Regenerative Therapy 26 (2024) 599–610

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Harnessing the potential of mesenchymal stem cells–derived exosomes in degenerative diseases

Hsiu-Jung Liao [a, b], Yi-Ping Yang [c, d], Yu-Hao Liu [c, e], Huan-Chin Tseng [c], Teh-Ia Huo [c, f, g], Shih-Hwa Chiou [c, d, g, **, 1], Chih-Hung Chang [h, i, *, 1]

[a] Department of Medical Research, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[b] Institute of Biopharmaceutical Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan
[c] Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
[d] School of Medicine, National Yang-Ming Chiao Tung University, Taipei, Taiwan
[e] Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei, Taiwan
[f] Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[g] Institute of Pharmacology, National Yang-Ming Chiao Tung University, Taipei, Taiwan
[h] Department of Orthopedic Surgery, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[i] Graduate School of Biotechnology and Bioengineering, Yuan Ze University, Taoyuan City, Taiwan

ARTICLE INFO

Article history:
Received 28 June 2024
Received in revised form
17 July 2024
Accepted 2 August 2024

Keywords:
Extracellular vesicles derived from mesenchymal stem cells (MSC-EVs)
Osteoarthritis
Rheumatoid arthritis
Cardiovascular disease
Age-related macular degeneration
Alzheimer's disease
microRNA

ABSTRACT

Mesenchymal stem cells (MSCs) have gained attention as a promising therapeutic approach in both preclinical and clinical osteoarthritis (OA) settings. Various joint cell types, such as chondrocytes, synovial fibroblasts, osteoblasts, and tenocytes, can produce and release extracellular vesicles (EVs), which subsequently influence the biological activities of recipient cells. Recently, extracellular vesicles derived from mesenchymal stem cells (MSC-EVs) have shown the potential to modulate various physiological and pathological processes through the modulation of cellular differentiation, immune responses, and tissue repair. This review explores the roles and therapeutic potential of MSC-EVs in OA and rheumatoid arthritis, cardiovascular disease, age-related macular degeneration, Alzheimer's disease, and other degenerative diseases. Notably, we provide a comprehensive summary of exosome biogenesis, microRNA composition, mechanisms of intercellular transfer, and their evolving role in the highlight of exosome-based treatments in both preclinical and clinical avenues.

© 2024 The Author(s). Published by Elsevier BV on behalf of The Japanese Society for Regenerative Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

* Corresponding author. Department of Orthopedic Surgery, Far Eastern Memorial Hospital, No. 21, Section 2, Nanya S. Road, Banqiao District, New Taipei City, 220216, Taiwan.
** Corresponding author. Department of Medical Research, Taipei Veterans General Hospital, No. 201, Section. 2, Shipai Rd, Beitou District, Taipei City, 11217, Taiwan.
E-mail addresses: shchiou@vghtpe.gov.tw (S.-H. Chiou), orthocch@mail.femh.org.tw (C.-H. Chang).
Peer review under responsibility of the Japanese Society for Regenerative Medicine.
[1] The authors contributed equally to this work.

https://doi.org/10.1016/j.reth.2024.08.001
2352-3204/© 2024 The Author(s). Published by Elsevier BV on behalf of The Japanese Society for Regenerative Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

1.1. The urgency of developing innovative approaches to address degenerative diseases

The global population is aging. By 2050, over 80% of older people are predicted to reside in low- and middle-income countries; this demographic shift will have considerable social and economic implications [1]. Therefore, prioritizing the development of new treatments and interventions for degenerative diseases is imperative to ensure enhanced health outcomes and improved quality of life for the aging global population (see Table 1).

Thus, innovative therapies and technologies for degenerative diseases must be explored. This involves genetics, regenerative medicine, and personalized treatment [2–4]. This review article explores new approaches in regenerative medicine, with a particular focus on the therapeutic applications of exosomes derived from MSCs. It further examines how MSC-derived exosomes (MSC-Exos) could potentially manage and reverse the effects of degenerative diseases, thereby opening new pathways to enhance the health and longevity of the aging population.

1.2. Mesenchymal stem cells and extracellular vesicles

Stem cells with multipotent differentiation potential and regenerative capacity can be broadly categorized into two groups: embryonic and adult stem cells [5]. Embryonic stem cells are derived from sources such as the term placenta, amniotic fluid, and umbilical cord. Adult stem cells are found in various tissues or organs, including the bone marrow (BM) [6], trabecular bone [7], adipose tissue [8], synovial fluid [9], synovium [10], and peripheral blood [11]. These cells are often used in treating knee osteoarthritis (OA). Stem cells from different sources exhibit varying differentiation capacities, clinical benefits, and culture characteristics. Therefore, selecting the appropriate cell source is crucial for successful mesenchymal stem cell therapies. Common sources include the bone marrow, adipose tissue, synovial fluid, and synovium. Several studies have indicated that bone marrow–derived MSCs (BM-MSCs) are often the primary cell source, followed by adipose tissue-derived MSCs (ADSCs).

Exosomes are a type of extracellular vesicle (EV) that range from 30 to 150 nm in diameter [12]. They are present in various cell types [13] and extracellular fluids, such as plasma [14], synovial fluid [15], urine [16], amniotic fluid [17], saliva [18], cerebrospinal fluid [19], breast milk [20], and tears [21]. MSC-Exos facilitate the transfer of bioactive lipids, nucleic acids (including DNA, mRNAs, and noncoding RNAs) [22], and proteins between cells. This transfer elicits biological responses such as gene regulation [23], proliferation, apoptosis [24], and immunomodulation [25] in recipient cells [26]. MSC-Exos exhibit heterogeneity, with extracellular RNA extracted from exosomes and nonvesicles derived from the same cell also displaying heterogeneity [27].

2. Osteoarthritis

Research on the effects of exosomes from various cell types on OA has yielded significant findings. For example, exosomes derived from chondrocytes (CC-Exos) have been demonstrated to enhance the proliferation of cartilage progenitor cells and significantly promote chondrogenesis-related factors. They also increase collagen deposition, reduce vascular ingrowth, and consistently develop into cartilage [28]. Additionally, studies have indicated that exosomes from bone marrow–derived mesenchymal stem cells (BMSC-Exos) alleviate cartilage damage in rats with OA by carrying high levels of miR-135b, which targets proinflammatory factors elevated in the serum and reduces cartilage tissue damage [29]. These exosomes also inhibit chondrocyte apoptosis and the expression of matrix metalloproteinases (MMPs) by regulating Drp1-mediated mitophagy [30]. Exosomes from embryonic MSCs (EMSC-Exos) contribute to maintaining the chondrocyte phenotype by increasing the synthesis of collagen type II and reducing the expression of ADAMTS5. The beneficial effects of EMSC-Exos may be linked to adenosine activation of protein kinases, transforming growth factor-β (TGF-β), and insulin-like growth factor (IGF) [31].

A key finding in recent research is the role of human synovial mesenchymal stem cell–derived exosomes (hSMSC-Exos) in stimulating chondrocyte proliferation and migration. This effect is mediated by the upregulation of Wnt5a, which activates yes-associated protein (YAP) signaling pathways and suppresses extracellular matrix formation [32,33]. YAP is a transcriptional coactivator in the Hippo signaling pathway, is crucial for promoting cell growth and inhibiting apoptosis when activated. The activation of YAP signaling by Wnt5a is pivotal for enhancing tissue regeneration processes. This discovery has significant therapeutic implications for treating osteoarthritis, offering a potential route to enhance joint repair and functionality.

Recent research has underscored the chondroprotective role of exosomes from subcutaneous adipose-derived stem cells (ADSC-Exos). These exosomes reduce senescence-associated β-galactosidase activity and the production of inflammatory mediators from OA osteoblasts and catabolic mediators from OA chondrocytes [34]. Furthermore, chondrocytes treated with exosomes isolated from infrapatellar fat pad mesenchymal stem cells (IPFP-Exos) were observed to exhibit upregulated Sox-9, aggrecan, and type II collagen expressions, outperforming exosomes derived from IPFP-MSCs pretreated with kartogenin [35]. These findings highlight the potential of ADSC-Exos in OA treatment.

3. MSC exosomal miRNA therapy for cartilage protection

Studies on periosteal cells treated with exosomes have revealed a correlation between elevated levels of miR-145 and miR-221 and enhanced proliferation and chondrogenic potential of these cells, respectively [36]. Additionally, miR-100-5p derived from IPFP-MSCs significantly promotes chondrocyte autophagy by inhibiting mTOR. The intra-articular injection of antagomir-100-5p has

Table 1
Current applications of MSC-EVs in treating degenerative conditions. *In vitro* and *in vivo* efficacy and promotion of cellular functions to facilitate tissue repair.

EV Source	Model	Results	Reference
Osteoarthritis			
Chondrocyte-derived exosomes (CC-Exos)	*In vitro*, chondrocyte	1. Enhanced cartilage progenitor cell expansion and increased expression of chondrogenesis-related factors. 2. Promoted collagen deposition, reduced vascular ingrowth, and developed into cartilage.	[28]
BMSC-derived exosomes (BMSC-Exos)	*In vivo*, anterior cruciate ligament transection (ACLT) + destabilization of the medial meniscus (DMM) OA model	1. Mitigated cartilage damage by targeting proinflammatory factors with miR-135b. 2. Inhibited chondrocyte apoptosis and MMP expression by modulating Drp1-mediated mitophagy.	[29,30]
Embryonic MSC-derived exosomes (EMSC-Exos)	*In vitro*, chondrocyte	1. Maintained chondrocyte phenotype with increased collagen type II synthesis and reduced ADAMTS5 expression. 2. Effects linked to adenosine-triggered protein kinases, TGF-β, and IGF activation.	[31]
Human synovial MSC-derived exosomes (hSMSC-Exos)	*In vitro*, chondrocyte	Promoted chondrocyte proliferation and migration by upregulating Wnt5a, activating YAP signaling pathways, and suppressing extracellular matrix formation.	[32,33]
ADSC-derived exosomes (ADSC-Exos)	*In vitro*, OA chondrocyte	Reduced senescence-associated β-galactosidase activity and the secretion of inflammatory mediators from OA osteoblasts and catabolic mediators from OA chondrocytes.	[34]
IPFP-derived exosomes (IPFP-Exos)	*In vitro*, chondrocyte	Elevated levels of Sox-9, aggrecan, and type II collagen expression, more effective than IPFP-Exos pretreated with kartogenin.	[35]
ADSC-Exos	*In vitro*, chondrocyte	Increased periosteal cell proliferation and chondrogenic capacity linked to miR-145 and miR-221, respectively.	[36]
IPFP-Exos	*In vivo*, DMM-induced OA animal model	1. Enhanced chondrocyte autophagy through miR-100-5p inhibition of mTOR. 2. Intra-articular administration of antagomir-100-5p protected cartilage from deterioration and improved gait by repressing chondrocyte apoptosis through the mTOR-autophagy pathway.	[37]
hSMSC-Exos	*In vivo*, ACLT-induced OA model	hSMSC-Exos overexpressing miR-140-5p augmented cartilage regeneration and slowed knee OA progression in a rat model.	[38]
BMSC-Exos	*In vivo*, collagenase-induced OA mouse model	BMSC-Exos overexpressing miR-92a-3p suppressed cartilage degradation by directly targeting WNT5A and preserving articular chondrocyte function.	[39]
BMSC-Exos	*In vivo*, ACLT + DMM OA surgery model	TGF-β1 promoted chondrocyte proliferation by modulating Sp1 through miR-135b sourced from BMSC-Exos, aiding cartilage restoration.	[40]
Cardiovascular disease			
HIF-1α engineered MSC-derived EVs (HIF-1α-EVs)	*In vitro*: cardiomyocytes and endothelial cells under hypoxia and serum deprivation (H/SD); *In vivo*: Sprague Dawley rats with acute myocardial infarction (AMI)	1. Reduced cardiomyocyte apoptosis and enhanced endothelial cell angiogenesis. 2. Reduced fibrosis and improved cardiac function in rats. 3. Enhanced effects with RGD-biotin hydrogels.	[81]
Human bone marrow MSC-derived EVs (MSC-EVs)	*In vitro*: human umbilical vein endothelial cells; *In vivo*: rat MI model	1. Promoted endothelial cell proliferation, migration, and tube formation *in vitro*. 2. Enhanced blood flow recovery, reduced infarct size, and preserved cardiac performance *in vivo*.	[84]
MSC-Exos derived from MSCs pretreated with ischemic rat heart extract (MSCE-Exos)	*In vitro*: human umbilical vein endothelial cells (HUVECs)	1. Enhanced HUVEC proliferation and migration. 2. Proteomic analysis revealed upregulation of angiogenesis-related proteins, including DMBT1. 3. DMBT1 delivery via MSCE-Exos was crucial for angiogenesis, with silencing of DMBT1 impairing HUVEC activity. 4. Ischemic heart extracts revealed increased levels of IL-22 and subsequent upregulation of VEGF and DMBT1 in MSCs, which	[85]

(*continued on next page*)

Table 1 (*continued*)

EV Source	Model	Results	Reference
		enhanced the angiogenic effects of the derived exosomes.	
Human umbilical cord MSC-derived exosomes (hucMSC-Exos)	*In vivo*: AMI rats; *In vitro*: hypoxic H9C2 cells	1. miR-19a was transferred, which offered protection for cardiomyocytes through the reduction of apoptosis and infarct size. 2. miR-19a targeted SOX6; inhibition of SOX6 reduced hypoxic damage. 3. Enhanced cardioprotection through the activation of AKT and inhibition of JNK3/caspase-3 pathway.	[86]
Mesenchymal stem cell–derived exosomes (MSC-Exos)	*In vivo*: mouse model of myocardial ischemia/reperfusion (I/R); *In vitro*: macrophage polarization studies	1. Reduced infarct size and inflammation postmyocardial I/R. 2. Facilitated macrophage polarization from M1 to M2, improving cardiac recovery. 3. miR-182 targeted TLR4, influencing macrophage polarization and reducing inflammation.	[87]
MicroRNA-1-transduced MSCs (MSC(miR-1))	*In vivo*: C57BL/6 mice with MI	1. Enhanced differentiation of transplanted MSCs into cardiomyocytes in the infarcted zone. 2. Improved cardiac function. 3. Increased cell survival and cardiomyogenic differentiation.	[88]
Age-related macular degeneration			
Human umbilical cord MSC-derived exosomes (hucMSC-Exos)	*In vitro*: RPE cells; *In vivo*: laser-induced CNV and subretinal fibrosis model in mice	1. Intravitreal injection of hucMSC-Exo reduced subretinal fibrosis and CNV. 2. Suppressed RPE cell migration and promoted mesenchymal–epithelial transition via miR-27b. 3. miR-27b targeted HOXC6, inhibiting the EMT process induced by TGF-β2.	[94]
Adipose-derived MSC exosomes (Ad-MSC-Exos)	*In vivo*: streptozotocin-induced diabetes in rabbits	1. Improved retinal structure, with SC and IO routes showing well-defined retinal layers similar to normal retina. 2. IV route resulted in less organized retinal layers. 3. Significant increase in micRNA-222 expression associated with retinal repair and regeneration.	[95]
MSC-derived exosomes (MSC-Exos)	*In vivo*: mouse models of photoreceptor loss (MNU-induced and Pde6bmut)	1. Intravitreal MSC transplantation and exosomal transplantation counteracted photoreceptor apoptosis and alleviated retinal degeneration. 2. Effects sustained for 1–2 months after a single injection. 3. miR-21 targeted Pdcd4, protecting photoreceptors and preventing retinal dysfunction.	[101]
Human bone marrow–derived MSCs (hBMSCs)	*In vitro*: Cultured hBMSCs	1. Overexpression of the miR-183/96/182 cluster upregulated neuroretinal genes such as OTX2, NRL, PKCα, and recoverin. 2. Ectopic expression of the miR-183 cluster increased CRX and rhodopsin levels at mRNA and protein levels, suggesting initiation of photoreceptor cell differentiation. 3. No morphological changes in cells despite gene expression alterations.	[102]
Alzheimer's disease			
Human adipose tissue-derived MSC exosomes (ADSC-Exos)	*In vitro*: N2a neuroblastoma cells	1. Carried enzymatically active neprilysin (NEP), a pivotal β-amyloid-degrading enzyme. 2. Transferred NEP into N2a cells, significantly reducing both secreted and intracellular Aβ levels. 3. More effective than bone marrow–derived MSC exosomes.	[118]
Mesenchymal stem cell–derived EVs (MSC-EVs)	*In vivo*: APP/PS1 mouse model of Alzheimer's disease	1. Reduced inducible nitric oxide synthase (iNOS) mRNA and protein levels in primary cultured neurons and APP/PS1 mice. 2. Improved cognitive behaviors and rescued synaptic transmission and long-term potentiation in the hippocampal CA1 region.	[119]
Mesenchymal stem cells and cell –derived EVs (MSC-EVs)	*In vitro*: Transwell cocultures with rat hippocampal neurons	1. Protected hippocampal neurons from amyloid-beta oligomer (AβO)-induced oxidative stress and synapse damage.	[120]

Table 1 (*continued*)

EV Source	Model	Results	Reference
		2. Protection involved internalization and degradation of AβOs, release of catalase-containing EVs, and secretion of anti-inflammatory cytokines and growth factors.	
Human Wharton's jelly MSC-derived EVs (hMSC-EVs)	*In vitro*: Primary hippocampal cultures exposed to AβOs	1. Internalized by hippocampal neurons, enhanced in the presence of AβOs. 2. Protected neurons from oxidative stress and synaptic damage induced by AβOs. 3. Neuroprotection mediated by catalase EVs, abolished by catalase inhibition.	[121]
Mesenchymal stem cell–derived exosomes (MSC-Exos)	*In vivo*: mouse model of Alzheimer's disease	1. Stimulated neurogenesis in the subventricular zone. 2. Alleviated beta-amyloid 1-42-induced cognitive impairment in Morris water maze and novel object recognition tests.	[123]
Human umbilical cord MSC-derived exosomes (hucMSC-Exos)	*In vivo*: AD mouse model; *In vitro*: BV2 microglial cells	1. Alleviated neuroinflammation and reduced amyloid-beta deposition in AD mouse models. 2. Improved cognitive function and modulated microglial activation. 3. Regulated inflammatory cytokine levels both *in vivo* and *in vitro*.	[125].
Allogenic human adipose MSC-derived exosomes (ahaMSCs-Exos)	Phase I/II clinical trial in patients with mild to moderate Alzheimer's disease	1. No adverse events were reported during the trial. 2. The medium-dose arm exhibited significant improvement in cognitive function, as measured using ADAS-cog and Montreal Cognitive Assessment scores. 3. Although no significant changes in amyloid or tau levels were observed, a reduction in hippocampal volume loss was noted in the medium-dose arm.	[129]

Choroidal Neovascularization (CNV); cone-rod homeobox (CRX); subconjunctival (SC); and intraocular (IO); yes-associated protein (YAP).

been demonstrated to protect cartilage from damage and improve gait patterns in mice with destabilization of the medial meniscus (DMM)-induced OA by suppressing chondrocyte apoptosis through the mTOR-autophagy pathway [37]. Furthermore, exosomes derived from human synovial MSCs overexpressing miR-140-5p were demonstrated to enhance cartilage regeneration and delay the progression of knee OA in a rat OA model [38]. Exosomes from human bone marrow–derived MSCs overexpressing miR-92a-3p inhibited cartilage degradation in a collagenase-induced OA mouse model by directly targeting WNT5A, thereby preserving articular chondrocyte the function [39]. Furthermore, in an animal study, TGF-β1 was demonstrated to promote chondrocyte proliferation and facilitate cartilage repair in a rat OA model by regulating Sp1 through miR-135b derived from BMSC exosomes [40]. These findings highlight the critical role of miRNA regulation in modulating gene expression during chondrogenic differentiation. Validating these miRNAs and their targets could support further research into safe and effective delivery systems, enhancing the therapeutic potential of miRNAs in OA treatment.

4. MSC-derived exosomal miRNA therapy for rheumatoid arthritis

Rheumatoid arthritis (RA) is a long-term inflammatory autoimmune disorder that mainly targets the joints. It is characterized by persistent synovial inflammation, which results in the deterioration of cartilage and bon [41]. Numerous genetic and environmental factors have been linked to a heightened risk of developing RA [42]. Along with synovial membrane hyperplasia and overactivation of osteoclasts, increased bone degradation is another key hallmark of RA [43,44]. Research has demonstrated that a range of immune cells, including T cells, B cells, and macrophages, play a role in the development of arthritis [45,46]. Despite the availability of conventional synthetic DMARDs (csDMARDs), biologic agents (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), these treatments often encounter challenges such as side effects [47]. Additionally, up to 40% of patients experience inadequate responses to these therapies (primary inefficacy) or lose their effectiveness over time (secondary inefficacy) [48]. Consequently, the potent immunomodulatory properties of MSC-Exos present a promising new approach for treating joint swelling and cartilage erosion.

While several clinical trials have demonstrated the effects of MSC-based therapy in RA patients, an optimal MSC-based therapeutic protocol has yet to be established [49]. Thus, utilizing MSCs for RA treatment remains challenging. Most studies have employed allogeneic MSCs, as obtaining and cultivating a sufficient quantity of autologous MSCs from RA patients can be difficult. Additionally, autologous MSCs from RA patients may possess intrinsic genetic defects that could impair their anti-inflammatory capabilities. MSC-Exos have not yet been utilized in the treatment of RA. However, the effectiveness of MSC-Exos-based therapy has been demonstrated in experimental animal models of RA. In these studies, MSC-Exos-based therapy has been shown to significantly reduce the onset and progression of experimental arthritis.

Li et al. reported that MSC-derived Exos expressing miRNA-150-5p reduced the secretion of inflammatory cytokines, such as TNF-α and IL-1β, in CIA mice, thereby suppressing RA progression *in vivo* [50]. Furthermore, MSC-derived exosomal circFBXW7 was shown to suppress the proliferation, migration, and inflammatory responses of rheumatoid fibroblast-like synoviocytes and mitigate RA in rats by sponging miR-216a-3p and activating HDAC4 [51]. Tavasolian et al. reported that in CIA mice, miR-146a-transduced ADSC-Exos increased the expression of FoxP3, TGFβ, and IL-10, while miR-155-transduced ADSC-Exos elevated levels of RORγt, IL-17, and IL-6

[52]. This indicates that Exos can serve as vehicles for the intracellular transfer of miRNAs, presenting a potential therapeutic strategy for RA. Moreover, other *in vitro* studies demonstrated that Exos derived from bone marrow stem cells contained increased levels of target miRNAs, such as miR-150-5p, miR-548e, miR-34a, miR-320a, miR-124a, miR-216a-3p, miR-192-5p, and miR-143-3p, which inhibited inflammation in mice with RA [51,53–58]. Therefore, MSC-Exos could potentially serve as innovative therapeutic agents for cell-free or cell-component-based treatment of RA.

5. Cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, accounting for approximately 17.9 million deaths annually. These diseases include various heart and vascular conditions such as coronary and cerebrovascular diseases [59]. More than 80% of these deaths result from heart attacks and strokes, with a significant number occurring prematurely in individuals under 70 years of age. Inflammation plays a crucial role in their development of CVDs, and anti-inflammatory therapies have been demonstrated to be effective in managing these conditions [60]. Myocardial infarction (MI) and ischemic heart disease are particularly influenced by inflammation and fibrosis. Various cell types produce EVs that influence these processes, making EVs valuable tools for diagnosis, prognosis, and treatment.

Following an acute MI, the body swiftly initiates immune responses at both cellular and humoral levels [61]. A notable reaction involves the differentiation of monocytes into macrophages [62]. A study indicated a substantial increase in EV release in the heart within 15–24 h post-MI [63]. These EVs, originating from cardiomyocytes and endothelial cells, trigger the release of chemokines and cytokines from monocytes and modulate macrophage inflammatory responses, depending on the donor cell's condition (ischemic vs. nonischemic) [64]. Post-MI, the interaction between cardiomyocytes extends beyond the heart, with myocardial microRNAs (miRNAs) such as miR-1, miR-208, and miR-499 transported via EVs to distant organs such as the bone marrow, where they suppress the expression of CXC chemokine receptor 4 (CXCR4) in mononuclear cells. This facilitates their release into the bloodstream [65]. Additionally, EVs originating from endothelial cells mobilize and activate monocytes from the spleen [66]. These EVs, regardless of their cell origin, recruit and alter the phenotype of peripheral mononuclear cells. Moreover, the quantity of EVs is strongly correlated with the severity of myocardial damage, indicating their potential as diagnostic and prognostic markers in MI [66]. Interestingly, EVs produced by endothelial cells overexpressing Krüppel-like factor 2 (KLF2) mitigate the recruitment of $Ly6C^{high}$ monocytes and reduce ischemia-reperfusion injury post-MI [67]. EVs released from cardiac stromal-progenitor cells across different species, including mice, rats, and humans, demonstrate immunomodulatory actions by influencing macrophage polarization in MI models, underscoring their therapeutic potential [68,69]. EVs from noncardiomyocyte sources also shape inflammatory and fibrotic responses post-MI. Macrophages release various noncoding RNAs via EVs, which influence the behavior of cardiac fibroblasts. Notably, EVs carrying circular RNA circUbe3a exacerbate myocardial fibrosis by altering cardiac fibroblast proliferation, migration, and phenotype [70]. Activated macrophages transport miR-155-rich EVs to cardiac fibroblasts, inhibiting their growth and enhancing inflammation, thereby increasing the risk of cardiac rupture [71]. Furthermore, the delivery of miR-155-loaded EVs from macrophages to endothelial cells exacerbates ischemic damage by inducing antiangiogenic effects [72]. Despite causing cardiac damage, EVs from innate immune cells offer beneficial effects post-MI. For instance, EVs from dendritic cells activate $CD4^{+}$ T cells, thereby improving cardiac function post-MI [73]. Recent research has increasingly focused on the therapeutic modulation of T cells in MI, mainly using regulatory T cells (Tregs) and their EVs. Studies have demonstrated that EVs from cardiac stromal-progenitor cells enhance Treg functions, promoting their proliferation and IL-10 production and contributing to cardioprotective outcomes in inflammation models [74]. The dynamic interplay between EVs and various cell types is critical in immune and repair responses post-MI. EVs contribute to inflammatory and fibrotic processes and have promising diagnostic and therapeutic applications, mainly through immune cell modulation. Approaches that leverage EV properties, particularly those derived from regulatory T cells and cardiac progenitor cells, are a promising avenue for improving outcomes in patients with cardiac injuries.

Heart failure (HF) is a chronic and progressive condition resulting from structural or functional cardiac irregularities, presenting primarily in two forms: heart failure with reduced ejection fraction and heart failure with preserved ejection fraction (HFpEF) [75]. Characterized by compromised ventricular blood ejection or filling, HF typically manifests as symptoms including fatigue, dyspnea, and edema, posing a considerable public health challenge globally and resulting in considerable morbidity and mortality. The mechanisms underlying HF are diverse and often linked to its root causes. EVs, extensively implicated in numerous aspects of HF pathophysiology, particularly chronic inflammation [76], play a critical role in intercellular communication in the context of HF. By transporting miRNAs and proinflammatory cytokines, EVs influence cardiac function and repair mechanisms. For instance, EVs derived from cardiac cells carrying miR-21-5p and miR-378 have been demonstrated to regulate angiogenesis, cardiomyocyte survival, and fibrosis, indicating their potential as modulators of disease progression [77]. Additionally, the bidirectional communication facilitated by specific miRNAs in EVs, such as miR-155 and miR-217, among cardiomyocytes, macrophages, and fibroblasts, underscores their role in either exacerbating or mitigating cardiac hypertrophy and ischemia [78]. Furtheremore, exosomes have been investigated as potential biomarkers for CVDs due to their ability to circulate in body fluids stably and because they encode information on a variety of disease status indicators [79]. Exosomes derived from cardiomyocytes, endothelial cells, and fibroblasts play a role in intercellular communication under both physiological and pathological conditions [80]. Their ability to mirror the cellular origin and the pathological disturbance renders them suitable for noninvasive diagnosis and prognosis of CVDs [79].

MSCs secrete exosomes that possess properties that boost cardiac repair, underscoring their therapeutic potential in CVDs [68,81–83]. Preclinical studies have revealed that MSC-Exos can interact with vascular endothelial cells, promoting angiogenesis, a pivotal process in heart tissue repair [84,85]. These exosomes, mainly originating from human umbilical cord mesenchymal stem cells (hucMSCs), have been observed to transport microRNA-19a (miR-19a) to cardiomyocytes, thereby promoting cell survival by targeting the SOX6 gene and modulating the AKT/JNK3/caspase-3 signaling pathway [86]. Furthermore, MSC-Exos can modulate the immune response in the heart by promoting the polarization of macrophages toward the anti-inflammatory M2 phenotype as opposed to the proinflammatory M1 phenotype, thereby mitigating inflammation and reducing infarct size in mouse models [87]. Additionally, studies have indicated that the transplantation of MSCs into the infarcted region enhances cardiac function, with further enhancement achieved by genetically modifying MSCs to overexpress miR-1, which enhances their survival and differentiation into cardiomyocytes [88]. Despite these promising findings, the practical application of MSC-Exos in CVD treatment faces challenges due to the limited expansion and survival of natural

MSCs posttransplantation. Therefore, ongoing efforts are directed toward optimizing and engineering MSCs to enhance their therapeutic efficacy in CVD treatment [89].

6. Age-related macular degeneration

Age-related macular degeneration (AMD), a leading cause of vision loss in older adults, has both dry and wet forms and is characterized by the accumulation of lysosomal lipofuscin, the formation of drusen, and the degeneration of retinal pigment epithelium (RPE) [90]. In wet AMD, neovascularization originating from the choriocapillaris leads to detrimental swelling due to increased VEGF expression. Despite the availability of current treatments such as anti-VEGF drugs, their efficacy varies, particularly in the advanced stages of the diseases. EVs, particularly those derived from aged RPEs and marked by lysosomal associated membrane protein 2 (LAMP2), CD63, and CD81, are implicated in drusen formation and may influence RPE function by enhancing exocytosis and releasing proteins that contribute to dysfunction through oxidative stress. Oxidative stress prompts EV release from RPEs, transferring stress signals to healthy cells and inducing apoptosis and inflammation [91]. In response to blue-light stimulation, EVs containing inflammasome mRNA contribute to AMD progression by stimulating angiogenesis and choroidal neovascularization. To address this problem, researchers have explored the therapeutic potential of ADSCs and MSCs [92]. Studies have indicated that ADSCs enhance their migratory capacity in response to conditioned medium derived from stressed RPE cells and effectively protect RPE cells from oxidative damage. Similarly, MSCs have been demonstrated to shield RPE cells from sodium iodate–induced death by suppressing the NF-kB pathway, which activates the NLRP3 inflammasome, while also preserving mitochondrial integrity [93].

These interventions significantly reduce the levels of inflammatory markers such as IL-6, iNOS, IFN-γ, and IL-17, but increase the levels of anti-inflammatory factor TGF-β, thereby alleviating inflammatory conditions in the eye and improve visual functions in AMD models. Such enhancements encompass improvements in visual acuity, visual field, and multifocal photopic electroretinogram (mf-ERG) findings in clinical settings. These results underscore the potential of MSC-Exos to complement RPE replacement therapies for patients with AMD.

The therapeutic and diagnostic potential of MSC exosomes in AMD has garnered considerable attention for their ability to regulate vital pathological processes in degenerative ocular diseases. Studies, such as those conducted by Li et al. and Safwat et al., have underscored the efficacy of exosomes derived from human umbilical cord and adipose tissue MSCs in addressing subretinal fibrosis, choroidal neovascularization, and retinal layer restoration. These exosomes transport essential miRNAs—such as miR-27b and proteins that promote cellular repair and inhibit processes, for example, the epithelial–mesenchymal transition (EMT)—effectively addressing the complex pathophysiology of neovascular AMD [94,95]. Moreover, MSC-Exos protect against degenerative retinal diseases through various pathways. These include the inhibition of retinal tissue inflammation [96,97], downregulation of VEGF expression to suppress choroidal neovascularization [98,99], amelioration of subretinal fibrosis [97], inhibition of microglial activation [100], and protection against photoreceptor apoptosis [101–103]. These multifaceted range of effects highlight the potential of MSC-Exos in AMD treatment in their targeting of the mechanisms underlying disease progression and enhancing of regenerative processes that are crucial for ocular tissue recovery and healing.

The role of exosomal cargos, such as miRNAs and proteins, extends to their potential as biomarkers for AMD diagnosis. Proteins released from RPE-derived EVs, including cathepsin D and Hsp70, detected in the aqueous humor of patients with AMD, suggest their use as biomarkers and therapeutic targets [104]. Exosomal miRNAs such as miR-410 and miR-19a play a role in critical VEGF signaling pathways, influencing apoptosis and angiogenesis, which are crucial for the development of choroidal neovascularization [105]. Studies have suggested that miRNA-410 may reduce VEGF expression and inhibit retinal angiogenesis. Furthermore, EVs released by retinal astrocytes exhibit antiangiogenic properties, inhibiting laser-induced choroidal neovascularization [106]. These findings underscore the dual potential of MSC-Exos in mitigating AMD symptoms and serving as diagnostic tools. However, despite promising preclinical results, more extensive studies on the safety, efficacy, and mechanisms of action of EVs must be conducted before they can be brought from the lab to the clinic. Continued research and clinical trials are imperative to establish the applicability and effectiveness of EV-based therapies in AMD, paving the way for new advancements in managing this debilitating condition.

7. Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia and accounts for 60%–80% of cases of dementia. AD is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles, leading to a progressive decline in neurological function [107]. The clinical symptoms of AD include memory loss and worsening cognitive impairment, severely affecting daily functioning and increasing dependency [108]. The FDA has approved several medications for AD treatment, including cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine, an NMDA receptor modulator [109]. Although these treatments aim to alleviate symptoms and enhance the patient's quality of life, they cannot effectively halt disease progression. This emphasizes the urgent need for identifying innovative therapeutic approaches that can directly target the underlying causes of AD.

The innovative use of MSC-Exos in treating AD highlights their remarkable multifunctionality and immense potential in modern medicine. MSC-Exos are ushering in a new era of medical advancements, offering hope to millions with AD through their extraordinary versatility. First, MSC-Exos are an ideal tool for “liquid biopsy.” They can be extracted from peripheral blood and enriched using immunoprecipitation techniques, providing a highly sensitive and specific method for early AD diagnosis [110–112]. Additionally, MSC-Exos serve as effective drug delivery vehicles. Their excellent biocompatibility and ability to cross the blood–brain barrier allow them to transport drugs directly to targeted brain areas [113,114]. MSC-Exos also play a crucial role in clearing pathogenic proteins. They facilitate the removal of beta-amyloid and tau proteins, which are associated with neuronal damage and death, leading to progressive memory and cognitive decline [115–121]. Furthermore, glycosphingolipids on the surface of exosomes can bind to Aβ, accelerating its clearance [122]. In terms of therapeutic applications, MSC-Exos are highly promising as a means to treat AD. Research conducted by Reza-Zaldivar et al. demonstrated that MSC-Exos can promote neurogenesis and alleviate cognitive impairments in an AD mouse model, indicating their potential in developing cell-free therapies [123]. These exosomes are particularly appealing due to their minimal immunogenicity. Guo et al. reviewed their ability to modify the progression of AD, emphasizing their suitability as a therapeutic tool [124]. Moreover, MSC-Exos derived from human umbilical cord mesenchymal stem cells can alleviate neuroinflammation and reduce amyloid-beta deposition in AD models by modulating microglial activation [125]. They regulate miRNA content and neuronal excitability, contribute to synaptic plasticity [126,127], enhance neuronal

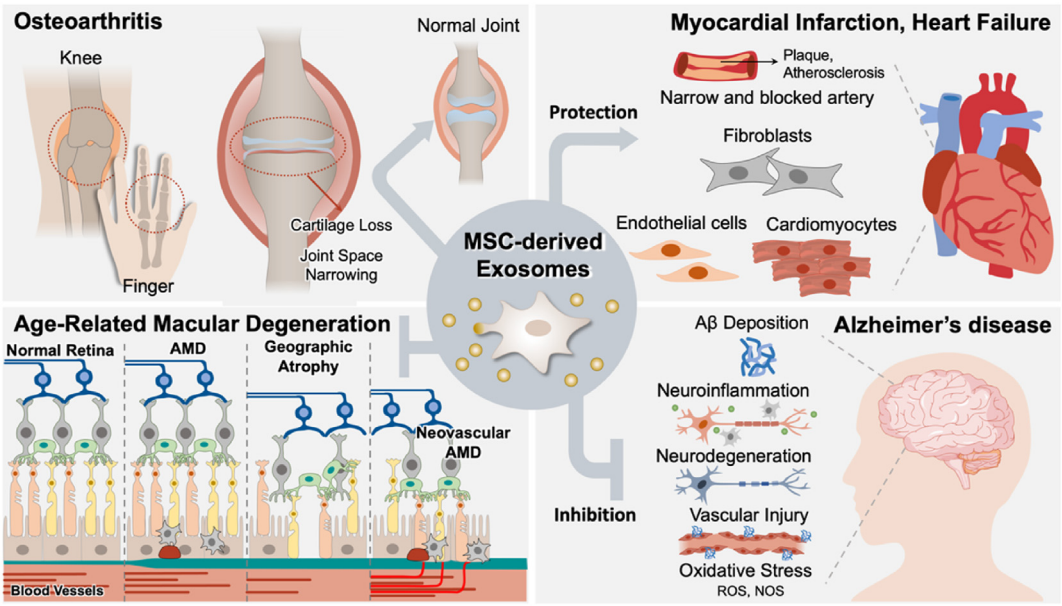

Fig. 1. Overview of the protective, regenerative, and immunomodulatory abilities of MSC-Exos in experimental models of various degenerative diseases. Exosomes have demonstrated potential across a range of degenerative diseases, offering a versatile platform for therapeutic intervention. These tiny vesicles, originating from various cell types, have a diverse range of functions depending on environmental cues and their source. They play crucial roles in intercellular signaling, immune regulation, and tissue repair mechanisms. Notably, MSC-Exos demonstrate the ability to modulate immune responses within cartilage, cardiac, ocular, and brain tissues. Furthermore, the miRNAs or proteomic carried by exosomes can reflect disease status, making them potential disease-specific biomarkers. Their inherent qualities as efficient drug carriers further enhance their appeal as optimal delivery systems. Therefore, the integration of exosome-based therapies and diagnostics presents a promising avenue for addressing age-related degenerative conditions in clinical settings.

activity, and regulate oxidative stress, thereby aiding in neural recovery [128]. Overall, MSC-Exos offer promising new diagnostic and therapeutic approaches for AD treatment strategies, making them a powerful tool against this increasingly severe neurodegenerative disease.

A clinical trial (NCT04388982), conducted in phases I and II, investigated the efficacy and safety of intranasally administered allogenic human adipose MSCs-derived exosomes (ahaMSCs-Exos) in patients with mild to moderate AD [129]. Over a period of 12 weeks, participants received the treatment twice weekly, with no adverse events reported, indicating the treatment's safety and tolerability. Notably, the group receiving a medium dose exhibited significant cognitive improvement. By the 12th week, a reduction in the Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog) scores by 2.33 points and an increase in the Montreal Cognitive Assessment scores by 2.38 points relative to the baseline were observed. These findings suggest enhanced cognitive function, with continued improvement in ADAS-cog scores observed up to week 36. Additionally, this group exhibited less hippocampal volume shrinkage, indicating potential benefits in preserving brain volume. These findings support further investigation into the use of ahaMSCs-Exos for AD treatment, particularly at dosages of at least 4×10^8 particles, given their potential to serve as a novel therapeutic approach.

Exosomes have also been explored as potential biomarkers for neurological disorders such as AD, Parkinson's disease, and stroke [130]. Exosomes originating from the central nervous system are detectable in cerebrospinal and peripheral bodily fluids, and the contents of these exosomes vary with disease status [130]. For example, exosomes isolated from plasma or cerebrospinal fluid samples of patients with AD have been observed to carry disease-related proteins, suggesting their utility as biomarkers for AD [130].

Exosomes derived from human umbilical cord mesenchymal stem cells (huc-MSCs) have shown promising therapeutic effects in a mouse model designed to mimic AD (AβPP/PS1 double transgenic mice). These exosomes improved cognitive abilities in the mice, particularly in spatial learning and memory. Furthermore, they led to a significant decrease in amyloid-beta plaques within the cortex and hippocampus. Additionally, the activity of enzymes responsible for degrading the Aβ peptide, namely neprilysin and insulin-degrading enzymes (IDE), increased upon exosome administration. The treatment also effectively reduced neuroinflammation, as evidenced by decreased levels of proinflammatory cytokines and increased production of anti-inflammatory cytokines. However, the precise mechanism underlying this inflammatory response remains unknown. In another study, the administration of exosomes secreted from MSC cells to an AD mouse model improved cognitive function by promoting neurogenesis in the subventricular zone. Exosomes derived from adipose stem cells also hold promise in protecting against AD and may serve as a novel therapeutic approach. These exosomes were found to reduce levels of Aβ, alter the Aβ1-42/1–40 ratio, and reduce neuronal apoptosis, all characteristic features of AD. Additionally, they were shown to promote neurite outgrowth. Neprilysin and IDE, enzymes responsible for degrading Aβ, were detected in these exosomes, further supporting their therapeutic potential in AD. Exosomes carrying neprilysin contribute to the reduction of Aβ levels when internalized, and statins have been found to increase the secretion of exosomes carrying IDE protein, aiding in Aβ clearance. However, the mechanisms involved remain unclear. Furthermore, other enzymes capable of degrading Aβ, such as endothelin-converting enzymes 1/2 and metalloproteinases, as well as cystatin C, a protein that inhibits cysteine protease and found to be imbalanced in AD, are released by exosomes. Studies on primary cortical neurons overexpressing PS2 mutations related to familial AD have demonstrated reduced levels of various forms of exosomal cystatin and Aβ1-40 concentrations.

Cystatin may offer therapeutic benefits in treating AD due to its potential positive effects on the brain, prompting considerable interest in regulating its levels for medical purposes. Exosomes, known for their ability to traverse the blood–brain barrier, offer a

promising avenue for AD therapy, particularly in gene therapy applications, where they can accurately deliver nucleic acids. A notable strategy involves the use of exosomes to transport short interfering RNA molecules that target and suppress the BACE1 enzyme responsible for cleaving APP and generating Aβ peptide. Studies have indicated that neuronal exosomes carry Aβ, contributing to the formation of amyloid plaques. Strategies for reducing the secretion or uptake of exosomes by neural cells might prove beneficial. For instance, inhibiting exosome uptake, which relies on the dynamin protein, has shown promise. In experimental models, blocking the enzyme-neutral sphingomyelinase 2, which is involved in ceramide production, may reduce exosome levels, plaque formation, and neuronal cell death. However, caution is warranted when considering the elimination of exosome secretion due to their beneficial roles in AD.

Exosomes have been used as vehicles for delivering therapeutic agents for AD. An innovative strategy entailed loading exosomes with curcumin to target disease mechanisms in an AD mouse model treated with okadaic acid. These curcumin-loaded exosomes effectively countered tau hyperphosphorylation, leading to enhanced cognitive functions. This improvement was attributed to the activation of AKT and inhibition of GSK-3β, a key player in neurofibrillary tangle formation. Although these results are promising, further research is necessary to confirm the therapeutic potential of exosomes in AD treatment.

8. Conclusion

Exosomes derived from stem cells play a pivotal role in transferring their cargo, including miRNA, to parenchymal cells under various conditions such as cartilage degradation, CVDs, brain disorders, and eye diseases. This ability makes exosomes essential for promoting plasticity and functional recovery in degenerative diseases. Given the necessity for complex paracrine signaling, exosomes offer a promising therapeutic approach for managing intricate conditions such as degenerative diseases. The diverse miRNA content in stem cell–derived exosomes allow for tailored therapeutic responses, enhancing their efficacy. Furthermore, exosomes exhibit considerable potential as diagnostic markers for these diseases.

Exosomes offer numerous advantages over traditional cell-based therapies for treating degenerative diseases, as evidenced by clinical trials. Unlike the systemic injection of cells into the bloodstream, which can cause vessel blockages, exosomes with diameters at the nanometer scale can swiftly penetrate the blood–brain barrier and reach the brain without obstructing small vessels. Moreover, exosomes can be effectively retained within joints to treat joint damage. Overall, exosome therapy offers a more targeted and efficient approach for tissue regeneration compared with MSC therapies.

Ongoing research explores the advantages of using stem cell–derived exosome therapy for degenerative diseases. These exosomes, whether natural or engineered, offer therapeutic potential. Although some studies have shown positive results in acute injury disease models, there remains a gap in research concerning chronic degenerative diseases such as OA, CVD, AMD, and AD and. Further investigations are necessary to understand the pathogenesis of these degenerative diseases and to assess the potential benefits of exosomes derived from various sources of MSCs, different preconditioning statuses, doses, and therapeutic regimens (Fig. 1).

9. Perspectives

Exosomes play crucial roles in intercellular communication and hold immense potential for advanced therapeutics. Their diverse origins and inherent targeting abilities make them effective in treating various diseases, including cancer, neurodegenerative disorders, and CVDs. Through the modulation of target cells, exosomes influence proliferation, differentiation, and immune responses as well as serve as carriers for therapeutic payloads, promoting tissue repair and enhancing treatment efficacy. This review explored the multifaceted role of exosomes, emphasizing their diverse sourcing from various cell types and organs, and their pivotal role in developing clinical treatments for cancers and regenerative medicine. Additionally, exosome biogenesis, molecular composition, and current advancements in exosome-based therapies were explored, and challenges and future directions in exosome research were addressed with the aim of translating these therapies into clinical practice. Understanding the complex molecular landscapes of exosomes is crucial for harnessing their diagnostic and therapeutic potentials, leading to innovative strategies in regenerative medicine and disease treatment.

Recent research has increasingly focused on leveraging the therapeutic potential of exosomes for the treatment of various diseases, including cancer, neurodegenerative disorders, CVDs, and regenerative medicine. Exosomes have unique properties, such as remarkable stability and inherent targeting capabilities, which make them promising candidates for therapeutic applications, particularly in cell therapy. Studies have demonstrated that exosomes differ in their biological activities depending on the cell source they are derived from and can effectively modulate various cellular processes, underscoring their potential in targeted drug delivery and therapy. Despite challenges such as their limited circulation lifetime and relatively weak targeting capacity, researchers are working to improve the performance and clinical utility of exosome engineering and therapies.

In conclusion, exosomes are promising therapeutic vehicles in cell therapy given their distinct properties and abilities. However, additional research is necessary to address current challenges and fully harness their potential in this field. This review offers a comprehensive overview of exosomes and their evolving role in intercellular communication, with a particular focus on their utility in cell therapy, along with discussions on exosome biogenesis, composition, mechanisms of intercellular transfer, and the current landscape of exosome-based treatments in both preclinical and clinical settings.

Funding

This research was funded by the Ministry of Science and Technology (MOST 111-2314-B-418-004, MOST 111-2321-B-418-002-, NSTC 112-2321-B-418-004- and NSTC 112-2314-B-418-010-MY3), Far Eastern Memorial Hospital (FEMH; 2022-C-042, 2022-C-123, 2023-C-124 and 2024-C-105), National Yang Ming Chiao Tung University–FEMH Cooperation (111DN12, 111DN22, 112DN13, 112DN22, 113DN09 and 113DN16), and National Taiwan University Hospital–FEMH Cooperation (111-FTN0012).

Declaration of competing interest

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

References

[1] Organization, W.H. Ageing and health.
[2] Khachaturian AS, Dengel A, Dočkal V, Hroboň P, Tolar M. Editorial: accelerating innovations for enhanced brain health. Can artificial intelligence advance new pathways for drug discovery for alzheimer's and other neurodegenerative disorders? J Prev Alzheimers Dis 2023;10:1–4.

[3] Khachigian LM, Liew G, Teo KYC, Wong TY, Mitchell P. Emerging therapeutic strategies for unmet need in neovascular age-related macular degeneration. J Transl Med 2023;21:133.
[4] Hammond MM, Everitt IK, Khan SS. New strategies and therapies for the prevention of heart failure in high-risk patients. Clin Cardiol 2022;45(Suppl 1):S13–25.
[5] Carstairs A, Genever P. Stem cell treatment for musculoskeletal disease. Curr Opin Pharmacol 2014;16:1–6.
[6] Johnson K, Zhu S, Tremblay MS, Payette JN, Wang J, Bouchez LC, et al. A stem cell-based approach to cartilage repair. Science 2012;336:717–21.
[7] Wu X, Wang W, Meng C, Yang S, Duan D, Xu W, et al. Regulation of differentiation in trabecular bone-derived mesenchymal stem cells by T cell activation and inflammation. Oncol Rep 2013;30:2211–9.
[8] Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase IIb, randomized, placebo-controlled clinical trial. Stem Cells Transl Med 2019;8:504–11.
[9] Neybecker P, Henrionnet C, Pape E, Mainard D, Galois L, Loeuille D, et al. In vitro and in vivo potentialities for cartilage repair from human advanced knee osteoarthritis synovial fluid-derived mesenchymal stem cells. Stem Cell Res Ther 2018;9:329.
[10] Greif DN, Kouroupis D, Murdock CJ, Griswold AJ, Kaplan LD, Best TM, et al. Infrapatellar fat pad/synovium complex in early-stage knee osteoarthritis: potential new target and source of therapeutic mesenchymal stem/stromal cells. Front Bioeng Biotechnol 2020;8:860.
[11] Turajane T, Chaveewanakorn U, Fongsarun W, Aojanepong J, Papadopoulos KI. Avoidance of total knee arthroplasty in early osteoarthritis of the knee with intra-articular implantation of autologous activated peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial with differential effects of growth factor addition. Stem Cell Int 2017;2017:8925132.
[12] Wortzel I, Dror S, Kenific CM, Lyden D. Exosome-mediated metastasis: communication from a distance. Dev Cell 2019;49:347–60.
[13] Sun Z, Yang S, Zhou Q, Wang G, Song J, Li Z, et al. Emerging role of exosome-derived long non-coding RNAs in tumor microenvironment. Mol Cancer 2018;17:82.
[14] Lobb RJ, Becker M, Wen SW, Wong CS, Wiegmans AP, Leimgruber A, et al. Optimized exosome isolation protocol for cell culture supernatant and human plasma. J Extracell Vesicles 2015;4:27031.
[15] Xu X, Liang Y, Li X, Ouyang K, Wang M, Cao T, et al. Exosome-mediated delivery of kartogenin for chondrogenesis of synovial fluid-derived mesenchymal stem cells and cartilage regeneration. Biomaterials 2021;269:120539.
[16] McKiernan J, Donovan MJ, O'Neill V, Bentink S, Noerholm M, Belzer S, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncol 2016;2:882–9.
[17] Dixon CL, Sheller-Miller S, Saade GR, Fortunato SJ, Lai A, Palma C, et al. Amniotic fluid exosome proteomic profile exhibits unique pathways of term and preterm labor. Endocrinology 2018;159:2229–40.
[18] Lasser C, Alikhani VS, Ekstrom K, Eldh M, Paredes PT, Bossios A, et al. Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. J Transl Med 2011;9:9.
[19] Jia L, Qiu Q, Zhang H, Chu L, Du Y, Zhang J, et al. Concordance between the assessment of Abeta42, T-tau, and P-T181-tau in peripheral blood neuronal-derived exosomes and cerebrospinal fluid. Alzheimers Dement 2019;15:1071–80.
[20] Nik Mohamed Kamal NNS, Awang RAR, Mohamad S, Shahidan WNS. Plasma- and saliva exosome profile reveals a distinct MicroRNA signature in chronic periodontitis. Front Physiol 2020;11:587381.
[21] Inubushi S, Kawaguchi H, Mizumoto S, Kunihisa T, Baba M, Kitayama Y, et al. Oncogenic miRNAs identified in tear exosomes from metastatic breast cancer patients. Anticancer Res 2020;40:3091–6.
[22] Cao Q, Guo Z, Yan Y, Wu J, Song C. Exosomal long noncoding RNAs in aging and age-related diseases. IUBMB Life 2019;71:1846–56.
[23] Whiteside TL. Exosome and mesenchymal stem cell cross-talk in the tumor microenvironment. Semin Immunol 2018;35:69–79.
[24] Liu Y, Lin L, Zou R, Wen C, Wang Z, Lin F. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. Cell Cycle 2018;17:2411–22.
[25] Ha DH, Kim HK, Lee J, Kwon HH, Park GH, Yang SH, et al. Mesenchymal stem/stromal cell-derived exosomes for immunomodulatory therapeutics and skin regeneration. Cells 2020;9.
[26] Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. Biomaterials 2018;156:16–27.
[27] Jeppesen DK, Fenix AM, Franklin JL, Higginbotham JN, Zhang Q, Zimmerman LJ, et al. Reassessment of exosome composition. Cell 2019;177:428–445 e418.
[28] Chen Y, Xue K, Zhang X, Zheng Z, Liu K. Exosomes derived from mature chondrocytes facilitate subcutaneous stable ectopic chondrogenesis of cartilage progenitor cells. Stem Cell Res Ther 2018;9:318.
[29] Wang R, Xu B. TGF-beta1-modified MSC-derived exosomal miR-135b attenuates cartilage injury via promoting M2 synovial macrophage polarization by targeting MAPK6. Cell Tissue Res 2021;384:113–27.
[30] Tang S, Tang T, Gao G, Wei Q, Sun K, Huang W. Bone marrow mesenchymal stem cell-derived exosomes inhibit chondrocyte apoptosis and the expression of MMPs by regulating Drp1-mediated mitophagy. Acta Histochem 2021;123:151796.
[31] Wang Y, Yu D, Liu Z, Zhou F, Dai J, Wu B, et al. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. Stem Cell Res Ther 2017;8:189.
[32] Wang Z, Yan K, Ge G, Zhang D, Bai J, Guo X, et al. Exosomes derived from miR-155-5p-overexpressing synovial mesenchymal stem cells prevent osteoarthritis via enhancing proliferation and migration, attenuating apoptosis, and modulating extracellular matrix secretion in chondrocytes. Cell Biol Toxicol 2021;37:85–96.
[33] Pourakbari R, Khodadadi M, Aghebati-Maleki A, Aghebati-Maleki L, Yousefi M. The potential of exosomes in the therapy of the cartilage and bone complications; emphasis on osteoarthritis. Life Sci 2019;236:116861.
[34] Tofino-Vian M, Guillen MI, Perez Del Caz MD, Castejon MA, Alcaraz MJ. Extracellular vesicles from adipose-derived mesenchymal stem cells down-regulate senescence features in osteoarthritic osteoblasts. Oxid Med Cell Longev 2017;2017:7197598.
[35] Shao J, Zhu J, Chen Y, Fu Q, Li L, Ding Z, et al. Exosomes from kartogenin-pretreated infrapatellar fat pad mesenchymal stem cells enhance chondrocyte anabolism and articular cartilage regeneration. Stem Cell Int 2021;2021:6624874.
[36] Zhao C, Chen JY, Peng WM, Yuan B, Bi Q, Xu YJ. Exosomes from adipose-derived stem cells promote chondrogenesis and suppress inflammation by upregulating miR-145 and miR-221. Mol Med Rep 2020;21:1881–9.
[37] Wu J, Kuang L, Chen C, Yang J, Zeng WN, Li T, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. Biomaterials 2019;206:87–100.
[38] Tao SC, Yuan T, Zhang YL, Yin WJ, Guo SC, Zhang CQ. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. Theranostics 2017;7:180–95.
[39] Mao G, Zhang Z, Hu S, Zhang Z, Chang Z, Huang Z, et al. Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A. Stem Cell Res Ther 2018;9:247.
[40] Wang R, Xu B, Xu H. TGF-beta1 promoted chondrocyte proliferation by regulating Sp1 through MSC-exosomes derived miR-135b. Cell Cycle 2018;17:2756–65.
[41] Peters MA, Wendholt D, Strietholt S, Frank S, Pundt N, Korb-Pap A, et al. The loss of alpha2beta1 integrin suppresses joint inflammation and cartilage destruction in mouse models of rheumatoid arthritis. Arthritis Rheum 2012;64:1359–68.
[42] Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 2014;506:376–81.
[43] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.
[44] Chen HW, Huang CH, Huang CF, Chang CH, Liao HJ. Distinct subsets of synovial fibroblasts control cartilage destruction in joint diseases. Clin Exp Rheumatol 2024;42:1118–26.
[45] Patlan M, Paez A, Masso F, Amezcua-Guerra LM. Relative increase of Th17 phenotype in senescent CD4+CD28null T cells from peripheral blood of patients with rheumatoid arthritis. Clin Exp Rheumatol 2021;39:925–6.
[46] Chang TH, Wu CS, Chiou SH, Chang CH, Liao HJ. Adipose-derived stem cell exosomes as a novel anti-inflammatory agent and the current therapeutic targets for rheumatoid arthritis. Biomedicines 2022;10.
[47] Gomez EA, Colas RA, Souza PR, Hands R, Lewis MJ, Bessant C, et al. Blood pro-resolving mediators are linked with synovial pathology and are predictive of DMARD responsiveness in rheumatoid arthritis. Nat Commun 2020;11:5420.
[48] Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther 2009;11(Suppl 1):S1.
[49] Lopez-Santalla M, Fernandez-Perez R, Garin MI. Mesenchymal stem/stromal cells for rheumatoid arthritis treatment: an update on clinical applications. Cells 2020;9.
[50] Li GQ, Fang YX, Liu Y, Meng FR, Wu X, Zhang CW, et al. MicroRNA-21 from bone marrow mesenchymal stem cell-derived extracellular vesicles targets TET1 to suppress KLF4 and alleviate rheumatoid arthritis. Ther Adv Chronic Dis 2021;12:20406223211007369.
[51] Chang L, Kan L. Mesenchymal stem cell-originated exosomal circular RNA circFBXW7 attenuates cell proliferation, migration and inflammation of fibroblast-like synoviocytes by targeting miR-216a-3p/HDAC4 in rheumatoid arthritis. J Inflamm Res 2021;14:6157–71.
[52] Tavasolian F, Hosseini AZ, Soudi S, Naderi M. miRNA-146a improves immunomodulatory effects of MSC-derived exosomes in rheumatoid arthritis. Curr Gene Ther 2020;20:297–312.
[53] Chen Z, Wang H, Xia Y, Yan F, Lu Y. Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF. J Immunol 2018;201:2472–82.

[54] Su Y, Liu Y, Ma C, Guan C, Ma X, Meng S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-kappaB pathway. J Orthop Surg Res 2021;16:116.
[55] Meng Q, Qiu B. Exosomal MicroRNA-320a derived from mesenchymal stem cells regulates rheumatoid arthritis fibroblast-like synoviocyte activation by suppressing CXCL9 expression. Front Physiol 2020;11:441.
[56] Meng HY, Chen LQ, Chen LH. The inhibition by human MSCs-derived miRNA-124a overexpression exosomes in the proliferation and migration of rheumatoid arthritis-related fibroblast-like synoviocyte cell. BMC Muscoskel Disord 2020;21:150.
[57] Wu H, Zhou X, Wang X, Cheng W, Hu X, Wang Y, et al. miR-34a in extracellular vesicles from bone marrow mesenchymal stem cells reduces rheumatoid arthritis inflammation via the cyclin I/ATM/ATR/p53 axis. J Cell Mol Med 2021;25:1896–910.
[58] Yan X, Cen Y, Wang Q. Mesenchymal stem cells alleviate experimental rheumatoid arthritis through microRNA-regulated IkappaB expression. Sci Rep 2016;6:28915.
[59] Organization WH. Cardiovascular diseases. 2023.
[60] Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. Signal Transduct Targeted Ther 2022;7:131.
[61] Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res 2002;53:31–47.
[62] Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. Circulation 2010;121:2437–45.
[63] Loyer X, Zlatanova I, Devue C, Yin M, Howangyin KY, Klaihmon P, et al. Intracardiac release of extracellular vesicles shapes inflammation following myocardial infarction. Circ Res 2018;123:100–6.
[64] Almeida Paiva R, Martins-Marques T, Jesus K, Ribeiro-Rodrigues T, Zuzarte M, Silva A, et al. Ischaemia alters the effects of cardiomyocyte-derived extracellular vesicles on macrophage activation. J Cell Mol Med 2019;23:1137–51.
[65] Cheng M, Yang J, Zhao X, Zhang E, Zeng Q, Yu Y, et al. Circulating myocardial microRNAs from infarcted hearts are carried in exosomes and mobilise bone marrow progenitor cells. Nat Commun 2019;10:959.
[66] Akbar N, Digby JE, Cahill TJ, Tavare AN, Corbin AL, Saluja S, et al. Endothelium-derived extracellular vesicles promote splenic monocyte mobilization in myocardial infarction. JCI Insight 2017;2.
[67] Qiao S, Zhang W, Yin Y, Wei Z, Chen F, Zhao J, et al. Extracellular vesicles derived from Krüppel-Like Factor 2-overexpressing endothelial cells attenuate myocardial ischemia-reperfusion injury by preventing Ly6C(high) monocyte recruitment. Theranostics 2020;10:11562–79.
[68] Cambier L, de Couto G, Ibrahim A, Echavez AK, Valle J, Liu W, et al. Y RNA fragment in extracellular vesicles confers cardioprotection via modulation of IL-10 expression and secretion. EMBO Mol Med 2017;9:337–52.
[69] de Couto G, Gallet R, Cambier L, Jaghatspanyan E, Makkar N, Dawkins JF, et al. Exosomal MicroRNA transfer into macrophages mediates cellular postconditioning. Circulation 2017;136:200–14.
[70] Wang Y, Li C, Zhao R, Qiu Z, Shen C, Wang Z, et al. CircUbe3a from M2 macrophage-derived small extracellular vesicles mediates myocardial fibrosis after acute myocardial infarction. Theranostics 2021;11:6315–33.
[71] Wang C, Zhang C, Liu L, A X, Chen B, Li Y, et al. Macrophage-derived mir-155-containing exosomes suppress fibroblast proliferation and promote fibroblast inflammation during cardiac injury. Mol Ther 2017;25:192–204.
[72] Liu S, Chen J, Shi J, Zhou W, Wang L, Fang W, et al. M1-like macrophage-derived exosomes suppress angiogenesis and exacerbate cardiac dysfunction in a myocardial infarction microenvironment. Basic Res Cardiol 2020;115:22.
[73] Liu H, Gao W, Yuan J, Wu C, Yao K, Zhang L, et al. Exosomes derived from dendritic cells improve cardiac function via activation of CD4(+) T lymphocytes after myocardial infarction. J Mol Cell Cardiol 2016;91:123–33.
[74] Akhmerov A, Rogers R, de Couto G, Valle J, Li L, Ibrahim A, et al. Regulatory T cell activation, proliferation, and reprogramming induced by extracellular vesicles. J Heart Lung Transplant 2021;40:1387–95.
[75] Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther 2021;11:263–76.
[76] Akhmerov A, Parimon T. Extracellular vesicles, inflammation, and cardiovascular disease. Cells 2022;11.
[77] Boen JR, Gevaert AB, De Keulenaer GW, Van Craenenbroeck EM, Segers VF. The role of endothelial miRNAs in myocardial biology and disease. J Mol Cell Cardiol 2020;138:75–87.
[78] Yang P, Chen Z, Huang W, Zhang J, Zou L, Wang H. Communications between macrophages and cardiomyocytes. Cell Commun Signal 2023;21:206.
[79] Moreira-Costa L, Barros AS, Lourenço AP, Leite-Moreira AF, Nogueira-Ferreira R, Thongboonkerd V, et al. Exosome-derived mediators as potential biomarkers for cardiovascular diseases: a network approach. Proteomes 2021;9.
[80] Jadli AS, Parasor A, Gomes KP, Shandilya R, Patel VB. Exosomes in cardiovascular diseases: pathological potential of nano-messenger. Front Cardiovasc Med 2021;8:767488.
[81] Wang Q, Zhang L, Sun Z, Chi B, Zou A, Mao L, et al. HIF-1α overexpression in mesenchymal stem cell-derived exosome-encapsulated arginine-glycine-aspartate (RGD) hydrogels boost therapeutic efficacy of cardiac repair after myocardial infarction. Mater Today Bio 2021;12:100171.
[82] Lai RC, Chen TS, Lim SK. Mesenchymal stem cell exosome: a novel stem cell-based therapy for cardiovascular disease. Regen Med 2011;6:481–92.
[83] Huang L, Ma W, Ma Y, Feng D, Chen H, Cai B. Exosomes in mesenchymal stem cells, a new therapeutic strategy for cardiovascular diseases? Int J Biol Sci 2015;11:238–45.
[84] Bian S, Zhang L, Duan L, Wang X, Min Y, Yu H. Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. J Mol Med (Berl) 2014;92:387–97.
[85] Xiao Y, Zhang Y, Li Y, Peng N, Liu Q, Qiu D, et al. Exosomes derived from mesenchymal stem cells pretreated with ischemic rat heart extracts promote angiogenesis via the delivery of DMBT1. Cell Transplant 2022;31:9636897221102898.
[86] Huang L, Yang L, Ding Y, Jiang X, Xia Z, You Z. Human umbilical cord mesenchymal stem cells-derived exosomes transfers microRNA-19a to protect cardiomyocytes from acute myocardial infarction by targeting SOX6. Cell Cycle 2020;19:339–53.
[87] Zhao J, Li X, Hu J, Chen F, Qiao S, Sun X, et al. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. Cardiovasc Res 2019;115:1205–16.
[88] Huang F, Li ML, Fang ZF, Hu XQ, Liu QM, Liu ZJ, et al. Overexpression of MicroRNA-1 improves the efficacy of mesenchymal stem cell transplantation after myocardial infarction. Cardiology 2013;125:18–30.
[89] Ahmed L, Al-Massri K. New approaches for enhancement of the efficacy of mesenchymal stem cell-derived exosomes in cardiovascular diseases. Tissue Eng Regen Med 2022;19:1129–46.
[90] Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci 2013;54:Orsf68–80.
[91] Datta S, Cano M, Ebrahimi K, Wang L, Handa JT. The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD. Prog Retin Eye Res 2017;60:201–18.
[92] Long C, Wang J, Gan W, Qin X, Yang R, Chen X. Therapeutic potential of exosomes from adipose-derived stem cells in chronic wound healing. Front Surg 2022;9:1030288.
[93] Holan V, Palacka K, Hermankova B. Mesenchymal stem cell-based therapy for retinal degenerative diseases: experimental models and clinical trials. Cells 2021;10.
[94] Li D, Zhang J, Liu Z, Gong Y, Zheng Z. Human umbilical cord mesenchymal stem cell-derived exosomal miR-27b attenuates subretinal fibrosis via suppressing epithelial-mesenchymal transition by targeting HOXC6. Stem Cell Res Ther 2021;12:24.
[95] Safwat A, Sabry D, Ragiae A, Amer E, Mahmoud RH, Shamardan RM. Adipose mesenchymal stem cells-derived exosomes attenuate retina degeneration of streptozotocin-induced diabetes in rabbits. J Circ Biomark 2018;7:1849454418807827.
[96] Li L, Lai K, Gong Y, Huang C, Xu F, Li Y, et al. Downregulation of miR-146a-5p inhibits choroidal neovascularization via the NF-κB signaling pathway by targeting OTUD7B. Curr Eye Res 2020;45:1514–25.
[97] Lian C, Lou H, Zhang J, Tian H, Ou Q, Xu J-Y, et al. MicroRNA-24 protects retina from degeneration in rats by down-regulating chitinase-3-like protein 1. Exp Eye Res 2019;188:107791.
[98] Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, et al. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell 2008;15:261–71.
[99] Wang L, Lee AYW, Wigg JP, Peshavariya H, Liu P, Zhang H. miR-126 regulation of angiogenesis in age-related macular degeneration in CNV mouse model. Int J Mol Sci 2016;17:895.
[100] Karali M, Guadagnino I, Marrocco E, De Cegli R, Carissimo A, Pizzo M, et al. AAV-miR-204 protects from retinal degeneration by attenuation of microglia activation and photoreceptor cell death. Mol Ther Nucleic Acids 2020;19:144–56.
[101] Deng C-L, Hu C-B, Ling S-T, Zhao N, Bao L-H, Zhou F, et al. Photoreceptor protection by mesenchymal stem cell transplantation identifies exosomal MiR-21 as a therapeutic for retinal degeneration. Cell Death Differ 2021;28:1041–61.
[102] Mahmoudian-Sani M-R, Forouzanfar F, Asgharzade S, Ghorbani N. Overexpression of MiR-183/96/182 triggers retina-like fate in human bone marrow-derived mesenchymal stem cells (hBMSCs) in culture. Journal of ophthalmology 2019;2019.
[103] Anasagasti A, Lara-López A, Milla-Navarro S, Escudero-Arrarás L, Rodríguez-Hidalgo M, Zabaleta N, et al. Inhibition of MicroRNA 6937 delays photoreceptor and vision loss in a mouse model of retinitis pigmentosa. Pharmaceutics 2020;12:913.
[104] Peng X, Zhang T, Liu R, Jin X. Potential in exosome-based targeted nanodrugs and delivery vehicles for posterior ocular disease treatment: from barriers to therapeutic application. Mol Cell Biochem 2023;479:1319–33.
[105] Flores-Bellver M, Mighty J, Aparicio-Domingo S, Li KV, Shi C, Zhou J, et al. Extracellular vesicles released by human retinal pigment epithelium mediate increased polarised secretion of drusen proteins in response to AMD stressors. J Extracell Vesicles 2021;10:e12165.
[106] Chen N, Wang J, Hu Y, Cui B, Li W, Xu G, et al. MicroRNA-410 reduces the expression of vascular endothelial growth factor and inhibits oxygen-induced retinal neovascularization. PLoS One 2014;9:e95665.

[107] Breijyeh Z, Karaman R. Comprehensive review on alzheimer's disease: causes and treatment. Molecules 2020;25.
[108] Tahami Monfared AA, Byrnes MJ, White LA, Zhang Q. Alzheimer's disease: epidemiology and clinical progression. Neurol Ther 2022;11:553–69.
[109] Alhazmi HA, Albratty M. An update on the novel and approved drugs for Alzheimer disease. Saudi Pharmaceut J 2022;30:1755–64.
[110] Eren E, Hunt JFV, Shardell M, Chawla S, Tran J, Gu J, et al. Extracellular vesicle biomarkers of Alzheimer's disease associated with sub-clinical cognitive decline in late middle age. Alzheimers Dement 2020;16:1293–304.
[111] Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 2006;59:512–9.
[112] Lowe VJ, Lundt ES, Albertson SM, Przybelski SA, Senjem ML, Parisi JE, et al. Neuroimaging correlates with neuropathologic schemes in neurodegenerative disease. Alzheimers Dement 2019;15:927–39.
[113] Iranifar E, Seresht BM, Momeni F, Fadaei E, Mehr MH, Ebrahimi Z, et al. Exosomes and microRNAs: new potential therapeutic candidates in Alzheimer disease therapy. J Cell Physiol 2019;234:2296–305.
[114] Qu M, Lin Q, Huang L, Fu Y, Wang L, He S, et al. Dopamine-loaded blood exosomes targeted to brain for better treatment of Parkinson's disease. J Contr Release 2018;287:156–66.
[115] DeLeo AM, Ikezu T. Extracellular vesicle biology in alzheimer's disease and related tauopathy. J Neuroimmune Pharmacol 2018;13:292–308.
[116] Yuyama K, Sun H, Mitsutake S, Igarashi Y. Sphingolipid-modulated exosome secretion promotes clearance of amyloid-β by microglia. J Biol Chem 2012;287:10977–89.
[117] Dinkins MB, Dasgupta S, Wang G, Zhu G, Bieberich E. Exosome reduction in vivo is associated with lower amyloid plaque load in the 5XFAD mouse model of Alzheimer's disease. Neurobiol Aging 2014;35:1792–800.
[118] Katsuda T, Tsuchiya R, Kosaka N, Yoshioka Y, Takagaki K, Oki K, et al. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Sci Rep 2013;3:1197.
[119] Wang SS, Jia J, Wang Z. Mesenchymal stem cell-derived extracellular vesicles suppresses iNOS expression and ameliorates neural impairment in alzheimer's disease mice. J Alzheimers Dis 2018;61:1005–13.
[120] de Godoy MA, Saraiva LM, de Carvalho LRP, Vasconcelos-Dos-Santos A, Beiral HJV, Ramos AB, et al. Mesenchymal stem cells and cell-derived extracellular vesicles protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers. J Biol Chem 2018;293:1957–75.
[121] Bodart-Santos V, de Carvalho LRP, de Godoy MA, Batista AF, Saraiva LM, Lima LG, et al. Extracellular vesicles derived from human Wharton's jelly mesenchymal stem cells protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers. Stem Cell Res Ther 2019;10:332.
[122] Yuyama K, Sun H, Sakai S, Mitsutake S, Okada M, Tahara H, et al. Decreased amyloid-β pathologies by intracerebral loading of glycosphingolipid-enriched exosomes in Alzheimer model mice. J Biol Chem 2014;289:24488–98.
[123] Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, Sandoval-Ávila S, Gomez-Pinedo U, Márquez-Aguirre AL, et al. Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res 2019;14:1626–34.
[124] Guo M, Yin Z, Chen F, Lei P. Mesenchymal stem cell-derived exosome: a promising alternative in the therapy of Alzheimer's disease. Alzheimer's Res Ther 2020;12:1–14.
[125] Ding M, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, et al. Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in alzheimer's disease. Neurochem Res 2018;43:2165–77.
[126] Delpech JC, Herron S, Botros MB, Ikezu T. Neuroimmune crosstalk through extracellular vesicles in health and disease. Trends Neurosci 2019;42:361–72.
[127] Bahrini I, Song JH, Diez D, Hanayama R. Neuronal exosomes facilitate synaptic pruning by up-regulating complement factors in microglia. Sci Rep 2015;5:7989.
[128] Paolicelli RC, Bergamini G, Rajendran L. Cell-to-cell communication by extracellular vesicles: focus on microglia. Neuroscience 2019;405:148–57.
[129] Xie X, Song Q, Dai C, Cui S, Tang R, Li S, et al. Clinical safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes in patients with mild to moderate Alzheimer's disease: a phase I/II clinical trial. Gen Psychiatr 2023;36:e101143.
[130] Liu W, Bai X, Zhang A, Huang J, Xu S, Zhang J. Role of exosomes in central nervous system diseases. Front Mol Neurosci 2019;12:240.