintain ECM homeostasis by upregulating type II collagen expression and downregulating ADAMTS5 expression [96]. Synovial MSC (SMSC)-derived exosomes (SMSC-EXOs) can inhibit ECM degradation and chondrocyte apoptosis by delivering exosomal miR-320c that targets ADAM19-dependent Wnt signalling and thereby repairs cartilage damage in OA rats [97]. SMSC-EXOs contents can also activate the YAP pathway through Wnt5a and Wnt5b, promoting chondrocyte proliferation and migration but inhibiting ECM secretion. However, miR-140-5p overexpression via SMSC-EXOs can counteract this inhibitory effect on ECM secretion [98]. Furthermore, SMSC-EXOs overexpressing miR-212-5p have been observed to suppress the production of inflammatory cytokines, including IL-6, MCP-1, TNF-α, COX-2, and iNOS, in OA chondrocytes [99].

Recently, various approaches have been employed to enhance the therapeutic effectiveness of these MSC-EXOs in OA treatment. For instance, 3D culture methods have been used to increase the yield of umbilical cord MSC–derived exosomes (UCMSC-EXOs), as well as their therapeutic effects on OA-related cartilage injuries. These methods include the use of a hollow-fibre bioreactor, rotary cell culture system, or a 3D porous scaffold culture [100–102]. A study integrated chondrocyte-targeting polymers onto the membrane of UCMSC-EXOs and encapsulated them in thiolated hyaluronic acid microgels to effectively target chondrocytes [103]. Combination with an acellular cartilage ECM scaffold can enhance the capacity of UCMSC-EXOs to promote OA cartilage defect repair [104].

Taken together, these results indicate that MSC-EXOs have a high therapeutic potential because they can promote chondrocyte proliferation, inhibit cell apoptosis, stimulate extracellular matrix synthesis, regulate inflammation, and ultimately effectively alleviating OA symptoms and pathology. The integration of multiple approaches, including genetic modification of MSC-EXOs, and combination of MSC-EXOs with biomaterials, has been noted to improve outcomes compared with those of each strategy individually [103]. Additional studies and integration of these approaches may further enhance the therapeutic potential of MSC-EXOs. For instance, a synergistic combination of MSC-EXOs with specific hydrogels may facilitate controlled and precise release of MSC-EXOs at designated sites and time points in response to stimuli, such as light and ultrasound. This is because some hydrogels can change their state after exposure to various stimuli; for instance, photosensitive hydrogels have been used to control the release of aspirin through light stimulation [105].

3. MSC-EVs in tendon and ligament injury treatment

Tendons and ligaments are fibrous connective tissues, a tendon connects muscles to bones, whereas a ligament connects bones within a joint for optimal functionality and stability. Structurally, tendons and ligaments are composed of collagen fibres at varying levels; for instance, the collagen fibre content of the rotator cuff tendon (RCT) is 66.6 % ± 5.3 %, whereas that of the anterior cruciate ligament (ACL) is approximately 75 % [106]. Tendon and ligament injuries are common musculoskeletal disorders, and they can lead to pain and disability [107,108]. Common tendon and ligament injury sites include the ACL, RCT, and Achilles tendon [108,109]. The treatment modalities used for tendon and ligament injuries can vary depending on their location and severity. Conservative treatment is typically used for minor injuries such as sprains, strains, and partial tears, whereas surgical repair or reconstruction is often employed for extensive tears and ruptures [110–112]. The challenges associated with conservative treatment and tendon repair surgery include slow tendon healing and scar tissue formation. Moreover, achieving optimal tendon–bone healing (TBH) at the graft

and bone tunnel interface after tendon reconstruction surgery can be difficult [3,6,113]. Nevertheless, many studies have demonstrated the therapeutic potential of MSC-EXOs for tendon repair and TBH (Fig. 3).

3.1. MSC-EVs for injured tendon repair

Both tendons and ligaments are primarily composed of collagen fibres, which in turn comprise collagen [114,115]. Under physiological conditions, type I collagen is the main component of tendons, affording them strong biomechanical properties, whereas type II collagen is mainly present near tendon–bone junctions, and type III collagen primarily occurs around tissues undergoing tendon repair [114,116]. The tendon repair process, however, often results in scar formation, characterised by suboptimal biomechanical properties. In the later stages of tendon repair, type I collagen gradually replaces some of the type III collagen [117,118]. Therefore, the ratio of type I collagen to type III collagen can indicate the extent of functional recovery after the repair of a damaged tendon.

The repair process of damaged tendons can be categorised into three primary phases: inflammatory, proliferative, and remodelling. The inflammatory phase, occurring in the first few days after injury, is characterised by red and white blood cell infiltration, as well as platelet-secreted growth and chemotactic factors. Subsequently, macrophages become activated and engulf dead cells, whereas tenocytes migrate to the affected region and proliferate [119]. The proliferative phase commences 2 days after injury, during which macrophages gradually transition from releasing proinflammatory factors to secreting growth factors. During this phase, tenocytes, fibroblasts, and inflammatory cells become recruited to the injured area, where the tenocytes secrete type III collagen. These recruited cells demonstrate upregulation of VEGF and bFGF expression, facilitating neovascularisation [120]. The remodelling phase, beginning at 1–2 months after injury, is characterised by the synthesis of type I collagen, which restores the physiological structure of the injured tendon. In adults, damaged tendon repair typically involves scar tissue healing. Therefore, it cannot restore the biomechanical strength of the affected tendon entirely [118].

3.1.1. MSC-EVs for inflammation during tendon repair

Recent studies have suggested that MSC-EXOs can accelerate tendon repair by regulating its various stages. During inflammation after tendon injury, MSC-EXOs facilitate tendon healing by inhibiting excessive inflammation. ADMSC-EXOs can inhibit M1 macrophage polarisation but promote M2 macrophage polarisation, resulting in decreased proinflammatory cytokine secretion [121]. Another study reported that TDSC-derived exosomes (TDSC-EXOs) upregulate the expression of IL-10 (M2 macrophage–stimulating factor) but significantly downregulate the expression of IL-6 (M1 macrophage–stimulating factor). COX-2 is strongly associated with fibrosis and adhesion subsequent to a tendon injury, whereas TDSC-EXOs treatment significantly attenuates COX-2 expression, thereby facilitating early inflammation alleviation and enhancing tendon regeneration [122]. In addition, MSC-EXOs have been used for pretreating macrophages, which can then be used for treating injured tendons. This approach can aid in effectively reducing the M1 macrophage population in the damaged area, increasing the M2 macrophage population, and mitigating postinjury scar formation [123].

3.1.2. MSC-EVs for TDSC and tenocyte function improvement during tendon repair

Tendon stem cells (TDSCs) and tenocytes play a crucial role in

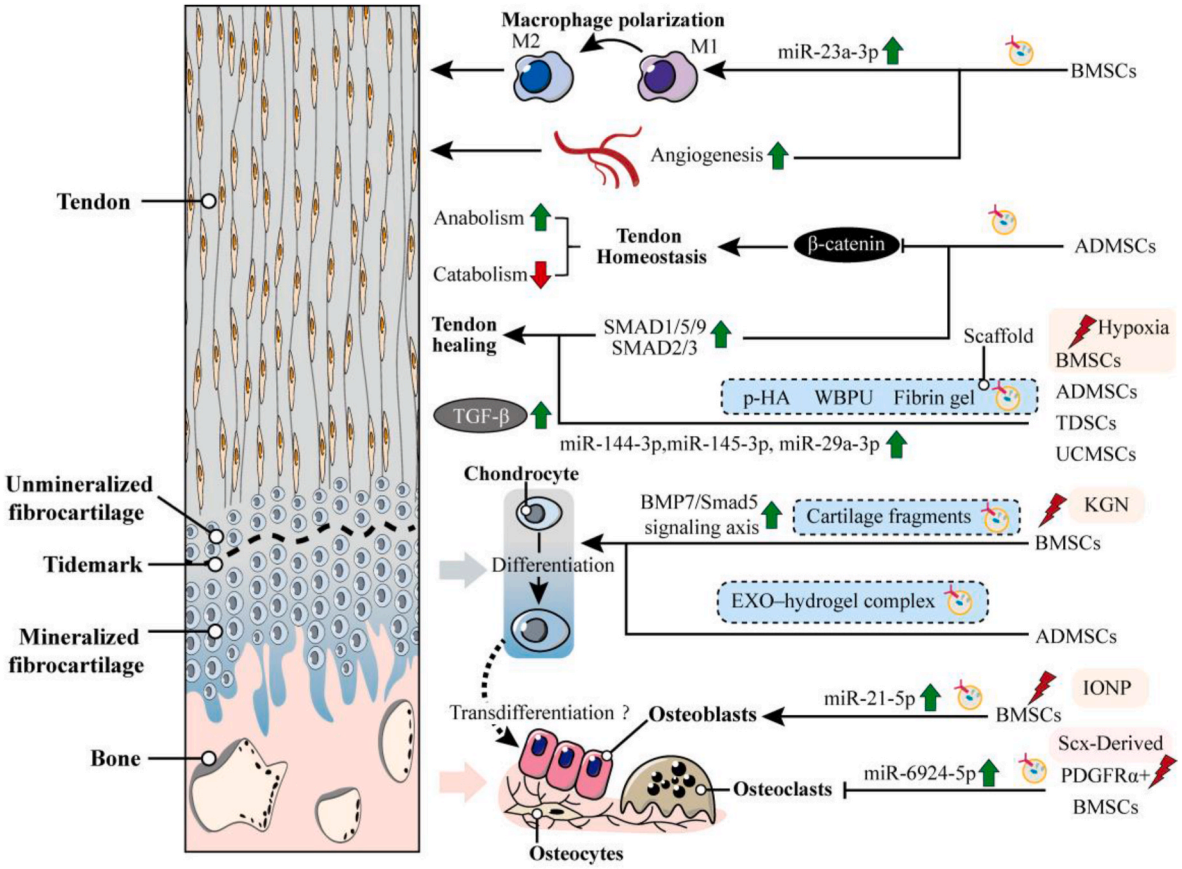

Figure 3. MSC-EXOs in tendon and ligament injury treatment. MSC-EXOs can accelerate the repair of damaged tendons by regulating the functions of TDSC. MSC-EXOs can also increase TBH by promoting bone and fibrocartilage formation at the tendon–bone interface. INOP, iron oxide nanoparticles; p-HA, photopolymerisable hyaluronic acid; PDGFR, platelet-derived growth factor receptors; WBPU, waterborne polyurethane.

damaged tendon repair. A study demonstrated that a dynamic wet-spinning system Rotator Cuff Patch loaded with BMSC-EXOs can effectively promote tenocyte proliferation and migration of tenocytes [124]. ADMSC-EXOs can restore damaged tendons by fostering TDSCs proliferation and migration. A study observed that GelMA-loaded ADMSC-EXOs promoted TDSCs proliferation by activating the SMAD2/3 and SMAD1/5/9 pathways [125]. Similarly, TDSC-EXOs can enhance TDSCs proliferation and migration by activating the TGF-β-SMAD2/3 and ERK1/2 pathways [126]. TDSC-derived EVs (TDSC-EVs) carrying miR-145-3p can also promote the proliferation, migration, and tendon differentiation of TDSCs. TDSC-EVs loaded using GelMA hydrogels demonstrate enhanced fixation and slow release and consequently exhibit high therapeutic efficacy [127]. UCMSC-EXOs carrying miR-29a-3p can activate the PTEN/mTOR/TGF-β1 pathway, facilitating the differentiation of TDSCs into tenocytes [128].

Tenocytes can directly mediate ECM synthesis, facilitating the repair of damaged tendons. MSC-EXOs can stimulate tenocyte proliferation and migration, as well as enhance tenocyte ECM secretion. Notably, TDSC-EXOs can activate the PI3K/AKT and MAPK/ERK1/2 pathways to promote tenocyte proliferation and migration [122]. Moreover, a scaffold of photopolymerisable hyaluronic acid loaded with TDSC-EXOs can achieve sustained TDSC-EXOs release at the injury site [129]. BMSC-EXOs can facilitate tenocyte proliferation and migration through TGF-β1 and enhance ECM synthesis by promoting the secretion of type III collagen, α-smooth muscle actin (α-SMA), scleraxis (Scx), and tenascin C [130]. A study combined BMSC-EXOs with fibrin and injected them into a tendon injury site, allowing for controlled release of BMSC-EXOs, which significantly increased the expression of type I collagen, thereby enhancing the ability of BMSC-EXOs to promote ECM synthesis [131].

During the remodelling phase of repairing damaged tendons, the content of type I collagen is strongly associated with the restoration of tendon physiological structure. ADMSC-EXOs can upregulate the ratio of type I collagen to type III collagen by activating the AMPK pathway and suppressing Wnt/β-catenin activity, ultimately enhancing the biomechanical properties of the healed tendons [132].

3.2. MSC-EVs for TBH improvement after ligament reconstruction

Severe tendon or ligament tears or ruptures typically require reconstruction surgery for damaged tissue repair. For instance, ACL reconstruction (ACLR) is commonly employed in cases of ACL tear or rupture, which surgical procedure involves creating a bone tunnel on the articular surface of the joint, inserting a tendon graft into the tunnel, and securing the graft with anchor pins or other methods [133]. However, ACLR is associated with a high incidence (11.9 %) of average failure, attributable to the related TBH limitations [134,135]. In physiological conditions, the tendon–bone junction consists of a tendon, non-mineralised fibrocartilage, mineralised fibrocartilage, and bone [6]. During the post-ACLR healing process, the tendon graft is initially connected to the bone tunnel by fibrous scar tissue. Trabecular remodelling is then performed around the bone tunnel, followed by bone infiltration of the tendon graft and ossification of the tendon graft [135,136]. However, compared with its normal physiological structure, the fibrous scar tissue exhibits inferior biomechanical properties, such as poorer tensile strength and impact resistance [137].

The TBH process can be divided into four stages: inflammation, proliferation, remodelling, and maturation [6]. The inflammation stage involves macrophage and neutrophil recruitment, subsequently leading to the formation of fibrovascular scar tissue connecting the tendon graft with the bone. The subsequent proliferation stage encompasses stem cell proliferation, migration, and differentiation, along with restoration of local blood circulation, prompted by cytokines and growth factors. The remodelling stage is primarily characterised by cell-secreted ECM at the graft–bone interface, which promotes the growth of bone into the graft and the formation of continuous collagen fibres between them. The final maturation stage is characterised by a gradual reduction in the number of cells and blood vessels at the bone–graft interface, parallel alignment of collagen fibres, and progressive restoration of biomechanical strength [6,138]. Bone formation enhancement and blood supply optimisation are considered essential for TBH improvement. Ameliorating inflammation, facilitating osteogenesis, and augmenting fibrocartilage formation might also enhance TBH [138].

MSC-EXOs have been reported to expedite the TBH process and enhance the joint's biomechanical strength, possibly by reducing inflammation at the tendon–bone interface, improving blood supply, promoting bone formation, and facilitating fibrocartilage formation [139].

3.2.1. MSC-EVs for inflammation alleviation in TBH

Macrophages play a central role in the inflammatory phase following tendon reconstruction. The early postoperative inflammation in the tendon–bone junction area after tendon reconstruction primarily occurs through the substantial influx of recruited macrophages [140,141]. The inflammatory phase of TBH involves M1 and M2 macrophages, and promoting the polarisation of M1 macrophages to M2 macrophages can effectively suppress inflammation at the tendon–bone interface and improve TBH [6]. Numerous studies have demonstrated the regulatory effects of BMSC-EXOs on macrophages, effectively suppressing polarisation towards the M1 phenotype, promoting differentiation into the M2 phenotype, and reducing the secretion of inflammatory cytokines. In a rat model of RCT reconstruction, articular cavity injection of BMSC-EXOs administration facilitated TBH and augmented its biological effects, possibly mediated by macrophages [139]. In a mouse model of Achilles tendon reconstruction, local injection of BMSC-EXOs reduced cell apoptosis and fibrotic tissue formation by inhibiting M1 macrophage polarisation, thereby improving biomechanical function of the reconstructed Achilles tendon [142]. Studies on rat models with ACLR have demonstrated that BMSC-EXOs or IPFP-MSC-EXOs can also accelerate TBH and promote recovery of postoperative function. The underlying mechanisms involve the downregulation of IRF1 and NF-κB pathway protein expression via miR-23a-3p, which promotes M2 polarisation and inhibits M1 polarisation of macrophages [141,143].

Recent research on MSC-EXOs in the inflammatory phase of TBH has primarily focused on macrophage regulation. In particular, neutrophils also play a role in inflammation regulation during this phase [6]. ADMSCs inhibit early inflammation during TBH and reduce the number of neutrophils [144]. Moreover, BMSC-EXOs reduce the number of neutrophils [145]. As such, investigating MSC-EXO-mediated regulation of neutrophils during TBH may provide new strategies for the treatment of the inflammatory phase.

3.2.2. MSC-EVs for angiogenesis improvement in TBH

Blood vessels are transportation channels for oxygen, cytokines, amino acids, glucose, and other metabolites, and local blood supply is crucial for tissue regeneration and repair [146]. The degree of postoperative regeneration of blood supply in the tendon–bone region significantly affects TBH. Insufficient local neovascularisation may result in nonunion at the tendon–bone interface [42,148,149]. MSC-EXOs lead to efficient angiogenesis when used to treat various diseases. For instance, UCMSC-EXOs can enhance fracture healing by promoting angiogenesis, and atorvastatin-pretreated BMSC-EXOs can promote diabetic wound healing through enhanced angiogenesis [151,152]. In a rat model of rotator cuff reconstruction, BMSC-EXOs can enhance angiogenesis, improve blood supply and tissue healing, and promote postoperative biological function. The underlying mechanisms may involve enhanced formation of new blood vessels during TBH through VEGF and Hippo pathway activation [139].

3.2.3. MSC-EVs for osteogenesis promotion in TBH

After ligament reconstruction, biomechanical strength is positively correlated with both the ingrowth of bone tissue into the tendon and the

ossification of the tendon [153]. In an ACLR rat model, both BMSC-EXOs and IPFP-MSC-EXOs reduced bone tunnel cross-sectional area and promoted bone tissue ingrowth into the graft [141,143]. Exosomes derived from magnetically actuated BMSCs can effectively enhance trabecular bone formation, reduce bone loss in the bone tunnel, promote osseous ingrowth into the tendon, and improve postreconstruction biomechanical function of the ACL [154]. Exosomes derived from hypoxia-stimulated BMSCs can facilitate the formation of specialised H-type vessels within the bone tissue, and promoting the differentiation of osteoprogenitor cells to osteoblasts. The differentiated osteoblasts contribute to the development of surrounding bone tissue around the tendon graft, stabilising the connection between the tendon and bone tunnel further and ultimately enhancing TBH [155]. Furthermore, exosomes derived from genetically modified Scleraxis-overexpressing PDGFRα(+) BMSCs, generated through Scx in BMSCs, can suppress osteoclastogenesis and inhibit bone resorption surrounding the bone tunnel, finally enhancing the mechanical strength of TBH. This effect is attributable to miR-6924-5p-mediated targeted downregulation of CXCL12 and OCSTAMP expression [156].

3.2.4. *MSC-EVs for fibrocartilage regeneration promotion in TBH*

As an intermediate structure between tendon and bone, fibrocartilage facilitates the efficient transmission and absorption of local tensile forces during movement [157]. During the tendon reconstruction process, the normal fibrocartilage structure becomes disrupted, which leads to disorganised fibrous scar tissue formation at the tendon–bone interface, which results in compromised mechanical properties [137,158]. MSC-EXOs can promote fibrocartilage regeneration and improve collagen fibre alignment. This enhancement eventually improves postoperative biomechanical function recovery [159,160].

In a rat model of Achilles tendon reconstruction, BMSC-EXOs can facilitate fibrocartilage regeneration at the tendon–bone interface, the underlying mechanism might be associated with the stimulation of M2 macrophage polarisation and promotion of local cell proliferation [142]. In an ACLR rat model, the therapeutic strategy combining cartilage fragments with BMSC-EXOs promoted fibrocartilage regeneration at the tendon–bone interface, of which possible underlying mechanisms include promotion of chondrocyte proliferation, upregulation of the expression of cartilage-related genes SOX9 and ACAN in chondrocytes, and activation of the BMP7/SMAD5 axis [161]. Moreover, IPFP-MSC-EXOs can enhance the regular arrangement of early collagen fibres and facilitate fibrocartilage regeneration, this effect may be attributing to the inhibitory effect of IPFP-MSC-EXOs on early inflammation [143]. In the rabbit model of chronic RCT tear, treatment with ADMSC-EXOs promoted fibrocartilage formation at the tendon–bone interface and improved the biomechanical properties of TBH, which may have occurred due to the anti-inflammatory effects of ADMSC-EXOs [162]. Compared with typical BMSC-EXOs, miR-21-5p-carrying exosomes derived from magnetically actuated BMSCs demonstrate a stronger role in facilitating fibrocartilage regeneration. The underlying mechanism may be attributable to miR-21-5p in the exosomes, which inhibits SMAD7 expression, consequently promoting fibroblast proliferation and migration and upregulating expression of fibrosis markers such as type I collagen and α-SMA [154]. A study pretreated BMSCs with KGN and then loaded them into sodium alginate hydrogel (SAH) to achieve slow BMSC-EXOs release at injury sites. Compared with the control group, treatment with BMSC-EXO-loaded SAH at the injury site increased the number of mature collagen fibres and formation of cartilage at the tendon–bone interface [163]. Tenocytes can transdifferentiate into chondrocytes, whereas chondrocytes can transdifferentiate into osteoblasts [164]. Moreover, some MSC-EXOs can regulate intercellular transdifferentiation; for instance, UCMSC-EXOs have been noted to inhibit epithelial–myofibroblast transdifferentiation [165]. Further research on the regulatory effects of MSC-EXOs on intercellular transdifferentiation may enable the discovery of newer strategies that facilitate fibrocartilage generation during TBH, thereby promoting functional recovery.

4. MSC-EVs in ONFH treatment

As a prevalent refractory orthopaedic disorder, ONFH is characterised by progressive osteonecrosis in the femoral head due to compromised blood supply [4,166]. ONFH can be caused by various factors including hip joint trauma, corticosteroids, alcohol, and genetic factors, and it can be divided into traumatic and nontraumatic types [7]. Nonoperative and operative interventions are used for ONFH treatments. The clinical effectiveness of nonoperative interventions, such as enoxaparin for coagulation inhibition and bisphosphonates for bone resorption inhibition, is limited by their uncertain therapeutic effect and considerable side effects. Moreover, the long-term outcomes of operative interventions, including core decompression, osteotomy, vascularised bone grafting, and joint replacement, tend to be unsatisfactory [7]. Recent studies have indicated that because they can promote microvascular regeneration, repair damaged microcirculation, and regulate bone metabolism, MSC-EXOs may represent an effective treatment strategy for ONFH (Fig. 4) [167,168].

4.1. *MSC-EVs for angiogenesis in ONFH*

Impaired blood supply due to exogenous or endogenous factors is considered a core pathogenic factor related to ONFH, as even short-term blood supply interruptions can lead to its development [4]. Commonly used animal models of ONFH include the glucocorticoid-induced ONFH (GC-ONFH), surgical vascular deprivation ONFH, and liquid nitrogen–induced ONFH models. In GC-ONFH, MSC-EXOs, such as exosomes derived from induced pluripotent stem cell–derived MSCs (iPSC-EXOs), ADMSC-EXOs and BMSC-EXOs, can promote vascular regeneration [167,169,170]. Furthermore, encapsulation with short interfering RNA (siRNA), such as those targeting FGF2, FSTL1, TNF-α, Wnt11, S100A9, and Caspase3, can enhance the vascular regeneration potential of BMSC-EXOs [169]. A study reported that when used for in the treatment of GC-ONFH, lithium ions–stimulated BMSC-EXOs incorporated into an ECM-mimicking hydrogel (i.e. Lightgel), demonstrating considerable angiogenic potential [171]. In the surgical vascular deprivation ONFH animal model, UCMSC-EXOs carrying miR-21-5p were reported to promote vascular regeneration by specifically inhibiting SOX5, thus downregulating the expression of enhancer of zeste homologue 2 (EZH2) [172]. A comparative study analysed the differential gene expression profiles between typical BMSC-EXOs from healthy volunteers and those from patients with traumatic ONFH (ONFH-EXOs). The results revealed that ONFH-EXOs carrying miR-224-3p-inhibited exhibited enhanced potential in promoting vascular regeneration through the upregulation of focal adhesion kinase family interacting protein of 200 kDa (FIP200) expression [173]. Therefore, MSC-EXOs may restore blood supply in patients with ONFH.

4.2. *Osteogenetic role of MSC-EVs in ONFH*

In ONFH, interruption of blood supply to the femoral head contributes to an increase in osteocyte apoptosis and a decrease in osteoblast number, potentially leading to microfractures and eventually causing subchondral bone damage and collapse in the femoral head [4,174]. In GC-ONFH, various MSC-EXOs, including BMSC-EXOs, SMSC-EXOs, UCMSC-EXOs, and iPSC-EXOs, can promote bone trabecula repair and reduce the necrotic area [168,175–178]. BMSC-EXOs can improve osteogenesis in GC-ONFH by enhancing the osteogenic differentiation of BMSCs. Pretreating BMSCs with lithium ions or transfecting tsRNA-10277 into BMSCs can further enhance the osteogenic differentiation effects of BMSC-EXOs [171,178,179]. SMSC-EXOs may facilitate osteogenesis in GC-ONFH by promoting proliferation and inhibiting apoptosis of in situ BMSCs [168]. UCMSC-EXOs carrying miR-365a-5p may increase osteogenesis in GC-ONFH by activating the Hippo

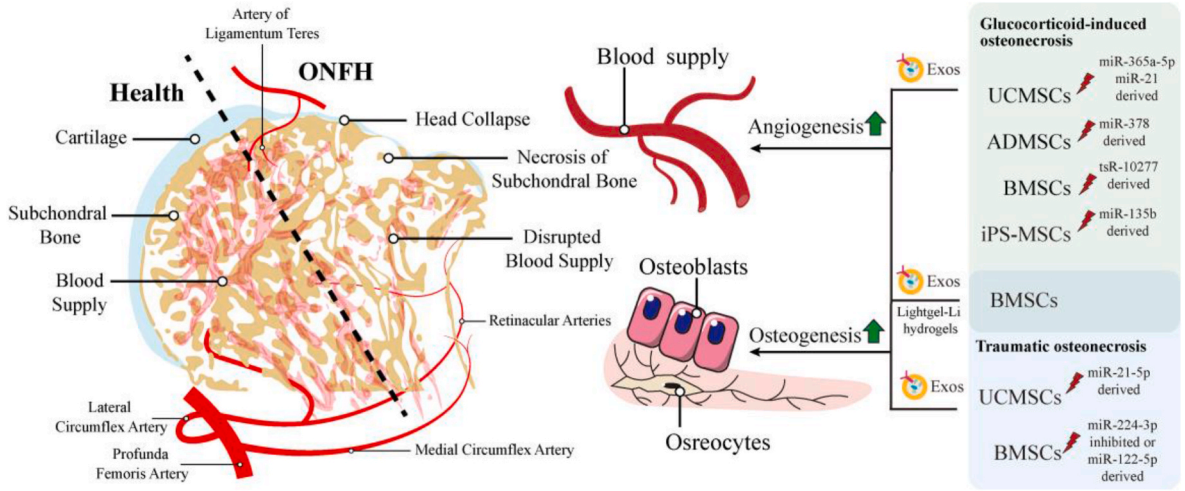

Figure 4. MSC-EXOs in ONFH treatment. Blood supply disruption and osteonecrosis are the main pathologic features of ONFH. MSC-EXOs can ameliorate ONFH by promoting angiogenesis and osteogenesis in damaged areas.

pathway [175]. IPSC-EXOs can reduce the apoptosis of osteocytes in GC-ONFH, and miR-135b overexpression can enhance the osteocyte apoptosis inhibition ability of iPSC-EXOs [176]. In surgical vascular deprivation ONFH animal models, UCMSC-EXOs carrying miR-21-5p were found to inhibit the expression of SOX5 and EZH2 in osteoblasts, thereby promoting osteogenesis and alleviating ONFH [172]. In the rabbit model of ONFH induced by liquid nitrogen, BMSC-EXOs carrying miR-122-5p can increase osteogenesis by promoting osteoblast proliferation and differentiation [180].

In sum, MSC-EVs can restore osteonecrosis by improving the functions of osteoblasts and osteocytes. As such, the effects of exosomes on osteoclasts and other inflammatory cells in ONFH warrant further investigation. Moreover, recent research on the effects of MSC-EVs in ONFH has mainly used ONFH animal models induced through glucocorticoid use, surgical vascular deprivation, and freezing with liquid nitrogen. Additional studies assessing the application of MSC-EVs in a broader range of ONFH models may yield novel therapeutic strategies for ONFH.

5. MSC-EVs in RA treatment

As a prevalent autoimmune disease, RA can affect multiple organs throughout the body, but it most commonly affects the joints. In the affected joints, RA primarily manifests as symmetrical chronic synovitis, cartilage damage, and bone erosion [181]. Given its global prevalence of approximately 0.27 %, RA imposes a large socioeconomic burden [182].

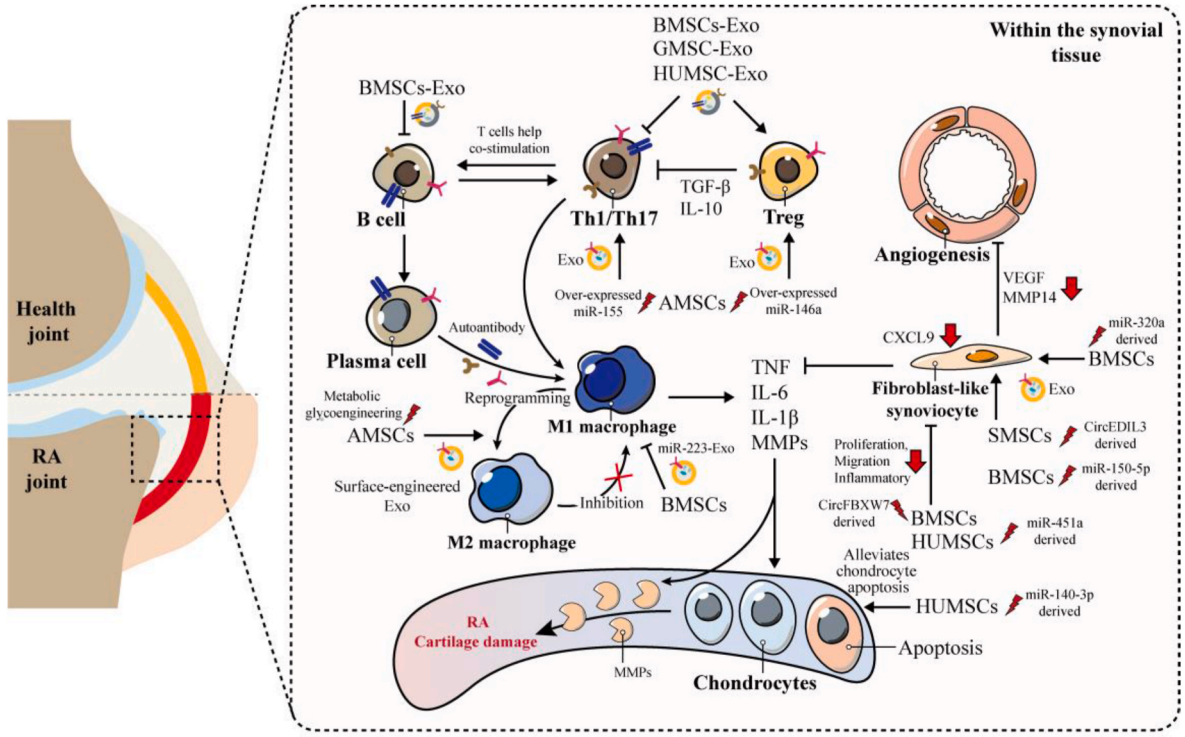

Figure 5. MSC-EXOs in RA treatment. RA pathogenesis is closely related to intraarticular immune inflammatory responses, including adaptive immunity with T and B cells, innate immunity with macrophages, and immune tissue responses involving synovial fibroblasts. MSC-EXOs can ameliorate RA through regulating the biological functions of different cells within the joint.

Pathogenic cells participating in adaptive immune responses (i.e. T and B cells), innate immune responses (i.e. macrophages), and mesenchymal tissue responses [i.e. fibroblast-like synoviocytes (FLSs)] contribute to the pathological damage at RA-affected joints [43,183]. Targeting the aforementioned pathogenic cells through MSC-EVs may represent a novel therapeutic approach for RA (Fig. 5).

5.1. MSC-EVs for targeting adaptive immunity in RA

Adaptive immunity mediated by T cells and B cells plays a central role in the early stage of synovitis in RA [43]. T cells are pivotal in the occurrence and development of RA. In particular, activated T cells can differentiate into different subsets under the stimulation of various cytokines in the surrounding environment. Among them, Th1 cells secrete interferon γ, whereas Th17 cells produce IL-17 and IL-22, both of which contribute to RA exacerbation through increased recruitment of macrophages and release of proinflammatory cytokines such as TNF-α and IL-6 [184]. Regulatory T cells (Tregs), which differentiate from CD4+ T cells, mainly exert immunosuppressive effects by inhibiting the proliferation and differentiation of Th17 cells, as well as the proinflammatory effects of Th1 and Th17 cells [185,186]. In RA, B cells can either become coactivated with Th1/Th17 cells or differentiate into plasma cells under antigen stimulation, promoting macrophage recruitment and activation through autoantibody production and cytokine secretion [187]. UCMSC-EXOs and gingival MSCs-EXOs (GMSC-EXOs) can alleviate joint swelling and synovial hyperplasia in collagen-induced arthritis (CIA) mice, the underlying anti-RA mechanisms might be related to reductions in the numbers of Th1 and Th17 cell proportions and significant increases of Tregs [188,189]. In RA, MSC-EXOs can exert their biological effects through the miRNA. Compared with normal ADMSC-EXOs, ADMSC-EXOs overexpressing miR-146a have an enhanced immunoregulatory capacity in RA, as evidenced by enhanced lymphocyte secretion of cytokines including TGF-β and IL-10 and increased proportions of Tregs [190]. Furthermore, BMSC-EXOs can suppress arthritic inflammation in RA animal models. In addition to regulating Th1/Th17 cells and Tregs, BMSC-EXOs can inhibit plasmablast differentiation, ultimately mediating inflammatory inhibition, in RA [191].

5.2. MSC-EVs targeting innate immune response in RA

In the innate immune response of RA synovitis, macrophages play a crucial role in synovial inflammation. Macrophages are recruited under the influence of T or B cells, and their differentiation is closely related to the surrounding environment. M1 and M2 macrophages, which secrete proinflammatory or anti-inflammatory cytokines, are involved in the regulation of synovial inflammation [43]. BMSC-EXOs can downregulate NLRP3 expression in macrophages through miR-223, thereby inhibiting the release of proinflammatory cytokines such as IL-1β and TNF-α [192]. ADMSC-EXOs can inhibit M1 macrophage polarisation. Moreover, the regulatory capacity of these exosomes can be enhanced using various bioengineering strategies. For instance, precise modification of the surface of ADMSCs through metabolic glycan engineering can improve the regulatory function of M1/M2 macrophage polarisation and increase M2 macrophage levels considerably, enhancing the therapeutic potential of ADMSC-EXOs in RA [193].

5.3. MSC-EVs targeting mesenchymal tissue responses in RA

Under the physiological state, FLSs actively secrete synovial fluid, contributing to the maintenance of the synovium's normal function and providing essential nutrition for the joint cartilage [43]. In patients with RA, FLSs proliferate and become activated, which leads to the secretion of MMPs, inflammatory cytokines (e.g. IL-6), chemokines (e.g. CXCL10), and angiogenic factors (e.g. VEGF). Through secretion of these molecules, FLSs can aid in mediating cartilage damage, synovial inflammation, lymphocyte recruitment, and angiogenesis. Furthermore, FLSs are invasive, facilitating the spread of RA to other unaffected joints [194,238].

A study reported that patients with RA may demonstrate significantly higher MMP14 and VEGF expression but significantly lower miR-150-5p expression than patients with OA. Moreover, observed human umbilical vein endothelial cells treated with the conditioned medium of inflammatory pretreated FLSs demonstrated significantly upregulated VEGF expression, as well as an increase in tube formation. However, treatment with miR-150-5p-overexpressing BMSC-EXOs reversed the proangiogenic effects of FLSs, and they also reduced the invasiveness of FLSs, potentially through the inhibition of MMP14 and VEGF expression in the FLSs. Finally, in CIA mice treated with miR-150-5p-overexpressing BMSC-EXOs, the synovium thickness and vascularisation reduced significantly compared with control mice [194,195].

BMSC-EXOs carrying miR-320a can inhibit FLS activation in RA by suppressing CXCL9 expression, whereas UCMSC-EXOs carrying miR-451a can inhibit FLS proliferation, migration, and invasion in RA by suppressing ATF2 expression [196,197]. In addition, SMSC-EXOs can delay RA progression by downregulating miR-216a-3p expression through circFBXW7, as well as inhibit the proangiogenic effects of FLS through circEDIL3 [198,199].

5.4. MSC-EVs for cartilage damage alleviation in RA

The pathological features of RA can also include cartilage damage and bone erosion. The mechanisms underlying cartilage damage in RA are closely associated with FLS adhesion and invasion. IL-1 and IL-6 released by FLSs can also aggravate cartilage damage. MMP14 mainly mediates ECM degradation, whereas IL-1 and IL-7A primarily mediate chondrocyte apoptosis [43]. Serum and glucocorticoid-induced protein kinase 1 (SGK1)—an important regulatory factor in chondrocyte differentiation and calcification—can facilitate tissue fibrosis by upregulating the NF-κB pathway. In rats with RA, UCMSC-EXOs carrying miR-140-3p can downregulate SGK1, thereby inhibiting chondrocyte apoptosis, promoting FLS apoptosis, and inhibiting FLS proliferation, ultimately alleviating cartilage damage [200]. In addition, chondrocytes can directly absorb BMSC-EXOs that promote their proliferation and migration and thereby reverse RA-related cartilage damage [201]. BMSC-EXOs also can downregulate MMP14 expression in RA, potentially alleviating cartilage damage [195].

Because RA pathogenesis involves autoimmune responses, therapeutically applied MSC-EVs primarily modulate immune cells to alleviate RA symptoms. Recent studies on the use of MSC-EVs in RA treatment have mainly focused on T cells, macrophages, and FLSs. However, B cells, playing a role in antigen presentation and T-cell activation, also participate in RA-related immune inflammation [147]. MSC-EXOs carrying miRNA-125b can alleviate experimental jogren's syndrome by inhibiting plasma cells [202]. MSC-EVs can also alleviate systemic lupus erythematosus by inhibiting B-cell proliferation and activation [203]. Therefore, further exploration of the regulatory effects of MSC-EXOs on B cells in RA may aid in the development of newer RA treatment strategies.

6. Limitations of MSC-EVs therapy

Further research on MSC-EVs and their clinical translation are faced with many challenges, involving large-scale production, safety concerns, efficacy, durability, storage, and transportation [204–206]. The challenges of large-scale production include achieving high yields, increasing recovery rates, and establishing MSC-EVs quality standards with each extraction [204]. Clinical therapeutic application of MSC-EVs is also associated with several risks, such as the potential for "off-target" side effects of including the risk of hypercoagulation [207]. Moreover, during therapeutic iPSC-EXO production, the conditioned media used for cell expansion may contain DNA fragments from apoptotic cells. In rare cases, the DNA from malignant cells may be transferred to normal

cells through the MSC-EVs cargo, promoting tumor formation [207]. Several studies have also suggested that the transfer of tumor-associated factors present in MSC-EVs can promote cancer cell proliferation [208]. MSC-EVs also have issues of relatively low efficacy, such as weak targeting and low content of functional components [26,150]. In the treatment of joint diseases such as OA and ONFH, the observation period for long-term efficacy of MSC-EVs administration typically spans from 8 to 12 weeks [92,180]. MSC-EVs are susceptible to metabolism and clearance at the administration site, this leads to the durability of MSC-EVs therapy needs to be further strengthened [210]. In addition, recent research indicates that the storage conditions for MSC-EVs are highly demanding, with temperature, pH, time and freeze–thaw cycles significantly impacting both quantity and quality of MSC-EVs, thus posing challenges for long-term storage and transportation [211].

Recent studies have proposed several strategies to address the aforementioned limitations of EVs application. Good manufacturing practice standards can be used to regulate the production of MSC-EVs through multiple aspects, such as cell control, culture medium composition, extraction methods, and initial product characterisation testing, so as to standardise the production process and establish a robust foundation for large-scale manufacturing [204]. There are also multiple strategies to improve the limitations of MSC-EVs in the treatment of joint diseases. Employing size-exclusion chromatography for MSC-EXOs purification can enhance exosome recovery rates, reduce impurity levels, and improve exosome therapeutic efficacy in OA chondrocytes [212]. Moreover, surface modification of BMSC-EXOs with hydrogels can enhance targeted delivery to OA chondrocytes and reduce local degradation [83]. Furthermore, pretreating MSCs with TGF-β1 can increase the miR-135b content in the exosomes, thereby augmenting the MSC-EXOs' capacity to stimulate OA chondrocyte proliferation [213]. Furthermore, the protective technologies of EVs such as cryopreservation, lyophilisation, and spray-drying can aid in overcoming storage and transportation challenges associated with EVs [26].

7. Conclusions and prospects

MSC-EVs, especially exosomes, exhibit remarkable therapeutic potential for joint disease treatment. Over the past decade, significant progress has been made in this field. As a novel treatment approach bridging the gap between pharmacological and surgical procedures, MSC-EVs use can ameliorate the symptoms of joint diseases or prevent their progression by promoting tissue regeneration, suppressing inflammation, and modulating immune responses [66,171,188,189]. Moreover, MSC-EVs can be used as an adjunct to surgical treatment of joint diseases, promoting postoperative functional recovery and preventing postoperative complications [6,139]. Although the potential therapeutic effects and applicability of MSC-EVs have been evaluated preclinically in small animal (mouse, rat, or rabbit) models of various joint diseases (e.g., OA, ONFH, and RA), their therapeutic effect in large animal studies or clinical trials have been mostly lacking until now. More strategies may be employed for the clinical translation of MSC-EV-based therapy in the future. In terms of basic research, the number of studies using large animal models should be increased, and the mechanism research should be deepened. For clinical research, large-scale, multi-center clinical trials with optimized statistical strategies are also warranted.

A major factor affecting the clinical translation of MSC-EVs is their heterogeneity, which is mainly influenced by different cell sources and culture conditions. MSC-EVs surface markers can vary across some different MSC sources. For instance, ADMSC-EXOs express CD9, CD63, and CD81, BMSC-EXOs express CD63, CD9, and TSG101, and iPSC-EXOs express CD9, TSG101, and SSEA1 [214]. Moreover, BMSC-EVs have a stronger ability to promote cell proliferation than ADMSC-EVs, whereas ADMSC-EVs are more prone to promote angiogenesis than BMSC-EVs [215]. The above function of EVs is closely associated with their cargo, which may include mRNAs, noncoding RNAs (miRNAs, circRNAs, siRNAs, or lncRNAs), lipids, and proteins [215]. Moreover, maintaining stable culture conditions aids in reducing MSC-EVs heterogeneity, which could also facilitate large-scale EV production.

Different EV types, such as BMSC-EVs, ADMSC-EVs, SMSC-EVs, and UCMSC-EVs, can demonstrate similarly high therapeutic efficacies for cartilage injury in different joint diseases [54,88,97,200]. Moreover, BMSC-EVs can enhance cartilage regeneration and repair in OA and tendon and ligament injuries, while they can also promote vascular regeneration in ONFH and tendon and ligament injuries. ADMSC-EVs can alleviate both OA and RA synovitis [55,57,139,142,172,191]. In addition, MSC-EVs derived from the same cell source can exert similar therapeutic effects for different joint diseases. Further research exploring the synergistic therapeutic effects of MSC-EVs from different sources on various cells is warranted.

MSC-EVs can also play a major role in regenerative medicine and tissue engineering, functioning as drug delivery systems and carriers for gene editing tools. In addition, combining novel biomaterials with EVs may aid in optimizing the therapeutic advantages of MSC-EVs. MSC-EVs with targeting and low immunogenicity characteristics can cross the biological barrier and thus be used as an efficient carrier for cargo delivery in vivo [216]. BMSC-EXOs loaded with ICA can synergistically enhance the cellular uptake and therapeutic effects of ICA in OA, partially though promoting chondrocyte proliferation and migration [82]. A study constructed a chondrocyte-targeting miRNA delivery system, which improved the targeting ability of exosomes to chondrocytes and promote cartilage regeneration of OA mice by loading of miR-199-3p [93]. Moreover, MSC-EVs combined with biomaterials, such as hydrogels, can further enhancing their therapeutic effects through improving their local targeting effects, and enhance their local retention [83,103,127,131].

In summary, MSC-EVs have potential clinical applicability to treat various joint diseases in the future. More studies should focus on elucidating their molecular mechanisms of action, determining the associated risks, and establishing administration protocols, aiming to promote the clinical translation of MSC-EVs.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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CRediT authorship contribution statement

Jinhui Wu: Visualization, Writing – original draft, Writing – review & editing. **Jiangyi Wu:** Funding acquisition, Writing – original draft, Writing – review & editing. **Zheng Liu:** Investigation, Writing – original draft, Writing – review & editing. **Yunquan Gong:** Writing – review & editing. **Daibo Feng:** Writing – review & editing. **Wei Xiang:** Funding acquisition, Writing – original draft, Writing – review & editing. **Shunzheng Fang:** Software, Writing – review & editing. **Ran Chen:** Software, Writing – review & editing. **Yaran Wu:** Formal analysis, Writing – review & editing. **Shu Huang:** Writing – review & editing. **Yizhao Zhou:** Writing – review & editing. **Ningning Liu:** Writing – review & editing. **Hao Xu:** Software, Writing – review & editing. **Siru**

Zhou: Visualization, Formal analysis, Software, Writing – review & editing. **Baorong Liu:** Investigation, Project administration, Supervision, Writing – review & editing. **Zhenhong Ni:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. The Editors of the Journal of Orthopaedic Translation strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

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