

Exosome-mediated crosstalk between the cardiovascular and musculoskeletal systems: Mechanisms and therapeutic potential (Review)

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Abstract. The cardiovascular and musculoskeletal systems are two core systems essential for maintaining human physiological functions and their dynamic interactions play a critical role in overall health. Exosomes, nanosized vesicles released by cells, contain bioactive substances including microRNA, long non-coding RNA, lipids and proteins and participate in the pathophysiological regulation of multiple organ systems by mediating intercellular communication. Bone-derived exosomes ameliorate cardiovascular diseases through the regulation of oxidative stress, inflammatory responses and apoptosis. Conversely, cardiovascular-derived exosomes enhance bone homeostasis by suppressing osteoclast activity or promoting osteogenic differentiation, but they may also exacerbate pathological progression in conditions such as osteoarthritis. Skeletal muscle-derived exosomes protect cardiomyocytes in muscular dystrophy through functional molecules delivery. However, under pathological conditions such as sarcopenia, skeletal muscle-derived exosomes may aggravate cardiac dysfunction by activating pro-apoptotic signals. Similarly, cardiovascular-derived exosomes exhibit dual roles in skeletal muscle regulation, promoting regeneration while potentially inducing atrophy during heart failure. In addition, exosomes demonstrate significant clinical value as diagnostic biomarkers and targeted drug delivery vehicles, both for early disease detection and regenerative therapies. The present review systematically outlined the mechanisms

underlying exosome-mediated bidirectional crosstalk between the cardiovascular and musculoskeletal systems and explores their clinical application potential. It provided theoretical insights and novel perspectives for further research into the pathogenesis and therapeutic strategies of cardiovascular and musculoskeletal diseases.

Contents

1. Introduction
2. Biogenesis and functional regulation of exosomes
3. The effects of bone-derived exosomes on the cardiovascular system
4. The effect of cardiovascular-derived exosomes on bone
5. The effect of skeletal muscle-derived exosomes on the cardiovascular system
6. The effect of cardiovascular-derived exosomes on skeletal muscle
7. Clinical applications of exosome therapy
8. Multiple factors influence the therapeutic efficacy of exosomes
9. Conclusions

1. Introduction

The organ systems within the human body are closely interconnected and respond coordinately to both internal and external demands and disruptions, dynamically maintaining internal balance and normal physiological activities through the transmission of various signals. The cardiovascular and musculoskeletal systems are two major systems within the human body and their interactions and crosstalk form an essential foundation for vital activities and the maintenance of health. Exosomes are defined as extracellular vesicles (EVs) originating from the endosomal compartment and secreted through the multivesicular body (MVB) pathway (1). They carry diverse bioactive molecules including proteins, lipids and nucleic acids, which are essential for facilitating communication between cells and play significant roles in the pathophysiological mechanisms underlying multiple

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diseases (2). For instance, specific microRNAs (miRNA/miR) carried by exosomes can serve as biomarkers for myocardial or skeletal muscle injury and even as potential therapeutic targets (3,4). As a crucial medium of intercellular communication, exosomes have garnered growing attention within the biomedical sector, especially concerning diseases related to the cardiovascular and musculoskeletal systems.

Cardiovascular diseases (CVDs) remain a major worldwide health threat. In recent years, growing research has shown that crosstalk between the cardiovascular and musculoskeletal systems can markedly improve CVDs. For example, musculoskeletal-derived exosomes can promote cardiac repair and regeneration (5,6). In addition, this crosstalk also contributes to the pathophysiological progression of CVDs. During sarcopenia, skeletal muscle-derived exosomes impair cardiac recovery after myocardial infarction (MI) by facilitating cardiomyocytes (CMCs) apoptosis (7). Bone marrow-derived fibroblast progenitor cells release extracellular vesicles that exacerbate cardiac fibrosis through mediating signaling pathways involving miR-21-5p and integrin α -V (ITGAV) (8). On the other hand, the homeostasis and functionality of the musculoskeletal system are influenced by exosomes as well. For example, exosomes secreted by cardiac progenitor cells markedly increase muscle fiber number and alleviate inflammatory responses and fibrosis in the skeletal muscle of X-linked muscular dystrophy (mdx) mice (9). As research into the endocrine, autocrine and paracrine functions of musculoskeletal tissues deepens, understanding of musculoskeletal molecular homeostasis has improved and the crosstalk between musculoskeletal and cardiac molecular homeostasis has also garnered increasing attention. Exosomes markedly contribute to this process. By delivering bioactive molecules, they affect the homeostasis and function of the musculoskeletal system, thus generating crosstalk with the cardiovascular system.

The present review is based on a comprehensive search of major databases such as PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Google Scholar ([/scholar.google.com](https://scholar.google.com)) and Web of Science (<https://www.webofscience.com>), as of March 2025, using keywords such as 'exosome', 'bone-derived exosomes AND cardiovascular', 'cardiovascular-derived exosomes AND bone', 'skeletal muscle-derived AND cardiovascular' and 'cardiovascular-derived exosomes AND skeletal muscle'. It provided an in-depth and detailed discussion of the molecular mechanisms and signaling pathways underlying exosomes-mediated crosstalk between the cardiovascular and musculoskeletal systems for the first time, to the best of the authors' knowledge. The present review introduced the processes involved in exosomes formation and the mechanisms governing their functional regulation. Moreover, it comprehensively reviewed the research progress on how bone- and skeletal muscle-derived exosomes mediate cardiac function and CVDs through the regulation of pathophysiological pathways. It also discussed the effects of cardiovascular-derived exosomes on bone and skeletal muscle under physiological and pathological conditions, along with their molecular mechanisms. Finally, it outlined the significant role of exosomes in clinical therapy, summarized current limitations and aimed to provide new perspectives and ideas for research in related fields.

2. Biogenesis and functional regulation of exosomes

Exosomes, characterized by a lipid bilayer membrane and a diameter ranging from 30-150 nm, represent a subtype of small EVs (1,10). They are detectable in diverse biological fluids, such as plasma (11), lymph (12), urine (13), gastric fluid (14) and saliva (15). Exosomes originate from early endosomes generated through the inward budding of the plasma membrane. After early endosomes develop into late endosomes, the late endosomes invaginate to form MVBs, which sequester intraluminal vesicles (ILVs) within their lumen (16). Following maturation and fusion of MVBs with the plasma membrane, ILVs are secreted into the extracellular environment as exosomes (17), eventually entering circulation and exerting local paracrine or distant systemic influences. Thus, exosomes are instrumental in intercellular crosstalk and communication systems, effectively mediating the transmission of biological signals across diverse cell types and tissues. The formation of exosomes is co-regulated by membrane skeleton proteins, including apoptosis-linked gene 2-interacting protein X and the Rab family. Furthermore, transmembrane protein superfamily members, including cluster of differentiation (CD)9, CD63 and CD81, play crucial roles in the fusion of exosomes with recipient cells. These proteins are pivotal markers for the isolation and identification of exosomes (18).

The discovery of exosomes dates back to 1983, stemming from *in vitro* studies involving sheep reticulocytes (19). However, this finding did not gather considerable attention initially, as researchers regarded exosomes merely as a way for cells to eliminate unnecessary components (20). As research advanced, scholars gradually recognized that exosomes are essential for intercellular communication, immune responses, disease diagnosis and therapy, tissue repair and regeneration. Currently, it is unclear to what extent the delivery of exosomes is random rather than specifically targeted (21). Nevertheless, existing studies have confirmed that exosomes can transport their cargo to recipient cells by three mechanisms. Exosomes can interact with plasma membrane receptors through surface proteins (22). For example, cardiac endothelial cell (EC)-specific receptors, including kinase insert domain receptor, scavenger receptor class B type 1 and CD36, recognize exosomal ligands such as clusterin, heparan sulfate proteoglycan 2 and extracellular matrix proteins to initiate angiogenic signaling (23). In addition, exosomes can directly fuse with cell membranes, or be internalized through endocytic pathways involving phagocytosis, macropinocytosis and endocytic mechanisms dependent on lipid rafts, clathrin or caveolae (22).

Exosomes contain complex cargo comprising proteins, lipids and various nucleic acids such as DNA, mRNA, miRNA and long non-coding RNA (lncRNA), which facilitate intercellular exchange of materials and biological signals among diverse tissues and organs. Proteins in exosomes, including titin antisense RNA 1, Ras-related protein Rab-27B and synaptotagmin-7, can influence tumor growth through multiple mechanisms. They not only directly promote cancer cell proliferation and metastasis (24,25) but also indirectly facilitate tumor growth by modulating the tumor microenvironment (26). Lipid molecules in exosomes also exhibit therapeutic potential. For instance, eicosanoids in exosomes

derived from different cell sources can serve as biomarkers for certain diseases and regulate distal immune responses (27). Exosomal DNA primarily originates from nuclear or mitochondrial DNA metabolic fragments or damage-induced DNA accumulation (28). These DNA molecules can circulate in the bloodstream and integrate into the genomes of specific immune cells, providing molecular markers for early cancer diagnosis and targeted therapy (29). As the key intermediary transferring genetic information from DNA to ribosomes, mRNA participates in various physiological and pathological processes by directing protein synthesis and has become an effective tool for treating diseases such as cancer. Yang *et al* (30) developed a cellular nanoporation technique to mass-produce exosomes loaded with therapeutic mRNA. These mRNA-loaded exosomes effectively restored tumor-suppressive functions in phosphatase and tensin homolog deleted on chromosome ten (PTEN)-deficient glioblastoma models, thereby inhibiting tumor progression and prolonging animal survival (30). Exosomal miRNAs modulate gene expression by binding target mRNAs and serve as key effector molecules mediating exosomal communication (31). In addition, exosomal lncRNAs demonstrate therapeutic effects in diverse diseases including cancer (32), metabolic disorders (33) and CVDs (34).

The composition and quantity of exosomal contents vary based on their cellular source and microenvironment and the number of exosomes released by a single cell can markedly fluctuate across various physiological and pathological states (35). Following acute myocardial infarction (AMI), damaged CMCs secrete a significant quantity of exosomes. Notably, under moderate hypoxic conditions for two hours, the secretion of exosomes from CMCs increases nearly threefold (36). In addition, exercise can increase the number of exosomal markers (such as TSG101, CD63 and CD81) as well as exosomal miRNAs (such as miR-125b-5p, miR-122-5p and miR-342-5p). These miRNAs mainly modulate the expression of mitogen-associated protein kinase (MAPK), nuclear factor- κ B (NF- κ B), vascular endothelial growth factor (VEGF) and cysteinyl aspartate specific proteinase (caspase), thereby contributing to cardiovascular protection (37) (Fig. 1).

3. The effects of bone-derived exosomes on the cardiovascular system

Bone-derived exosomes demonstrate multi-organ targeting capabilities through secretion into the extracellular environment and subsequent entry into bodily fluids or tissue interstitium, enabling their action on various organ systems including neural (38), tendinous (39) and cardiovascular systems (40). Consequently, bone-derived exosomes may similarly be internalized by target cells such as CMCs through membrane fusion or endocytosis, or alternatively regulate cardiac function via interactions between exosomal surface proteins and cardiac cell receptors. Bone marrow mesenchymal stem cells (BMSCs) are a type of non-hematopoietic stem cell originating from the bone marrow (BM) (41). They exhibit self-renewal capabilities and can extensively proliferate and differentiate into multiple cell types (42). Extensive research in recent years has demonstrated that exosomes released by BMSCs through paracrine mechanisms serve as critical membrane vesicles. These exosomes are crucial

for mediating intercellular communication and exhibiting unique functions in disease diagnosis and treatment (43,44). BMSC-derived exosomes (BMSC-Exos) can regulate multiple signaling pathways in cells such as CMCs and macrophages. Through the synergistic action of various mechanisms, they exert therapeutic effects on CVDs, including MI, myocardial ischemia-reperfusion injury (MIRI), atherosclerosis (AS) and doxorubicin (DOX)-induced cardiomyopathy (DIC).

Amelioration of myocardial infarction. The mortality rate associated with MI is high (45). It is caused by the blockage of coronary arteries, resulting in abrupt interruption of blood flow and subsequent myocardial ischemia and hypoxia. It is often accompanied by severe oxidative stress and inflammatory responses, leading to extensive damage to cardiac tissue and a sharp decline in heart function (46). BMSC-Exos carry various bioactive molecules and can ameliorate MI through multiple mechanisms, including modulating oxidative stress, inflammation, autophagy, apoptosis, angiogenesis and fibrosis.

Oxidative stress. Oxidative stress arises from a disruption in the equilibrium between reactive oxygen species (ROS) generation and the antioxidant mechanisms of the body (47). Following MI, oxidative stress develops in both infarcted and non-infarcted regions of the myocardial tissues. Ischemic myocardium produces ROS, which, particularly following reperfusion, causes direct damage to cellular membranes, triggering cell death (48,49). ROS-induced oxidative stress is a major trigger for CMCs death following MI and contributes to the decline in cardiac contraction and relaxation function (47). Wang *et al* (40) found that BMSC-Exos can markedly reduce the apoptosis rate and ROS levels of cardiac stem cells (CSCs) following oxidative stress injury, inhibit malondialdehyde (MDA) levels and upregulate the expression of superoxide dismutase (SOD). Among these effects, miR-214, as a key functional molecule within BMSC-Exos, safeguards CSCs against oxidative stress by targeting and inhibiting calcium-calmodulin-dependent protein kinase II expression (40). Under lipopolysaccharide stimulation, BMSC-Exos exhibit a more significant inhibitory effect on oxidative stress (50). This is accompanied by an elevation in miR-181a-5p levels, which is transported to CMCs via exosomes, where miR-181a-5p targets and inhibits activating transcription factor 2 expression, leading to increased SOD1 and SOD2 production and suppressing oxidative stress in CMCs (50). Overexpression of PTEN inhibits the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) axis, which is a pathway widely acknowledged as a key mechanism driving cell apoptosis following oxidative stress (51). miR-21 in BMSC-Exos has been shown to effectively internalize into C-kit⁺ CSCs, inhibiting PTEN expression to activate PI3K/AKT pathway, thereby protecting CSCs from apoptosis under oxidative stress conditions (52).

Inflammation. MI facilitates the release of danger-associated molecular patterns from necrotic cells into the extracellular space, transmitting danger signals to surrounding CMCs via pattern recognition receptors, thus triggering strong inflammatory responses (53). The inflammatory response and oxidative stress following MI are key processes that contributing to myocardial injury, repair and remodeling (54). Research has shown that BMSC-Exos can

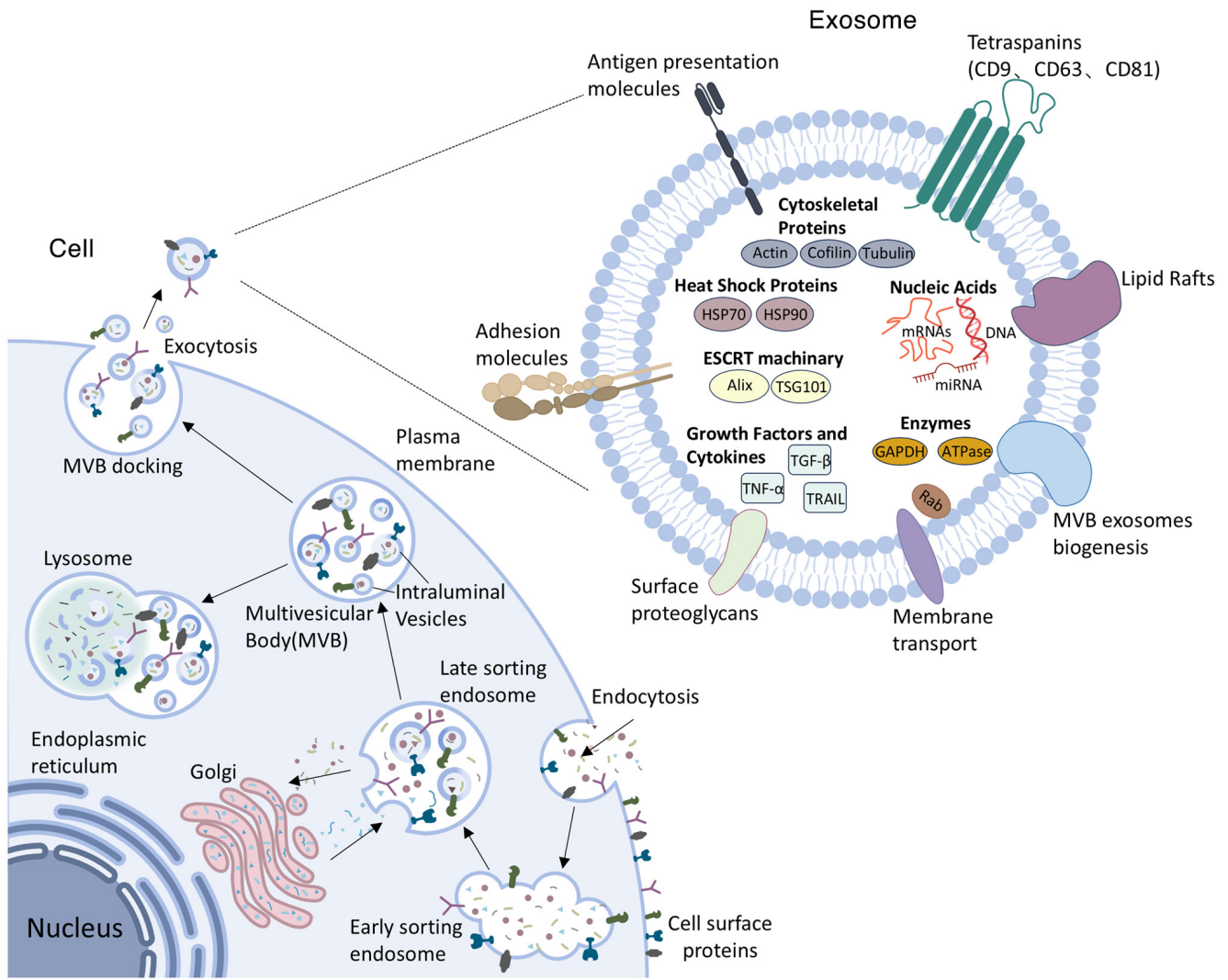


Figure 1. Biogenesis and cargo composition of exosomes. Initially, the plasma membrane invaginates, leading to the formation of early endosomes in the cytoplasm. These mature into late endosomes and a second invagination generates MVBs containing ILVs, which will eventually become exosomes. MVBs can fuse with lysosomes for degradation or release exosomes through exocytosis. Exosomes are composed of diverse proteins, including tetraspanins, adhesion molecules, cytoskeletal proteins, heat shock proteins, membrane transport proteins as well as nucleic acids such as mRNA, DNA and miRNAs, along with various lipids and enzymes. MVBs, multivesicular bodies; ILVs, intraluminal vesicles; miR/miRNAs, microRNAs; HSP, heat shock protein; ESCRT, endosomal sorting complex required for transport; TSG101, tumor susceptibility gene 101; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; Alix, apoptosis-linked gene 2-interacting protein X; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor- α ; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

effectively inhibit the levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), tumor necrosis factor- α (TNF- α) and monocyte chemoattractant protein-1 in MI mouse heart tissue (55). This effect is mediated through the expression of miR-182-5p, which suppresses Toll-like receptor 4 (TLR4) expression, thus inhibiting the TLR4/NF- κ B signaling pathway (55). Moreover, exosomes secreted by BMSCs with overexpressed miR-182-5p markedly enhance heart function recovery in MI mice, enhancing left ventricular ejection fraction while simultaneously reducing left ventricular end-diastolic pressure compared with normal exosomes (55). In addition, BMSC-Exos can reduce the activity of the nucleotide-binding domain and leucine-rich repeat pyrin domain-containing-3 (NLRP3) inflammasome in a left anterior descending coronary artery ligation mouse model, particularly in the peri-infarct region, by inhibiting inflammatory responses

and pro-apoptotic mechanisms (56). This brings about a decrease in MI size as well as an enhancement of cardiac function (56).

Macrophages participate in the onset, progression and resolution of inflammation after MI. They are categorized into two principal types: Classically activated or pro-inflammatory macrophages (M1) and alternatively activated or anti-inflammatory macrophages (M2) (57). In the early stages following MI, M1 macrophages are recruited to the infarcted myocardial area, exhibiting potent phagocytic capabilities and pro-inflammatory effects. Subsequently, M2 macrophages gradually predominate and are instrumental in the process of resolving inflammation and repairing cardiac tissue (58). BMSC-Exos have been shown to promote M2 macrophage polarization while inhibiting M1 macrophage polarization, thereby alleviating myocardial injury and reducing inflammation after MI. The underlying mechanisms encompass the partial activation

of the AKT1/AKT2 signaling pathway or direct inhibition of the NF- κ B pathway (59,60). Furthermore, BMSCs treated with fibronectin type III domain-containing protein 5 effectively improve exosomal capacity to facilitate the transformation of M1 macrophages to the M2 phenotype, thereby alleviating inflammation following an infarction through the inhibition of the NF- κ B pathway (60).

Autophagy. Autophagy can degrade proteins and organelles that are aged or damaged, converting them into amino acids and fatty acids which are utilized for energy production and recycling purposes (61). However, during severe myocardial ischemia, excessive autophagic flux promotes cell death and impairs cardiac function (62). The modulation of the autophagy process involves at least two signaling pathways: one centered on mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) (63) and the other involving tumor suppressor p53 and Bcl-2/adenovirus E1B 19-kDa interacting protein 3 (Bnip3) (64). Hypoxia leads to a marked upregulation of p53 and Bnip3 expression. In addition, overexpression of p53 further induces Bnip3 expression, increasing autophagic flux and inducing CMCs death (62). Xiao *et al* (62) revealed that miR-125b-5p within BMSC-Exos interferes with the p53/Bnip3 signaling, reducing the microtubule-associated protein 1 light chain 3-II (LC3-II) level while elevating the autophagy receptor P62 expression, thus providing cardioprotection. The authors showed that the benefits associated with BMSC transplantation following MI are partly due to the suppression of autophagy triggered by ischemic conditions (62). Overexpression of miR-301 in BMSC-Exos from MI rats markedly improve cardiac functional indicators, including an elevation in left ventricular ejection fraction and left ventricular fractional shortening, alongside a reduction in both the left ventricular end-diastolic and end-systolic diameters (65). Simultaneously, it reduces the LC3-II/LC3-I ratio in infarcted myocardial tissue and increases the relative expression of P62, effectively inhibiting autophagic processes in CMCs (65). Conversely, Zou *et al* (66) revealed that BMSC-Exos protect the myocardium by promoting autophagy. The authors showed that BMSC-Exos clearly upregulate autophagy-related protein 13 (ATG13) and Bcl-2-interacting protein 1 (Beclin-1) expression and that the autophagy inhibitor 3-methyladenine can reverse this protective effect (66). This indicates that the beneficial influence of BMSC-Exos on CMCs depends on their positive regulation of autophagic flux. A recent study demonstrated that pretreatment with Danshen decoction enhances the therapeutic effects of BMSC-Exos on MI, primarily by promoting CMCs autophagy to reduce infarcted areas and cardiac fibrosis (67). These findings further highlight the value of autophagy regulation in MI therapy.

Apoptosis. Apoptosis is a programmed cell death process. CMCs apoptosis initiates in the myocardial border zone affected by infarction within hours to days after AMI (68). It has been proved that miR-210 and miR-338 in BMSC-Exos can respectively regulate PI3K/AKT and the mitogen-activated protein kinase kinase 2 (MAP3K2)/c-Jun N-terminal kinase (JNK) signaling pathways, reducing apoptosis-related genes expression, including Bcl-2 associated X protein (Bax), Bcl-xL/Bcl-2 associated death promoter and caspase-3, thus

improving cardiac function following MI (69,70). Notably, inducing changes in gene expression of parental BMSCs can affect the apoptosis-suppressing capabilities of BMSC-Exos. For instance, exosomes released from GATA-binding protein-4 (GATA-4)-overexpressing BMSCs have been demonstrated to exhibit improved anti-apoptotic impacts on CMCs compared with control group, while also promoting BMSCs differentiation into CMC-like cells and increasing myocardial vascular density (71). According to Ning *et al* (72), BMSC-Exos with low expression of miR-153-3p enhance the phosphorylation of PI3K, AKT and endothelial nitric oxide synthase, thus reducing ECs and CMCs apoptosis and preventing hypoxic injury. miR-144 in BMSC-Exos is delivered to target cells, activating the PTEN/AKT pathway and exerts anti-apoptotic effects on hypoxic CMCs (73).

Ubiquitination, a crucial post-translational modification process of proteins, has also been shown to contribute to the cardiac protective mechanisms mediated by BMSC-Exos. For example, the itchy E3 ubiquitin ligase carried by BMSC-Exos can mediate the ubiquitination and degradation of apoptosis signal-regulated kinase-1, effectively inhibiting CMCs apoptosis and enhancing their viability, providing new insights for alleviating myocardial injury after MI (74).

Notably, pretreatment strategies further broaden the application prospects of BMSC-Exos in MI therapy. Hypoxic preconditioning of BMSC-Exos markedly upregulated miR-24 expression in myocardial tissue of rats with AMI and downregulated apoptosis-related proteins Bax, caspase-3 and cleaved-caspase-3, resulting in a reduction of the infarct size (75). Under conditions of hypoxic treatment for BMSCs, BMSC-Exos have been shown to reduce CMCs apoptosis by delivering miR-125b-5p and enhance CMCs viability via the miR-873-5p/X-linked inhibitor of apoptosis protein (XIAP) axis regulated by lncRNA-UCA1, thereby facilitating ischemic heart recovery and diminishing infarct size in an MI mouse model (6,76). Moreover, BMSC-Exos preconditioned with Danshen decoction showed superior efficacy in improving cardiac function, morphology, histopathology and CMCs ultrastructure compared with untreated groups (67). This effect involves the suppression of CMCs apoptosis, thus reducing the infarct area and cardiac fibrosis (67).

Angiogenesis. Angiogenesis refers to the biological mechanism through which new blood vessels originated from pre-existing vasculature. The occlusion of blood flow is the direct pathogenic mechanism of MI, whereas vascular reconstruction and the formation of new collateral circulation are critical steps in recovery following MI (77). In an AMI rat model, Teng *et al* (78) revealed the effects of BMSCs on both angiogenesis and anti-inflammatory responses through paracrine mechanisms. Specifically, BMSC-Exos enhance the angiogenic capacity of human umbilical vein endothelial cells (HUVECs), inhibit T-cell proliferation and, furthermore, decrease the size of infarcts, preserve cardiac contraction and relaxation performance and promote blood flow restoration (78). Zheng *et al* (79) showed that miR-29b-3p in BMSC-Exos targets a disintegrin-like metalloproteinase with thrombospondin motifs-16, reducing its expression levels and promoting myocardial angiogenesis and ventricular remodeling. This leads to a reduction in myocardial fibrosis and collagen volume fraction, upregulation of VEGF expression

and increased capillary density, while effectively inhibiting CMCs apoptosis and alleviating MI symptoms in rats (79). A recent study found that hypoxia-inducible factor-1 (HIF-1 α) expression is elevated in MI mice (80). BMSC-Exos preconditioned with Astragaloside IV can target and inhibit HIF-1 α through miR-411, promoting neovascularization. This finding offers a new approach for MI treatment (80).

Fibrosis. Myocardial fibrosis, a significant pathophysiological process following MI, is mainly categorized into replacement fibrosis and reactive fibrosis (81). Replacement fibrosis occurs when CMCs in the infarcted area are replaced by a large number of fibrotic cells, forming scar tissue to prevent ventricular wall rupture (82). By contrast, reactive fibrosis involves the abnormal proliferation of connective tissue in the infarcted and distal myocardial regions, often leading to a decrease in ventricular compliance and increased stiffness (81). In addition, research indicates that BMSC-Exos can inhibit enhancer of zeste 2 polycomb repressive complex 2 subunit to activate high mobility group AT-hook 2 (HMGA2) (83). This action delays the epithelial-mesenchymal transition process and fibrosis progression in the myocardial tissue of MI rats (83). According to Wang *et al.* (84), BMSC-Exos carrying miR-19a/19b reduce the fibrosis area in cardiac tissue of MI mouse models, leading to a reduction in collagen I and collagen III levels in the infarcted myocardium. Notably, BMSC-Exos that overexpress miR-129-5p enhance cardiac performance in MI mice, inhibit cell apoptosis and reduce fibrosis (85). They also decrease high mobility group box 1 (HMGB1) expression and inflammatory cytokines production, further suppressing inflammation (85). It has been demonstrated that BMSC-Exos pretreated with Vericiguat show superior efficacy in AMI therapy (86). Mechanistically, BMSC-Exos pretreated with Vericiguat are enriched with miR-1180-3p, which inhibits the ETS1 signaling, causing a marked suppression in the proliferation and migration of cardiac fibroblasts along with decreased collagen I and collagen III expression (86). Animal experiments have confirmed that Vericiguat-pretreated BMSC-Exos, compared with normal BMSC-Exos, more effectively improve cardiac contractile function and alleviates the extent of fibrosis (86).

To summarize, BMSC-Exos exhibit remarkable potential in the treatment of MI, improving cardiac function through multiple mechanisms, including modulation of oxidative stress, inflammatory response, autophagy, apoptosis, angiogenesis and fibrosis. BMSC-Exos carry various miRNAs, regulating key signaling pathways such as PI3K/AKT, TLR4/NF- κ B, p53/Bnip3 and HIF-1 α , to exert cardioprotective effects. Furthermore, preconditioning strategies, such as hypoxic preconditioning and drug induction, further enhance the cardiac repair function of BMSC-Exos (Fig. 2).

Alleviation of myocardial ischemia-reperfusion injury. MIRI refers to the phenomenon in which damage is exacerbated upon the restoration of blood flow after myocardial tissue ischemia, posing a serious threat to human health (87). During MI, a thrombus occludes a coronary artery, causing severe and extended myocardial ischemia, followed by local necrosis. In clinical interventions, such as thrombolytic treatment or percutaneous coronary intervention to restore blood circulation, ischemia/reperfusion (I/R) injury can occur (87,88).

BMSC-Exos are crucial in alleviating MIRI and enhancing the survival of CMCs.

Oxidative stress. Oxidative stress is a vital pathological mechanism resulting in myocardial injury following reperfusion. It induces excessive ROS production, disrupts the redox balance and triggers CMCs apoptosis, autophagy, inflammation and mitochondrial dysfunction, ultimately resulting in irreversible myocardial damage and heart failure (89). HIF-1 α is recognized as the central transcriptional regulator mediating the hypoxic adaptive response of tissue cells under ischemic conditions (90). A recent study uncovered that miR-101a-3p in BMSC-Exos activates the PI3K/AKT pathway, inhibits pathological autophagy in CMCs (91). It may also alleviate myocardial oxidative stress by inducing upregulation of HIF-1 α , which subsequently enhances SOD production in CMCs and reduces MDA and ROS generation, thereby mitigating myocardial damage in I/R rats and potentiating cardioprotective effects (91). In addition, exosomes can deliver miR-149-5p, let-7c-5p and lncRNA A2M-AS1 molecules, which regulate the fas ligand gene, Wnt/ β -catenin signaling pathway or miR-556-5p/XIAP signaling axis (92,93). This ameliorates oxidative stress in CMCs induced by hypoxia/reoxygenation (H/R) and markedly enhances the protective effects on CMCs. Another study demonstrated that BMSC-Exos reduce lactate dehydrogenase (LDH) and MDA levels in H/R CMCs and increase SOD levels (94). This protective effect results from modulating miR-17-5p expression in CMCs (94). The therapeutic effects of BMSC-Exos alone exhibits limitations, thus exploring methods to enhance their efficacy is crucial. Following pretreatment with Irisin, BMSC-Exos exhibit markedly stronger antioxidant effects compared with the control group (95). They reduce ROS production and inhibit oxidative stress in CMCs after H/R injury (95). This finding provides fresh perspectives for further optimizing cardioprotective strategies of BMSC-Exos.

Inflammation. During myocardial ischemia, CMCs death has already induced inflammation. However, when blood flow and oxygen supply are restored during reperfusion, inflammatory signaling pathways become further activated, exacerbating myocardial injury (87). Research has shown that hypoxia-induced BMSC-Exos with upregulated miR-98-5p reduce TLR4 expression in myocardial tissue and activate the PI3K/AKT signaling pathway (96). This mechanism effectively inhibits I/R injury, downregulates TNF- α , IL-1 β and IL-6 expression, suppresses inflammatory responses and macrophage infiltration, thereby promoting cardiac function recovery (96). BMSC-Exos can also promote MIRI repair by facilitating M2 macrophage polarization. BMSC-Exos carrying specific miRNAs (such as miR-25-3p, miR-182, miR-21-5p and miR-125a-5p) attenuate MIRI by inhibiting the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway or targeting the TLR4/NF- κ B/PI3K/Akt signaling cascade (97-100). These mechanisms induce the polarization of macrophages from the pro-inflammatory M1 state to the anti-inflammatory M2 state, reducing inflammation and promoting myocardial repair. Notably, the miR-125a-5p agomir treatment provides an efficient and safe strategy for utilizing stem cells and exosomes in the therapy of I/R (100).

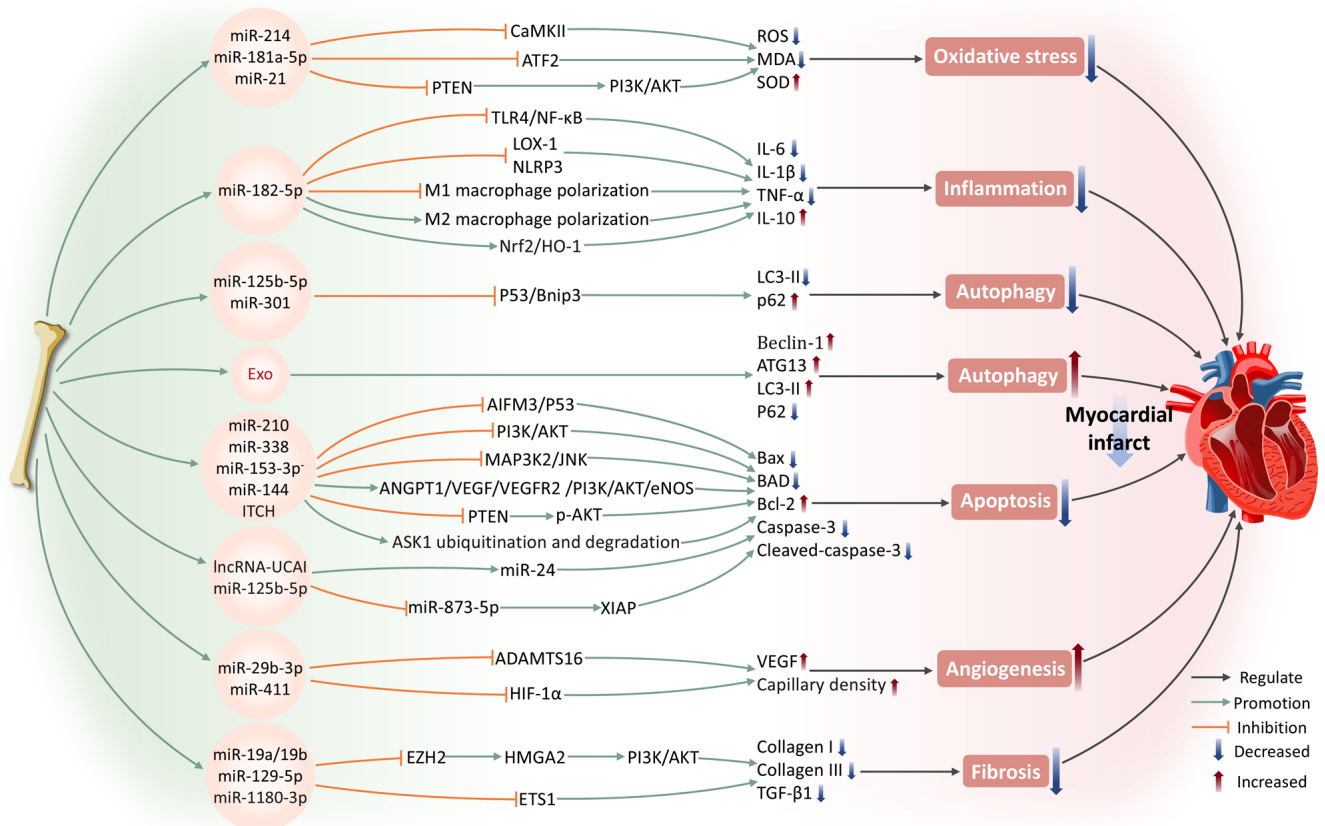


Figure 2. BMSC-Exos ameliorate MI. miR-214, miR-181a-5p and miR-21 in BMSC-Exos can inhibit CaMKII and ATF2 expression, respectively and regulate the PTEN/PI3K/AKT axis, resulting in downregulation of ROS and MDA expression upregulation of SOD and then inhibit MI oxidative stress. In addition, miR-182-5p and other molecules in BMSC-Exos can inhibit MI inflammation by suppressing the TLR4/NF-κB pathway, reducing LOX-1 and NLRP3 inflammasome expression, regulating macrophage polarization, or activating the Nrf2/HO-1 axis, thereby suppressing the release of pro-inflammatory factors while upregulating anti-inflammatory cytokines IL-10 expression. BMSC-derived exosomal miR-125b-5p and miR-301 can suppress p53/Bnip3 signaling, reduce the LC3-II/I ratio and inhibit excessive autophagy. BMSC-Exos can also promote the expression of Beclin-1, ATG13 and LC3-II, while decreasing P62 gene expression to enhance protective autophagy, improving MI. Notably, miR-210, miR-338 and miR-144 in BMSC-Exos can inhibit AIFM3/P53, PI3K/AKT, MAP3K2/JNK and PTEN/AKT signaling pathways, while BMSC-Exos with low expression of miR-153-3p can activate ANGPT1-mediated VEGF/PI3K/AKT/eNOS signaling, thereby inhibiting apoptosis. ITCH carried by BMSC-Exos enhances ASK1 ubiquitination and degradation. BMSC-Exos containing lncRNA-UCA1, miR-125b-5p and others can upregulate miR-24 in CMCs and inhibit apoptosis via the miR-873-5p/XIAP axis, exerting cardioprotective effects. miR-29b-3p and miR-411 in BMSC-Exos target and inhibit ADAMTS16 and HIF-1α, enhance VEGF secretion and increase capillary density, thereby promoting angiogenesis after MI. miR-19a/19b, miR-129-5p, miR-1180-3p and other molecules in BMSC-Exos can inhibit EZH2 to promote HMGA2 expression and activate the PI3K/AKT pathway, or inhibit ETS1 signaling to downregulate collagen I, collagen III and TGF-β1, alleviating cardiac fibrosis. BMSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; MI, myocardial infarction; miR/miRNA, microRNA; CaMKII, calcium-calmodulin-dependent protein kinase II; ATF2, activating transcription factor 2; PTEN, phosphatase and tensin homolog deleted on chromosome ten; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; TLR4, toll-like receptor 4; NF-κB, nuclear factor-κB; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; NLRP3, nucleotide-binding domain and leucine-rich repeat pyrin domain-containing-3; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; Bnip3, Bcl-2/adenovirus E1B 19-kDa interacting protein 3; LC3-II, microtubule-associated protein 1 light chain 3-II; Beclin-1, Bcl-2-interacting protein 1; ATG13, autophagy-related protein 13; AIFM3, apoptosis-inducing factor, mitochondrion-associated 3; MAP3K2, mitogen-activated protein kinase kinase kinase 2; JNK, c-Jun N-terminal kinase; ANGPT1, angiopoietin 1; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; ITCH, itchy E3 ubiquitin ligase; ASK1, apoptosis signal-regulated kinase-1; ADAMTS16, a disintegrin-like metalloproteinase with thrombospondin motifs-16; HIF-1α, hypoxia-inducible factor-1; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HMGA2, high mobility group AT-hook 2; ETS1, ETS proto-oncogene 1; TGF-β1, transforming growth factor-β1.

Apoptosis. During MIRI, apoptosis serves as a critical event in the progression of myocardial injury. Apoptosis not only exacerbates myocardial tissue damage but also leads to a decline in cardiac function. Studies have shown that BMSC-Exos regulate apoptosis during I/R, providing diverse protective effects through the delivery of specific miRNAs. Specifically, BMSC-Exos carrying miR-125b negatively regulate sirtuin 7, downregulating the protein expression of Bax and caspase-3, while upregulating Bcl-2 levels, effectively alleviating MIRI (101). miR-183-5p in BMSC-Exos targets

forkhead box transcription factor O1 (FOXO1) and reduces caspase-3 expression in the I/R rat model (102). Markedly, *in vitro* experiments demonstrated that overexpression of FOXO1 counteracted the protective role of miR-183-5p in CMCs induced by H/R, further confirming the importance of this regulatory pathway (102). A study using both an *in vivo* rat cardiac I/R model and *in vitro* H/R models of cardiac microvascular endothelial cells also demonstrated that BMSC-Exos restore heart function by inhibiting apoptosis (103). The authors revealed that BMSC-Exos promote

microvascular regeneration during stress. They also protect cardiac microvascular endothelial cells from apoptosis and inhibit fibrosis by modulating platelet-derived growth factor receptor- β (103). The PI3K/AKT signaling pathway has a fundamental effect on the regulation of cell survival and apoptosis (104). miR-486-5p in BMSC-Exos inhibits PTEN expression, leading to the activation of the PI3K/AKT pathway, thus suppressing CMCs apoptosis and alleviating MIRI (105). In addition, lncRNA HCP5 inhibits insulin-like growth factor 1 expression via sponging miR-497, thereby activating PI3K/AKT pathway to enhance cell viability and contributing to the attenuation of MIRI (106). According to Yu *et al.* (107), GATA-4-overexpressing BMSC-Exos deliver miR-19a to ischemic myocardium, activating the AKT and extracellular signal-regulated kinase (ERK) signaling pathways to mediate myocardial protection and promote *in vivo* ischemic myocardial repair.

Ferroptosis. Ferroptosis represents a type of programmed cell death induced by lipid peroxidation dependent on iron (108). In recent years, numerous studies have indicated that ferroptosis is another important form of CMCs death. Under myocardial ischemia, iron accumulates extensively within the heart tissue and the elevated iron levels in the myocardium exacerbate I/R injury, ultimately leading to CMCs ferroptosis (109,110). According to Zhang *et al.* (109), BMSC-Exos clearly inhibit CMCs ferroptosis through the RNA-binding protein Pumilio2 (Pum2)/ peroxiredoxin 6 (PRDX6) axis, mitigating cardiac injury caused by I/R and enhancing heart function. Specifically, lncRNA Mir9-3hg is enriched in mouse BMSC-Exos. It downregulates Pum2 expression which is promoting the activation of PRDX6 and demonstrates inhibition of ferroptosis marker proteins such as Acyl-CoA synthetase long-chain family member 4 (ACSL4) in H/R-induced HL-1 mouse cardiac tissue in *in vivo* and *in vitro* experiments (109). Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) is considered a key regulatory pathway in ferroptosis (111). A recent study suggested that GATA-4 overexpression in BMSC-Exos can effectively inhibit H/R-induced CMCs ferroptosis through upregulating miR-330-3p (112). This process involves the regulation of the BRCA1-associated protein 1 (BAP1)/solute carrier family 7a member 11 (SLC7A11)/inositol 1,4,5-triphosphate receptor (IP3R) axis, along with the opening of the mitochondrial permeability transition pore (112). In addition, it may also be related to the H₂S-mediated regulation of the Keap1 signaling pathway, wherein elevated H₂S concentrations lead to reduced Keap1 levels and heightened Nrf2 expression. In *in vitro* experiments, BAP1 downregulates SLC7A11 expression, reversing the inhibitory effect of GATA-4-overexpressing BMSC-Exos on H/R-induced CMCs ferroptosis (112).

In conclusion, BMSC-Exos deliver specific miRNAs and lncRNAs, regulating vital signaling pathways such as PI3K/AKT and Wnt/ β -catenin, effectively inhibiting oxidative stress, inflammatory responses, apoptosis and ferroptosis, thereby demonstrating significant protective effects against MIRI (Fig. 3).

Improvement of AS. AS is a progressive inflammatory disorder that markedly endangers cardiovascular health. Its pathological features primarily include lipid accumulation, fibrous

proliferation and calcium deposition within the vascular structure (113). These changes may eventually lead to hemorrhage, plaque rupture and localized thrombosis, triggering CVDs (114). Regarding the complex pathogenesis of AS, growing evidence suggests that BMSC-Exos exhibit significant potential in mitigating AS progression.

Endothelial cells. Oxidized low-density lipoprotein (ox-LDL) is a critical pathogenic factor in AS (115). It promotes the formation and progression of AS plaques through various mechanisms, including inducing EC activation and dysfunction, promoting foam cell formation in macrophages and the migration and proliferation of smooth muscle cells. (116). ECs dysfunction and damage are widely recognized as primary triggers for AS initiation and progression (117). A study confirmed that BMSC-Exos overexpressing miR-512-3p are internalized by ECs, markedly improving ox-LDL-induced ECs damage (117). miR-512-3p in ECs targets Keap1, inhibiting its expression and increasing Nrf2 protein levels, thereby reducing EC apoptosis and inflammatory responses (117). In addition, BMSC-Exos expressing the lncRNA FENDRR are internalized by HUVECs, regulating miR-28/ TEA domain transcription factor 1 (TEAD1) expression to attenuate HUVECs damage and AS formation (118).

Macrophage function. Macrophages are of pivotal importance in the pathogenesis of AS. They modulate inflammatory signal integration and cell death pathways, particularly necrotic cell death, which aggravates inflammation and facilitates plaque rupture, causing acute cardiovascular incidents (119). BMSC-Exos regulate macrophage function through specific molecular pathways, highlighting their potential for the treatment of AS. Specifically, through the miR-let7/HMGA2/NF- κ B pathway, BMSC-Exos facilitate the polarization of M2 macrophages (120). They also inhibit macrophage infiltration in plaques via the miR-let7/insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1)/PTEN pathway, ameliorating AS pathology in the apolipoprotein E-deficient mouse model (120). Sun *et al.* (121) further reveal that the transport of small interfering RNA (siRNA/si)-LOC100129516 by BMSC-Exos effectively promotes cholesterol efflux while simultaneously inhibiting lipid deposition in foam cells derived from THP-1 macrophages. This effect is facilitated by the activation of the signaling pathway of peroxisome proliferator-activated receptor γ (PPAR γ)/liver X receptor α (LXR α)/ATP-binding cassette transporter A1 (ABCA1), where PPAR γ serves as a cholesterol sensor (122), enhancing cholesterol efflux through the induction of LXR α and ABCA1 transcription (123) and ultimately alleviating AS progression. These results underscore the essential contribution of BMSC-Exos to macrophage regulation and their value for therapeutic application in AS.

Pyroptosis. Pyroptosis is a type of inflammatory cell death that fundamentally relies on the activation of caspase-1 (124). This process involves the formation and activation of inflammasomes, which culminate in the rupture of the cell membrane and the release of cellular contents, triggering a strong inflammatory response (125). Pyroptosis is a key pathophysiological mechanism in AS, contributing to its initiation and progression (126). Therefore, inhibiting pyroptosis is a promising target for both the prevention and treatment of AS. Research indicates that BMSC-Exos alleviate inflammation by blocking

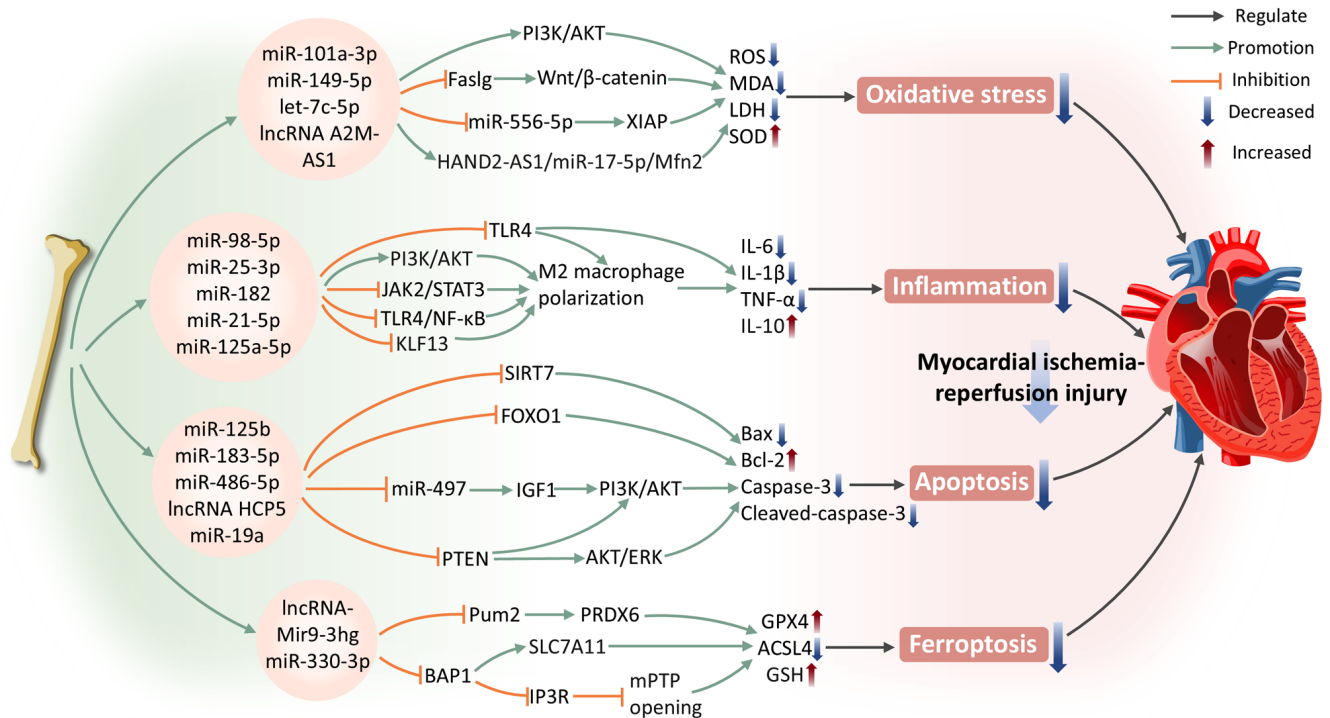


Figure 3. BMSC-Exos alleviate MIRI. miR-101a-3p, miR-149-5p and let-7c-5p in BMSC-Exos can activate the PI3K/AKT signaling pathway or inhibit Faslg, further activating the Wnt/β-catenin pathway, enhancing SOD activity and reducing ROS, MDA and LDH levels. BMSC-derived exosomal lncRNA A2M-AS1 can target miR-556-5p and upregulate XIAP expression, alleviating oxidative damage. BMSC-Exos can also activate the HAND2-AS1/miR-17-5p/Mfn2 pathway to reduce H/R-induced myocardial injury. miR-98-5p in BMSC-Exos suppresses cardiac inflammation by inhibiting TLR4 expression and activating the PI3K/AKT pathway. BMSC-derived exosomal miR-25-3p, miR-182 and miR-21-5p can inhibit JAK2/STAT3 and TLR4/NF-κB signaling while targeting the TLR4/PI3K/AKT pathway, promoting macrophage polarization toward the M2 phenotype. Notably, KLF13 is one of the target genes of miR-125a-5p in BMSC-Exos that promotes M2 macrophage polarization, downregulating IL-6, IL-1β and TNF-α expression and upregulating IL-10 expression to suppress inflammation and improve MIRI. miR-125b, miR-183-5p, miR-486-5p, lncRNA HCP5 and miR-19a in BMSC-Exos inhibit SIRT7, FOXO1 and regulate miR-497/IGF1/PI3K/AKT or PTEN/AKT/ERK signaling pathways, downregulating Bax, caspase-3, cleaved-caspase-3 and upregulating Bcl-2 to inhibit MIRI apoptosis. In addition, the lncRNA Mir9-3hg in BMSC-Exos can alleviate ferroptosis by downregulating ACSL4 expression and upregulating GPX4 and GSH expression through the Pum2/PRDX6 axis. miR-330-3p in BMSC-Exos targets and inhibits BAP1 to regulate the SLC7A11/IP3R pathway and suppress mPTP opening, thereby inhibiting ferroptosis. BMSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; MIRI, myocardial ischemia-reperfusion injury; miR/miRNA, microRNA; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Faslg, fas ligand gene; SOD, superoxide dismutase; ROS, reactive oxygen species; MDA, malondialdehyde; LDH, lactate dehydrogenase; lncRNA, long non-coding RNA; XIAP, X-linked inhibitor of apoptosis protein; Mfn2, mitofusin 2 protein; H/R, hypoxia/reoxygenation; TLR4, toll-like receptor 4; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor-κB; KLF13, Krüppel-like transcription factor 13; TNF-α, tumor necrosis factor-α; SIRT7, sirtuin 7; FOXO1, forkhead box transcription factor 1; IGF1, insulin-like growth factor 1; PTEN, phosphatase and tensin homolog deleted on chromosome ten; ERK, extracellular signal-regulated kinase; Bax, Bcl-2 associated X protein; ACSL4, Acyl-CoA synthetase long-chain family member 4; GPX4, glutathione peroxidase 4; GSH, glutathione; Pum2, RNA-binding protein Pumilio2; PRDX6, peroxiredoxin 6; BAP1, BRCA1-associated protein 1; SLC7A11, solute carrier family 7a member 11; IP3R, inositol 1,4,5-trisphosphate receptor; mPTP, mitochondrial permeability transition pore.

the activation of the NLRP3/caspase-1/gasdermin-D (GSDMD) pathway in aortic tissue pyroptosis, thereby suppressing lipid buildup and inflammatory damage in aortic tissue affected by AS (127). The regulation of macrophage pyroptosis pathways in AS is gaining increasing attention. Lin *et al* (128) first demonstrated that BMSC-derived microvesicles can decrease the vulnerability index of atherosclerotic plaques and the thickness of the intimal layer, decreasing macrophage pyroptosis. The authors revealed that miR-223 carried by BMSC-derived microvesicles mediates this process by inhibiting NLRP3 expression (128). lncRNAs are becoming recognized as key modulators of macrophage pyroptosis pathways in AS. A recent study shows that BMSC-Exos deliver lncRNA AU020206, which obstructs the transcriptional activation of NLRP3 mediated by CCAAT/enhancer-binding protein beta (CEBPB), leading to a reduction in cleaved-caspase-1 and GSDMD expression (129). This process inhibits macrophage pyroptosis and alleviates AS symptom.

To summarize, BMSC-Exos exhibit multiple therapeutic mechanisms in alleviating AS pathological progression by regulating EC and macrophage function, inhibiting apoptosis, inflammation and pyroptosis. These findings not only enhance our comprehension of the function of BMSC-Exos in AS pathophysiology but also provide a foundation for developing novel exosome-based therapies for AS (Fig. 4).

Mitigation of doxorubicin-induced cardiomyopathy. DOX, belonging to the anthracycline class of medications, is commonly employed in cancer treatment (130). Nonetheless, long-term DOX chemotherapy can induce cardiotoxicity, leading to various cardiac complications (131). The mechanism of DIC is complex, primarily involving inflammatory and pyroptosis pathways (132). BMSC-Exos can exert beneficial effects on DIC.

Inflammation. BMSC-Exos modulate the ras-related C3 botulinum toxin substrate 1 (Rac1)/NF-κB pathway by

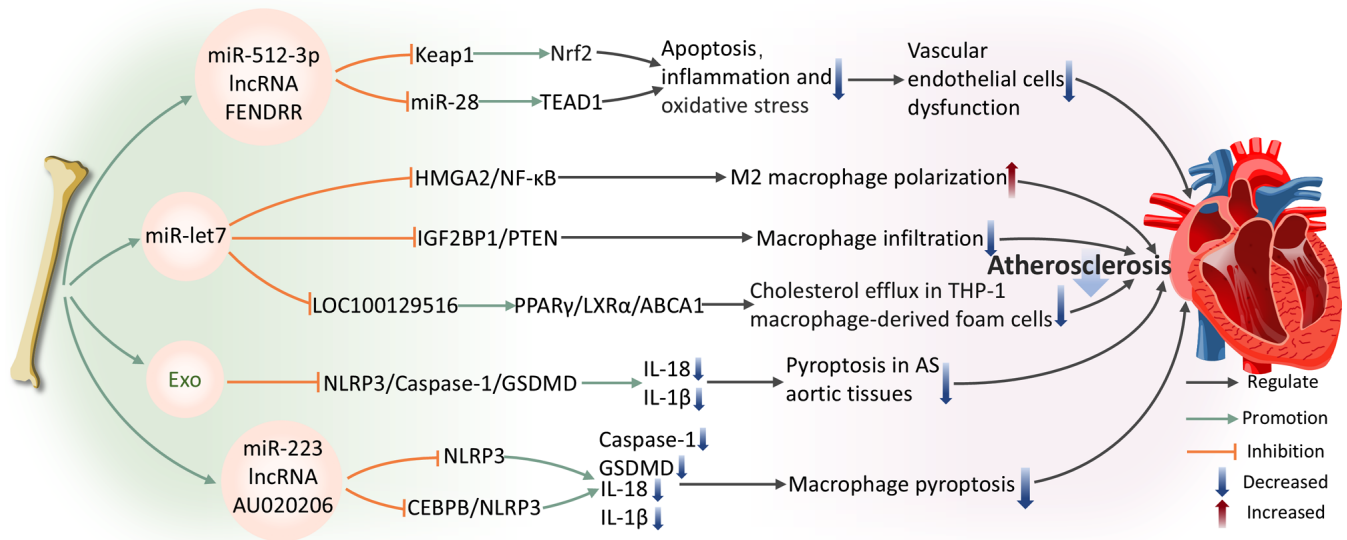


Figure 4. BMSC-Exos improve AS. miR-512-3p and lncRNA FENDRR delivered by BMSC-Exos can inhibit Keap1 and upregulate Nrf2 expression, or interact with miR-28 to regulate TEAD1 expression, respectively, thereby inhibiting AS apoptosis, inflammation and oxidative stress, which alleviates endothelial dysfunction. miR-let7 in BMSC-Exos can inhibit the HMGA2/NF- κ B and IGF2BP1/PTEN signaling pathways, promoting M2 macrophage polarization and suppressing plaque infiltration. Knockdown of LOC100129516 in BMSC-Exos can activate the PPAR γ /LXR α /ABCA1 pathway, enhancing cholesterol efflux from THP-1 macrophage-derived foam cells. miR-223 and lncRNA AU020206 in BMSC-Exos can directly inhibit NLRP3 expression or suppress the CEBPB/NLRP3 axis, downregulating caspase-1 and GSDMD expression and reducing the release of IL-1 β and IL-18, thereby inhibiting AS macrophage pyroptosis. BMSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; AS, atherosclerosis; miR/miRNA, microRNA; lncRNA, long non-coding RNA; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; TEAD1, TEA domain transcription factor 1; HMGA2, high mobility group AT-hook 2; NF- κ B, nuclear factor- κ B; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; PTEN, phosphatase and tensin homolog deleted on chromosome ten; PPAR γ , proliferator-activated receptor γ ; LXR α , liver X receptor α ; ABCA1, ATP-binding cassette transporter A1; NLRP3, nucleotide-binding domain and leucine-rich repeat pyrin domain-containing-3; CEBPB, CCAAT/enhancer-binding protein beta; GSDMD, gasdermin-D.

delivering miR-96 (133). The gene Rac1, which is a target of miR-96, is suppressed by this miRNA, resulting in the downregulation of NF- κ B signaling transduction and protecting myocardium against DOX-induced toxicity (133). In addition, BMSC-Exos reduce pro-inflammatory cytokines (TNF- α , IL-1 β and IL-6) expression and collagen fiber deposition in the myocardium of DOX-treated rats. This suggests their potential to alleviate cardiac inflammation and fibrosis (133). Tian *et al* (134) constructed a DOX-induced CMCs damage model and performed transcriptome sequencing to analyze lncRNA expression in CMCs before and after co-culture with BMSCs. The results revealed that BMSC-Exos deliver multiple lncRNAs, thus inhibiting CMCs inflammatory responses and alleviating DIC. Among these, MSTRG.58791.2 was identified as a potential exosome-derived lncRNA with cardiotoxicity-ameliorating effects (134).

Pyroptosis. Inflammation and pyroptosis are closely interconnected. Pyroptosis, a type of programmed cell death driven primarily by Gasdermin proteins, especially the crucial protein GSDMD, can exacerbate the inflammatory response (119,135). In turn, the inflammatory response can further activate pyroptosis-related signaling pathways, promoting more cells to undergo pyroptosis, thereby creating a vicious cycle that aggravates tissue damage (136). BMSC-Exos phosphorylate FOXO1 and downregulate GSDMD expression by activating the PI3K-AKT pathway, which results in alleviating DOX-induced CMCs pyroptosis (137). Ali and Singla (138) also confirm that BMSC-Exos inhibit the NLRP3 inflammatory cascade mediated by the HMGB1/TLR4 axis, suppress GSDMD activation and reduce pyroptosis, thereby improving

DIC. Notably, compared with exosomes originating from endothelial progenitor cells, BMSC-Exos exhibit superior efficacy in suppressing CMCs pyroptosis and improving DIC (139). This is partly due to the lncRNA GHET1 in BMSC-Exos, which binds to IGF2BP1, inhibiting its transcriptional activity and downregulating NLRP3 expression, thereby effectively improving DIC and pyroptosis (139).

In summary, the protective effects of BMSC-Exos in DIC are primarily achieved by regulating inflammation and pyroptosis-related signaling pathways. They effectively alleviate cardiac damage and provide novel strategies for treating DIC.

Amelioration of other cardiovascular diseases. Heart failure (HF) is a pathophysiological condition characterized by a reduced ability of the heart to pump effectively, causing insufficient cardiac output to fulfill metabolic requirements or systemic venous congestion (140). CMCs hypertrophy is a fundamental pathological feature of HF. According to Chen *et al* (141), BMSC-Exos are capable of alleviating CMCs hypertrophy, inhibiting CMCs apoptosis and reducing fibrosis in a mouse model of myocardial hypertrophy induced by pressure overload. These effects help preserve myocardial structure, delay cardiac remodeling and exert cardioprotective effects (141). In addition, BMSC-Exos reduce apoptosis and inflammation in hypertrophic CMCs, effectively inhibiting HF progression. This mechanism may involve the suppression of the Hippo-YAP pathway (142). Various lncRNAs play key roles in mediating the advantageous impacts of BMSC-Exos. For example, the upregulation of lncRNA GAS5 in BMSC-Exos contributes to alleviating HF by regulating

the UL3/Hippo pathway and inhibiting ferroptosis (143). miR-30e in rat BMSC-Exos can markedly inhibit recombinant lectin-like oxidized low-density lipoprotein receptor 1 expression, downregulating NF- κ B p65/caspase-9 signaling and improving HF post-MI in rats (144). A recent study indicated that BMSC-Exos alleviate inflammation in HF by increasing Krüppel-like factor 4 (KLF4) expression in CMCs (145). In a model of myocardial injury induced by DOX, BMSC-Exos treatment leads to a decrease in levels of inflammatory factors including TNF- α , IL-6 and IL-1 β . KLF4 gene knockout experiments confirmed its role as a core molecular target for exosome-mediated anti-inflammatory effects, offering new avenues for HF treatment (145).

Atrial fibrillation (AF) is a prevalent arrhythmia, with the primary histological feature being atrial fibrosis, which is often caused by extracellular matrix metabolic dysregulation leading to excessive fibrinogen deposition (146,147). Xu *et al* (148) focused on the effect of Nrf2 in AF-specific atrial fibrosis, finding that BMSC-Exos derived from Nrf2-transfected cells effectively inhibit atrial fibrosis and excessive myofibroblast proliferation in AF rats. This mechanism involves the increased expression of Nrf2 and its target, heme oxygenase-1 (148). In another study, miR-148a overexpression in BMSC-Exos alleviates CMCs apoptosis in AF by targeting and suppressing secreted modular calcium-binding protein 2 (149).

Sepsis arises from a dysregulated host reaction to infection, leading to organ dysfunction marked by severe oxidative stress and inflammation (150,151). It can cause endothelial, coagulation and cellular dysfunction, often resulting in cardiovascular impairment (152,153). In this area, BMSC-Exos have also shown potential therapeutic benefits. BMSC-derived exosomal circular RNA RTN4 directly targets miR-497-5p, upregulating the expression of mitsugumin 53 in CMCs, enhancing cell survival rate and mitigating sepsis-induced myocardial injury (154). Moreover, downregulation of miR-141 in BMSC-Exos can reduce PTEN levels and increase β -catenin expression (155). This suggests that miR-141 may alleviate CMCs apoptosis and myocardial injury through the PTEN/ β -catenin signaling cascade, thus reducing myocardial dysfunction in septic mice (155). Notably, a recent study has revealed the unique therapeutic value of Apelin-pretreated BMSC-Exos in sepsis-induced myocardial dysfunction (156). Mechanistically, Apelin-pretreated BMSC-Exos efficiently deliver miR-34a-5p to target and inhibit the HMGB1/AMPK signaling pathway, markedly reducing CMCs pyroptosis (156). This effect has been confirmed to effectively improve cardiac contractile function in mice with sepsis-induced myocardial dysfunction (Fig. 5).

Bone-derived exosomes impair the cardiovascular system. Under specific pathological conditions, bone-derived exosomes can also exert detrimental effects on the cardiovascular system. Pressure overload represents a pathophysiological state of the heart induced by sustained mechanical stress, such as hypertension or aortic stenosis, leading to compensatory myocardial hypertrophy and interstitial fibrotic remodeling (157). Initially manifesting as adaptive myocardial thickening, prolonged overload results in pathological cardiac remodeling characterized by CMCs apoptosis, excessive extracellular matrix deposition and aberrant activation of

myofibroblasts, ultimately progressing to systolic dysfunction and HF (158). Ranjan *et al* (8) demonstrate that under pressure overload conditions, small EVs derived from inflammatory BM fibrogenic progenitors exacerbate cardiac fibrosis through the miR-21a-5p/ITGAV/collagen type I α 1 (Col1 α) signaling pathway. The core mechanism involves miR-21a-5p-mediated upregulation of ITGAV expression, enhancing its interaction with Col1 α and thereby irreversibly transforming fibroblasts into contractile myofibroblasts (8). Notably, inhibition of miR-21a-5p in small EVs markedly attenuates pressure overload-induced cardiac fibrosis and improves cardiac function (8). This finding suggests miR-21a-5p as a promising molecular target for developing miRNA-modified small EVs therapies to treat hypertrophic cardiac remodeling and HF.

In summary, bone-derived exosomes serve as vehicles for miRNAs, lncRNAs and other biomolecules that markedly influence the regulation of various CVDs by suppressing pathophysiological processes including oxidative stress, inflammation, apoptosis and pyroptosis. However, under specific pathological conditions, the exosomes may conversely induce detrimental effects on the cardiovascular system. Importantly, beyond BMSC-Exos, other bone-derived exosomes such as those from cortical bone stem cells exhibit distinct cardioprotective properties (159). They promote cardiac repair by inhibiting fibroblast activation and reducing scar formation (159). However, current understanding of the mechanisms underlying non-BMSC-Exos in the cardiovascular system remains limited, necessitating broader investigations to advance knowledge in this field. These discoveries not only uncover the complex regulatory mechanisms of bone-derived exosomes in the cardiovascular system but also offer novel strategies and perspectives for CVDs treatment.

4. The effect of cardiovascular-derived exosomes on bone

Positive regulation of bone homeostasis. ECs are a layer of flat epithelial cells that cover the inner surfaces of the heart, blood vessels and lymphatic vessels (160), with functions such as regulating vascular tone, maintaining vascular structure and participating in inflammatory responses (161). During the last several years, the expanding body of literature has highlighted the important role of exosomes secreted by ECs (EC-Exos) in maintaining bone homeostasis.

Osteoporosis (OP) is a systemic skeletal disease marked by a decline in bone mass and deterioration of the bone microarchitecture, often causing increased bone fragility and an elevated risk of fractures (162). It is a primary clinical issue in aging populations. Research has demonstrated that EC-Exos possess effective bone-targeting capabilities and hold promise for treating OP (163). *In vivo*, EC-Exos precisely deliver miR-155 to macrophages derived from bone marrow, inhibiting osteoclast activity (163). This clearly slows the pathological progression of OP in ovariectomized mouse models, resulting in a marked increase in bone mineral density (BMD) and bone volume per total volume (BV/TV) compared with the control group (163). This finding not only validates the natural ability of EC-Exos to target bone tissue but also shows their capacity to impede osteoclastogenesis *in vitro* and decrease bone resorption in animal models, revealing their unique advantages over osteoblasts and BMSC-Exos. In

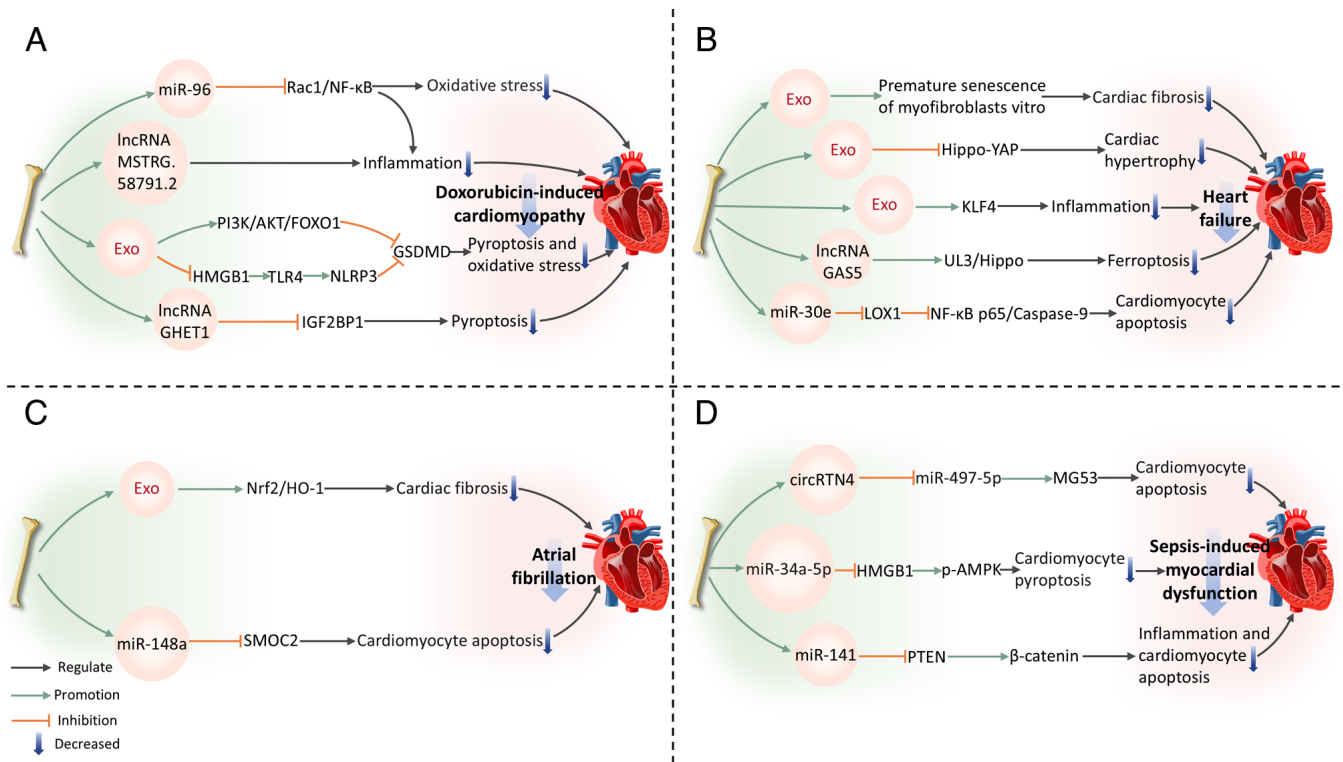


Figure 5. BMSC-Exos ameliorate other CVDs. (A) BMSC-Exos alleviate DIC. miR-96 carried by BMSC-Exos targets and inhibits the Rac1/NF- κ B signaling axis, suppressing oxidative stress and inflammation. lncRNA MSTRG.58791.2 in BMSC-Exos can inhibit inflammation. BMSC-Exos can also regulate the PI3K/AKT/FOXO1 and HMGB1/TLR4/NLRP3 pathways, reducing GSDMD expression and inhibiting DOX-induced CMCs pyroptosis and oxidative stress. lncRNA GHET1 in BMSC-Exos targets IGF2BP1 to reduce NLRP3 mRNA stability, ameliorating DOX-induced CMCs pyroptosis. (B) BMSC-Exos mitigate HF. BMSC-Exos can exert anti-fibrotic effects, inhibit CMCs hypertrophy and suppress inflammation by inducing myfibroblast senescence, inhibiting the Hippo-YAP signaling axis, or enhancing KLF4 expression. (C) BMSC-Exos improve AF. Nrf2-overexpressing BMSC-Exos can reduce cardiac fibrosis through the Nrf2/HO-1 pathway. miR-148a carried by BMSC-Exos targets and binds to SMOC2 mRNA to inhibit its expression, thereby suppressing CMCs apoptosis. (D) BMSC-Exos alleviate sepsis-induced myocardial dysfunction. CircRTN4, miR-34a-5p and miR-141 carried by BMSC-Exos can inhibit CMCs apoptosis by interacting with miR-497-5p to upregulate MG53, regulating the HMGB1/AMPK signaling pathway to reduce CMCs pyroptosis and binding and inhibiting PTEN expression to activate the β -catenin signaling axis, thereby alleviating inflammation and CMCs apoptosis. BMSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; CVDs, cardiovascular diseases; DIC, doxorubicin-induced cardiomyopathy; miR/miRNA, microRNA; Rac1, ras-related C3 botulinum toxin substrate 1; NF- κ B, nuclear factor- κ B; lncRNA, long non-coding RNA; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; FOXO1, forkhead box transcription factor 1; HMGB1, high mobility group box 1; TLR4, toll-like receptor 4; NLRP3, nucleotide-binding domain and leucine-rich repeat pyrin domain-containing-3; GSDMD, gasdermin-D; DOX, doxorubicin; CMCs, cardiomyocytes; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; HF, heart failure; KLF4, Krüppel-like factor 4; AF, atrial fibrillation; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; SMOC2, secreted modular calcium-binding protein 2; circRNA, circular RNA; MG53, mitsugumin 53; AMPK, AMP-activated protein kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten.

a glucocorticoid dexamethasone-induced OP mouse model, researchers found that EC-Exos slow disease progression by preventing apoptosis and ferroptosis of osteoblasts induced by dexamethasone (164). This restores BMD and BV/TV in OP mice, although the specific exosomes components remain unidentified (164). A recent study also revealed the synergistic effect between EC-Exos and curcumin in preventing OP (165). Mechanistically, miR-3p-975_4191 targets tumor necrosis factor and directly regulates the differentiation of BMSCs, promoting osteogenic differentiation while inhibiting adipogenic differentiation (165). The combined intervention of EC-Exos and curcumin leads to enhanced therapeutic effects.

Osteonecrosis of the femoral head (ONFH) is a prevalent and refractory disorder in orthopedics, often leading to structural degradation and collapse of the femoral head (166). In a steroid-induced femoral head ischemic necrosis model, Wu *et al* (167) found that through the activation of the MAPK/ERK pathway, VEGF-modified vascular EC-Exos can promote the differentiation of osteoblasts while concurrently

inhibiting adipogenic differentiation of BMSCs, thus accelerating bone tissue regeneration and repair. The Wnt signaling pathway is a vital regulatory mechanism in bone development. In the classical Wnt/ β -catenin pathway, when Wnt ligands bind to receptors, they inhibit the activity of the β -catenin degradation complex (168). β -catenin levels rise and it translocates into the nucleus, where it binds with T-cell factors and lymphoid enhancer-binding factors to activate downstream gene transcription (168). However, in bone diseases, Wnt signaling is disrupted or blocked by various molecules such as the Dickkopf (DKK) protein family, Kremen and sclerostin (169). A study shows that EC-Exos overexpressing miR-27a can target DKK2 in osteoblasts and reduce its expression, relieving the suppressive effect of DKK2 on the Wnt pathway, thereby facilitating osteogenesis and improving glucocorticoid-induced ONFH (170).

Furthermore, Cheng *et al* (171) conducted a thorough analysis of how circulating exosomes mediate the function of miRNAs between ischemic hearts and BM in mice. After AMI, circulating exosomes become the main carriers of

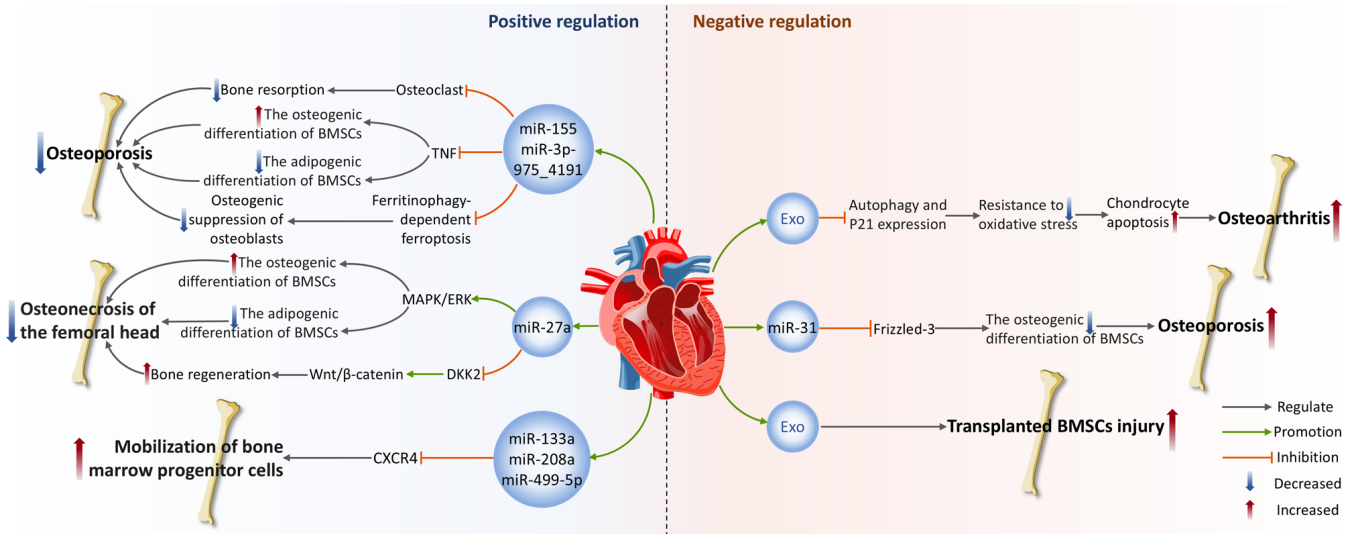


Figure 6. Cardiovascular-derived exosomes regulate the bone. Cardiovascular-derived exosomes exhibit a dual role in regulating skeletal diseases. Positive regulation: Cardiovascular-derived exosomal miR-155 and miR-3p-975_4191 can inhibit osteoclast activity and reduce bone resorption, inhibit TNF to regulate BMSC differentiation, suppress adipogenic differentiation and promote osteogenic differentiation to prevent the development of osteoporosis. Cardiovascular-derived exosomes can also inhibit osteoblast suppression by suppressing ferritin autophagy-dependent ferroptosis. Cardiovascular-derived exosomal miR-27a and other molecules can activate the MAPK/ERK pathway to promote BMSC osteoblast differentiation and inhibit adipogenic differentiation, or directly target DKK2 and activate the Wnt/ β -catenin signaling pathway to promote bone formation and improve femoral head necrosis. Moreover, miR-133a, miR-208a, miR-499-5p and other miRNAs in cardiovascular-derived exosomes can target bone marrow mononuclear cells, downregulating CXCR4 expression and mobilize progenitor cells to participate in bone remodeling. Negative regulation: Cardiovascular-derived exosomes reduce chondrocyte resistance to oxidative stress and induce apoptosis by inhibiting autophagy and p21 expression, thus promoting the progression of OA. Cardiovascular-derived exosomes can act on mesenchymal stem cells, accelerating BMSC damage in MI heart transplants. miR/miRNA, microRNA; TNF, tumor necrosis factor; BMSC, bone marrow mesenchymal stem cell; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase; DKK2, dickkopf 2; CXCR4, CXC motif chemokine receptor type 4; OA, osteoarthritis; MI, myocardial infarction.

specific myocardial miRNAs, including miR-133a, miR-208a and miR-499-5p (171). These miRNAs selectively enter peripheral organs, especially BM, where they reduce the CXC motif chemokine receptor type 4 (CXCR4) expression in BM cells, mobilizing BM progenitor cells and promoting their proliferation, thus coordinating the body's systemic response to myocardial injury (171).

Negative regulation of bone homeostasis. However, some cardiovascular-derived exosomes also exhibit negative regulatory effects on bone homeostasis. Yang *et al* (172) discovered through *in vivo* and *in vitro* experiments that EC-Exos inhibit autophagy and the multifunctional cellular protein p21 expression, weakening chondrocyte resistance to oxidative stress. This leads to a rise in ROS levels and induces apoptosis, thus aggravating the progression of osteoarthritis (OA) (172). A clinical study found that older adults and OP patients exhibited increased plasma levels of miR-31, with aging ECs being a potential source of secretion (173). miR-31 is secreted in microvesicles derived from aging ECs and absorbed by mesenchymal stem cells. It hampers osteogenic differentiation by downregulating the expression of its target gene, Frizzled-3 and enhances osteoclast activity, leading to bone loss and decreased BMD (173). Oxidative stress damage is a significant pathological feature of tissue injury following MI. Stem cell-based therapies offer a promising approach for repairing and regenerating the harmed cardiac tissue. Researchers collected exosomes released from hydrogen peroxide (H_2O_2)-treated CMCs and co-cultured them with BMSCs exposed to H_2O_2 , to simulate the severe microenvironment

encountered by CMCs or transplanted BMSCs after MI (174). The results showed that oxidative stress promoted CMCs to secrete exosomes and exosomes derived from H_2O_2 -pretreated CMCs accelerated BMSCs damage and apoptosis under oxidative stress (174). This finding provides a possible strategy to improve the survival rate of implanted BMSCs after MI.

In summary, cardiovascular-derived exosomes exert multifaceted regulatory effects on bone homeostasis, with distinct functional effects mediated by their specific cargo compositions. Current evidence demonstrates that under skeletal disease conditions, certain cardiovascular-derived exosomes exert protective effects by precisely delivering miRNAs to regulate cellular differentiation, indicating significant therapeutic potential for OP and ONFH. However, under sustained pathological microenvironments such as aging or oxidative stress, cardiovascular-derived exosomes may negatively regulate bone homeostasis by suppressing osteogenesis while enhancing osteoclast activity, thereby exacerbating OA progression. Other cardiac cell types (such as fibroblasts and inflammatory cells) also secrete substantial amounts of exosomes, yet their specific effects on the skeletal system remain unexplored. Consequently, future investigations should elucidate the potential regulatory roles of these cell-specific exosomes in bone homeostasis (Fig. 6).

5. The effect of skeletal muscle-derived exosomes on the cardiovascular system

Protection of cardiomyocytes. Duchenne muscular dystrophy (DMD) is an X-linked recessive genetic disease resulting

from mutations in the dystrophin gene (175), often affecting the heart. Common cardiovascular complications include dilated cardiomyopathy, arrhythmias and congestive heart failure (176,177). Studies by Su *et al* (178-180) reveal the capability of exosomes derived from myogenic progenitor cells (MPC-Exos) in cardiac protection in DMD. MPC-Exos carry mRNA encoding dystrophin. Transplantation of MPC-Exos can enhance dystrophin gene expression in the cardiac tissue of mdx mice, improving heart function (178). They also show significant anti-apoptotic and anti-inflammatory properties by downregulating MAPK8 and IL-6 expression levels and upregulating Bcl-2 levels, providing new insights into the cardiac protection mechanisms in DMD (180).

In addition, the positive effects of remote ischemic conditioning (RIC) during HF have also garnered attention. Myocardial ischemia is a frequent contributor to HF. The core mechanism of RIC therapy is that it activates the body's endogenous protective pathways through brief, repeated I/R stimuli applied to distant limbs, thus providing systemic protection to the heart (181). Homme *et al* (5) induced cardiopulmonary heart failure in mice by constructing an aorta-vena-cava fistula and used hind-limb RIC as a treatment method. The authors found that RIC induced the release of skeletal muscle-derived exosomes containing musclin and myokines. These exosomes can alleviate HF in mice and protect CMCs (5). This provides further evidence of the skeletal endocrine function mediated by exosomes in regulating heart function. Exosomes derived from skeletal myoblasts pretreated with hypoxia may play a role in conveying protective signals produced by RIC in distant limbs to the targeted tissues. These exosomes promote connexin 43 expression in ventricular muscles, improving ventricular myocardial conduction and reducing reperfusion arrhythmias under the condition of hypothermic I/R (182).

Promotion of cardiomyocyte apoptosis. In some cases, skeletal muscle-derived exosomes may have detrimental effects on the heart. Sarcopenia is a disease characterized by the gradual decline of skeletal muscle, causing a decrease in both muscle mass and functionality (183). It is closely associated with negative consequences, including increased fall risk, functional decline, frailty and higher mortality rates (184). Sarcopenia-induced cardiac cachexia has been noted to be connected to poor cardiac prognosis (7). In MI patients, concomitant HF often delays the transition from bed rest to early activity, causing a decline in life quality and reduction in skeletal muscle mass, eventually inducing sarcopenia (7,185). Sarcopenia has significant adverse effects on heart disease patients with skeletal muscle loss, which can lead to cardiac cachexia. This process is often accompanied by disturbances in nutrition and metabolic functions, thereby forming a malignant cycle that results in continuous deterioration of heart function (186-188). Hayasaka *et al* (7) induced skeletal muscle atrophy in mice after I/R by continuous tail suspension and further revealed the potential mechanisms of impaired cardiac repair associated with sarcopenia. The authors found that sarcopenia following I/R interfered with cardiac recovery and increased miR-16-5p levels in circulating exosomes secreted by the atrophied limbs and hearts of continuously tail-suspended mice (7). miR-16-5p directly inhibits sestrin 1 transcription, activating mTOR signaling, which subsequently

promotes CMCs apoptosis and exacerbates impaired cardiac repair (7). This suggests that the pro-apoptotic effect of miR-16-5p derived from sarcopenia might contribute to the deterioration of MI.

Collectively, skeletal muscle-derived exosomes exhibit a dual role in cardiac health regulation. They can promote cardiac protection and functional recovery, promote angiogenesis and optimize cardiac blood supply by delivering therapeutic miRNAs and other active molecules to regulate the relevant signaling pathways. However, they can also induce CMCs apoptosis, exacerbating impaired cardiac repair. Therefore, precise regulation and rational use of skeletal muscle-derived exosomes are essential in CVDs treatment.

6. The effect of cardiovascular-derived exosomes on skeletal muscle

Improvement of skeletal muscle injury and promotion of regeneration. Cardiovascular-derived exosomes can be delivered to skeletal muscle tissue via peripheral circulation, where they interact with skeletal muscle cells, thereby regulating skeletal muscle physiological functions. Cardiac-derived progenitor cells (CDCs) possess properties that are anti-inflammatory, antioxidant, anti-fibrotic and cardiogenic (189). Rogers *et al* (190) found that CDCs can improve the functionality of both cardiac and skeletal muscles in DMD mice and enhance skeletal muscle regenerative capacity. Further research showed that CDCs secrete exosomes that deliver miR-148a to skeletal muscle, promoting muscle regeneration (190). In another DMD animal study, researchers directly injected CDC-derived exosomes into the soleus muscle of mdx mice and observed a rise in the total quantity of muscle fibers with a shift in size distribution toward a smaller diameter and this phenomenon was not influenced by the insulin-like growth factor 1 receptor. Simultaneously, with enhanced muscle regeneration, CDC-derived exosomes injection reduced skeletal muscle inflammation and fibrosis and increased contractile force (9). On the other hand, research has demonstrated that mechanical stress, under both *in vitro* hypotonic conditions and *in vivo* pressure overload, induces CMCs to release exosomes carrying angiotensin II type 1 receptor (AT1R). Skeletal muscle cells are one of the target cells, thus regulating the vascular response to neurohormonal stimulation (191). This finding provides strong evidence for the crosstalk between the cardiovascular system and skeletal muscle.

Induction of skeletal muscle atrophy. A class of miRNAs specifically expressed in muscle tissue is called myomiRs (192). The majority of myomiRs, such as miR-1, miR-133a and miR-499, are present in both skeletal muscle and myocardium. By contrast, miR-206 is exclusive to skeletal muscle and miR-208a is exclusive to myocardium (192,193). In HF-related studies, a series of specific miRNAs frequently appear (194), including miR-1, miR-21, miR-24, miR-29b, miR-133a and b, miR-199, miR-208, miR-214 and miR-499. Notably, most of these miRNAs belong to the sequences of myomiRs and they change in the cardiac tissue of HF patients with various causes and severity. This not only reveals the complexity of the pathological mechanisms of HF but also

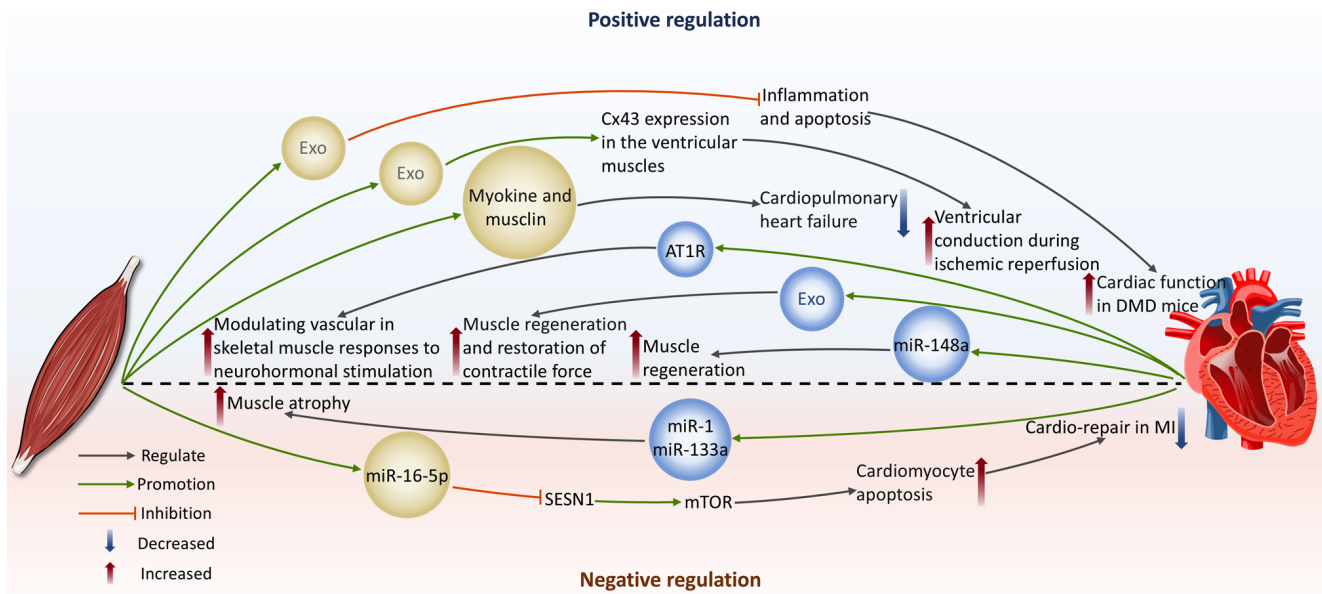


Figure 7. Exosome-mediated crosstalk between skeletal muscle and cardiovascular system. Skeletal muscle and cardiovascular system exhibit both positive and negative regulatory crosstalk mediated by exosomes. Positive regulation: Skeletal muscle-derived exosomes contain myokine and musclin that can inhibit cardiopulmonary heart failure. Skeletal muscle-derived exosomes can promote the expression of Cx43 in ventricular myocardium, enhance I/R ventricular conduction and inhibit inflammation and apoptosis to improve cardiac function in DMD mice. Cardiovascular-derived exosomal miR-148a promotes muscle regeneration, while AT1R modulates skeletal muscle vascular responses to neurohormonal stimulation. Cardiovascular-derived exosomes can also promote muscle regeneration and the restoration of contractile force. Negative regulation: Skeletal muscle-derived exosomes rich in miR-16-5p directly inhibit SESN1 transcription, leading to mTOR signaling upregulation, promoting CMCs apoptosis and exacerbating repair impairment after myocardial infarction. Cardiovascular-derived exosomal miR-1 and miR-133a can promote muscle atrophy. Cx43, connexin 43; I/R, ischemia/reperfusion; DMD, Duchenne muscular dystrophy; miR/miRNA, microRNA; AT1R, angiotensin II type I receptor; SESN1, sestrin 1; CMCs, cardiomyocytes; mTOR, mechanistic target of rapamycin; MI, myocardial infarction.

strongly suggests that these molecules could serve as important mediators of communication between the cardiovascular and skeletal muscle through the release of miRNA-rich exosomes during the progression of HF. In instances of overload-induced hypertrophy in skeletal muscles, reduced expression levels of miR-1 and miR-133a have been observed (195). Therefore, the increased circulation of miR-1 and miR-133a caused by HF (196) are hypothesized to be important promoting factors of skeletal muscle atrophy after the onset of CVDs (193).

Taken together, cardiovascular-derived exosomes can promote skeletal muscle function improvement and regeneration by delivering beneficial molecules, but they may also transmit HF-related miRNAs that exacerbate skeletal muscle atrophy. These findings reveal the complex effects of cardiovascular-derived exosomes in the pathological progression of skeletal muscle (Fig. 7).

7. Clinical applications of exosome therapy

Diagnostic biomarkers. The ubiquitous distribution of exosomes in biological fluids provides new avenues for diagnosing musculoskeletal diseases and CVDs. Research reveals that compared with men, female OA patients have more differentially regulated miRNAs in their synovial fluid, such as miR-16-2-3p, miR-26a-5p, miR-146a-5p and miR-6821-5p (197). The exosome miRNAs specifically expressed in the synovial fluid of women with OA react to estrogen and influence the TLR signaling pathway. These exosome miRNAs can serve as sex-specific biomarkers for

diagnosing OA (197). In addition, Zhao *et al* (198) mention the potential of lncRNAs in exosomes as OA biomarkers. The authors conducted a comparative analysis of exosome lncRNAs from synovial fluid and plasma to evaluate the progression of OA. The findings indicate that there are no notable discrepancies in the expression of plasma exosome lncRNAs, while the levels of synovial fluid exosome lncRNAs (HOTAIR, PCGEM1 and GAS5) are markedly elevated in both early and late OA patients compared with healthy controls. Notably, the expression of exosome lncRNA PCGEM1 was greater in individuals with late-stage OA relative to those with early-stage OA. For CVDs, exosomal lncRNAs also show potential diagnostic value. Specifically, plasma levels of exosomal lncRNA UCA1 are elevated in AMI patients compared with healthy individuals, suggesting that circulating exosomal lncRNA UCA1 could function as an effective biomarker for diagnosing AMI (76). To develop more efficient biomarkers for effectively monitoring disease onset and progression, it is critical to investigate the sorting mechanisms of exosome contents and their secretions and to clarify their stability levels under different physiological and pathological conditions (199).

Biologically engineered drug delivery vectors. Exosomes have a nanometer-scale size and a lipid bilayer membrane structure that protects bioactive molecules. They can cross cell membranes rapidly and have the advantages of low immunogenicity and toxicity as well as organ-targeting properties, demonstrating tremendous potential as drug delivery vehicles (200). Exosomes can be modified with

the specific ligand, such as hyaluronic acid, enabling the delivery of Forsythoside A-loaded exosomes to recipient cells and forming a targeted ligand-receptor interaction with the cell surface adhesion molecule CD44. This approach enhances the hepatoprotective effect of Forsythoside A against fibrosis (201). Exosomes released by macrophages carrying paclitaxel are capable of specifically targeting cancer cells to deliver the drug, suppressing their proliferation and addressing issues related to multidrug resistance (202). Through bioengineering modifications, the targeting ability and therapeutic efficiency of exosomes are further enhanced. For example, after the modification of surfaces using anti-CD20 monoclonal antibodies, exosomes loaded with zinc oxide nanocrystals can specifically recognize and target lymphoma cells, showing higher cytotoxicity (203). Meanwhile, adipose-derived mesenchymal stem cells (ADSCs), owing to their easy accessibility and unique capacities for self-renewal and differentiation, have been widely applied in targeted therapy for musculoskeletal disorders (including fractures, OP, OA and tendon injuries) through their secreted exosomes serving as nanoscale drug carriers (204). Hydrogels, as ideal delivery vehicles, have been demonstrated to effectively enhance the *in vivo* stability and targeted distribution of MSC-Exos, thereby showing promising applications in regenerative medicine for age-related musculoskeletal diseases (205). In addition, the combined use of exosomes with biological scaffolds can more effectively utilize their unique advantages in drug delivery and tissue repair and reconstruction. A minimally invasive exosome spray composite material integrating MSC-Exos into a fibrin scaffold was designed by Yao *et al* (206). It promotes the retention of MSC-Exos within cardiac tissue, enhancing heart function and angiogenesis in MI mouse models. Subsequent experiments in rat and pig models confirmed that exosomes effectively reduce surgical stress and inflammation, verifying their clinical translation feasibility (206). Chen *et al* (207) designed an extracellular matrix/gelatin methacrylate scaffold to deliver exosomes. Experimental data showed that transplanting exosome-combined scaffolds into a rabbit osteochondral defects model markedly improved cartilage repair efficiency.

Novel therapeutic approaches for tissue repair and regeneration post-injury. Within the domain of regenerative medicine, exosomes have attracted significant attention for their remarkable tissue repair-promoting abilities, as well as their low-risk and high-treatment efficacy advantages compared with traditional stem cell transplantation therapies. Compared with stem cell therapy, exosomes can precisely deliver bioactive molecules to target tissues, improving treatment targeting and efficiency and effectively avoiding immune rejection issues that may be induced by stem cell transplantation, providing novel therapeutic approaches for repair and regeneration following tissue damage. Specifically, BMSC-Exos overexpressing miR-486-5 have been demonstrated to activate the matrix metalloproteinase MMP19 and VEGF signaling pathways, facilitating angiogenesis and decreasing infarct area in a MI monkey model (208). In addition, as mentioned earlier, MSCs and their exosomes can regulate macrophage polarization. With the capacity to swiftly alter their phenotype and

functional traits, macrophages are essential in the process of tissue regeneration (209). For example, in the MI pig model, CDC-derived exosomes reduce infarct myocardial area, which is mediated by the exosomal transfer of miR-181b to macrophages to regulate their polarization (210). In musculoskeletal diseases, amniotic fluid stem cells-derived exosomes promote cartilage formation and inhibit inflammation by mediating M2 macrophage polarization (211). An emerging finding indicates that synovial MSC-Exos preconditioned with growth differentiation factor 5 enhances chondrogenesis through activation of the lysine-specific demethylase 2A/SRY-box transcription factor 2 pathway (212). When combined with digitally light-processed bio-printed scaffolds composed of glycyrrhizic acid/methacrylated-acylated hyaluronic acid, this system achieves sustained-release delivery and promotes articular cartilage regeneration in rat models (212). Tendinopathy ranks among the most prevalent musculoskeletal disorders globally (213). Song *et al* (214) used a rat model with the tendon defect, discovering that exosomes derived from tendon-derived stem cells containing miR-144-3p promote the proliferation and migration of tendon cells by targeting AT-rich interaction domain 1A. Exosomes, owing to their minute size and lipid bilayer structure, can also traverse the blood-brain barrier, target specific cells and regulate pathological processes in neural tissue. It has been reported that BMSC-Exos can stimulate the proliferation of hippocampal neurons and decrease apoptosis in rats through the upregulation of miR-26a, improving symptoms in a depression model (215).

8. Multiple factors influence the therapeutic efficacy of exosomes

The therapeutic effects of exosomes are highly dependent on their cellular origin, administration dosage, frequency and recipient species. In diabetic ulcer mouse models, EVs derived from BMSCs and ADSCs exhibit distinct therapeutic effects on wound healing (216). BMSC-EVs primarily stimulate cell proliferation, whereas ADSC-EVs accelerate wound closure through pro-angiogenic mechanisms (216). A study demonstrated dose-dependent neuroprotective effects of BMSC-Exos in cerebral ischemia models (217). Compared with controls and low-dose groups (80 $\mu\text{g}/\text{rat}$), medium (100 $\mu\text{g}/\text{rat}$) and high-dose (120 $\mu\text{g}/\text{rat}$) BMSC-Exos administration markedly reduces cerebral infarction area and alleviates brain edema, with the highest dose showing most pronounced effects (217). Zhou *et al* (218) found that ADSC-Exos administered three times daily promoted skin wound healing more effectively than single or twice-daily dosing, suggesting increased administration frequency enhances tissue repair. Species-matched exosomes demonstrate superior therapeutic efficacy for ischemic stroke (219). In middle cerebral artery occlusion mouse models, murine cerebral EC-derived exosomes more effectively improve mitochondrial function in recipient cells, reduce infarct volume and decrease neurological deficit scores compared with human-derived exosomes (219). This finding supports using species-matched exosomes in preclinical studies to optimize outcomes. Notably, current exosomal research remains predominantly animal-based, with limited clinical trials. In existing clinical studies, human-derived exosomes (from adipose, BM, or umbilical cord MSCs) and

plant-derived exosomes represent the two most commonly used types (199). Adipose tissue has become a preferred MSC-Exos source due to its accessibility, with applications in seven clinical trials (220). Common administration routes include intravenous infusion, inhalation and local delivery. However, dosage standards vary depending on disease type and administration method, with some studies quantifying exosomes by weight (mg) while others use particle counts or parental cell equivalents as metrics (220).

9. Conclusions

As soluble mediators of intercellular communication, exosomes can load and transport mRNAs, lipids, proteins, miRNAs, lncRNAs and other bioactive molecules to adjacent or distant cells, playing an essential part in intercellular communication. Substantial evidence demonstrates that exosomes play pivotal roles in bone-muscle crosstalk, not only promoting skeletal muscle regeneration and repair (221,222) but also critically regulating bone metabolic homeostasis and remodeling (223,224). However, the mechanisms underlying exosomes-mediated inter-organ communication between the cardiovascular and musculoskeletal systems remain poorly investigated. The present review provided the first comprehensive synthesis of the complex bidirectional regulatory networks mediated by exosomes across these two major systems, encompassing both beneficial effects and potential adverse impacts. BMSC-Exos and other bone-derived exosomes show significant promise for therapeutic applications in CVDs such as MI, I/R, AS and DIC. They provide strong support for cardiovascular repair and regeneration through mechanisms such as modulating oxidative stress, inflammation, autophagy, apoptosis, fibrosis, ferroptosis, pyroptosis and promoting angiogenesis. Nevertheless, under specific pathological conditions, such as pressure overload-induced pathological cardiac remodeling, bone-derived exosomes may also exert detrimental effects on the cardiovascular system. Meanwhile, cardiovascular-derived exosomes also have beneficial effects on bone diseases such as OP and ONFH. However, some exosomes may have negative effects on bones, such as inhibiting osteogenic differentiation or reducing bone mineral density. On the other hand, skeletal muscle-derived exosomes provide new therapeutic perspectives for CVDs recovery through mechanisms such as promoting angiogenesis. However, these exosomes also have adverse effects, such as promoting CMCs apoptosis. In addition, cardiovascular-derived exosomes exhibit positive effects on skeletal muscle regeneration and repair, but under pathological conditions such as HF, some exosomes may induce skeletal muscle atrophy, leading to adverse consequences.

Although exosome-based therapies have broad prospects, several challenges still need to be overcome. First, the extraction, purification and identification techniques for exosomes still need further improvement. There is a need for rapid and inexpensive methods, as well as straightforward, standardized processes for separation and purification, to achieve high yields of exosomes with high purity. Second, the specific molecular mechanisms by which exosomes implement their reparative and protective functions remain inadequately elucidated and their long-term therapeutic effects are still in the exploratory

stage. Exosomes derived from various tissues contain different bioactive molecules, thus generating varying degrees of reparative effects in different disease injuries. Finally, issues related to the stability, targeting ability and biosafety of exosomes *in vivo* need to be thoroughly investigated. These challenges may be addressed through tissue engineering approaches to functionally optimize exosomes by modifying their surface properties and drug-loading capacity, thereby enhancing their therapeutic efficacy and expanding potential clinical applications. Currently, the complete understanding of exosomal biodistribution, metabolism and immunogenicity remains lacking and appropriate animal models for evaluating the required medicine concentration and duration of its effectiveness for large-scale manufacturing are unavailable. Future research should encompass a broader spectrum of *in vivo* studies and clinical trials, with the objective of evaluating the safety and efficacy of drug formulations based on exosomes.

In conclusion, exosomes serve significant functions that contribute to the crosstalk between the cardiovascular and musculoskeletal systems, showing great potential and application prospects in addressing CVDs and musculoskeletal-related diseases. As investigations into exosomes deepens, those released from cultured cells are anticipated to emerge as novel, efficient and versatile drug carriers, driving innovative development in drug delivery systems, tissue engineering, as well as regenerative therapies. This will further unveil their roles in intercellular communication and disease mechanisms, contributing to human health.

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Availability of data and materials

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Authors' contributions

QL was responsible for conceptualization, investigation, methodology, writing the original draft and illustration. HG was responsible for conceptualization, investigation, software, writing the original draft, illustration, reviewing and editing. XM was responsible for writing the original draft, reviewing and editing. ZW was responsible for illustration, reviewing and editing. LZ was responsible for conceptualization, reviewing and editing. WX was responsible for funding, supervision,

visualization, reviewing and editing. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors used ChatGPT to improve readability and language quality. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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