Review article

Cardioprotective microRNAs: Lessons from stem cell-derived exosomal microRNAs to treat cardiovascular disease

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HIGHLIGHTS

- MSC-derived exosomal miRs can reduce infarct size and improve cardiac survival and function after heart failure.
- MSC-derived exosomal miRs exert cardioprotective effects through induction of angiogenesis in ischemic heart after MI.
- CPC-derived exosomal miRs show therapeutic potential for mitral regurgitation, atrial enlargement, and heart failure.

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ABSTRACT

The stem cell-based therapy has emerged as a promising therapeutic strategy for treating cardiovascular ischemic diseases (CVIDs), such as myocardial infarction (MI). However, some important functional shortcomings of stem cell transplantation, such as immune rejection, tumorigenicity and infusional toxicity, have overshadowed stem cell therapy in the setting of cardiovascular diseases (CVDs). Accumulating evidence suggests that the therapeutic effects of transplanted stem cells are predominantly mediated by secreting paracrine factors, importantly, microRNAs (miRs) present in the secreted exosomes. Therefore, novel cell-free therapy based on the stem cell-secreted exosomal miRs can be considered as a safe and effective alternative tool to stem cell therapy for the treatment of CVDs. Stem cell-derived miRs have recently been found to transfer, via exosomes, from a transplanted stem cell into a recipient cardiac cell, where they regulate various cellular process, such as proliferation, apoptosis, stress responses, as well as differentiation and angiogenesis. The present review aimed to summarize cardioprotective exosomal miRs secreted by transplanted stem cells from various sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and cardiac stem/progenitor cells, which showed beneficial modulatory effects on the myocardial infracted heart. In summary, stem cell-exosomal miRs, including miR-19a, mirR-21, miR-21-5p, miR-21-a5p, miR-22 miR-24, miR-26a, miR-29, miR-125b-5p, miR-126, miR-201, miR-210, and miR-294, have been shown to have cardioprotective effects by enhancing cardiomyocyte survival and function and attenuating cardiac fibrosis. Additionally, MCS-exosomal miRs, including miR-126, miR-210, miR-21, miR-23a-3p and miR-130a-3p, are found to exert cardioprotective effects through induction of angiogenesis in ischemic heart after MI.

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1. Introduction

## 1.1. Cardiovascular diseases and stem cell-based regenerative medicine

Cardiovascular disease (CVD) is still the major leading pathological cause of morbidity and mortality worldwide [1–4]. Cardiovascular ischemic diseases (CVIDs) or ischemic heart diseases (IHDs), such as acute myocardial infarction (MI), myocardial ischemia/reperfusion (MIR) damage, and heart failure, generate huge amounts of reactive oxygen species (ROS) in the ischemic zone [5,6], which is a major contributor to cardiomyocyte necrosis/apoptosis and death, and exacerbates cardiac disease [7]. Typically, the damaged, relatively non-regenerative myocardium undergoes a degenerative remodeling process. The heart shows limited potential for endogenous cardiomyocyte renewal after survival of an MI, which leads to the irreversible loss of a large numbers of cardiomyocytes, causing left ventricular remodeling and progressive heart failure [8]. The main therapeutic options in patients with MI are to reduce infract size and myocardial injury, induce replacement or improve repair of a damaged myocardium, as well as diminish myocardial remodeling. Over the past years, regenerative medicine has been recognized to be effective for preventing and treating cardiac diseases [9]. Transplantation of stem/progenitor cells showing regenerative potential has been well established as one promising approach for CVD therapy to replace apoptotic or dead cardiomyocytes and enhance contractility [10,11]. These cells include embryonic stem cells (ESCs) [12], induced pluripotent stem cells (iPSCs) [13], mesenchymal stem cells (MSCs) [14,15], and cardiac stem/progenitor cells [16–19]. Transplantation of stem/progenitor cells into the heart *via* infusion and/or intramyocardial injection has been used for the treatment of coronary artery disease, MI, and heart failure, in which it can foster heart repair and regeneration, and enhance cardiac functions in patients with CVD [18,19] and animal models following MIR [20–22]. Despite these promising results, some shortcomings, such as the need of a consistent supply of cells with stable phenotype, the infusional toxicity caused by transplanted cells lodged in the pulmonary microvasculature, low survival and poor differentiation into functional new cardiomyocytes, immune rejection and tumorigenicity, ectopic tissue formation, high costs and delays for the generation and handling of these cells, as well as ethical and safety challenges, are the major concerns in clinical practice [23–26].

Since the cardioprotective effect of the administrated stem cells could not be illustrated by direct *trans*-differentiation of the injected stem cells into cardiomyocytes, this effect is proposed to be mediated by paracrine communication between donor and recipient cells accompanied with exosomes secreted by stem (donner) cells. Therefore, a cell-free approach, such as therapy based on stem cell-derived exosomes, can be an effective optional choice to overcome the above-mentioned stem cell therapy-related drawbacks to treat heart disease [27,28].

1.2. Stem cell-derived exosomes as an efficient alternative to stem cell therapy of CVD

Exosomes are secreted small membrane vesicles (30–100 nm) originating from intracellular endosomes, which contain a wide variety of proteins, lipids, mRNAs, and microRNAs (miRs) and that are representative of their cellular origin (Fig. 1) [29,30], Hence, exosomes carry a multitude of signals and merge their membrane contents into the recipient cell membrane, delivering complex cargos of signaling molecules into recipient cells [31]. Exosomes function as an important mode of cell-to-cell communication to modulate or mediate a variety of cellular processes in target cells, comprising both neighboring cells and distant parts of the body [32]. Exosomes can be secreted by numerous cell types, including platelets [33], lymphocytes [34], adipocytes [35], as well as muscle [36,37], glial [38] and stem cells [39–41].

Therapeutic potential of stem cell-derived exosomes for ischemic tissue repair and regeneration has been reported by several preclinical
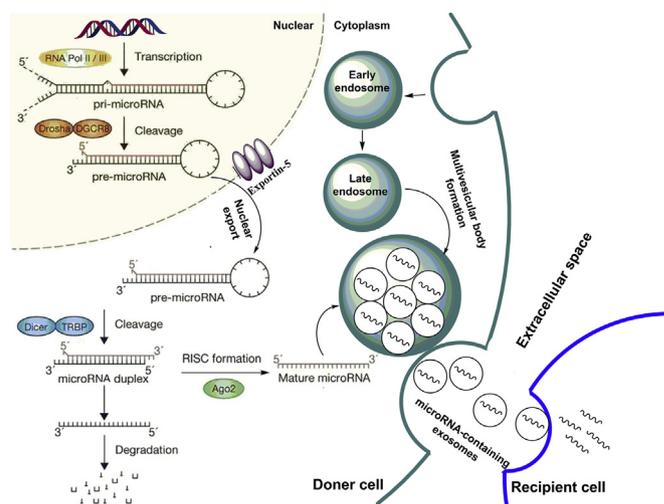
Fig. 1. A schematic view of trafficking of microRNA-containing exosomes. Small vesicles originating invaginations of the plasma membrane are fused and form early endosomes, in which protein composition and acidification are changed, to finally mature into late endosomes. Inward budding of the limiting membrane of late endosomes produces cytoplasm-containing exosomes. Upon accumulation of exosomes within the late endosome, a multivesicular body (MVB) is formed. MicroRNAs (miRs) are primarily transcribed as long pri-miRs comprising one or more pre-miR hairpin structures. Within the nucleus, the class 2 ribonuclease III Drosha cleaves these pri-miRs to form miR hairpins termed pre-miR. These pre-miR hairpins are exported into the cytoplasm and further processed into the mature miR, which is loaded into exosomes. Finally, MVB is fused to the plasma membrane and releases exosomes into the extracellular space, including blood stream and other biological fluids. Circulating exosomes are recognized and bound by a variety of receptors on recipient cells. The receiving cell then performs endocytosis, receiving the exosome cargo.

experiments [42–45]. Studies have shown that exosomes derived from stem cells efficiently recapitulate the therapeutic activities of live cells in models of myocardial IR, infarction and remodeling [46–48]. Exosomes show advantages over the corresponding stem cells: they are less complex and smaller than cells and have the potential to nullify some of the regulatory issues facing stem cells [49]. Exosomes derived from various stem cells have recently appeared as effective regulators of the heart restorative process [44,50] and angiogenesis [51,52], whereby participate in cardiac protection and repair and consequently improve heart function after infarction [47,51–54].

Despite the increasing amount of data have revealed the beneficial effects and therapeutic potentials in the field of CVDs, the exosome-based therapy in clinical practice is still debated and impeded by some important issues, such as the limited efficiency due to their time-consuming and poor purification [55] and the uncharacterized off-target and undesirable/side effects for the heart tissue due to their heterogeneous components that can arise concerns about the potential risk of tumor formation and the effects of immunogenicity [56].

Such limitations can be conquered on the basis of the growing evidence of the therapeutic effects of transplanted stem cells predominately mediated by secreting paracrine factors [57,58], typically microRNAs (miRs) presenting in secreted exosomes [59–61]. Several studies have shown beneficial effects of stem cell-derived exosomes on cardioprotection by carrying and transferring cardioprotective miRs to the injured heart cells [31,62]. Exosomal miRs confer important roles in the regulation of intracellular cell signaling, proliferation, differentiation, apoptosis, stress response, and cell/exosome therapy [46,63–66]. In the present review, we summarize all reported cardioprotective exosomal miRs derived from stem cells, their potential cardio benefits, and underlying mechanisms to heal the injured heart, and provide translational perspectives for the clinical treatment of patients with CVDs in the future.

Table 1
In vitro studies of cardioprotective exosomal miRs derived from stem cells.

Exosomal miR	Exosome source	Target cell	Protective effects	Molecular targets	Ref.
Exosomes containing miR-21-5p	Human BMSCs	Human engineered cardiac tissue	Enhance cardiac tissue contractility and calcium handling gene expression responses	Reduce expression of genes involved in cell survival/death, including Peli1, PDCD4, FasL, and PTEN	[1]
	Human BMSCs	Hypoxic-cultured H9c2 cardiomyocytic cells			[2]
Exosomes containing -higher levels of miR-29, miR-24 -lower levels of miR-21, miR-15, miR-34, miR-130, miR-378	Human BMSCs	H9C2 cardiomyocyte cell	Induce cell proliferation Inhibit oxidative stress-induced apoptosis Suppress TGF-induced transformation of fibroblast cells into myofibroblasts		[3]
Exosomes containing miR-19a	Hypoxic-human MSCs	Primary cultured rat neonatal cardiomyocytes	Enhance survival Decrease apoptosis Preserve mitochondrial membrane potential in cardiomyocytes	Decrease expression of PTEN Activate the Akt/ERK signaling pathways	[4]
Exosomes containing miR-126	AMCSs	Hypoxia-induced H9c2 myocardial cells	Protect myocardial cells against apoptosis and fibrosis		[5]
Exosomes containing miR- 125b-5p	Hypoxic-MSCs	Neonatal mouse cardiomyocytes	Decrease autophagic flux and cell death	Modulate autophagy-regulating pathway p53-Bnip3 signaling	[6]
Exosomes containing miR-21	CPCs	H9C2 cardiomyocytes	Protect against oxidative stress-related apoptosis	Downregulate oxidative stress-induced PDCD4	[7]
Exosomes containing miR-451	CPCs	H9C2 cardiomyocytes	Protect against oxidative stress-related apoptosis		[8]
Exosomes containing miR 290–295 cluster	Mouse ESCs	H9C2 cardiomyocytes HUVECs CPCs	Enhance neovascularization and cardiomyocyte survival		[9]
Exosomes containing miR-21 and miR-210	iPSCs	H9C2 cardiomyocytes	Protect against oxidative stress-induced apoptosis	Suppress caspase 3/7 activation	[10]
Exosomes containing miR-126	AMCSs	Hypoxia-induced H9c2 myocardial cell injury	Induce the microvascular generation and migration of endothelial progenitor cells	Inhibit Spred1 and PI3KR2 Enhance the VEGF signaling pathway	[10]
Exosomes containing miR-210	BMSCs	HUVECs	Promote capillary-like tube formation and angiogenesis	Inhibit expression of *Efna3* gene	[11]

Adipose-derived mesenchymal stem cells, AMCSs; Bone marrow-derived mesenchymal stem cells, BMCSs; Cardiac progenitor cells, CPCs; Embryonic stem cells, ESCs; Induced pluripotent stem cells, iPSCs.

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Table 2
In vivo studies of cardioprotective exosomal miRs derived from stem cells.

microRNA	Source of exosome	Animal model	Protective effects	Molecular targets	Ref.
Exosomes containing miR-21-5p	hBMSCs	Mouse myocardial ischemia/reperfusion model	Myocardial salvage	Reduce MI-mediated cell apoptosis and death in cardiomyocytes	[2]
Exosomes containing miR-22	Mouse BMSCs	Mouse model of MI	Decrease ischemia-induced apoptosis / Ameliorate fibrosis / Improve cardiac function	Suppress Mecp2	[12]
Exosomes containing -higher levels of miR-29, miR-24 -lower levels of miR-21, miR-15, miR-34, miR-130, miR-378	hBMSCs	Rat model of MI	Reduce cardiomyocyte apoptosis / Decrease infarct size / Attenuate cardiac dysfunction		[3]
Exosomes containing miR-26a	Hypoxic-human MSCs	Rat model of IR injury	Attenuate degree of infarct size / Reduce arrhythmias / Restore electrical conduction	Reduce GSK3β expression / Elevate Cx43 expression	[5]
Exosomes containing miR-210	Hypoxic-human MSCs	Mouse model of MI	Increase survival / Decrease scar size / Recover cardiac functions / Elevate vascular density / Decrease cardiomyocyte apoptosis / Decrease fibrosis / Enhance recruitment of cardiac progenitor cells		[13]
Exosomes containing miR-126	Adipose-derived MCSs	Rat model of MI	Decrease the size of MI / Reduce cardiac fibrosis		[10]
Exosomes containing miR-125b-5p	Hypoxic-cultured MSCs CPCs	Mouse model of MI	Improve cardiac function and infract size / Inhibit cardiomyocyte apoptosis	Inhibit autophagic flux	[6]
Exosomes containing miR-451		Mouse myocardial ischemia/reperfusion model			[8]
Exosomes containing miR 290–295 cluster	Mouse ESC	Mouse model of MI	Reduce fibrosis / Revival of cardiac proliferative response / Enhance cardiac progenitor cell survival and proliferation, as well as cardiac commitment		[9]
Exosomes containing miR-21 and miR-210	iPSCs	Mouse myocardial ischemia/reperfusion model	Protect against MIR injury	Suppress caspase 3/7 activation	[14]
Exosomes containing miR-126	AMSCs	Rat model of MI	Induce angiogenesis / Inhibit inflammation	Inhibit Spred1 and PI3KR2 / Enhance the VEGF signaling pathway	[10]
Exosomes containing miR-210	BMSCs	Mouse model of MI	Improve angiogenesis / Limit fibrosis / Enhance cardiac function in ischemic hearts	Inhibit expression of *Efna3* gene	[11,15]
Exosomes containing miR-21	Endometrium MSCs	Rat model of MI	Enhance cardiac cell survival and angiogenesis	Modulate the PTEN/Akt pathway	[16]

Adipose-derived mesenchymal stem cells, AMCSs; Bone marrow-derived mesenchymal stem cells, BMCSs; Cardiac progenitor cells, CPCs; Embryonic stem cells, ESCs; Induced pluripotent stem cells, iPSCs; Myocardial infarction, MI.

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2. Cardioprotective exosomal miRs derived from stem cells

miRs are small single-stranded noncoding RNAs (18–25 nucleotides) that negatively regulate the expression of target genes by either inducing mRNA degradation or inhibiting translation through direct binding to the 3′ untranslated region (3′UTR) of their target mRNAs [65]. miRs are typically synthesized as longer pri-miRs comprising one or more pre-miR hairpin structures (~80 nucleotides). Within the nucleus, the class 2 ribonuclease III Drosha cleaves these pri-miRs to form miR hairpins termed pre-miR. These pre-miR hairpins are exported to the cytoplasm and further cleaved by the endoribonuclease Dicer into two separate miRs, commonly called as the mature and passenger (or * strand) miR. The mature miR is loaded into the RNA-induced silencing complex (RISC), while the passenger miR is often (but not always) degraded (Fig. 1) [67]. miRs contain a 6-nucleotide seed-match site, from position 2 to 7 in their 5′ end that is complementary to the 3′ UTR region of mRNAs. Within the RISC complex, a miR binds to an mRNA, which will either results in translation inhibition or mRNA degradation, leading to lower protein levels [68]. Because of the relatively short complementary sequence and the functional suppression despite imperfect nucleotide matches, each miR can modulate hundreds of different proteins [69].

miRs have been found to exert an established role in cardiovascular function and disease [70–73] by modulating cardiac survival, apoptosis, proliferation, differentiation, autophagy, and reprogramming [74–76]. miRs have shown a crucial influence in the inflammation and regeneration phases of cardiac repair after MI [77], and also in regulation of ROS-mediated heart disease [78,79]. Recent researches have shown that the cardioprotective effect of stem cell therapy is predominantly achieved by exosomal miRs from various sources of stem cells.

2.1. Protective effects of stem cell-exosomal miRs on cardiomyocyte apoptosis and proliferation

In the process of MI, regional myocardial ischemia subsequent to a significant reduction or cessation of coronary arterial blood flow promotes myocardial injury, including apoptosis of cardiomyocyte and cardiac fibrosis leading to the irreversible acute and chronic losses of cardiomyocytes, which results in heart failure and death [80,81]. As discussed in the following sections, exosomal miRs from bone marrow mesenchymal stem cells (BMSCs) (and hypoxic BMSC), pluripotent stem cells, and cardiac progenitor cells were found to enhance cardiac function by improving cardiomyocytes survival and proliferation.

2.1.1. Myocardioprotective exosomal miRs derived from BMCSs

BMSCs are among the most promising cell-based strategies for myocardial repair after ischemic and non-ischemic cardiomyopathies [82–85]. Although the safety and efficacy of BMSCs for cardiovascular indications have frequently been approved in vigorous preclinical and clinical trials [86–89], cell transplantation related contamination, cell death, and immune rejection are the major concerns in clinical practice. Transplantation of BMSCs into the heart after MI or ischemia/reperfusion (IR) injury has been found to improve infarct size and heart function, which are accompanied by reductions in cardiomyocyte death [46,90], and these cardioprotective effects are widely accepted to be mediated by exosome-delivered paracrine factors, particularly miRs [48,51,52,90–93]. Therefore, cell-free therapies using MSCs exosomes can be a choice of procedure to treat heart disease. There has been growing evidence showing MSCs exosomes carrying miRs, which mediate cardioprotective effect of these cells.

Mayourian et al. found that exosomal miR-21-5p secreted form human BMSCs could efficiently enhance cardiac tissue contractility and calcium handling gene expression responses in mature ischemic adult human cardiomyocytes [94]. This is further confirmed by another study that showed mouse BMSCs-exosomes containing high levels of miR-21-

a5p could protect ischemic cardiomyocytes in hypoxic-cultured H9c2 cardiomyocytic cells, and in a mouse model of myocardial IR. miR-21-a5p could exert cardioprotective effects by reducing MI-mediated cell apoptosis and death in cardiomyocytes via synergic downregulation of protein levels of several genes implicated in distinct portions of cell death/survival signaling pathways, including Peli1, PDCD4, FasL, and PTEN, whereby contributing to myocardial salvage [95]. Additionally, Feng et al. reported that miR-22-enriched exosomes were secreted by mouse BMSCs following ischemic preconditioning and moved to cardiomyocytes where they decreased ischemia-induced apoptosis, ameliorated fibrosis and improved cardiac function post-myocardial infarction. miR-22 was found to exert the anti-apoptotic effects in the cardiomyocytes at least partially via suppression of methyl CpG binding protein 2 (Mecp2) [96], which is known to be overexpressed in the ischemic heart [97] as well as in the developmental cardiac and skeletal abnormalities [98]. Further, Shao et al. demonstrated that BMSC-derived exosomes contain higher levels of miR-29 and miR-24 and lower levels of miR-21, miR-15, miR-34, miR-130, and miR-378, when compared with BMMSCs. These exosomes could repair the injured myocardium by suppressing cardiac fibrosis, inflammation, and improving cardiac function in a rat model of MI. A mechanistic study showed that exosomes induced H9C2 cardiomyocyte cell proliferation, inhibited oxidative stress-induced apoptosis, and suppressed TGF-induced transformation of fibroblast cell into myofibroblasts [99]. Particularly, it was shown that over-expression of miR-24 could significantly reduce cardiomyocyte apoptosis, decrease infarct size, and attenuate cardiac dysfunction in a mouse model of MI [100]. Another study showed that elevated expression of miR-29 could prevent tissue fibrosis by inhibiting the expression of collagen [101]. It was also reported that in vivo inhibition of miR-34 could enhance cardiomyocyte survival after MI and thereby preserve the cardiac contractile function [102,103]. Additionally, other reports revealed that high expression of miR-130 and miR-378, which showed low levels in exosomes, could lead to dysfunctionality of the K-ion channel in cardiac stem cells and cardiac hypertrophy [104,105]. Likewise, it was also found that downregulation of miR-21 prevented hypertrophy [106] and suppression of miR-15 prevented cardiac ischemic injury [107].

In conclusion, the increased expression of miR-21-5p, miR-21-a5p, miR-22 miR-24, and miR-29, as well as the reduced expression of miR-21, miR-15, miR-34, miR-130, and miR-378, is suggested to be responsible for the beneficial cardioprotective effects of BMSC-derived exosomes, such as inducing cardiomyocyte proliferation and survival, suppression of cardiomyocyte apoptosis, attenuating infract size and cardiac fibrosis, improving cardiac function after MI and IR injury.

2.1.2. Myocardioprotective exosomal miRs derived from hypoxic-cultured BMCSs

Hypoxic precondition of MSCs has been shown to improve their biological activities and, therefore, enhance the efficacy of MSCs transplantation for treatment of MI [90,108,109]. The salutary effects of hypoxia preconditioning on MSCs therapy for cardiovascular diseases were suggested to be mediated in part or in whole by parallel effects on exosomes. In this way, miR cargoes of BMSCs exosomes have been found to exert a critical effect.

Park et al. demonstrated that expression of miR-26a was significantly elevated in exosomes derived from hypoxic-human MSCs, compared with those derived from normoxic-human MSCs. It was shown that systemic injection of hypoxic exosomes containing increased levels of miR-26a levels could attenuate the degree of infract size and reduce arrhythmias by restoring electrical conduction after IR injury in a rat model. Mechanistically, the cardioprotective effect of miR-26a was found to be attributed to reduction of increase in GSK3β expression and elevation of decrease in Cx43 expression, which are dysregulated in the process of IR injury [110]. Furthermore, Zhu et al. reported that hypoxia treatment of BMSCs could elevate the expression of miR-210 in exosomes secreted from hypoxia-treated BMSCs.

Intramyocardial injection of hypoxic exosomes containing over-expressed miR-210 into the infarcted heart of C57BL/6 mice led to significantly higher survival, smaller scar size and better recovery of cardiac functions. Hypoxic exosomes with high levels of miR-210 donated elevated vascular density, lower cardiomyocytes apoptosis, decreased fibrosis and enhanced recruitment of cardiac progenitor cells in the infarcted heart relative to null exosomes [111]. Accordingly, Yu et al. showed that exosomes from BMSCs cultured under hypoxic conditions can serve as a reservoir of anti-apoptotic miRs, particularly miR-19a for cardioprotection, in comparison with those from normoxic-cultured MSCs. Investigation of cell injury in primary cultured rat neonatal cardiomyocytes and in the rat heart revealed that hypoxic exosomes carrying high levels of miR-19a could enhance survival, decrease apoptosis, and preserve mitochondrial membrane potential in cardiomyocytes cultured under a hypoxic condition. The observed protective effect in the myocardium treated with hypoxic exosomes was found to be mediated by overexpressed miR-19a in cardiomyocytes, which was accompanied by decreased expression of miR-19a target PTEN, resulting in the activation of the Akt/ERK signaling pathways [48]. Additionally, Luo et al. demonstrated that exosomes isolated from miR-126-overexpressing adipose-derived MCSs prevented hypoxia-induced H9c2 myocardial cell damage by protecting myocardial cells against apoptosis and fibrosis. The cardioprotective effects of miR-126 was confirmed by *in vivo* studies that showed miR-126-enriched exosomes derived from ADSCs can significantly decrease the size of MI and reduce cardiac fibrosis in a rat model of MI [112]. Likewise, as revealed by Xiao et al. exosomal miR-125b-5p derived from hypoxic-cultured MSCs could exert a cardioprotective effect through modulation of autophagic flux [113]. Autophagy can protect cell viability, attenuate infarct size, and reduce adverse left ventricular remodeling under conditions of mild ischemia by degrading injured organelles for ATP production [114–116], however, under prolonged or severe ischemia, it can cause cardiomyocyte cell death [116–118] and worsen myocardial performance [119]. An *in vitro* study by Xiao et al. showed that exosomal miR-125b-5p could decrease autophagic flux and cell death *via* modulation of thr autophagy-regulating pathway p53-Bnip3 signaling in neonatal mouse cardiomyocytes co-cultured with MSCs-secreting exosomes on hypoxia and serum deprivation conditions. More importantly, an *in vivo* study on a mouse model of MI revealed that treatment with transplanted MSCs secreting exosomes containing mainly miR-125b-5p could improve measurements of cardiac function and infract size after MI through modulation of the autophagic flux [113].

In conclusion, hypoxic condition can increase levels of cardioprotective miRs carried by ScExo, including miR-26a, miR-210, miR-19a, miR-126, miR-125b-5p, which were found to be associated with higher survival and lower apoptosis of cardiomyocytes, attenuated degree of infract size and arrhythmias, elevated vascular density, decreased fibrosis, as well as better recovery of cardiac functions and enhanced recruitment of cardiac progenitor cells in the infarcted heart.

2.1.3. Myocardioprotective exosomal miRs derived from cardiac progenitor cells

Cardiac progenitor cells (CPCs), a small population of stem-like cells residing in the adult heart, are the most promising stem cell types for cardiac protection and repair. CPCs-derived exosomal miRs have been found to be the main cardioprotective mediators of CPCs against heart injury during oxidative stress. Oxidative stress originates primarily in mitochondria from ROS and can be critical in many important steps in cardiac diseases, such as mitral regurgitation [120], atrial enlargement [121], and heart failure [122]. Actually, in the same oxidative environment, oxidative stress causes apoptosis of resident cardiomyocytes whereas enhances the production of transplanted CPC derived cardioprotective exosomes. For example, the *in vitro* studies by Xiao et al. showed that miR-21 in CPC-derived exosomes up-regulated under the oxidative stress, potentially protect recipient H9C2 cardiomyocytes against oxidative stress-related apoptosis. CPC-derived exosomal miR-

21 could suppress the apoptosis pathway in the receptor cardiomyocytes through downregulating oxidative stress-induced PDCD4 [123], an inducer of tumor cell apoptosis and inhibitor of tumor metastasis, as a predicted target gene of miR-21 in tumor cells [124]. The other study conducted by Chen et al. revealed that CPC-derived exosomes contained high levels of miR-451 and can protect cardiomyocytes from oxidative stress-induced apoptosis *in vitro* and IR injury *in vivo* [125].

Therefore, the oxidative stress-treated CPCs can secret exosomes containing cardioprotective miRs, such as miR-21 and miR-451, that can protect cardiomyocytes against oxidative stress-induced apoptosis, suggesting that theses miRs can be therapeutic tools for treatment of mitral regurgitation, atrial enlargement, and heart failure arisen during oxidative stress injury [122].

2.1.4. Myocardioprotective exosomal miRs derived from pluripotent stem cells

Both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are pluripotent cells with unparalleled differentiation ability, which possess great potential for cardiac regeneration [126]. Although cardiomyocytes isolated from ESCs and iPSCs have been found to enhance cardiac regeneration and function in animal models of heart failure, some complications, such as elevated arrhythmogenic response [127,128], immune rejection, and teratoma formation, have been observed after transplantation of an unpurified ESC or iPSCs derived cardiomyocyte population [129,130]. Additionally, ESC/iPSC derived cells also suffer some deficiencies in cell retention, coupling and survival in ischemic myocardium, as it is known for adult stem cells. It has been found that cell-free components of ESC/iPSC, such as exosomes, which carry ESC-specific miRs, can provide a potential alternative for cardiac protection and regeneration [41,46]. In this regard, Khan et al. showed that mouse ESC-exosomes containing elevated levels of miR 290–295 cluster (particularly miR-294) hold ability to improve the function in infarcted hearts. miR-294-contained exosomes were found to enhance neovascularization and cardiomyocyte survival *in vitro* and reduced fibrosis post infarction, consistent with revival of the cardiac proliferative response in mice with MI. Interestingly, ESC-exosomes carrying mir-294 could enhance cardiac progenitor cell survival and proliferation, as well as cardiac commitment, 8 weeks after *in vivo* transfer, along with formation of *bona-fide* new cardiomyocytes in the ischemic heart [131]. Wang et al. have reported that exosomes from iPSCs transmit cardioprotective miRs, including miR-21 and miR-210, and prevent cardiomyocyte apoptosis in the ischemic myocardium. The delivered exosomal miR-21 and miR-210 were found to protect recipient H9C2 cardiomyocytes *in vitro* against oxidative stress-induced apoptosis by suppressing caspase 3/7 activation. This effect was confirmed by an *in vivo* study showing that intramyocardial administration of iPSCs-exosomes into mouse ischemic myocardium can protect against MIR injury [132].

2.2. Cardioprotective exosomal angiogenic miRs-derived from MCSs

In myocardial ischemia during MI, blood flow and oxygen to the heart are impaired. It occurs when an artery becomes narrows or blocks for a short time, preventing oxygen-rich blood from reaching the heart. Angiogenesis in the post-MI heart is crucial for promoting reperfusion and function of the ischemic heart [133,134].

Neoangiogenesis can be enhanced by MCSs exosomes, supplying angiogenic miRs. For example, miR-126 is expressed in vascular endothelial cells and vascular smooth muscle cells and has been found to be a master regulator of angiogenesis through the regulation of cell proliferation, differentiation, and apoptosis [135–137]. Luo et al. have reported that miR-126-enriched exosomes isolated from adipose tissue MSCs (AMSCs) can significantly induce the micro vascular generation and migration of endothelial progenitor cells during hypoxic injury. Pro-angiogenic effects of exosomal miR-126 are supported by *in vivo* studies that showed blood vessel formation was induced in the

infarction region of treated AMI rats [112]. miR-126 can directly inhibit Spred1 and PI3KR2 and consequently enhance the VEGF signaling pathway. When miR-l26 is downregulated, the overexpression of Spred1 and PI3KR2 suppresses the MAPK and PI3K signaling pathway, which impacts angiogenic factor signals and leads to angiogenesis disruption [138,139]. miR-126 not only can induce angiogenesis but also shows anti-inflammatory effects through direct targeting of inflammatory factors SPRED1, PIK3R2, and VCAM1 [140,141]. miR-126-enriched exosomes derived form AMSCs were also found to decrease inflammation, as detected by decreased levels of inflammatory cytokines IL-1β, IL-6, and TNF-α in hypoxic H9c2 myocardial cells, and in serum of treated AMI rats [112]. To sum up, exosomal miR-126 derived from AMSCs can improve infarcted cardiac performance through induction of angiogenesis and inhibition of inflammation in a rat model of AMI [112]. In another study, Wang et al. reported that BMSCs-derived exosomes, *via* miR-210, can improve infarcted cardiac function by promotion of angiogenesis. As revealed by an *in vitro* study, miR-210-enriched exosomes can significantly promote capillary-like tube formation and angiogenesis through facilitation of HUVEC migration and proliferation by inhibiting the *Efna3* gene [142] which plays a vital role in angiogenesis [143–145]. *In vivo* studies in mice with AMI injury showed that intravenous injection of miR-210-enriched exosomes can profoundly improve angiogenesis, limit fibrosis, and enhance reduced cardiac function in ischemic hearts [142]. Pro-angiogenic and cardioprotective effects of miR-210 are further confirmed by another study that evaluated its effect in a murine model of MI [143]. In addition, Wang et al. evaluated the cardioprotective effect of MSCs from three different sources -bone marrow, adipose, endometrium- and found that endometrium MSCs (EMSCs) secreting miR-21-enriched exosomes confer superior cardioprotection relative to BMSCs or AMSCs. miR-21 was found to mediate cardioprotective effects of EMSC therapy by enhancing cardiac cell survival and angiogenesis through the PTEN/Akt pathway in a rat model of MI [146]. Likewise, according to bioinformatics analyses performed by Ferguson et al., MSC-derived exosomal miR-23a-3p and miR-130a-3p were predicted to target the most genes involved in angiogenesis and vasculature development [147]. The pro-angiogenic effect of MSC-derived exosomal miR-130a-3p is supported by another study that showed miR-130a-3p induces angiogenesis through inhibition of the antiangiogenic homeobox genes *GAX* and *HOXA5* [148]. MCS exosomal miRs, including miR-126, miR-210, miR-21, miR-23a-3p and miR-130a-3p, are suggested to exert cardioprotective effects through induction of angiogenesis in ischemic heart after MI.

3. Conclusion and future translational perspectives

In the present review, we discuss miRs from stem cell-exosomes, which show therapeutic potential of stem cells for heart injury caused by MI and/or MIR, while covering cell/exomes therapy related drawbacks (Tables 1 and 2). Stem cell-derived exosomal miRs are powerful regulators of survival and functional properties of cardiomyocyte, cardiac progenitor and endothelial cells, whereby enhance cardiac function and angiogenesis after heart injury by improving regeneration of both injured myocardium and blood vessels in the infarcted heart, and therefore possess a huge therapeutic capacity in prevention/treatment of CVDs. Correspondingly, novel therapeutic approaches will set translational perspectives for clinical treatment of patients with CVDs in the future. By specific modulation of stem cell-derived cardioprotective miRs expression in cardiac or endothelial cells, we are able to improve cardiac and/or vascular regeneration. Still, the ideal miR cocktail has not reached the bar yet. Different combinations of miR targets should be tested in different cell types, in various cardiovascular settings, with attention for both safety and efficacy. As reviewed above, stem cell-derived exosomal cardioprotective miRs have been verified by *in vivo* studies in animal models and could be valuable candidates for first clinical testing in humans, appearing to hold a significant share in

the "Wall Street" of new therapeutic modalities for CVDs. However, future research is needed for further testing and fine-tuning in a clinical setting.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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