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REVIEW

Mesenchymal Stem Cell-Derived Exosomal Noncoding RNAs as Alternative Treatments for Myocardial Ischemia-Reperfusion Injury: Current Status and Future Perspectives

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Abstract

Ischemic cardiomyopathy is treated mainly with thrombolytic drugs, percutaneous coronary intervention, and coronary artery bypass grafting to recanalize blocked vessels. Myocardial ischemia-reperfusion injury (MIRI) is an unavoidable complication of obstructive revascularization. Compared with those of myocardial ischemic injury, few effective therapeutic options are available for MIRI treatment. The pathophysiological mechanisms of MIRI involve the inflammatory response, the immune response, oxidative stress, apoptosis, intracellular Ca^{2+} overload, and cardiomyocyte energy metabolism. These mechanisms exacerbate MIRI. Mesenchymal stem cell-derived exosomes (MSC-EXOs) can alleviate MIRI through these mechanisms and, to some extent, prevent the limitations caused by direct MSC administration. Therefore, using MSC-EXOs instead of MSCs to treat MIRI is a potentially beneficial cell-free treatment strategy. In this review, we describe the mechanism of action of MSC-EXO-derived noncoding RNAs in the treatment of MIRI and discuss the advantages and limitations of this strategy, as well as possible future research directions.

Keywords Mesenchymal stem cells · Exosomes · Myocardial ischemia-reperfusion injury · Oxidative stress · Inflammation · Regulated cell death · ncRNAs

Introduction

The concept of myocardial ischemia-reperfusion injury (MIRI) was first introduced by Jennings et al. [1] in 1960. MIRI is characterized by a pathological process in which local myocardial tissue is normally perfused after recanalization of obstructed coronary vessels for a certain period of time, but myocardial damage increases and exceeds the damage caused by simple myocardial ischemia (MI) [2]. MIRI is an unavoidable complication after reperfusion therapy. Currently, effective countermeasures against MIRI are lacking [3]. Reperfusion therapy not only exacerbates damage to ischemic myocardial tissue but also causes further damage to previously uninvolved myocardial tissue [4]. In addition, reperfusion-induced injury can account for up to 50% of overall myocardial injury, frequently resulting in serious adverse outcomes [4]. MIRI usually causes conditions such as fatal arrhythmias, heart failure, and even sudden cardiac death [5]. Up to 10% of patients with acute myocardial infarction (AMI) die due to MIRI even after early reperfusion therapy [5]. MIRI involves multiple pathological mechanisms, including oxidative stress, inflammation, metabolic disruption, mitochondrial damage, and regulated cell death (RCD) [6, 7]. In recent years, mesenchymal stem cell-derived exosomes (MSC-EXOs) have shown tremendous potential in the treatment of diseases.

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Mesenchymal stem cells (MSCs) are derived from the early developmental mesoderm and are pluripotent stem cells with self-renewal and multidirectional differentiation capabilities [8]. MSCs can be differentiated into adipose, muscle, bone and cartilage cells under specific conditions in vivo and in vitro [9]. Furthermore, MSCs mainly exert immunomodulatory effects on innate and adaptive immune cells [10]. However, the direct application of MSCs has some limitations, such as the introduction of damaged cells, low-temperature storage and transport, and ethical concerns. Interestingly, numerous studies have shown that the pleiotropy of stem cells is closely associated with soluble factors and paracrine secretion but not their differentiation capacity [11, 12]. The efficacy of stem cell therapy is largely dependent on exosomes released through stem cell paracrine effects, and MSCs are the preferred source of exosomes [8]. MSC-derived exosomes MSC-EXOs preserve the therapeutic properties of MSCs while overcoming the limitations of using live MSCs [13]. Exosomes are membrane-enclosed extracellular vesicles 30-150 nm in diameter [14]. The term "extracellular vesicles" describes different types of membrane-bound vesicles, including exosomes, microvesicles, and apoptotic vesicles. These vesicles are formed by the invagination of intracellular lysosomal particles and are released into the extracellular space through fusion of the outer membrane of the multivesicular body with the cell membrane [15]. Exosomes can carry multiple types of molecules, such as proteins, lipids and noncoding RNAs (ncRNAs), which are required for various physiological and pathological processes [16, 17]. Exosomes may act on target cells through three mechanisms: (1) fusion with the plasma membrane, (2) endocytosis, and (3) the activation of target cells by specific surface ligands [18]. Recently, numerous studies have shown that MSC-EXOs are closely associated with various human diseases, such as autoimmune diseases, hematological diseases, cancer, neurodegenerative diseases, and coronavirus disease 2019 [19–23]. In addition, MSC-EXOs have shown great potential as adjuvant therapies for not only MI but also MIRI [24]. Notably, MSC-derived exosomal ncRNAs show therapeutic potential in MIRI [24–26].

The transcription of the human genome produces a large number of noncoding RNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), in addition to ribosomal RNAs and transfer RNAs [27]. MiRNAs are commonly found in eukaryotic organisms and are approximately 20 nt in length [28]. In 1993, Lee et al. [29] first demonstrated that the miRNA lin-4 regulates the translation of lin-14 through antisense RNA-RNA interactions. There are many types of miRNAs, and one miRNA can target multiple messenger RNAs (mRNAs) to regulate gene expression [30]. LncRNAs are more than 200 nt in length and can regulate gene expression at multiple levels [31]. The internal regulatory mechanism of ncRNAs is complex, and lncRNAs can function as molecular sponges of miRNAs to regulate the expression and function of mRNAs of target genes through a competing endogenous RNA network [32]. CircRNAs constitute a class of endogenous closed-loop RNA molecules that are produced mostly by reverse splicing of precursor mRNA exons, and similar to lncRNAs, they can function as molecular sponges for miRNAs to regulate gene expression [33]. In addition, circRNAs can function as molecular protein sponges, protein scaffolds, and protein recruiters and can even translated into proteins [34].

Overall, ncRNAs constitute a large and diverse family, and many studies have shown that these factors are closely associated with MIRI [35–37]. In this review, we focus on the mechanism of MSC-EXO-delivered ncRNAs in the treatment of MIRI. In addition, we discuss the advantages and limitations of this strategy and predict future research directions in this field.

MSC-EXO-Derived ncRNAs in MIRI

We have summarized articles on MSC-EXO-derived ncRNA-mediated regulation of MIRI in recent years (Table 1). Notably, recent studies on MSC-EXO-derived ncRNAs have focused on miRNAs, while relatively few studies have directed to other types of ncRNAs (Fig. 1). In this regard, experiments have been conducted mainly with rat and mouse models of I/R or hypoxia/reoxygenation (H/R) and rarely on large animal models or humans. MSC-EXO-derived ncRNAs regulate MIRI through multiple mechanisms such as the oxidative stress response, mitochondrial function, the inflammatory response, the immune response, and RCD. Because studies on the efficacy of MSC-EXO-derived ncRNAs against MIRI are still in an initial stage, more in vivo and in vitro studies are needed to explore the related mechanisms.

MSC-EXO-Derived ncRNAs Attenuate MIRI by Regulating Oxidative Stress

The cardiac dysfunction caused by MIRI can be partially explained by an imbalance between reactive oxygen species (ROS) production and activation of antioxidant defense systems such as superoxide dismutase, catalase, and glutathione peroxidase [7]. Excess ROS act on lipids, proteins, nucleic acids, and other biomolecules, resulting in the loss of cell membrane integrity, changes in protein structure and function, and nucleic acid damage [56]. MSC-EXO-derived ncRNAs can alleviate MIRI by regulating the processes triggered by excessive ROS levels.

Table 1 List of MSC-EXO-derived ncRNAs and their role in MIRI

Ref.	Species	Model	Origin	Component	Target cells	Function
Wang et al. [38]	Rat	Myocardial I/R	BMSCs	miR-126	Cardiomyocytes	Inhibiting ERRFI1 expression to alleviate oxidative stress
Zhang et al. [25]	Rat	Myocardial I/R	BMSCs	miR-98-5p	Cardiomyocytes	Activating the PI3K/Akt signaling pathway to reduce myocardial infarct size
Mao et al. [39]	Rat	Myocardial I/R	BMSCs	miR-183-5p	Cardiomyocytes	Targeting FOXO1 to reduce apoptosis and oxidative stress
Chen et al. [40]	Rat	Myocardial I/R	BMSCs	miR-125b	Cardiomyocytes	Targeting SIRT7 to inhibit apoptosis, autophagy and inflammation
Ou et al. [41]	Rat	Myocardial I/R	BMSCs	miR-150-5p	Cardiomyocytes	Targeting TXNIP to inhibit cardiomyocyte apoptosis and reverse myocardial remodeling
Wang et al. [42]	Rat	Myocardial I/R	BMSCs	miR-455-3p	Cardiomyocytes	Targeting the MEKK1/MKK4/JNK axis to inhibit apoptosis and regulate autophagic flux
Li et al. [43]	Mice	Myocardial I/R	BMSCs	miR-29c	Cardiomyocytes	Inhibiting cardiomyocyte apoptosis and regulating autophagic flux
Shen et al. [44]	Mice	Myocardial I/R	BMSCs	miR-21-5p	Macrophages	Promoting macrophage polarization toward the M2 phenotype
Zhang et al. [45]	Rat	Myocardial I/R	BMSCs	miR-21-5p	Cardiomyocytes	Targeting PDC4 to inhibit apoptosis
Zhao et al. [46]	Mice	Myocardial I/R	BMSCs	miR-182	Macrophages	Promoting macrophage polarization toward the M2 phenotype
Zhang et al. [47]	Mice	Myocardial I/R	BMSCs	lncRNA Mir9-3hg	Cardiomyocytes	Targeting the Pum2/PRDX6 axis to inhibit ferroptosis in cardiomyocytes
Wei et al. [48]	Mice	Myocardial I/R	HUCMSCs	miR-181a-5p	Peripheral blood mononuclear cells	Inhibiting MIRI-induced inflammatory responses
Li et al. [49]	Rat	Myocardial H/R	BMSCs	miR-29a	Cardiomyocytes	Inhibiting the JAK2/STAT3 pathway and promoting myocyte apoptosis
Zou et al. [50]	Rat	Myocardial H/R	BMSCs	miR-149-5p	Cardiomyocytes	Targeting the wnt/β-catenin signaling pathway by miR-149-5p
Chen et al. [51]	Rat	Myocardial H/R	BMSCs	miR-143-3p	Cardiomyocytes	Targeting the CHK2/Beclin2 pathway to regulate autophagic flux and alleviate MIRI
Li et al. [52]	Rat	Myocardial H/R	BMSCs	lncRNA HCP5	Cardiomyocytes	Targeting miR-497/IGF1/PI3K/AKT pathway to inhibit apoptosis
Diao et al. [53]	Rat	Myocardial H/R	HUCMSCs	lncRNA UCA1	Cardiac microvascular endothelial cells	Targeting miR-143/Bcl-2 to regulate autophagy and protect the myocardium
Yu et al. [24]	Human	Myocardial H/R	BMSCs	lncRNA A2M-AS1	Cardiomyocytes	Targeting miR-556-5p/XIAP to inhibit oxidative stress and apoptosis
Liu et al. [54]	Rat	MI	BMSCs	miR-181a-5p	Cardiomyocytes	Targeting ATF2 to inhibit myocardial inflammation and oxidative stress
Zhu et al. [55]	Mice	MI	HUCMSCs	miR-24-3p	Macrophages	Promoting macrophage polarization toward the M2 phenotype

BMSCs bone marrow stem cells, *H/R* hypoxia-reoxygenation, *HUCMSCs* human umbilical cord mesenchymal stem cells, *I/R* ischemia−reperfusion, *MI* myocardial ischemia

MiR-126 is located in intron 7 of the EGFL7 gene and is expressed in human tissues with high vascularization, such as the myocardium, endothelium, and lung [57]. H/R induces bone marrow MSC (BMSC)-EXOs to overproduce miR-126, which alleviates tissue damage [58]. Exosome-delivered miR-126 counteracts oxidative stress by negatively regulating the expression of ERBB receptor feedback inhibitor (ERRFI) 1 [38]. Downregulation of ERRFI1 expression not only facilitates ROS clearance, but also further activates the epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) signaling pathway to promote angiogenesis [38, 59]. The overexpression of miR-126 not

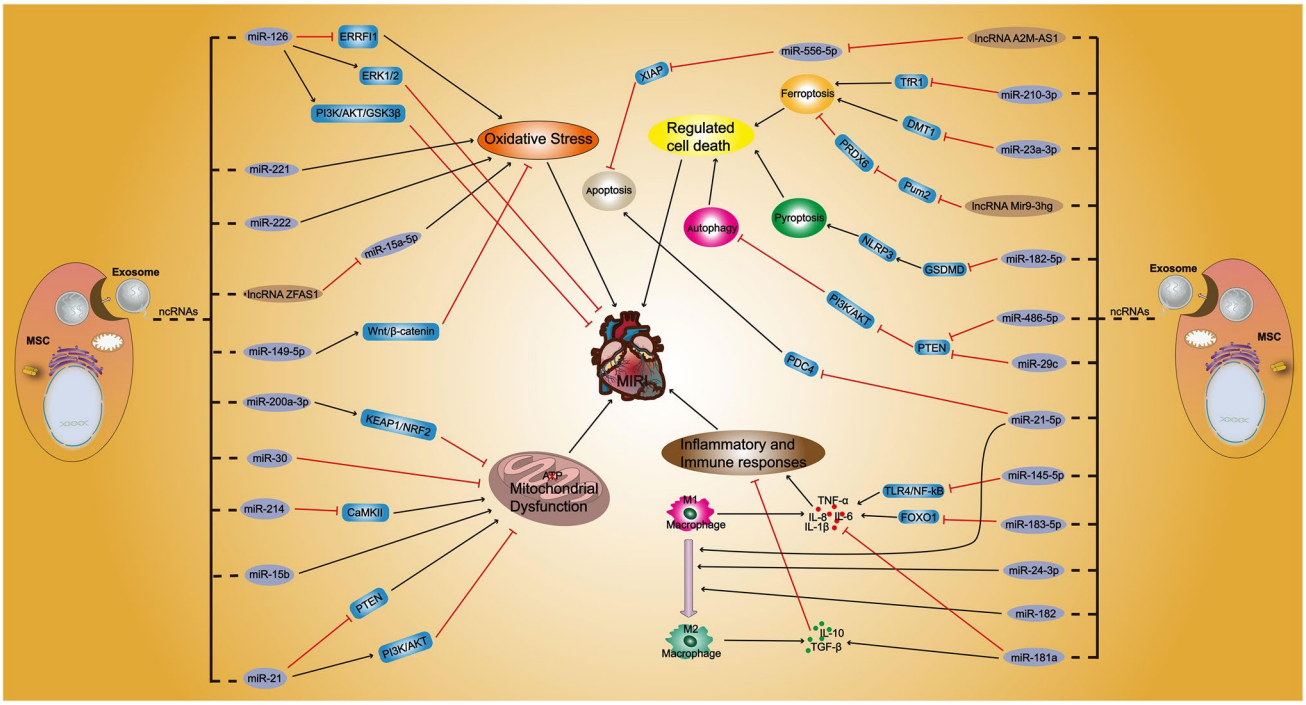

Fig. 1 Schematic diagram of MSC-EXO-derived ncRNAs regulatory network in MIRI. MSC-EXO-derived ncRNAs alleviate or exacerbate MIRI by mediating processes such as oxidative stress, mitochondrial dysfunction, inflammation, immune response, and regulated cell death. Among them, miR-126, miR-221, miR-222, miR-15a-5p, and lncRNA ZFAS1 were closely associated with oxidative stress. miR-149-5p, miR-200a-3p, miR-30, miR-214, miR-15b, and miR-21 are involved in the regulation of mitochondrial function. miR-181a, miR-182, miR-24-3p, miR-183-5p, miR-145-5p, and miR-21-5p are closely related to inflammation and immune response. miR-29c, miR-486-5p, miR-182-5p, miR-23a-3p, miR-210-3p, miR-556-5p, lncRNA A2M-AS1, and lncRNA Mir9-3hg are associated with regulated cell death. Akt, protein kinase B; DMT1, downregulating divalent metal transporter 1; ERK1/2, extracellular signal-regulated kinase 1/2; ERRFI1, ERBB receptor feedback inhibitor 1; FOXO1, Forkhead box protein O1; GSDMD, gasdermin-D; GSK3β, glycogen synthase kinase 3-beta; IL, interleukin; KEAP1, Kelch-like ECH-associated protein 1; MIRI, myocardial ischemia-reperfusion injury; MSC, mesenchymal stem cell; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NRF2, nuclear factor erythroid2-related factor 2; PDC4, pyruvate decarboxylase 4; PI3K, phosphatidylinositol 3-kinase; PRDX6, peroxiredoxin-6; PTEN, phosphatase and tensin homolog deleted on chromosome ten; Pum2, Pumilio homolog 2; TfR1, transferrin receptor 1; TGF, transforming growth factor; TLR4, Toll-like receptor 4; XIAP, X-linked inhibitor of apoptosis protein

only inhibits H2O2-induced oxidative stress but also targets the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase 3 beta (GSK3β) and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways to promote endothelial cell migration and maturation [60]. Overexpression of miR-15a-5p has been reported to exacerbate oxidative stress-induced tissue damage [61]. As a downstream target of the lncRNA ZFAS1, miR-15a-5p is efficiently downregulated by BMSC-EXOs loaded with lncRNA ZFAS1 [62]. A possible mechanism for this action involves the activation of the lncRNA ZFAS1/miR-15a-5p axis to enhance the activity of an antioxidant reductase and inhibit the expression of inflammatory factors such as IL-1β, IL-6, and TNF-α, inhibiting lesion tissue damage [62]. The downregulation of β-catenin in an H/R rat model induced ROS production and myocardial apoptosis [50]. BMSC-EXO-delivered miR-149-5p reversed this effect to some extent by regulating the wnt/β-catenin signaling pathway [50]. Lai et al. [63] demonstrated that adipose-derived MSCs reduced ROS production by downregulating miR-221 and miR-222 levels.

The protective effect of MSC-EXO-derived ncRNAs on oxidative stress has been verified in numerous experiments. However, the precise molecules carried by MSC-EXOs and the cellular components to which they localize, as well as the molecular mechanisms involved, need to be explored in depth. In addition, further studies to explore to induce MSC-EXOs to stably express a target molecule are needed.

MSC-EXO-Derived ncRNAs Attenuate MIRI by Regulating Mitochondrial Dysfunction

MIRI induces mitochondrial dysfunction and changes such as the uncoupling of respiratory chains, reduced adenosine triphosphate (ATP) synthesis and the overproduction of superoxide anions [64]. In addition, homeostatic regulation

of the mitochondrial Ca^{2+} level is a key factor in the initiation of mitochondrial metabolism and the regulation of mitochondrial activity [65]. In MIRI, an increase in cytoplasmic calcium leads to further calcium entry into mitochondria via the mitochondrial calcium uniporter, triggering mitochondrial permeability transition pore (mPTP) opening and promoting cell death [66]. MSC-EXO-derived ncRNAs reverse MIRI by exerting mitochondrion-protective effects.

Overexpression of miR-15b leads to the loss of mitochondrial membrane potential and promotes H/R-induced myocardial apoptosis in rats [67]. Moreover, BMSC-EXOs are enriched in miR-15b [68]. Theoretically, the induction of BMSC-EXOs by the downregulation of miR-15b could protect mitochondrial function in MIRI. Cardiac stem cells (CSCs) are mainly involved in regeneration and repair of the heart after injury [69]. Due to their reduced productivity and implantation rates, MSC-EXO-delivered ncRNAs can improve endogenous CSC functions [69]. Circulating miR-30 is overexpressed in AMI patients compared to healthy subjects, suggesting that miR-30 may be associated with AMI and its prognosis [70]. MSC-EXOs were shown to protect against renal I/R injury by delivering miR-30 to inhibit mitochondrial fission [69]. Therefore, a similar effect is possible in MIRI, which requires experimental support. Human placental MSC-EXO-delivered miR-200a-3p increases the integrity of the mitochondrial structure, stimulates ATP production and exerts antioxidant effects by activating the Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid2-related factor 2 (NRF2) signaling pathway [71]. The transfer of miR-214 from BMSC-EXOs may be a major factor in protecting CSCs from oxidative damage in myocardial infarction [72]. A previous study showed that miR-214 was upregulated by hypoxic stress to protect cardiomyocytes from injury [73]. BMSC-EXOs deliver miR-214 and maintain Ca^{2+} homeostasis by inhibiting CaMKII expression [72]. It is clear that the cardioprotective effect of miR-214 is partly due to the suppression of sodium/calcium exchanger 1 and the inhibited activation of the downstream Ca^{2+} signaling pathway [74]. MiR-21 expression was significantly downregulated in a MIRI model [75]. In addition, BMSC-EXO-delivered miR-21 exerted a cardioprotective effect [76]. These outcomes may be related to the inhibition of phosphatase and tensin homolog deleted on chromosome ten (PTEN), which is a direct target protein of miR-21, and activation of the PI3K/Akt axis [76]. Overexpression of miR-21-5p attenuates lipid levels and lipid peroxidation in cardiomyocytes [77]. This effect is partly attributed to enhanced basal and maximal mitochondrial respiration [77].

Functionally complete mitochondria are important for maintaining physiological activity in the heart [78]. However, MIRI can lead to mitochondrial damage, including the production of large amounts of ROS that further attack normal mitochondria, leading to cardiomyocyte death [78]. In conclusion, mitochondrial dysfunction is considered a main mechanism underlying MIRI [79].

MSC-EXO-Derived ncRNAs Attenuate MIRI by Regulating Inflammatory and Immune Responses

Inflammation is a defense response, but when this response is overactivated by various factors, it exacerbates tissue damage. The hosts immune defense mechanisms can be classified into innate immune and adaptive immune responses. Inflammatory responses and activation of the innate immune system are important features of MIRI [80]. MIRI involves the release of a large number of proinflammatory factors and inflammatory mediators that are not confined to myocardial tissue but reach all parts of the body via the circulatory system, potentially causing multiorgan dysfunction [81]. Moreover, reperfusion treatment leads to cell damage or even death, prompting cells to release molecules with immunomodulatory effects, such as heat shock proteins, ATP, and high mobility group protein B1 [82]. These molecules are endogenous damage-associated molecular pattern factors that signal imbalances in intracellular homeostasis to induce the innate immune response. Innate immunity is a host's first line of defense against pathogenic microorganisms and is dependent on germline-encoded receptors known as pattern recognition receptors (PRRs) [82]. Numerous studies have shown that PRRs are closely associated with MIRI [83–85]. PRRs activate downstream signaling pathways to induce intrinsic immune responses by recognizing and binding to the corresponding pathogen-associated molecular patterns (PAMPs) [86]. Therefore, suppressing inflammatory and immune responses is essential for MIRI treatment.

MSC-EXO pretreatment of a mouse I/R model significantly reduced neutrophil and macrophage infiltration and decreased the size of the myocardial infarct area [87]. The overexpression of miR-181a had a protective effect on the myocardial tissue of MI rats and could regulate myocardial remodeling by inhibiting the aldosterone/mineralocorticoid pathway [88]. Furthermore, BMSC-EXOs overexpressing miR-181a not only downregulated TNF-α and IL-6 in the I/R model but also upregulated the anti-inflammatory cytokine IL-10 in monocytes [48]. The luciferase reporter gene assay and western blotting showed that miRNA-181a could directly bind to the 3′-UTR of the cellular oncogene fos (c-Fos) and inhibit the expression of c-Fos to exert anti-inflammatory effects [48]. Macrophages affected by the microenvironment can polarize toward the M1 or M2 phenotype [89]. The M1 phenotype has upregulated expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8, whereas the M2 phenotype has upregulated expression of the anti-inflammatory factors IL-10 and transforming growth factor (TGF)-β [90]. BMSC-EXOs loaded with

miR-182 can promote the polarization of M1 macrophages to the M2 phenotype, not only alleviating the MIRI-induced inflammatory response but also facilitating the repair of lesioned tissues [46]. Animal experiments have confirmed that the mechanisms may involve Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) pathway inhibition and PI3K/Akt pathway activation [46]. It is possible that myeloid differentiation primary response protein MyD88 (MyD88) binds to the p85 regulatory subunit of PI3K after separation from the TIR structural domain, prompting a shift from TLR4/NF-κB activation to TLR4/PI3K/AKT pathway activation, which alleviates MIRI [91, 92]. MiR-182 delivered by human umbilical cord MSC (HUCMSC)-EXOs can inhibit the inflammatory response and thus alleviate MIRI [93]. In addition to miR-182, miR-24-3p and miR-21-5p can be delivered by HUCMSC-EXOs and shift the polarization M1 macrophages to the M2 phenotype, not only suppressing the inflammatory response but also promoting the repair of diseased myocardial tissue [44, 94]. Forkhead box protein O1 (FOXO1) is highly expressed in myocardial tissue and is closely associated with inflammatory signaling-related pathways [95]. BMSC-EXOs overexpressing miR-183-5p were recently shown to alleviate MIRI by downregulating FOXO1 expression [39]. Knockdown of the foxo1 gene in a mouse liver I/R model has been reported to alleviate the I/R-induced inflammatory response by inhibiting the NimA-related protein kinase 7 (NEK7)/NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) signaling pathway [96]. Whether BMSC-EXOs overexpressing miR-183-5p can inhibit the NEK7/NLRP3 signaling pathway by downregulating FOXO1 in a myocardial I/R model requires further experimental validation because exosomes are strongly affected by the environment. Mild and moderate hypothermia are potentially effective therapeutic measures for MIRI. The cardioprotective effect of hypothermia treatment involves reducing the heart rate and myocardial oxygen consumption and inhibiting metabolism to reduce oxygen demand, as well as modulating the mPTP and inhibiting the inflammatory response [97]. Notably, changes in temperature affect the efficacy of adipose MSC-EXOs, suggesting the need for in-depth studies on the optimal low temperature for different individuals. TLR4 is abundantly expressed in myocardial tissue and regulates innate immunity by activating downstream signaling pathways in response to lipopolysaccharides [98]. The overexpression of miR-145-5p in BMSC-EXOs reduces TLR4 expression levels in spinal cord tissue and further inhibits the TLR4/NF-κB pathway to alleviate spinal cord tissue injury [99]. MiR-145-5p was shown to be significantly downregulated in a rat I/R model, and further upregulation of miR-145-5p reversed MIRI to some extent [100]. Several studies have reported that inhibiting the TLR4/NF-κB pathway significantly reduces MIRI-related immune inflammation [101, 102]. The levels of the cargoes carried by BMSC-EXOs are susceptible to changes in the microenvironment. Thus, the role of BMSC-EXOs in the delivery of miR-145-5p during MIRI needs to be supported by extensive animal experiments. MiR-21a-5p is a paracrine cytokine with cardioprotective effects, and cardiac MSC (CMSC)-EXOs act mainly through paracrine secretion [103]. Although animal experiments have demonstrated that CMSC-EXOs can promote cytokine activity and facilitate the repair of damaged myocardial tissues, further experiments are needed to verify whether the mechanism is associated with CMSC-EXO-mediated delivery of miR-21a-5p [103]. PCI is the preferred option for ST segment elevation myocardial infarction patients [104]. PCI causes atherosclerotic plaques to rupture, form microscopic emboli and block the coronary microcirculatory system, leading to coronary microembolization (CME) [105]. CME is a complication of reperfusion therapy and an exacerbating factor for MIRI [106, 107]. Su et al. [108] showed that the TLR4/MyD88/NF-κB signaling pathway plays a key role in CME-induced myocardial injury. Pathological examination of many patients with sudden coronary death revealed massive occlusion of coronary vessels less than 200 μm in diameter due to microemboli [109]. However, coronary angiography can only detect vessels larger than 500 μm in diameter. Wang et al. [110] constructed a porcine I/R model and intravenously transplanted allogeneic porcine umbilical cord MSCs (PUCMSCs), and the occurrence of CME was significantly lower than that in the model group. The exosomes involved and the related molecular functions need to be further investigated. Overall, the treatment of MIRI by MSC-EXO-derived ncRNAs is multifaceted.

MSC-EXO-derived ncRNAs attenuate MIRI by modulating inflammation and immunity, shedding new light on the treatment of MIRI. Scholars are testing different methods to optimize the ability of MSC-EXOs to regulate inflammatory and immune responses to improve the efficacy and safety of MSC-EXOs [111, 112].

MSC-EXO-derived ncRNAs Attenuate MIRI by Regulating RCD

Typically, cell death is regulated by two types of mechanisms: accidental cell death (ACD) and RCD [113]. ACD is often initiated by an accidental injury or attack that overwhelms any possible molecular control mechanisms [114]. However, RCD has a precise molecular mechanism that can be regulated at the genetic and pharmacological levels [115]. MSC-EXO-derived ncRNAs are associated with multiple RCD modalities, such as apoptosis, ferroptosis, pyroptosis and autophagy [116–119].

Multiple studies have shown that MSC-EXOs are closely associated with RCD in MIRI [43, 53]. The overexpression of miR-21-5p exerts cardioprotective effects by promoting

macrophage polarization toward the M2 phenotype [44]. Our previous study showed that myeloid BMSC-EXOs expressing miR-21-5p inhibited myocardial apoptosis by downregulating pyruvate decarboxylase 4 (PDC4) expression, and interestingly, knockdown of circRNA_0031672 produced a similar effect [45]. CircRNA_0031672 acts as a molecular sponge for miR-21-5p, and knockdown of circRNA_0031672 enhanced the inhibition of PDC4 by miR-21-5p to achieve cardioprotection [45]. PTEN shows protein phosphatase and lipid phosphatase activities and reverses the conversion of PIP2 to PIP3, thereby inhibiting PI3K/Akt signaling pathway activation [120]. MiR-29c expression is reduced in mouse I/R models, suggesting that it may be associated with MIRI [121]. Further experiments revealed that miR-29c delivered by BMSC-EXOs targeted PTEN and activated the AKT/mammalian target of rapamycin signaling pathway to regulate autophagic flux to alleviate MIRI [121]. Additionally, miR-486-5p delivered by BMSC-EXOs could downregulate PTEN expression and activate the PI3K/AKT signaling pathway, alleviating myocardial apoptosis [122]. Whether the effect of miR-486-5p delivered by BMSC-EXOs in combination with miR-29c enhances the treatment of MIRI needs to be further verified *ex vivo*. Additionally, miR-98-5p delivered by BMSC-EXOs could activate the PI3K/AKT signaling pathway to exert myocardial protective effects [123]. In addition to miRNAs, MSC-EXOs can carry lncRNAs, which play a regulatory role. BMSC-EXOs deliver lncRNA A2M-AS1, which acts as a molecular sponge for miR-556-5p to regulate X-linked inhibitor of apoptosis protein (XIAP) expression [24]. The downregulation of XIAP leads to an increase in NLRP3 inflammasomes, which exacerbates the inflammatory response and promotes apoptosis [124]. BMSC-EXO delivery of lncRNA A2M-AS1 downregulated miR-556-5p but upregulated XIAP, further alleviating MIRI by inhibiting apoptosis and counteracting oxidative stress [24]. Gasdermin-D (GSDMD) is a key protein in NLRP3-induced pyroptosis [125]. Yue et al. [93] showed that miR-182-5p delivered by BMSC-EXOs could downregulate GSDMD and further inhibit NLRP3-mediated pyroptosis to protect myocardial tissue. BMSC-EXOs inhibit apoptosis by delivering miR-148a to fight multiple diseases [126, 127]. Furthermore, M2 macrophage-derived exosomes inhibited the TLR4/NF-κB/NLRP3 axis by delivering miR-148a and reduced pyroptosis to alleviate MIRI [128]. Therefore, the induction of BMSC-EXOs to overexpress miR-148a to attenuate MIRI is theoretically feasible, but this needs to be further validated *in vivo* and *in vitro*. Recently, Zhang et al. [47] found that BMSC-EXOs were enriched in lncRNA Mir9-3hg, which targets the Pumilio homolog 2 /Peroxiredoxin-6 axis to inhibit cardiomyocyte ferroptosis and alleviate MIRI. HUCMSC-EXO-delivered miR-23a-3p inhibits ferroptosis by downregulating divalent metal transporter 1 expression to attenuate AMI-induced myocardial injury [129]. Furthermore, hypoxia-induced CMEC-derived exosomal miR-210-3p alleviated H/R-induced myocardial cell injury by inhibiting transferrin receptor 1-mediated ferroptosis [130].

The role of MSC-EXO-derived ncRNAs in MIRI involves multiple forms of RCD, such as apoptosis, pyroptosis, autophagy, and ferroptosis. To maximize the improvements in MIRI, the relationship between other RCD modalities and MIRI should be further investigated. Current studies are inadequate, and it is unclear whether these known RCDs act as independent death programs or as amplification mechanisms for necrotic cell death [114]. Although other RCD modalities have been less frequently reported in MIRI, their roles in MIRI cannot be ignored. Therefore, further in-depth investigation of the relationship between MIRI and RCD is warranted to improve the mitigation of MIRI.

Current Challenges

MSC-EXOs play important roles in MIRI; however, our understanding of these factors is still in the exploratory stage. Various challenges limit the translation of findings from various studies into clinical applications. For instance, there are technical limitations regarding exosome preparation, storage, and drug delivery. Exosome standardization is also a major challenge. Exosomes are characterized by a highly heterogeneous nature, and the small molecules they carry vary depending on cell source. Exosomes are highly sensitive to the environment, and even homologous exosomes can be significantly affected by different processing techniques [8].

Challenges in Exosomal Drug Delivery

Preparation of Exosomes

The clinical value of exosomes has yet to be fully established. To evaluate the biological functions of exosomes, they must be isolated and purified. Based on whether they have been artificially modified, exosomes are classified as natural exosomes or engineered exosomes [131]. Natural exosomes can be classified as animal-derived or plant-derived. Due to the heterogeneity in size, origin, content, and function of exosomes, there is no standard, universal technique for exosome isolation [132, 133].

The most commonly used isolation method is ultracentrifugation, which is simple and limits the chances of cross-contamination [134]. However, its limitations include possible impairment of exosome integrity, time, and high costs. In addition, centrifugation time, centrifugal force, and parameters can affect the purity and yield of exosomes. Densitometric gradient centrifugation is often used in combination with

ultracentrifugation to purify exosomes, but it is time-consuming [134]. The polyethylene glycol-based precipitation method is simple and time-consuming and is mostly used to process large sample volumes. However, purity and recovery are low, and this process is accompanied by the formation of polymers that are difficult to remove [135]. Wang et al. [136] developed a simple light-responsive magnetic bead sorting system that was based on a conventional immunomagnetic separation technique. The immunomagnetic separation technique is highly specific, does not affect the morphological integrity of exosomes and is suitable for the characterization and quantification of exosomal proteins [134]. This method may be difficult to scale up because of its low efficiency and unsuitability for large numbers of samples, which may result in the loss of functional activities of exosomes and is not conducive for downstream experiments.

Exosome purity and recovery also limit their applications. Beyond the search for new methods of preparation, a rational combination of existing methods can be used to efficiently prepare exosomes to meet the current clinical need.

Storage of Exosomes

Exosome therapy is a type of cell-free therapy. Long-term exosome storage is a major challenge. To protect their biological activities and facilitate clinical applications, there is a need to develop appropriate exosome preservation techniques. Common storage methods include cryopreservation, freeze-drying, and spray-drying.

Temperature is of great importance in the preservation of exosomes. Compared to -20 °C, preservation conditions of -80 °C can better maintain the biological functions of proteins in exosomes [137]. Different sources of exosomes require different preservation conditions. Human saliva-derived exosomes can remain morphologically unchanged for 20 months at 4 °C [138]. Human urine- and semen-derived exosomes are better suited for storage at -80 °C [137, 139]. Higher freezing rates and higher protectant concentrations are more effective, while slower freezing rates can lead to nanoparticle aggregation [140]. Furthermore, acidity, alkalinity, and the materials used to store exosomes all have effects [141].

The optimal preservation conditions for exosomes are still being determined, and the preservation of exosomes may be strongly influenced by their source materials.

Exosome Drug-Loading Methods

Drug delivery approaches are classified based on whether the therapeutic drug is loaded directly onto the exosome: presecretory and postsecretory drug delivery. The former refers to direct loading of therapeutic agents on parental cells, which then secrete engineered exosomes. Presecretory drug delivery is convenient; however, it is not possible to control the drug delivery efficiency and may disrupt the natural physiological functions of membrane proteins [134]. The latter refers to the direct addition of therapeutic agents to exosomes; however, this method is associated with exosome aggregation, membrane damage, and low production rates [134].

Electroporation, ultrasonic treatment, and coculture are commonly used methods of drug loading [142]. Coculture is simple, time-consuming, and inefficient, while electroporation and ultrasonication are not conducive for maintaining the integrity of exosomal membranes. The drug loading rates of exosomes may be related to drug hydrophobicity, the drug loading method, and the lipid composition of exosomes [143]. Therefore, understanding exosomes and their molecular transfer mechanisms will mediate the development of appropriate drug loading methods.

Current Problems Associated with MSC-EXOs in MIRI

The importance of MSC-EXOs in MIRI is still being investigated. First, the pathological mechanisms of MIRI are complex and have yet to be fully established. Second, current studies on MSC-EXOs in MIRI mainly focus on elucidating the downstream molecular mechanisms of miRNA regulation, ignoring the upstream mechanisms. Various miRNAs have been shown to be important in disease regulation. In animal experiments, only one pathway is usually studied, which deviates from the complex mechanisms of MIRI. The crosstalk among signaling pathways is also a difficult area of study. The miRNAs involved in general studies are those that are significantly differentially expressed in disease, and the roles of miRNAs with nonsignificant changes in expression in disease processes are often overlooked.

In addition to ncRNAs, the small molecules carried by MSC-EXOs include mRNAs, cytokines, lipids and growth factors [144]. Most of the current studies only focus on miRNAs, and less research has been performed on other small molecules. When drugs are loaded into exosomes, it is not clear what molecular mechanisms are involved in how these loaded small molecules react with other components in exosomes before they are released from the vesicle. There is a need to establish appropriate processes to induce MSC-EXOs to stably express target proteins and to determine how MSC-EXOs mediate intercellular communication. Furthermore, exosomes from different sources are significantly different and are influenced by microenvironmental changes. The safety and efficacy of MSC-EXOs should be ensured to enhance their use in treating MIRI. However, most of the current experiments are conducted in animals, and human-based experiments are inadequate.

Treatment of MIRI is not fixed to one drug or one method. To maximize relief from MIRI, treatment is often performed using a combination of drugs or a combination of drugs and surgery. Findings on how MSC-EXOs mitigate MIRI are inconclusive. Therefore, studies on MSC-EXOs in MIRI should be improved from all aspects.

Prospects for MSC-EXO Applications

Exosomes are membranous extracellular vesicles with a diameter of 30-150 nm [14]. They can effectively escape phagocytosis by mononuclear macrophages and freely cross vessel walls and the extracellular matrix [145]. During physiological and pathological processes, exosomes can be secreted by any cell and can act as carriers for drug delivery [146]. MSCs are multipotent stem cells with self-renewal and multidirectional differentiation abilities [147]. They have been shown to adapt to the tumor microenvironment, exhibit strong paracrine activities, and secrete various exosomes [148]. The positive efficacy of stem cell therapy is largely attributed to the release of exosomes with paracrine activity from stem cells [8]. Therefore, MSCs are the preferred sources of exosomes. Human-derived exosomes carry various molecules, including proteins, lipids, miRNAs, and mRNAs, which make them unique in mediating intercellular communication [149]. Compared to MSCs, MSC-Exos are less immunogenic, more stable, and easier to manage [150, 151]. In addition, MSC-EXOs preserve the therapeutic properties of MSCs while overcoming the limitations of using MSCs as viable cells [13]. Direct applications of MSCs are subject to storage, transportation, and ethical problems. MSC-EXOs show great potential in treatment of cardiovascular diseases [152]. MSC-EXOs rapidly activate multiple cardioprotective pathways to reduce infarct area size and alleviate MIRI-induced cardiac dysfunction [87]. MSC-EXOs can alleviate MIRI by regulating various processes, such as oxidative stress, intracellular Ca^{2+} overload, inflammatory responses, immune responses, and cell death. Therefore, the use of MSC-EXOs instead of MSCs to treat MIRI is a potential cell-free therapeutic strategy.

Conclusions

MSCs can be obtained from different sources including bone marrow, adipose tissue, umbilical cord, and placenta [153]. The pathophysiological mechanisms of MIRI involve processes such as inflammatory responses, immune responses, oxidative stress, apoptosis, intracellular calcium overload, and cardiomyocyte energy metabolism. MSC-EXO-derived ncRNAs participate in the aforementioned processes to inhibit MIRI. Although the use of MSC-EXOs as carriers of therapeutic drugs or genes is still in its infancy, exosome-related research continues to advance the development of MSC-EXOs in medical therapeutics and diagnostics. Studies should assess the significance of MSC-EXOs in tissue regeneration, organ degeneration, and intractable diseases. Furthermore, MSC-EXO-mediated therapies may eventually lead to significant advances in macromolecular drug or gene delivery.

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Declarations

Ethics Approval No human or animal studies were carried out by the authors for this article.

Consent for Publication All authors have given consent for publication.

Conflict of Interest The authors declare no competing interests.

References

1. Jennings RB, Sommers HM, Smyth GA, et al. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. Arch Pathol. 1960;70:68–78.
2. Wei B, Li WW, Ji J, et al. The cardioprotective effect of sodium tanshinone IIA sulfonate and the optimizing of therapeutic time window in myocardial ischemia/reperfusion injury in rats. Atherosclerosis. 2014;235:318–27. https://doi.org/10.1016/j.atherosclerosis.2014.05.924.
3. Nie C, Ding XAR, et al. Hydrogen gas inhalation alleviates myocardial ischemia-reperfusion injury by the inhibition of oxidative stress and NLRP3-mediated pyroptosis in rats. Life Sci. 2021;272:119248. https://doi.org/10.1016/j.lfs.2021.119248.
4. Li Y, Li Z, Liu J, et al. miR-190-5p alleviates myocardial ischemia-reperfusion injury by targeting PHLPP1. Dis Markers. 2021;2021:8709298. https://doi.org/10.1155/2021/8709298.
5. Lv XW, He ZF, Zhu PP, et al. miR-451-3p alleviates myocardial ischemia/reperfusion injury by inhibiting MAP1LC3B-mediated autophagy. Inflamm Res. 2021;70:1089–100. https://doi.org/10.1007/s00011-021-01508-4.
6. Li L, Wang Y, Guo R, et al. Ginsenoside Rg3-loaded, reactive oxygen species-responsive polymeric nanoparticles for alleviating myocardial ischemia-reperfusion injury. J Control Release. 2020;317:259–72. https://doi.org/10.1016/j.jconrel.2019.11.032.
7. Xiang M, Lu Y, Xin L, et al. Role of oxidative stress in reperfusion following myocardial ischemia and its treatments. Oxid Med

Cell Longev. 2021;2021:6614009. https://doi.org/10.1155/2021/6614009.
8. Ha DH, Kim HK, Lee J, et al. Mesenchymal stem/stromal cell-derived exosomes for immunomodulatory therapeutics and skin regeneration. Cells. 2020;9. https://doi.org/10.3390/cells9051157
9. Crisan M, Yap S, Casteilla L, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell. 2008;3:301–13. https://doi.org/10.1016/j.stem.2008.07.003.
10. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;110:3499–506. https://doi.org/10.1182/blood-2007-02-069716.
11. Nikfarjam S, Rezaie J, Zolbanin NM, et al. Mesenchymal stem cell derived-exosomes: a modern approach in translational medicine. J Transl Med. 2020;18:449. https://doi.org/10.1186/s12967-020-02622-3.
12. Enam SF, Kader SR, Bodkin N, et al. Evaluation of M2-like macrophage enrichment after diffuse traumatic brain injury through transient interleukin-4 expression from engineered mesenchymal stromal cells. J Neuroinflammation. 2020;17:197. https://doi.org/10.1186/s12974-020-01860-y.
13. Fernández-Francos S, Eiro N, González-Galiano N, et al. Mesenchymal stem cell-based therapy as an alternative to the treatment of acute respiratory distress syndrome: Current Evidence and Future Perspectives. Int J Mol Sci. 2021;22. https://doi.org/10.3390/ijms22157850
14. Whiteside TL. The emerging role of plasma exosomes in diagnosis, prognosis and therapies of patients with cancer. Contemp Oncol (Pozn). 2018;22:38–40. https://doi.org/10.5114/wo.2018.73882.
15. Hade MD, Suire CNSuo Z. Mesenchymal stem cell-derived exosomes: applications in regenerative medicine. Cells. 2021;10. https://doi.org/10.3390/cells10081959
16. Zheng D, Huo M, Li B, et al. The role of exosomes and exosomal microRNA in cardiovascular disease. Front Cell Dev Biol. 2020;8:616161. https://doi.org/10.3389/fcell.2020.616161.
17. Wu SC, Kuo PJ, Rau CS, et al. Subpopulations of exosomes purified via different exosomal markers carry different microRNA contents. Int J Med Sci. 2021;18:1058–66. https://doi.org/10.7150/ijms.52768.
18. Luo H, Li X, Li T, et al. microRNA-423-3p exosomes derived from cardiac fibroblasts mediates the cardioprotective effects of ischaemic post-conditioning. Cardiovasc Res. 2019;115:1189–204. https://doi.org/10.1093/cvr/cvy231.
19. Shen Z, Huang W, Liu J, et al. Effects of mesenchymal stem cell-derived exosomes on autoimmune diseases. Front Immunol. 2021;12:749192. https://doi.org/10.3389/fimmu.2021.749192.
20. Shen M, Chen T. Mesenchymal stem cell-derived exosomes and their potential agents in hematological diseases. Oxid Med Cell Longev. 2021;2021:4539453. https://doi.org/10.1155/2021/4539453.
21. Muralikumar M, Manoj Jain S, Ganesan H, et al. Current understanding of the mesenchymal stem cell-derived exosomes in cancer and aging. Biotechnol Rep (Amst). 2021;31:e00658. https://doi.org/10.1016/j.btre.2021.e00658.
22. Riazifar M, Mohammadi MR, Pone EJ, et al. Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. ACS Nano. 2019;13:6670–88. https://doi.org/10.1021/acsnano.9b01004.
23. Jayaramayya K, Mahalaxmi I, Subramaniam MD, et al. Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment. BMB Rep. 2020;53:400–12. https://doi.org/10.5483/BMBRep.2020.53.8.121.
24. Yu H, Pan Y, Dai M, et al. Mesenchymal stem cell-originated exosomal Lnc A2M-AS1 alleviates hypoxia/reperfusion-induced apoptosis and oxidative stress in cardiomyocytes. Cardiovasc Drugs Ther. 2022. https://doi.org/10.1007/s10557-022-07339-7.
25. Zhang L, Wei Q, Liu X, et al. Exosomal microRNA-98-5p from hypoxic bone marrow mesenchymal stem cells inhibits myocardial ischemia-reperfusion injury by reducing TLR4 and activating the PI3K/Akt signaling pathway. Int Immunopharmacol. 2021;101:107592. https://doi.org/10.1016/j.intimp.2021.107592.
26. Sun XH, Wang X, Zhang Y, et al. Exosomes of bone-marrow stromal cells inhibit cardiomyocyte apoptosis under ischemic and hypoxic conditions via miR-486-5p targeting the PTEN/PI3K/AKT signaling pathway. Thromb Res. 2019;177:23–32. https://doi.org/10.1016/j.thromres.2019.02.002.
27. Zhang S, Li P, Zhao L, et al. LINC00210 as a miR-328-5p sponge promotes nasopharyngeal carcinoma tumorigenesis by activating NOTCH3 pathway. Biosci Rep. 2018;38. https://doi.org/10.1042/bsr20181168.
28. Kong Y, Liang X, Liu L, et al. High throughput sequencing identifies microRNAs mediating α-synuclein toxicity by targeting neuroactive-ligand receptor interaction pathway in early stage of drosophila Parkinson's disease Model. PLoS One. 2015;10:e0137432. https://doi.org/10.1371/journal.pone.0137432.
29. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–54. https://doi.org/10.1016/0092-8674(93)90529-y.
30. Gomes CPC, Schroen B, Kuster GM, et al. Regulatory RNAs in heart failure. Circulation. 2020;141:313–28. https://doi.org/10.1161/circulationaha.119.042474.
31. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016;17:47–62. https://doi.org/10.1038/nrg.2015.10.
32. Filippov-Levy N, Reich R, Davidson B. The biological and clinical role of the long non-coding RNA LOC642852 in ovarian carcinoma. Int J Mol Sci. 2020;21. https://doi.org/10.3390/ijms21155237
33. Zhou WY, Cai ZR, Liu J, et al. Circular RNA: metabolism, functions and interactions with proteins. Mol Cancer. 2020;19:172. https://doi.org/10.1186/s12943-020-01286-3.
34. Huang A, Zheng H, Wu Z, et al. Circular RNA-protein interactions: functions, mechanisms, and identification. Theranostics. 2020;10:3503–17. https://doi.org/10.7150/thno.42174.
35. Bai XF, Niu RZ, Liu J, et al. Roles of noncoding RNAs in the initiation and progression of myocardial ischemia-reperfusion injury. Epigenomics. 2021;13:715–43. https://doi.org/10.2217/epi-2020-0359.
36. Zhao Z, Sun W, Guo Z, et al. Long Noncoding RNAs in Myocardial Ischemia-Reperfusion Injury. Oxid Med Cell Longev. 2021;2021:8889123. https://doi.org/10.1155/2021/8889123.
37. Han Y, Wu N, Xia F, et al. Long non-coding RNA GAS5 regulates myocardial ischemia-reperfusion injury through the PI3K/AKT apoptosis pathway by sponging miR-532-5p. Int J Mol Med. 2020;45:858–72. https://doi.org/10.3892/ijmm.2020.4471.
38. Wang W, Zheng Y, Wang M, et al. Exosomes derived miR-126 attenuates oxidative stress and apoptosis from ischemia and reperfusion injury by targeting ERRFI1. Gene. 2019;690:75–80. https://doi.org/10.1016/j.gene.2018.12.044.
39. Mao S, Zhao J, Zhang ZJ, et al. MiR-183-5p overexpression in bone mesenchymal stem cell-derived exosomes protects against myocardial ischemia/reperfusion injury by targeting FOXO1. Immunobiology. 2022;227:152204. https://doi.org/10.1016/j.imbio.2022.152204.
40. Chen Q, Liu Y, Ding X, et al. Bone marrow mesenchymal stem cell-secreted exosomes carrying microRNA-125b protect against myocardial ischemia reperfusion injury via targeting SIRT7.

Mol Cell Biochem. 2020;465:103–14. https://doi.org/10.1007/s11010-019-03671-z.
41. Ou H, Teng H, Qin Y, et al. Extracellular vesicles derived from microRNA-150-5p-overexpressing mesenchymal stem cells protect rat hearts against ischemia/reperfusion. Aging (Albany NY). 2020;12:12669–83. https://doi.org/10.18632/aging.102792.
42. Wang Y, Shen Y. Exosomal miR-455-3p from BMMSCs prevents cardiac ischemia-reperfusion injury. Hum Exp Toxicol. 2022;41:9603271221102508. https://doi.org/10.1177/09603271221102508.
43. Li T, Gu J, Yang O, et al. Bone marrow mesenchymal stem cell-derived exosomal miRNA-29c decreases cardiac ischemia/reperfusion injury through inhibition of excessive autophagy via the PTEN/Akt/mTOR signaling pathway. Circ J. 2020;84:1304–11. https://doi.org/10.1253/circj.CJ-19-1060.
44. Shen D, He Z. Mesenchymal stem cell-derived exosomes regulate the polarization and inflammatory response of macrophages via miR-21-5p to promote repair after myocardial reperfusion injury. Ann Transl Med. 2021;9:1323. https://doi.org/10.21037/atm-21-3557.
45. Zhang J, Luo CJ, Xiong XQ, et al. MiR-21-5p-expressing bone marrow mesenchymal stem cells alleviate myocardial ischemia/reperfusion injury by regulating the circRNA_0031672/miR-21-5p/programmed cell death protein 4 pathway. J Geriatr Cardiol. 2021;18:1029–43. https://doi.org/10.11909/j.issn.1671-5411.2021.12.004.
46. Zhao J, Li X, Hu J, et al. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. Cardiovasc Res. 2019;115:1205–16. https://doi.org/10.1093/cvr/cvz040.
47. Zhang JK, Zhang Z, Guo ZA, et al. The BMSC-derived exosomal lncRNA Mir9-3hg suppresses cardiomyocyte ferroptosis in ischemia-reperfusion mice via the Pum2/PRDX6 axis. Nutr Metab Cardiovasc Dis. 2022;32:515–27. https://doi.org/10.1016/j.numecd.2021.10.017.
48. Wei Z, Qiao S, Zhao J, et al. miRNA-181a over-expression in mesenchymal stem cell-derived exosomes influenced inflammatory response after myocardial ischemia-reperfusion injury. Life Sci. 2019;232:116632. https://doi.org/10.1016/j.lfs.2019.116632.
49. Li KS, Jiang WP, Li QC, et al. MiR-29a in mesenchymal stem cells inhibits FSTL1 secretion and promotes cardiac myocyte apoptosis in hypoxia-reoxygenation injury. Cardiovasc Pathol. 2020;46:107180. https://doi.org/10.1016/j.carpath.2019.107180.
50. Zou L, Ma X, Wu B, et al. Protective effect of bone marrow mesenchymal stem cell-derived exosomes on cardiomyoblast hypoxia-reperfusion injury through the miR-149/let-7c/Faslg axis. Free Radic Res. 2020;54:722–31. https://doi.org/10.1080/10715762.2020.1837793.
51. Chen G, Wang M, Ruan Z, et al. Mesenchymal stem cell-derived exosomal miR-143-3p suppresses myocardial ischemia-reperfusion injury by regulating autophagy. Life Sci. 2021;280:119742. https://doi.org/10.1016/j.lfs.2021.119742.
52. Li KS, Bai Y, Li J, et al. LncRNA HCP5 in hBMSC-derived exosomes alleviates myocardial ischemia reperfusion injury by sponging miR-497 to activate IGF1/PI3K/AKT pathway. Int J Cardiol. 2021;342:72–81. https://doi.org/10.1016/j.ijcard.2021.07.042.
53. Diao L, Zhang Q. Transfer of lncRNA UCA1 by hUCMSCs-derived exosomes protects against hypoxia/reoxygenation injury through impairing miR-143-targeted degradation of Bcl-2. Aging (Albany NY). 2021;13:5967–85. https://doi.org/10.18632/aging.202520.
54. Liu HY, Yu LF, Zhou TG, et al. Lipopolysaccharide-stimulated bone marrow mesenchymal stem cells-derived exosomes inhibit H2O2-induced cardiomyocyte inflammation and oxidative stress via regulating miR-181a-5p/ATF2 axis. Eur Rev Med Pharmacol Sci. 2020;24:10069–77. https://doi.org/10.26355/eurrev_202010_23224.
55. Zhu F, Chen Y, Li J, et al. Human umbilical cord mesenchymal stem cell-derived exosomes attenuate myocardial infarction injury via miR-24-3p-promoted M2 macrophage polarization. Adv Biol (Weinh). 2022;e2200074. https://doi.org/10.1002/adbi.202200074
56. Shen ZJ, Liu YJ, Gao XH, et al. Molecular identification of two thioredoxin genes from grapholita molesta and their function in resistance to emamectin benzoate. Front Physiol. 2018;9:1421. https://doi.org/10.3389/fphys.2018.01421.
57. Casciaro M, Di Salvo E, Brizzi T, et al. Involvement of miR-126 in autoimmune disorders. Clin Mol Allergy. 2018;16:11. https://doi.org/10.1186/s12948-018-0089-4.
58. Pan Q, Wang Y, Lan Q, et al. Exosomes derived from mesenchymal stem cells ameliorate hypoxia/reoxygenation-injured ECs via transferring microRNA-126. Stem Cells Int. 2019;2019:2831756. https://doi.org/10.1155/2019/2831756.
59. Wang M, Zhao Y, Yu ZY, et al. Glioma exosomal microRNA-148a-3p promotes tumor angiogenesis through activating the EGFR/MAPK signaling pathway via inhibiting ERRFI1. Cancer Cell Int. 2020;20:518. https://doi.org/10.1186/s12935-020-01566-4.
60. Wu Q, Qi B, Duan X, et al. MicroRNA-126 enhances the biological function of endothelial progenitor cells under oxidative stress via PI3K/Akt/GSK3β and ERK1/2 signaling pathways. Bosn J Basic Med Sci. 2021;21:71–80. https://doi.org/10.17305/bjbms.2019.4493.
61. Wang Z, Na Z, Cui Y, et al. LncRNA ZFAS1 regulates the hippocampal neurons injury in epilepsy through the miR-15a-5p/OXSR1/NF-κB pathway. Metab Brain Dis. 2022. https://doi.org/10.1007/s11011-022-01013-5.
62. Yang H, Chen J. Bone marrow mesenchymal stem cell-derived exosomes carrying long noncoding RNA ZFAS1 alleviate oxidative stress and inflammation in ischemic stroke by inhibiting microRNA-15a-5p. Metab Brain Dis. 2022. https://doi.org/10.1007/s11011-022-00997-4.
63. Lai TC, Lee TL, Chang YC, et al. MicroRNA-221/222 mediates ADSC-exosome-induced cardioprotection against ischemia/reperfusion by targeting PUMA and ETS-1. Front Cell Dev Biol. 2020;8:569150. https://doi.org/10.3389/fcell.2020.569150.
64. Marin W, Marin D, Ao X, et al. Mitochondria as a therapeutic target for cardiac ischemia-reperfusion injury (Review). Int J Mol Med. 2021;47:485–99. https://doi.org/10.3892/ijmm.2020.4823.
65. Wang F, Meng TG, Li J, et al. Mitochondrial Ca^{2+} is related to mitochondrial activity and dynamic events in mouse oocytes. Front Cell Dev Biol. 2020;8:585932. https://doi.org/10.3389/fcell.2020.585932.
66. Parks RJ, Menazza S, Holmström KM, et al. Cyclophilin D-mediated regulation of the permeability transition pore is altered in mice lacking the mitochondrial calcium uniporter. Cardiovasc Res. 2019;115:385–94. https://doi.org/10.1093/cvr/cvy218.
67. Liu L, Zhang G, Liang Z, et al. MicroRNA-15b enhances hypoxia/reoxygenation-induced apoptosis of cardiomyocytes via a mitochondrial apoptotic pathway. Apoptosis. 2014;19:19–29. https://doi.org/10.1007/s10495-013-0899-2.
68. Luo F, Guo W, Liu W. Exosomes derived from bone marrow mesenchymal stem cells inhibit human aortic vascular smooth muscle cells calcification via the miR-15a/15b/16/NFATc3/OCN axis. Biochem Biophys Res Commun. 2022;635:65–76. https://doi.org/10.1016/j.bbrc.2022.09.076.
69. Loussouarn C, Pers YM, Bony C, et al. Mesenchymal stromal cell-derived extracellular vesicles regulate the mitochondrial metabolism via transfer of miRNAs. Front Immunol. 2021;12:623973. https://doi.org/10.3389/fimmu.2021.623973.

70. Long G, Wang F, Duan Q, et al. Circulating miR-30a, miR-195 and let-7b associated with acute myocardial infarction. PLoS One. 2012;7:e50926. https://doi.org/10.1371/journal.pone.0050926.
71. Cao H, Cheng Y, Gao H, et al. In vivo tracking of mesenchymal stem cell-derived extracellular vesicles improving mitochondrial function in renal ischemia-reperfusion injury. ACS Nano. 2020;14:4014–26. https://doi.org/10.1021/acsnano.9b08207.
72. Wang Y, Zhao R, Liu D, et al. Exosomes derived from miR-214-enriched bone marrow-derived mesenchymal stem cells regulate oxidative damage in cardiac stem cells by targeting CaMKII. Oxid Med Cell Longev. 2018;2018:4971261. https://doi.org/10.1155/2018/4971261.
73. Lv G, Shao S, Dong H, et al. MicroRNA-214 protects cardiac myocytes against H2O2-induced injury. J Cell Biochem. 2014;115:93–101. https://doi.org/10.1002/jcb.24636.
74. Yang Y, Ding S, Xu G, et al. MicroRNA-15a inhibition protects against hypoxia/reoxygenation-induced apoptosis of cardiomyocytes by targeting mothers against decapentaplegic homolog 7. Mol Med Rep. 2017;15:3699–705. https://doi.org/10.3892/mmr.2017.6466.
75. Wang J, Yue J, Xia Q, et al. Angiotensin II type i receptor agonistic autoantibodies induces apoptosis of cardiomyocytes by downregulating miR21 in preeclampsia: a mechanism study. Am J Transl Res. 2019;11:2339–49.
76. Shi B, Wang Y, Zhao R, et al. Bone marrow mesenchymal stem cell-derived exosomal miR-21 protects C-kit+ cardiac stem cells from oxidative injury through the PTEN/PI3K/Akt axis. PLoS One. 2018;13:e0191616. https://doi.org/10.1371/journal.pone.0191616.
77. Nasci VL, Chuppa S, Griswold L, et al. miR-21-5p regulates mitochondrial respiration and lipid content in H9C2 cells. Am J Physiol Heart Circ Physiol. 2019;316:H710-h721. https://doi.org/10.1152/ajpheart.00538.2017.
78. Yang L, Wu J, Xie P, et al. Sevoflurane postconditioning alleviates hypoxia-reoxygenation injury of cardiomyocytes by promoting mitochondrial autophagy through the HIF-1/BNIP3 signaling pathway. PeerJ. 2019;7:e7165. https://doi.org/10.7717/peerj.7165.
79. Forini F, NicoliniGIervasi G. Mitochondria as key targets of cardioprotection in cardiac ischemic disease: role of thyroid hormone triiodothyronine. Int J Mol Sci. 2015;16:6312–36. https://doi.org/10.3390/ijms16036312.
80. Bonaventura A, Montecucco F, Dallegri F. Cellular recruitment in myocardial ischaemia/reperfusion injury. Eur J Clin Invest. 2016;46:590–601. https://doi.org/10.1111/eci.12633.
81. Naito H, Nojima T, Fujisaki N, et al. Therapeutic strategies for ischemia reperfusion injury in emergency medicine. Acute Med Surg. 2020;7:e501. https://doi.org/10.1002/ams2.501.
82. Silvis MJM, KaffkaGenaamdDengler SE, Odille CA, et al. Damage-associated molecular patterns in myocardial infarction and heart transplantation: the road to translational success. Front Immunol. 2020;11:599511. https://doi.org/10.3389/fimmu.2020.599511.
83. Fang Y, Hu J. Toll-like receptor and its roles in myocardial ischemic/reperfusion injury. Med Sci Monit. 2011;17:Ra100-109. https://doi.org/10.12659/msm.881709.
84. Liu Y, Yang H, Liu LX, et al. NOD2 contributes to myocardial ischemia/reperfusion injury by regulating cardiomyocyte apoptosis and inflammation. Life Sci. 2016;149:10–7. https://doi.org/10.1016/j.lfs.2016.02.039.
85. Jordan JE, Montalto MC, Stahl GL. Inhibition of mannose-binding lectin reduces postischemic myocardial reperfusion injury. Circulation. 2001;104:1413–8. https://doi.org/10.1161/hc3601.095578.
86. Zhu X, Huang H, Zhao L. PAMPs and DAMPs as the bridge between periodontitis and atherosclerosis: the potential therapeutic targets. Front Cell Dev Biol. 2022;10:856118. https://doi.org/10.3389/fcell.2022.856118.
87. Arslan F, Lai RC, Smeets MB, et al. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. Stem Cell Res. 2013;10:301–12. https://doi.org/10.1016/j.scr.2013.01.002.
88. Garg A, Foinquinos A, Jung M, et al. MiRNA-181a is a novel regulator of aldosterone-mineralocorticoid receptor-mediated cardiac remodelling. Eur J Heart Fail. 2020;22:1366–77. https://doi.org/10.1002/ejhf.1813.
89. Al-Omar MS, Jabir M, Karsh E, et al. Gold nanoparticles and graphene oxide flakes enhance cancer cells' phagocytosis through granzyme-perforin-dependent biomechanism. Nanomaterials (Basel). 2021;11. https://doi.org/10.3390/nano11061382
90. Pérez S, Rius-Pérez S. Macrophage polarization and reprogramming in acute inflammation: a redox perspective. Antioxidants (Basel). 2022;11. https://doi.org/10.3390/antiox11071394
91. O'Neill LA, Bowie AG. The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. Nat Rev Immunol. 2007;7:353–64. https://doi.org/10.1038/nri2079.
92. Yuan X, Juan Z, Zhang R, et al. Clemastine fumarate protects against myocardial ischemia reperfusion injury by activating the TLR4/PI3K/Akt Signaling Pathway. Front Pharmacol. 2020;11:28. https://doi.org/10.3389/fphar.2020.00028.
93. Yue R, Lu S, Luo Y, et al. Mesenchymal stem cell-derived exosomal microRNA-182-5p alleviates myocardial ischemia/reperfusion injury by targeting GSDMD in mice. Cell Death Discov. 2022;8:202. https://doi.org/10.1038/s41420-022-00909-6.
94. Zhu F, Chen Y, Li J, et al. Human umbilical cord mesenchymal stem cell-derived exosomes attenuate myocardial infarction injury via miR-24-3p-promoted M2 macrophage polarization. Adv Biol. 2022;e2200074. https://doi.org/10.1002/adbi.202200074
95. Han R, Huang H, Xia W, et al. Perspectives for Forkhead box transcription factors in diabetic cardiomyopathy: Their therapeutic potential and possible effects of salvianolic acids. Front Cardiovasc Med. 2022;9:951597. https://doi.org/10.3389/fcvm.2022.951597.
96. Li C, Sheng M, Lin Y, et al. Functional crosstalk between myeloid Foxo1-β-catenin axis and Hedgehog/Gli1 signaling in oxidative stress response. Cell Death Differ. 2021;28:1705–19. https://doi.org/10.1038/s41418-020-00695-7.
97. Jung KT, Bapat A, Kim YK, et al. Therapeutic hypothermia for acute myocardial infarction: a narrative review of evidence from animal and clinical studies. Korean J Anesthesiol. 2022;75:216–30. https://doi.org/10.4097/kja.22156.
98. Frantz S, Kobzik L, Kim YD, et al. Toll4 (TLR4) expression in cardiac myocytes in normal and failing myocardium. J Clin Invest. 1999;104:271–80. https://doi.org/10.1172/jci6709.
99. Jiang Z, Zhang J. Mesenchymal stem cell-derived exosomes containing miR-145-5p reduce inflammation in spinal cord injury by regulating the TLR4/NF-κB signaling pathway. Cell Cycle. 2021;20:993–1009. https://doi.org/10.1080/15384101.2021.1919825.
100. Liang C, Wang S, Zhao L, et al. Effects of miR-145-5p on cardiomyocyte proliferation and apoptosis, GIGYF1 expression and oxidative stress response in rats with myocardial ischemia-reperfusion. Cell Mol Biol (Noisy-le-grand). 2022;68:147–59. https://doi.org/10.14715/cmb/2022.68.1.19.
101. Bai Y, Li Z, Liu W, et al. Biochanin A attenuates myocardial ischemia/reperfusion injury through the TLR4/NF-κB/NLRP3

signaling pathway. Acta Cir Bras. 2019;34:e201901104. https://doi.org/10.1590/s0102-865020190110000004.
102. Liu Y, Qu X, Zhang J, et al. Effects of dexmedetomidine on the degree of myocardial ischemia-reperfusion injury, oxidative stress and TLR4/NF-κB signaling pathway in rats. Pak J Pharm Sci. 2021;34:2047–51.
103. Ju C, Shen Y, Ma G, et al. Transplantation of cardiac mesenchymal stem cell-derived exosomes promotes repair in ischemic myocardium. J Cardiovasc Transl Res. 2018;11:420–8. https://doi.org/10.1007/s12265-018-9822-0.
104. Vogel B, Claessen BE, Arnold SV, et al. ST-segment elevation myocardial infarction. Nat Rev Dis Primers. 2019;5:39. https://doi.org/10.1038/s41572-019-0090-3.
105. Su Q, Li L, Sun Y, et al. Effects of the TLR4/Myd88/NF-κB signaling pathway on NLRP3 inflammasome in coronary microembolization-induced myocardial injury. Cell Physiol Biochem. 2018;47:1497–508. https://doi.org/10.1159/000490866.
106. Chen ZQ, Zhou Y, Chen F, et al. miR-200a-3p attenuates coronary microembolization-induced myocardial injury in rats by inhibiting TXNIP/NLRP3-mediated cardiomyocyte pyroptosis. Front Cardiovasc Med. 2021;8:693257. https://doi.org/10.3389/fcvm.2021.693257.
107. SkyschallyWalter AB, Heusch G. Coronary microembolization during early reperfusion: infarct extension, but protection by ischaemic postconditioning. Eur Heart J. 2013;34:3314–21. https://doi.org/10.1093/eurheartj/ehs434.
108. Su Q, Lv X, Sun Y, et al. Role of TLR4/MyD88/NF-κB signaling pathway in coronary microembolization-induced myocardial injury prevented and treated with nicorandil. Biomed Pharmacother. 2018;106:776–84. https://doi.org/10.1016/j.biopha.2018.07.014.
109. Schwartz RS, Burke A, Farb A, et al. Microemboli and microvascular obstruction in acute coronary thrombosis and sudden coronary death: relation to epicardial plaque histopathology. J Am Coll Cardiol. 2009;54:2167–73. https://doi.org/10.1016/j.jacc.2009.07.042.
110. Wang J, Chen Z, Dai Q, et al. Intravenously delivered mesenchymal stem cells prevent microvascular obstruction formation after myocardial ischemia/reperfusion injury. Basic Res Cardiol. 2020;115:40. https://doi.org/10.1007/s00395-020-0800-8.
111. Cao J, Wang B, Tang T, et al. Three-dimensional culture of MSCs produces exosomes with improved yield and enhanced therapeutic efficacy for cisplatin-induced acute kidney injury. Stem Cell Res Ther. 2020;11:206. https://doi.org/10.1186/s13287-020-01719-2.
112. Alzahrani FA. Melatonin improves therapeutic potential of mesenchymal stem cells-derived exosomes against renal ischemia-reperfusion injury in rats. Am J Transl Res. 2019;11:2887–907.
113. Zhang Y, Huang X, Qi B, et al. Ferroptosis and musculoskeletal diseases: "Iron Maiden" cell death may be a promising therapeutic target. Front Immunol. 2022;13:972753. https://doi.org/10.3389/fimmu.2022.972753.
114. Del Re DP, Amgalan D, Linkermann A, et al. Fundamental mechanisms of regulated cell death and implications for heart disease. Physiol Rev. 2019;99:1765–817. https://doi.org/10.1152/physrev.00022.2018.
115. Bumiller-Bini V, Cipolla GA, Spadoni MB, et al. Condemned or not to die? Gene polymorphisms associated with cell death in Pemphigus foliaceus. Front Immunol. 2019;10:2416. https://doi.org/10.3389/fimmu.2019.02416.
116. Ibrahim MA, Khalifa AM, Mohamed AA, et al. Bone-marrow-derived mesenchymal stem cells, their conditioned media, and olive leaf extract protect against cisplatin-induced toxicity by alleviating oxidative stress, inflammation, and apoptosis in rats. Toxics. 2022;10. https://doi.org/10.3390/toxics10090526
117. Xiong Y, Chen L, Lin Z, et al. The regulatory role of ferroptosis in bone homeostasis. Stem Cells Int. 2022;2022:3568597. https://doi.org/10.1155/2022/3568597.
118. Zhao Y, Chen Y, Wang Z, et al. Bone marrow mesenchymal stem cell exosome attenuates inflammasome-related pyroptosis via delivering circ_003564 to improve the recovery of spinal cord injury. Mol Neurobiol. 2022. https://doi.org/10.1007/s12035-022-03006-y.
119. Xiao Q, Zhao Z, Teng Y, et al. BMSC-derived exosomes alleviate intervertebral disc degeneration by modulating akt/mtor-mediated autophagy of nucleus pulposus cells. Stem Cells Int. 2022;2022:9896444. https://doi.org/10.1155/2022/9896444.
120. Liu A, Zhu Y, Chen W, et al. PTEN dual lipid- and protein-phosphatase function in tumor progression. Cancers (Basel). 2022;14. https://doi.org/10.3390/cancers14153666
121. Li T, Gu J, Yang O, et al. Bone marrow mesenchymal stem cell-derived exosomal miRNA-29c decreases cardiac ischemia/reperfusion injury through inhibition of excessive autophagy via the PTEN/Akt/mTOR signaling pathway. Circ J Off J Jpn Circ Soc. 2020;84:1304–11. https://doi.org/10.1253/circj.CJ-19-1060.
122. Sun X, Wang X, Zhang Y, et al. Exosomes of bone-marrow stromal cells inhibit cardiomyocyte apoptosis under ischemic and hypoxic conditions via miR-486-5p targeting the PTEN/PI3K/AKT signaling pathway. Thrombosis Res. 2019;177:23–32. https://doi.org/10.1016/j.thromres.2019.02.002.
123. Zhang L, Wei Q, Liu X, et al. Exosomal microRNA-98-5p from hypoxic bone marrow mesenchymal stem cells inhibits myocardial ischemia-reperfusion injury by reducing TLR4 and activating the PI3K/Akt signaling pathway. Int Immunopharmacol. 2021;101:107592. https://doi.org/10.1016/j.intimp.2021.107592.
124. Xin R, Sun X, Wang Z, et al. Apocynin inhibited NLRP3/XIAP signalling to alleviate renal fibrotic injury in rat diabetic nephropathy. Biomed Pharmacother. 2018;106:1325–31. https://doi.org/10.1016/j.biopha.2018.07.036.
125. He WT, Wan H, Hu L, et al. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Res. 2015;25:1285–98. https://doi.org/10.1038/cr.2015.139.
126. Zhou Q, Rong C, Gu T, et al. Mesenchymal stem cells improve liver fibrosis and protect hepatocytes by promoting microRNA-148a-5p-mediated inhibition of Notch signaling pathway. Stem Cell Res Ther. 2022;13:354. https://doi.org/10.1186/s13287-022-03030-8.
127. ZhangMan WY, Chen Z. microRNA-148a in exosomes derived from bone marrow mesenchymal stem cells alleviates cardiomyocyte apoptosis in atrial fibrillation by inhibiting SMOC2. Mol Biotechnol. 2022;64:1076–87. https://doi.org/10.1007/s12033-022-00487-z.
128. Dai Y, Wang S, Chang S, et al. M2 macrophage-derived exosomes carry microRNA-148a to alleviate myocardial ischemia/reperfusion injury via inhibiting TXNIP and the TLR4/NF-κB/NLRP3 inflammasome signaling pathway. J Mol Cell Cardiol. 2020;142:65–79. https://doi.org/10.1016/j.yjmcc.2020.02.007.
129. Song Y, Wang B, Zhu X, et al. Human umbilical cord blood-derived MSCs exosome attenuate myocardial injury by inhibiting ferroptosis in acute myocardial infarction mice. Cell Biol Toxicol. 2021;37:51–64. https://doi.org/10.1007/s10565-020-09530-8.
130. Lei D, Li B, Isa Z, et al. Hypoxia-elicited cardiac microvascular endothelial cell-derived exosomal miR-210-3p alleviate hypoxia/reoxygenation-induced myocardial cell injury through inhibiting transferrin receptor 1-mediated ferroptosis. Tissue Cell. 2022;79:101956. https://doi.org/10.1016/j.tice.2022.101956.
131. Ma X, Liu B, Fan L, et al. Native and engineered exosomes for inflammatory disease. Nano Res. 2022;1-16. https://doi.org/10.1007/s12274-022-5275-5

132. Yue B, Wang H, Cai X, et al. Adipose-secreted exosomes and their pathophysiologic effects on skeletal muscle. Int J Mol Sci. 2022;23. https://doi.org/10.3390/ijms232012411
133. Song B, Chen Q, Li Y, et al. Functional roles of exosomes in allergic contact dermatitis. J Microbiol Biotechnol. 2022;32:1506–14. https://doi.org/10.4014/jmb.2206.06024.
134. Zhang Y, Bi J, Huang J, et al. Exosome: a review of its classification, isolation techniques, storage, diagnostic and targeted therapy applications. Int J Nanomedicine. 2020;15:6917–34. https://doi.org/10.2147/ijn.S264498.
135. RiderHurwitz MASN, Meckes DG Jr. ExtraPEG: A Polyethylene Glycol-Based Method for Enrichment of Extracellular Vesicles. Sci Rep. 2016;6:23978. https://doi.org/10.1038/srep23978.
136. Wang C, Zhang D, Yang H, et al. A light-activated magnetic bead strategy utilized in spatio-temporal controllable exosomes isolation. Front Bioeng Biotechnol. 2022;10:1006374. https://doi.org/10.3389/fbioe.2022.1006374.
137. Zhou H, Yuen PS, Pisitkun T, et al. Collection, storage, preservation, and normalization of human urinary exosomes for biomarker discovery. Kidney Int. 2006;69:1471–6. https://doi.org/10.1038/sj.ki.5000273.
138. Kumeda N, Ogawa Y, Akimoto Y, et al. Characterization of membrane integrity and morphological stability of human salivary exosomes. Biol Pharm Bull. 2017;40:1183–91. https://doi.org/10.1248/bpb.b16-00891.
139. Welch JL, Madison MN, Margolick JB, et al. Effect of prolonged freezing of semen on exosome recovery and biologic activity. Sci Rep. 2017;7:45034. https://doi.org/10.1038/srep45034.
140. Lee MK, Kim MY, Kim S, et al. Cryoprotectants for freeze drying of drug nano-suspensions: effect of freezing rate. J Pharm Sci. 2009;98:4808–17. https://doi.org/10.1002/jps.21786.
141. Evtushenko EG, Bagrov DV, Lazarev VN, et al. Adsorption of extracellular vesicles onto the tube walls during storage in solution. PLoS One. 2020;15:e0243738. https://doi.org/10.1371/journal.pone.0243738.
142. Wang X, Zhang H, Yang H, et al. Cell-derived exosomes as promising carriers for drug delivery and targeted therapy. Curr Cancer Drug Targets. 2018;18:347–54. https://doi.org/10.2174/1568009617666170710120311.
143. Fuhrmann G, Serio A, Mazo M, et al. Active loading into extracellular vesicles significantly improves the cellular uptake and photodynamic effect of porphyrins. J Control Release. 2015;205:35–44. https://doi.org/10.1016/j.jconrel.2014.11.029.
144. Joo HS, Suh JH, Lee HJ, et al. Current knowledge and future perspectives on mesenchymal stem cell-derived exosomes as a new therapeutic agent. Int J Mol Sci. 2020;21. https://doi.org/10.3390/ijms21030727
145. Kooijmans SA, Vader P, van Dommelen SM, et al. Exosome mimetics: a novel class of drug delivery systems. Int J Nanomed. 2012;7:1525–41. https://doi.org/10.2147/ijn.S29661.
146. Mentkowski KI, Lang JK. Exosomes engineered to express a cardiomyocyte binding peptide demonstrate improved cardiac retention in vivo. Sci Rep. 2019;9:10041. https://doi.org/10.1038/s41598-019-46407-1.
147. Ji R, Zhang X, Qian H, et al. miR-374 mediates the malignant transformation of gastric cancer-associated mesenchymal stem cells in an experimental rat model. Oncol Rep. 2017;38:1473–81. https://doi.org/10.3892/or.2017.5831.
148. Sun Z, Zhang J, Li J, et al. Roles of mesenchymal stem cell-derived exosomes in cancer development and targeted therapy. Stem Cells Int. 2021;2021:9962194. https://doi.org/10.1155/2021/9962194.
149. Willms E, Johansson HJ, Mäger I, et al. Cells release subpopulations of exosomes with distinct molecular and biological properties. Sci Rep. 2016;6:22519. https://doi.org/10.1038/srep22519.
150. Abbaszadeh H, Ghorbani F, Derakhshani M, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles: A novel therapeutic paradigm. J Cell Physiol. 2020;235:706–17. https://doi.org/10.1002/jcp.29004.
151. Abbaszadeh H, Ghorbani F, Derakhshani M, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles: a novel therapeutic paradigm. J Cell Physiol. 2020;235:706–17. https://doi.org/10.1002/jcp.29004.
152. Yang Z, Li Y, Wang Z. Recent advances in the application of mesenchymal stem cell-derived exosomes for cardiovascular and neurodegenerative disease therapies. Pharmaceutics. 2022;14. https://doi.org/10.3390/pharmaceutics14030618
153. Hsuan YC, Lin CH, Chang CP, et al. Mesenchymal stem cell-based treatments for stroke, neural trauma, and heat stroke. Brain Behav. 2016;6:e00526. https://doi.org/10.1002/brb3.526.