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Review Article

Extracellular vesicles: Potential role in osteoarthritis regenerative medicine

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ABSTRACT

Osteoarthritis (OA) is a prevalent whole joint disease characterised by cartilage degradation, subchondral bone sclerosis and bone remodelling, and synovium inflammation, leading to pain, deformity, and cartilage dysfunction. Currently, there is no appropriate therapy for OA, and available treatments simply aim to reduce pain and swelling. Exosomes are membrane-bound extracellular vesicles secreted by almost all cells, receiving increasing interest because of their effect in cell-to-cell communication. Increasing evidence suggests that exosomes play an important role in cartilage physiological and pathological effects. This article reviews the potential role of exosomes in OA regenerative medicine. Special attention is given to mesenchymal stem cells-derived exosomes due to the extensive research on their cartilage repair property and their function as miRNA cargo. More investigations are needed for the effects of exosomes from synovial fluid and chondrocytes in joints. A better understanding of the mechanisms will contribute to a novel and promising therapy for OA patients.

The translational potential of this article: A better understanding of the role of extracellular vesicles in regenerative medicine will contribute to a novel and promising therapy for OA patients.

Introduction

Osteoarthritis (OA) is a leading cause of pain and disability in the elderly, affecting more than 250 million people worldwide. OA is mainly characterised by inflammation in the synovium, progressive loss of articular cartilage, degradation and degeneration of menisci and ligaments, thickening of the subchondral bone, and formation of osteophytes [1]. Multiple pathophysiological processes are involved in OA progression, including the activation of the innate and immune systems and imbalance between the anabolic and catabolic factors, eventually leading to the degradation of cartilage and bone [2]. Numerous risk factors may be associated with OA, such as aging, obesity, and trauma. To date, drugs for OA patients can only relieve pain without actually curing the disease. The treatment for OA has always been a problem because of the lack of blood supply to the articular cartilage, the poor proliferation, and the migration potential of chondrocytes [3]. The most widely used treatment in end-stage patients is surgical therapy, which is not only expensive, but also needs a second surgery in some cases [4]. Therefore, an appropriate disease-modifying therapy that targets the onset and progression of OA is urgently needed. In recent years, exosomes have been proposed to play important roles in the pathogenesis and progression of OA, thus providing exciting therapeutic prospects.

Exosomes are membrane-bound extracellular vesicles (EVs) surrounded by a phospholipid bilayer that can be released from normal and pathological cells existing in the blood, urine, saliva, breast milk, bronchoalveolar lavage, pleural effusions, malignant ascites, and amniotic

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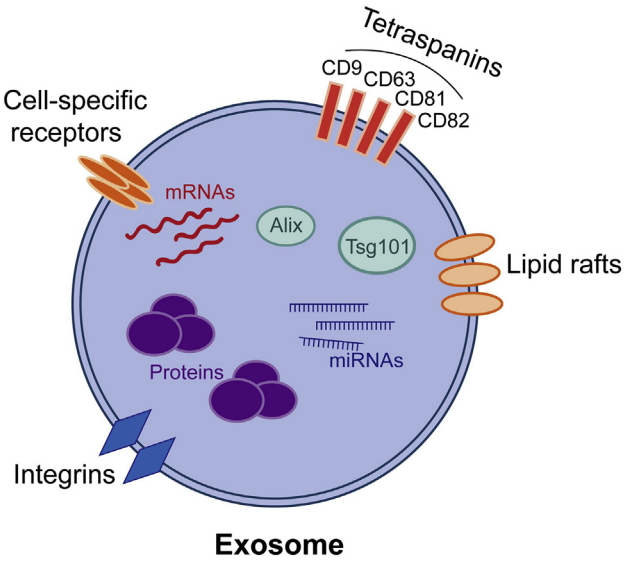

Figure 1. Diagram of the exosome. Exosomes are membrane-bound extracellular vesicles and have an endosome origin, with a size ranging from 30 nm to 100 nm. Cell-specific receptors, integrins, and lipid rafts can be found in the phospholipid bilayer of the membrane, participating in cell-to-cell communication. Almost all exosomes contain tetraspanins (CD9, CD63, CD81, CD82), multivesicular body biogenesis-related proteins (Alix, Tsg101), heat shock proteins, and some phospholipases. Besides proteins, exosomes also contain mRNAs as well as miRNAs. The composition of exosomes not only reflects the biological state of their parent cells but also affects their functions.

Table 1
Different types of extracellular vesicles.

Characteristics	Exosomes	Microvesicles	Apoptotic bodies
Size	30–100 nm [7]	50–1000 nm [13]	1–5000 nm [13]
Morphology	Cup-shaped [14]	Heterogeneous [14]	Heterogeneous [14]
Origin	Luminal budding into multivesicular bodies (MVBs); release by fusion of MVBs with the cell membrane [13]	Budding off the plasma membrane [15]	Outward blebbing of the cell membrane [13]
Composition	Coding RNA, noncoding RNA, proteins, antigen presentation molecules, DNA [10, 14]	miRNA, mRNA, proteins, lipids, cytosol [15]	Proteins, lipids, DNA, rRNA, cytosol [15]

and synovial fluids (Figure 1) [5,6]. EVs are divided into three categories: exosomes, microparticles, and apoptotic bodies (Table 1). Exosomes, the diameters of which vary from 30 to 100 nm, originate from the cell membrane during endocytic internalisation [7]. Previously, the size was considered to be a main determining factor in distinguishing these three particles [8], but recent research points to the fact that protein composition may be a major mechanism in identifying them as well [9]. In this review, EVs refer to exosomes. Exosomes contain RNAs, DNAs, mRNAs, microRNA (miRNAs), proteins, and lipids [10], and their cargo reflects the biological state of the parent cell. They mostly function during cell-to-cell communication via paracrine, juxtacrine, and endocrine signalling [11]. The mRNAs contained in exosomes can be translated within the recipient cells via exosome–cell interaction for silencing gene expression and posttranscriptional regulation [10]. Besides, the bilayer phospholipid membranes of exosomes offer a controlled internal microenvironment, as well as protection, to its contents that guarantee degradation-free travel over cell distances [12]. In OA pathogenesis, exosomes can be pathogenic or protective [2,7]. Since exosomes are secreted by almost all cell types, in this review, we demonstrate the role of exosomes derived from certain typical cell types that are involved in OA, such as mesenchymal stem cells (MSCs), fibroblast-like synoviocytes (FLS), and articular chondrocytes.

Role of mesenchymal stem cell-derived exosomes in OA

Characteristics of mesenchymal stem cells

MSCs can be divided into three types: embryonic stem cells, pluripotent stem cells, and adult stem cells [16]. Multipotent MSCs have been isolated from various tissues, such as bone marrow, adipose tissue, dental pulp, umbilical cord, and others [17]. MSCs display remarkable antiinflammatory functions and immunosuppressive properties in terms of decreasing inflammation and activating monocytes. They can also modulate immune responses by interacting with cells existing in both the innate and adaptive immune systems. Furthermore, they inhibit macrophage polarisation toward proinflammatory macrophages (M1), and instead favor the antiinflammatory macrophage (M2) phenotype. Additionally, MSCs have the potential to differentiate into chondrocytes, osteoblasts, adipocytes, endothelial cells, neurogenic cells, and cardiovascular cells [18,19]. They can also secrete other bioactive molecules such as insulin-like growth factor 1 (IGF-1), interleukin 6 (IL-6), prostaglandin E2 (PGE2), matrix metalloproteinase-2 (MMP-2), MMP-9 and platelet-derived growth factor (PDGF), which culminate in anti--apoptotic, immunomodulatory, hematopoietic stem cell support, and anti-fibrotic functions [20]. As MSCs are able to mediate inflammation, modulate immune responses, differentiate into chondrocytes, and accelerate tissue repair, they are considered to be a suitable form of therapy for cartilage repair. Previously, Murphy et al. [21] reported the regeneration of the medial meniscus and a reduction in articular cartilage degradation after intraarticular injection of bone marrow MSCs in goats with surgery-induced knee joint OA. At one point, their ability to repair cartilage damage was attributed to chondrocyte differentiation; however, emerging evidence suggests the MSC secretome (mainly referring to exosomes) as an important component in modulating abnormal injury tissue microenvironments and regenerative processes, such as cell migration, proliferation, and matrix synthesis [22]. Although MSC-derived exosomes have been proven to be therapeutically efficient in different studies spanning cardiovascular disease, graft-versus-host disease, and bone fracture, their potential mechanisms in OA still remain unclear. Here, we attempt to summarise the role of MSC-derived exosomes in OA.

Potential role of MSC-Derived exosomes in OA

MSC-derived exosomes in cartilage repair and OA therapy

The articular cartilage, which is mostly responsible for distributing loads evenly and reducing friction, is a unique hypocellular and avascular tissue. In this case, the common regenerative processes upon damage (with respect to stem cell recruitment through the blood) do not occur easily [23], which means that it has very limited capability of self-repair. Therefore, a chronic articular cartilage defect would ultimately cause OA. One of the current surgical treatment options involves autologous chondrocyte implantation, which is still confronted with several problems, including donor site morbidity, shortage of cell source, tissue hypertrophy, and high surgery costs [24]. Another option is joint arthroplasty, which could possibly cause severe complications and injuries at a later stage. Hence, a safe and promising cell-based therapy is urgently needed in terms of regenerative medicine. Although MSC therapy is safer than other types of stem cells, the direct application of stem cells has many limitations, such as tumor growth stimulation, bio-distribution, or ectopic grafting, and immune rejection [25]. Notably, research has increasingly indicated that the therapeutic effects of MSCs may not be limited merely in terms of cell differentiation, but also with

respect to their paracrine secretion of bioactive molecules and trophic factors.

Several studies conducted on animals suggested that MSC exosomes possibly facilitated cartilage repair and contributed to promoting articular conditions. Zhang et al. first reported that femurs treated with human embryonic MSC-derived exosomes showed thorough rehabilitation of the subchondral bone and cartilage along with a smooth, regular surface on the hyaline cartilage and almost normal extracellular matrix (ECM) deposition in a surgical rat model. Similar results showed that EVs released by human bone marrow-derived MSCs (hBMSC-EVs) were able to accelerate OA cartilage repair not only by promoting ECM production via OA chondrocytes, but also ameliorating inflammatory responses [26]. Despite their ability to regenerate, MSC exosomes exhibit antiapoptotic capabilities, which may also relate to cartilage repair. Since chondrocytes are the only resident cells in the cartilage, their apoptosis is of great pathogenic importance in OA. Zhang et al. further observed an increase in proliferating nuclear antigen + cells and a different change in cyclic citrullinated peptide 3 + apoptotic cells in exosome-treated groups, which implied that MSC-derived exosomes possibly induced cell proliferation and weakened apoptosis [27]. Similarly, Cosenza et al. also reported that MSC exosomes influenced apoptotic chondrocyte levels in a murine apoptosis model [28].

For many years, stem cell therapy has been considered to be an effective and promising strategy in treating many diseases. Exosome-based therapy is obviously superior when compared to MSC therapy not only because exosomes are relatively more sustainable and reproducible, but also because of their probable safety levels, which is enforced by their reduced toxicity and immunogenicity issues [29,30]. In addition, MSC-derived exosomes could communicate with their target cells directly, which significantly reduces the risks and limits of carrying toxicity and rapid clearance [31]. They can also maintain the immune-privileged characteristics of their parental cells and prevent immunogenicity because of the absence of cell surface major histocompatibility complex I/II proteins [14]. Previously, a study showed that

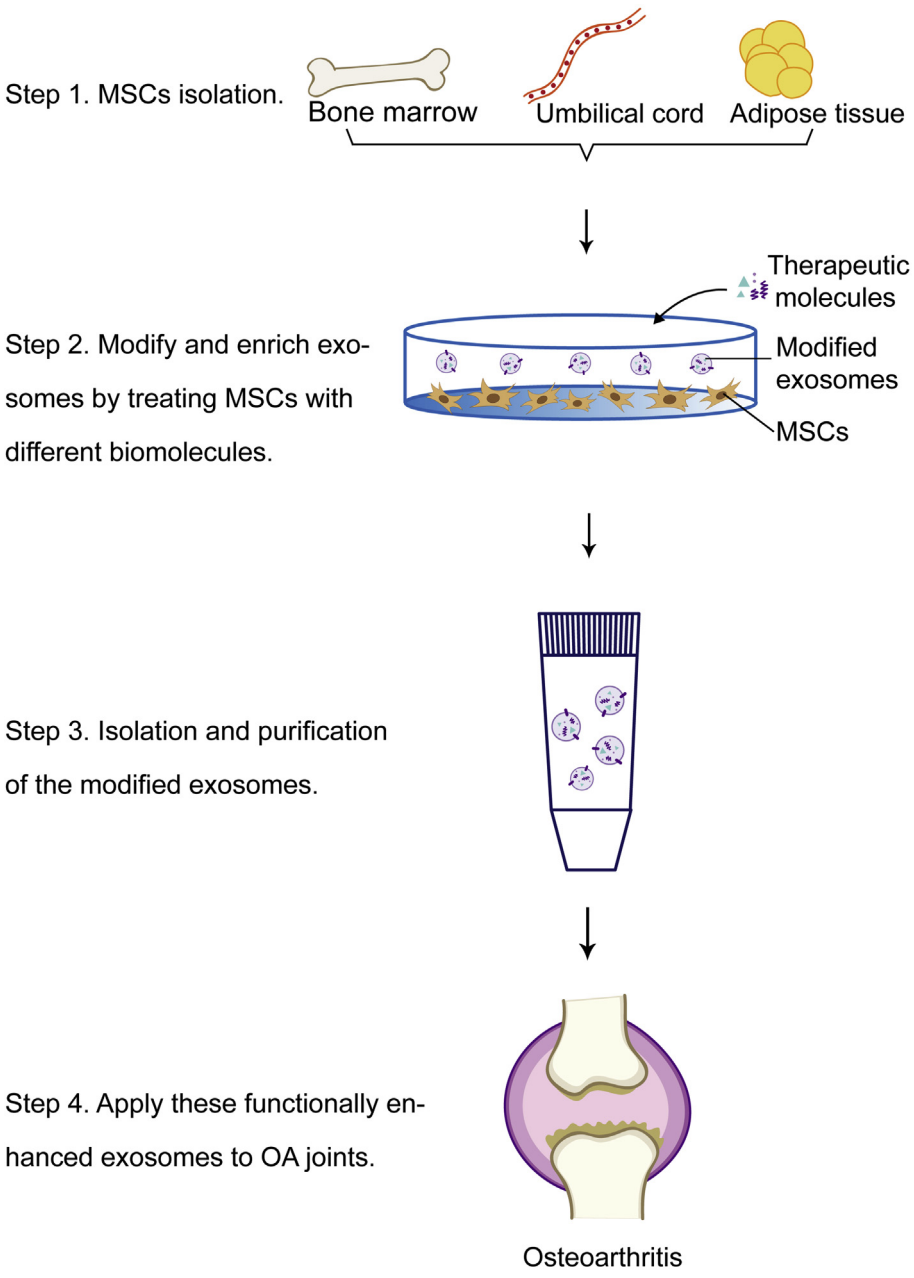

Figure 2. Schematic diagram of modified MSC-derived exosomes production and their application in treating OA.

MSC-derived EVs induced antiinflammatory cytokine expression, while simultaneously triggering cell death in activated T cells [32]. Exosomes can also be engineered by changing their contents (proteins, miRNAs, nucleic acids, etc.) so that they can be used in various treatments [33]. To date, exosome-based therapies have been reportedly applied in different disease investigations, such as graft-versus-host disease [34] and cardiovascular disease [30]. In terms of treating OA, exosomes from different kinds of MSCs have shown different effects. For instance, Zhu et al. reported that injecting exosomes secreted by both human-induced pluripotent stem cell-derived MSCs (iMSCs-Exos) and synovial membrane-derived MSCs suppressed OA in a mouse model; however, iMSCs-Exos demonstrated superior therapeutic abilities as they were able to better stimulate chondrocyte migration and proliferation [35]. According to this study, exosome therapy for OA is possible because of the non-invasive collection process, inexhaustible cell source, and immunosuppressive properties of iMSCs. Another study by Wang et al. reported that embryonic stem cell-induced MSC-derived exosomes could alleviate OA by balancing the formation and degradation of chondrocyte ECM [36]. Recently, MSCs derived from adipose tissue have shown promising therapeutic prospects in treating OA. In recent research, Wu et al. [37] reported that exosomes secreted by infrapatellar fat pad MSCs (IPFP-MSCs) had the potential to protect the cartilage and prevent its destruction and meanwhile attenuate gait abnormality in OA mice models. In addition, they also found a significant enhancement of the chondrocyte autophagy level via inhibiting the mammalian target of the rapamycin signalling pathway, which was closely related to exosomes derived from IPFP-MSCs. Taken together, these findings above point out that exosome-based therapy may have the great potential to open new possibilities for cell-free treatments in the future. In addition to the direct application of exosomes, modified exosomes have also attracted remarkable scientific interest (Figure 2). Parental cells are well-known to impact the properties and functions of their exosomes by affecting their bioactive cargos. Besides, their specific cell-targeting potential is also noteworthy. Increasing investigations regarding exosomal enrichment with biomolecules for therapeutic purposes suggested another novel strategy for OA treatment based on gene targeting (also known as genetically engineered exosome therapy). Such functionally enhanced exosomes have already been applied successfully in other fields to treat cancer, mediate immune responses, and ameliorate neural deficits. In a recent study, modified exosomes were used to deliver siRNA to human epidermal growth factor receptor 2-positive breast cancer cells [38].

Despite the advantages and potential of MSC-derived exosome therapy, certain limitations and risks, in terms of uncontrolled transfer of gene information [10] and problems associated with biodistribution, still exist. Moreover, many challenges with respect to the intrinsic properties of exosomes, such as the lack of targeting property, and the difficulty to load specific biomolecules [39], should be given due attention. In addition, this application requires high-quality standardisation of isolation and professional techniques to harvest sustainable and reproducible exosomes Future investigations may focus on the method to purify exosomes, simultaneously lowering the cost and time of exosome production.

Exosomal miRNA derived from MSCs

As demonstrated above, exosomes can contain RNAs, DNAs, mRNAs, miRNAs, and other biomolecules, through which miRNAs have constantly received increased research interest. Among the different small RNAs, the proportion of exosomal miRNAs has been reported to be higher than miRNAs in their respective parent cells [40].

Notably, particular miRNAs are closely associated with cartilage formation and degeneration. For example, a study by Miyaki suggested that miRNA-140, known to be the most cartilage-specific miRNA, was significantly downregulated in OA articular cartilage and was involved in both chondrocyte differentiation and the imbalance of anabolic and catabolic processes in OA [41]. To be more specific, some other studies implied that exosomal miR-140-5p was of great importance in cartilage homeostasis and slowing down OA progression. Furthermore, Tao et al. found that exosomes derived from miR-140-5p-overexpressed synovial mesenchymal cells (SMSC-140-Exos) enhanced chondrocyte migration and proliferation in a rat OA model [42]. Another study showed that miR-320c enhanced human MSC chondrogenesis and downregulated MMP-13 expression [43]. Sun et al. demonstrated that exosomes derived from hBMSCs overexpressing miR-320c increased SOX9 [SRY (Sex determining region Y)-box 9] and decreased MMP-13 expression in OA chondrocytes, thereby indicating its potent effects in promoting chondrogenesis [44]. Exosomal miR-92a-3p derived from MSCs was also found to mediate cartilage development and homeostasis via WNT5A. Moreover, cartilage proliferation and matrix gene expression were both found to be promoted after MSC-miR-92a-3p-Exosome treatment in OA primary human chondrocytes [45]. The main role of miRNAs in OA pathogenesis is summarised in Table 2. It is important to note that the amount and composition of the miRNAs packaged into exosomes follow diverse disciplines and that exosomal miRNAs are expressed at different levels under various physiological conditions [46]. Unfortunately, present research regarding these topics is very limited. Therefore, the role of MSC-derived exosomal miRNAs in OA needs further investigation.

Role of exosomes in OA synovial inflammation

Synovial inflammation in OA

Synovial inflammation is a potential cause of OA progression. The synovial membrane is a membranous structure lining the cavities of joints, and its main functions are to secrete synovial fluid and provide nutrients to the cartilage [59]. Evidence-based medicine shows that OA patients experience acute or chronic synovitis in varying degrees [59]. Although OA is always considered to be a degenerative disease with significant debilitating cartilage disorder, research increasingly indicates that chronic, low-grade inflammatory processes leading to synovial inflammation also contribute to OA pathogenesis and disease progression. The underlying mechanisms probably involve the activation of macrophages by some cartilage matrix catabolic molecules and stimulation of other immune cells that release inflammatory cytokines, gradually resulting in chondrocyte dysfunction [60].

Table 2
Role of microRNAs in the pathogenesis of OA.

miRNAs	Roles	Reference
miR-93	Inhibit chondrocyte apoptosis and inflammation in OA	[47]
miR-31	Promote chondrocyte proliferation by targeting C-X-C motif chemokine ligand 12	[48]
miR-485-5p	Increase the release of inflammatory factors and inhibit the cartilage differentiation	[49]
miR-486-5p	Inhibit chondrocyte proliferation and migration by suppressing Mothers against decapentaplegic homolog 2 (SMAD2)	[50]
miR-10a-5p	Promote chondrocyte apoptosis in OA by targeting Homeobox A1 (HOXA1)	[51]
miR-92a	Involved in chondrogenesis and positively regulate co19a2 and aggrecan expression	[52]
miR-320	Inhibit MMP-13 expression in chondrogenesis	[43]
miR-181b	Negatively regulate the cartilage development and chondrocyte differentiation	[53]
miR-125b	Suppress the expression of ADAMTS-4 mRNA in osteoarthritic chondrocytes	[54]
miR-455	Exacerbate cartilage destruction through diminishing TGFβsignalling	[55]
miR-27b	Regulate MMP-13 expression in human osteoarthritis chondrocytes	[56]
miR-146a	Intensely expressed in low-grade OA cartilage and decrease in parallel with the level of MMP-13 expression	[57]
miR-9	Inhibit secretion of the collagen type II-targeting metalloproteinase MMP-13 in OA chondrocytes	[58]

Exosomes in synovial inflammation

During the synovial inflammation process, macrophages play a significant role in disease progression [61]. Macrophage accumulation in the synovial lining is a significant characteristic of synovitis. Once stimulated by certain environmental stimuli and inflammatory mediators, these highly plastic cells can change their phenotype, going from M1 macrophages to M2 macrophages [62]. M1 macrophages are capable of presenting antigen and activating Th1 responses, thus displaying proinflammatory functions. M2 macrophages can be divided into three different subtypes: M2a, which are stimulated by IL-4 or IL-13 and are considered to ameliorate proinflammatory stimuli [63]; M2b, which are induced by immune complexes and Toll-like receptors or IL-1 receptor agonists [64]; and M2c, which are stimulated by IL-10 or transforming growth factor beta (TGF-β) and glucocorticoids and suppress inflammation by downregulating proinflammatory cytokines while promoting neovascularisation and tissue remodelling [64,65]. Generally, M2 macrophages contribute to antiinflammation and the repair of injured tissue [66]. Lo Sicco et al. reported for the first time that exosomes secreted by adipose tissue-derived MSCs induced the polarisation of macrophages toward the M2 phenotype, which exhibited antiinflammatory ability [67]. Similarly, Cosenza et al. showed that BMSC-derived exosomes inhibited macrophage activation and likely induced a shift to the M2 phenotype [68]. Interestingly, M2 macrophages have been widely reported to show an antiinflammatory effect during the immune response process, which could promote cartilage repair and ideal joint conditions by suppressing inflammation in arthrosis. Therefore, the immunological property of exosomes may also lay a foundation for clinical therapy in OA patients by manipulating macrophage polarisation in synovial tissues (Figure 3).

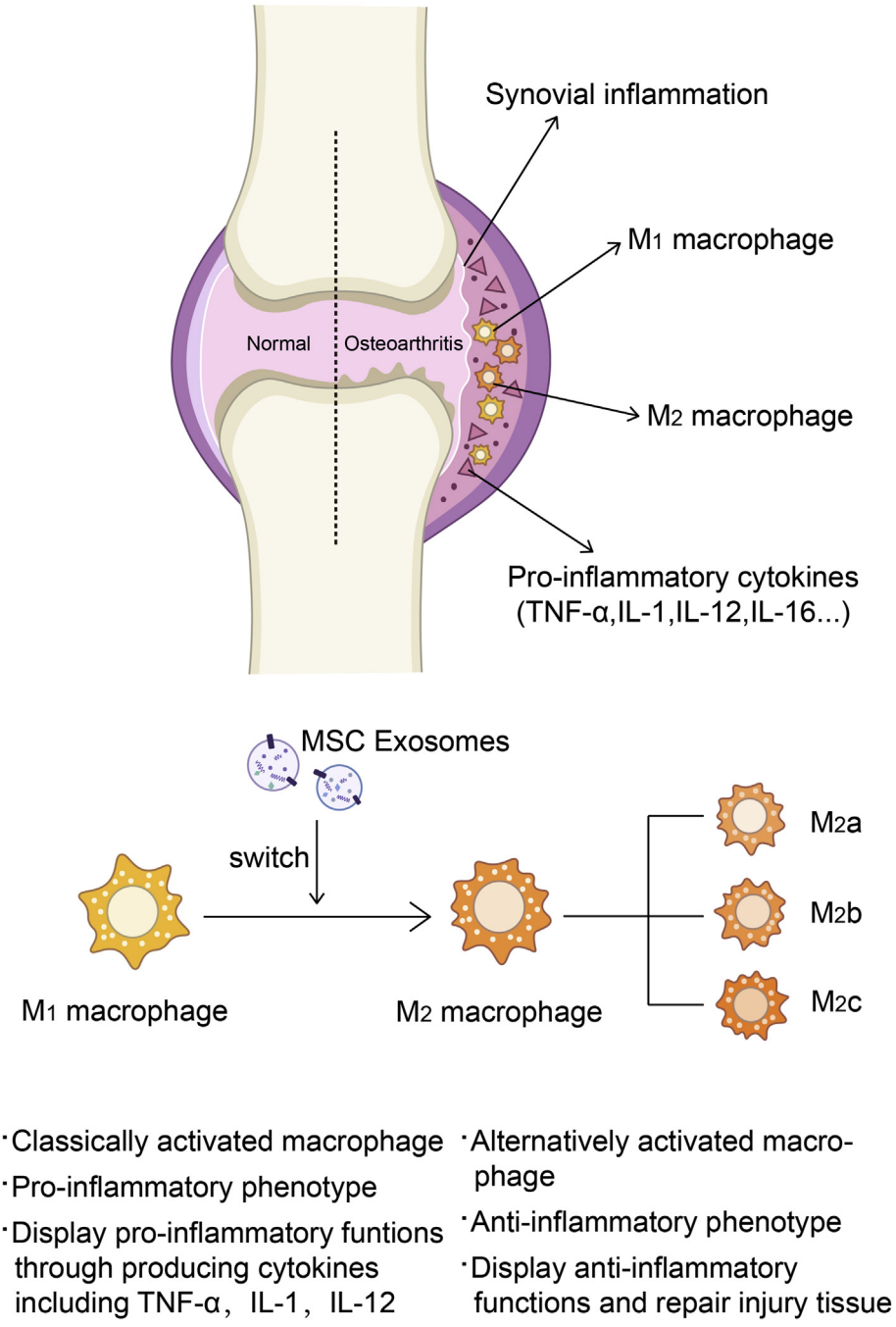

Figure 3. Macrophage cell accumulation in the synovial lining is one of the characteristics of synovial inflammation. Synovial inflammation promotes the polarisation of macrophages into the M1 phenotype, and they could produce pro-inflammatory cytokines. TNF-α, IL-1, IL-12, and IL-16 abound in inflamed synovium. Previous studies showed that MSCs could change the phenotype of macrophage. Consistent with this, exosomes derived from MSCs may also be macrophage polarisation switchers. Polarised from the M1 phenotype into the M2 phenotype (subdivided into M2a, M2b, and M2c), macrophages could display anti-inflammatory functions and repair the injured tissue.

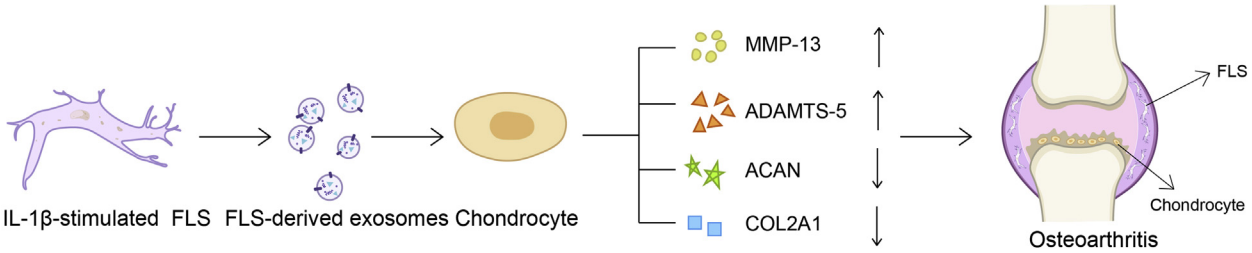

Figure 4. FLS-derived exosomes induce the gene expression patterns related to OA. Exosomes secreted by IL-1β-stimulated FLS promote MMP-13 and TNF-α expression while inhibiting ACAN and COL2A1 expression. MMP-13 is the most important collagenase that causes type II collagen degradation. The upregulation or aberrant activation of MMP-13 contributes to the progression of different stages of OA. TNF-α is also involved in the cartilage degradation process. Simultaneously, the expression of anabolic genes (ACAN and COL2A1) is decreased.

Fibroblast-like synoviocyte-derived exosomes in OA

Unfortunately, the role of FLS-derived exosomes in OA has not been investigated as much as MSC-derived exosomes (Figure 4). FLS, also known as synovial fibroblasts, are important constituents of the intimal lining layer of the synovial membrane. They are mesenchymal-derived cells, and their main function is to maintain the normal structure and integrity of the joints by stabilising ECM and synovial fluid homeostasis [69]. FLS are capable of releasing exosomes, and a recent study reported that IL-1β-stimulated FLS could increase exosomes secretion [70]. FLS-derived exosomes in OA might be pathogenic because they contribute to OA pathogenesis mainly by inducing OA-related gene expression and promoting angiogenic activities. Kato et al. showed that FLS-derived exosomes induced OA-like changes in articular chondrocytes by upregulating MMP-13 and A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) and downregulating Aggrecan (ACAN) and Collagen type II alpha 1 (COL2A1), which suggested that FLS-derived exosomes induced OA-related gene expression patterns, especially in articular chondrocytes. Another study by Kato et al. demonstrated that exosomes from IL-1β-stimulated FLS also induced angiogenesis [70]. The formation of new capillary blood vessels is commonly found in the OA synovium, which is closely associated with chronic inflammation. Exosomes are also involved in chondrocytes-FLS communication. Investigations showed that chondrocyte-derived exosomes treated with inflammatory cytokines could increase COX-2, IL-1β, tumor necrosis factor alpha (TNF-α), and MMP-13 production via FLS, which contributed to ECM degradation, thereby promoting OA progression.

Besides inflammatory cytokines and chemokines, miRNAs have also attracted great interest because miRNAs expressed in exosomes play different roles in chondrocytes. Notably, a selective process to miRNA release is likely to exist. Kato et al. reported the differences in miRNA expression in exosomes derived from IL-1β-stimulated FLS. This study observed that while 340 miRNAs were upregulated in FLS, only 11 miRNAs were upregulated in exosomes and that, while 24 miRNAs were downregulated in FLS, 39 were downregulated in exosomes. 5 miRNAs were upregulated in both FLS and exosomes, namely miR-720, miR-199b-5p, miR-500b, miR-4454, and miR-3154 [70]. Research showed that miR-720 promoted cell migration in cancer tissues [71,72], while miR-199b-5p was associated with the osteogenesis process in hBMSCs by promoting osteoblast differentiation [73] and that it was also upregulated in chondrogenesis [74]. Unfortunately, research related to miR-500b, miR-4454, and miR-3154 in the musculoskeletal system remains poorly understood. Moreover, miR-200c in EVs derived from the synovial fluid of OA patients was shown to increase by 2.5-fold when compared to non-OA subjects. It was also reported to promote the expression of type II collagen while ameliorating IL-6-dependent inflammation [68]. Interestingly, Kolhe et al. found that miRNAs detected in the EVs of FLS-secreted synovial fluids in OA patients differed with gender, i.e., a greater amount of differentially-regulated miRNAs were observed in the female OA group when compared to the male OA group. They also revealed that OA-specific miRNAs in women were estrogen responsive and were involved in Toll-like receptor signalling pathways, thereby indicating that these gender-specific miRNAs were likely related to the higher incidence and severity of OA in females [75].

Role of chondrocyte-derived exosomes in OA

Chondrocytes are extremely important in maintaining normal cartilage function as they are the only cells in the cartilage that produce ECM. Chondrogenesis is essential in forming cartilage and involves several processes, such as mesenchymal cell recruitment and migration, condensation of progenitors, and chondrocyte differentiation/maturation [76]. Various underlying mechanisms contribute to the pathogenesis of OA, and aside from the potential risk factors mentioned previously, increasing evidence suggests that epigenetic factors are also involved. Histone modifications, DNA methylation, and non-coding RNAs form the basic regulatory mechanisms in epigenetics [77]. These epigenetic regulatory processes in chondrocytes are related to the catabolic and anabolic factor instability, which results in articular cartilage injury that gradually leads to OA [78]. In a recent investigation, Mao et al. showed the potential role of miRNAs secreted by exosomes derived from chondrocytes in both cartilage development and OA pathogenesis. Twenty-two miRNAs were found to be upregulated, while 29 miRNAs were downregulated in OA chondrocyte-derived exosomes when compared to the control, among which miR-95-5p was the most studied. They found that miR-95-5p was reduced 2.54-fold in OA chondrocyte exosomes. Furthermore, exosomal miR-95-5p could not only delay the development of OA and maintain cartilage homoeostasis but could also directly inhibit histone deacetylases 2/8, thereby possibly regulating chondrocyte development and participating in hypertrophic responses [79]. Therefore, exosomes derived from miR-95-5p-overexpressing chondrocytes exhibit the potential to be novel therapeutic drugs for OA patients [45]. Other findings also demonstrate the potential role of extracellular vesicles secreted by chondrocytes in OA. Kirsch et al. reported that matrix vesicles (MVs) derived from OA chondrocytes contained annexins II, V, and VI, which were closely associated with the pathological mineralisation of the cartilage. These MVs also contained alkaline phosphatase, which participates in mineral formation [80]. Since excessive and pathological mineralisation may contribute to OA, the components of those MVs released from chondrocytes can provide a therapeutic target for OA. To the best of our knowledge, investigations concerning the potential role of chondrocyte-derived exosomes in OA are very limited, and the mechanisms are poorly understood. Therefore, the role of chondrocyte-derived exosomes in OA needs to be further elucidated.

Conclusions

OA is a very common and complex joint disease, which unfortunately still lacks appropriate clinical therapy options. In this review, we illustrated the potential role of exosomes in OA regenerative medicine and

paid special attention to exosomes derived from MSCs. MSC-derived exosomes have been widely investigated. Their efficacy in terms of cartilage repair, miRNA transport, and several other functions showcase their great potential and enable them to be promising cell-free therapeutic agents with respect to OA treatments. However, their clinical application in patients requires abundant clinical trials. Unfortunately, studies concerning exosomes from the synovial fluid and chondrocytes are limited; thus, their role in OA is not yet fully understood.

Significantly, much research is ongoing on the role of other biomolecules in OA, which would help in promoting the development of OA diagnosis and treatments. For instance, long noncoding RNA (lncRNA) is a type of RNA consisting of more than 200 nucleotides, and the regulated expression of lncRNAs plays an important role in many diseases. It is reported that over 24 kinds of lncRNAs were upregulated in different *vivo* or *vitro* OA models, but only a few now focus on those derived from extracellular vesicles. A recent study reported that the expression of lncRNA Prostate-specific transcript 1 increased gradually in normal, early, and late-stage OA, which indicated that some lncRNA could be used as an indicator for distinguishing the different stages of OA [81]. In another study, it was reported that MSC-derived exosomal lncRNA Kruppel Like Factor 3 Antisense RNA 1 (KLF3-AS1) promoted cartilage repair and chondrocyte proliferation by inhibit apoptosis of chondrocytes via KLF3-AS1/miR206/GTPase-activating Protein axis in OA [82,83]. More future work needs to emphasise the underlying mechanisms and the role of other extracellular vesicles derived from different categories of cells apart from what has been discussed above, such as subchondral bone, which is believed to change earlier than cartilage [84,85]. Besides, we are still confronted with various obstacles, such as the time-consuming and expensive isolation and purification processes in exosome production. Therefore, continued investigation in this field is needed so that these different exosomes may benefit OA patients in the future.

Declaration of competing interest

The authors declare no competing interests.

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