



# Mesenchymal Stem Cell-Derived Exosomes and Their MicroRNAs in Heart Repair and Regeneration

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## Abstract

Mesenchymal stem cells (MSCs) can be differentiated into cardiac, endothelial, and smooth muscle cells. Therefore, MSC-based therapeutic approaches have the potential to deal with the aftermaths of cardiac diseases. However, transplanted stem cells rarely survive in damaged myocardium, proposing that paracrine factors other than trans-differentiation may involve in heart regeneration. Apart from cytokines/growth factors, MSCs secrete small, single-membrane organelles named exosomes. The MSC-secreted exosomes are enriched in lipids, proteins, nucleic acids, and microRNA (miRNA). There has been an increasing amount of data that confirmed that MSC-derived exosomes and their active molecule microRNA (miRNAs) regulate signaling pathways involved in heart repair/regeneration. In this review, we systematically present an overview of MSCs, their cardiac differentiation, and the role of MSC-derived exosomes and exosomal miRNAs in heart regeneration. In addition, biological functions regulated by MSC-derived exosomes and exosomal-derived miRNAs in the process of heart regeneration are reviewed.

**Keywords** Cardiovascular diseases · Mesenchymal stem cells · Extracellular vesicles · Exosomes · Heart regeneration · MicroRNA

## Abbreviations

CVDs	Cardiovascular diseases	EVs	Extracellular vesicles
MSCs	Mesenchymal stem cells	ILVs	Intraluminal vesicles
miRNAs	microRNA	MVB	Multivesicular body
BM-MSCs	Bone marrow MSCs	ESCRT	Endosomal sorting complexes required for transport
AT-MSCs	Adipose tissue-derived MSCs	VEGF	Vascular endothelial growth factor
UC-MSCs	Umbilical cord MSCs	MI	Myocardial infarction
ESC-MSCs	Embryonic stem cell-derived MSCs	HUVEC	Human umbilical vein endothelial cell
iPSC-MSCs	Induced pluripotent stem cell-derived MSCs	EGF	Epidermal growth factors
5-aza	5-Azacytidine	PDGF	Platelet-derived growth factors
AA	Ascorbic acid	FGF	Fibroblast-derived growth factors
BMP2	Bone morphogenetic protein	TGF	Transforming growth factors
DMSO	Dimethylsulfoxide	NF-κB	Nuclear factor κB
		Ang1	Angiopoietin-1
		Flk1	Fetal liver kinase-1
		Vash1	Vasohibin-1
		EPHB2	Ephrin type-B receptor-2
		NRP2	Neuropilin-2
		SEMA5B	Semaphoring-5B
		NCOA1	Nuclear receptor coactivator-1
		MAZ	MYC-associated zinc finger protein
		ALOX5	Arachidonate 5-Lipoxygenase
		PPM1A	Protein phosphatase-1A
		ROS	Reactive oxygen species

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PI3K	Phosphoinositide 3-kinase
miRISC	miRNA-induced silencing complex
SRF	Serum response factor
MEF2	Myosin enhancer factor-2
MRF	Myogenic regulatory factor
CHD	Congenital heart disease
Tbx5	T-box transcription factor-5
ANF	Atrial natriuretic factor
BNP	Brain natriuretic peptide
PTEN	Phosphatase and tensin homolog
SOX-6	SRY-box transcription factor-6
CTGF	Connective tissue growth factor
HDAC4	Histone deacetylase-4
Hand	Hand transcription factor-2
Dll-1	Delta-like 1
Dab2	Disabled homolog-2
IGF1	Insulin-like growth factor-1
CXCR4	Chemokine receptor type 4
CMs	Cardiomyocytes
DU145	Human prostate cancer cell line
hECTs	Human-engineered cardiac tissue
CSCs	Cardiac stem cells
HMGA2	High-mobility group AT-Hook 2
EZH2	Enhancer of zeste homolog 2
EMT	Epithelial-mesenchymal transition
LV	Left ventricular
AMP	Adenosine 5'-monophosphate
OS	Oxidative stress
TIMPs	Tissue inhibitor of matrix metalloproteinases
MMPs	Matrix metalloproteinases

## Introduction

Cardiovascular diseases (CVDs) are the major cause of death throughout the world [1, 2]. A number of therapeutic approaches for CVDs are currently under practice such as drugs (ACEI/ARB/ $\beta$ -blockers), percutaneous coronary intervention, and artery bypass grafting [3–6]. However, all of the above mentioned strategies only allow to relieve the symptoms and delay the offset of disease progression but cannot assist to resolve the fundamental problems of regeneration in damaged cardiac tissue. Cardiomyocytes are terminally differentiated cells and thus fail to repair themselves after the damage occurs by CVDs. Therefore, fibroblasts take the place of injured cardiomyocytes and ultimately lead to ventricular remodeling and heart failure [7]. Modern techniques such as cell-based regenerative approach intend to replace the dead cardiomyocytes with healthy cardiac cells.

Mesenchymal stem cells (MSCs) are considered an ideal candidate for cardiac repair and regeneration due to their remarkable properties such as abundant availability, immune

modulation, and non-teratogenicity [8, 9]. The role of MSCs in cardiac differentiation is demonstrated by numerous studies [10, 11]. Various pharmacological, chemical, genetic, and biological factors have been reported in multiple studies for inducing cardiac differentiation [12–15]. However, stem cell-based therapies have generally failed to produce significant improvement in heart function [16]. Studies show that the anti-apoptotic, anti-inflammatory, and anti-fibrotic properties of MSCs are mediated through paracrine factors (i.e., secretion of cytokines, growth factors, exosomes, and microRNA (miRNAs)) [17–21]. Exosomes are enriched in cytokines, growth factors, lipids, and miRNAs and actively participate in cell communication and signaling processes [22]. More recently, studies using MSC-derived exosomes and exosomal miRNAs have shown encouraging outcomes in terms of the regeneration of damaged hearts [23].

Numerous cutting-edge studies have demonstrated the regulatory potential of miRNAs generated from exosomes to support myocardial regeneration. Herein, we review the cardiomyogenic potential of mesenchymal stem cells with a focus on the involvement of MSC-derived exosomes and exosomal miRNAs in the process and also present an overview focusing on the cellular functions affected by MSC-secreted exosomes and exosomal miRNAs in the process of heart regeneration.

## Mesenchymal Stem Cells

MSCs are non-hematopoietic, multipotent, adherent cells that can be differentiated into osteoblasts, chondrocytes, and adipocytes [24–26]. Phenotypically, MSCs comprise a population of cells with distinct physiology, morphology, and surface markers [27]. There is a vast variety of surface receptors present on MSCs such as extracellular matrix proteins, adhesion protein molecules, cytokines, and growth factor that gives MSCs particular functions and properties. The MSCs express cluster of differentiation (CD) markers, such as CD-44, CD-105, CD-106, CD-166, CD-29, CD-73, CD-90, CD-117, Sca-1, and STRO-1 [28–31]. Similarly, the identification of MSCs can be confirmed by the absence of hematopoietic stem cell-related differentiation markers, i.e., CD-11, CD-14, CD-34, and CD-45 [17, 29]. In addition to strong self-renewal and multipotency, MSCs also have the following three major properties: (i) immune-regulation, (ii) low immunogenicity, and (iii) homing potential [32]. Therefore, MSCs are a reliable cell source that can be used in damaged tissue/organs caused by aging and pathological changes. MSCs can be isolated from nearly all the tissues of the body, including adult tissues (i.e., bone marrow, adipose tissues, peripheral blood, skeletal muscles, tendons, synovial fluid, brain, dermis, and dental pulp), perinatal tissues (i.e., umbilical cord and amnion), and pluripotent stem cells (i.e., induced pluripotent stem cells and embryonic cells) [33, 34].

Bone marrow MSCs (BM-MSCs), adipose tissue-derived MSCs (AT-MSCs), and umbilical cord MSCs (UC-MSCs) have been reported to be safe in clinical settings. However embryonic stem cell-derived MSCs (ESC-MSCs) and induced pluripotent stem cell-derived MSCs (iPSC-MSCs) have the advantage over other sources in terms of their high proliferation and unlimited expansion with consistent quality [34].

### Cardiac Differentiation of Mesenchymal Stem Cells

Regenerative medicine uses the differentiation and homing potential of MSCs to treat injured tissues [35, 36]. The clinical use of MSCs started in the late 90s and continued and consequently established the virtue of MSCs in the treatment of ischemic heart diseases. There are multiple cell culture conditions that are being used to induce cardiac differentiation in MSCs [37]. Chemical analogs such as 5-azacytidine (5-aza), ascorbic acid (AA), glycoproteins such as bone morphogenetic protein (BMP2), and some other compounds like angiotensin II and dimethylsulfoxide (DMSO) are in practice to enhance cardiac differentiation. Moreover, genetic modification, transcription factors, and cardiomyocyte lysis medium have also been used in various studies [12, 21, 38–40]. In 2022, Poomani et al. [41] extensively reviewed the research studies conducted to evaluate the therapeutic effects of MSCs in cardiac diseases and highlighted the three main functions of MSCs that involve in cardiac repair and regeneration. These include (1) the mass production of new cardiomyocytes, (2) the development and stimulation of endogenous cardiac stem cells (CSCs), and (3) the maintenance of a new vascular system [41]. However, the respective study indicates the unsatisfactory results of MSC transplantation due to the poor viability and survival in infarcted tissue of the myocardium. To overcome that inauspicious outcome, researchers are focusing on exosomes and exosomal miRNA-based cell free therapeutic approaches, which may represent promising treatment options for heart patients.

### Exosomes

Extracellular vesicles (EVs) such as apoptotic bodies, exosomes, microvesicles, and macrovesicles have different structural and functional characteristics [42, 43]. The term ‘EVs’ has been suggested to be used in modern nomenclature by the International Society for Extracellular Vesicles, which is employed for two or more classes of EVs, which may be due to the lack of standardization procedures for both isolation and characterization of EVs. In this review, we use the term ‘exosome’ because of their specific origin and presence of widely accepted surface markers [44]. EVs secrete proteins, lipids, nucleic acids, and miRNAs which play a vital role in intercellular signaling [45]. Exosomes are the

class of EVs with a size range between 30–150nm in diameter [46]. The biogenesis of exosomes occurs by two pathways: (i) classic pathway and (ii) direct pathway. Exosome synthesis in the classic pathway starts with the endocytosis of transmembrane proteins, followed by their trafficking to early endosomes, then in late endosomes, where they mature into intraluminal vesicles (ILVs). The late endosomes with loaded ILVs are termed as ‘multivesicular body (MVB).’ MVBs are formed by two mechanisms, i.e., endosomal sorting complexes required for transport (ESCRT) dependent and independent mechanisms. MVBs either undergo fusion with lysosomes and get degraded or get infused with the plasma membrane and release the mature exosome in extracellular space by exocytosis [44, 46, 47]. The direct pathway of exosome biogenesis is more immediate in which cells like T cells and erythroleukemia cell lines directly release exosomes from the plasma membrane. However, the exosomes synthesized from both pathways are indistinguishable [46]. The composition and functions of exosomes depend on the site of release, parental cell, and secretion pathways [48–50]. Exosomes are believed to be the key players in various pivotal biological processes such as immunological responses, cellular homeostasis, autophagy, cell signaling, and cell to cell interactions [51]. Exosomes connect with target cells via endocytosis to facilitate intercellular communication between cells [52]. Exosomes exert their effects on recipient cells through various molecular mechanisms, such as epigenetic reprogramming, transfer of activated receptors, and target cell stimulation via surface-bound ligands [53, 54]. Exosomes disseminate their intercellular signaling actions by releasing the cargo of biological molecules such as nucleic acids (DNAs and RNAs), lipids, metabolites, and soluble and integral proteins [46].

### Role of MSC-Derived Exosomes in Heart Regeneration

A number of in vitro and in vivo studies show encouraging results of MSC-based therapies in heart regeneration. However, cell-based therapeutic approach is still hampered by some of the major limitations such as cell death and low engraftment in recipient’s hearts [55–57]. Recent research provides shreds of evidence that the paracrine factors produce the regenerative effects of cellular therapy rather than stem cell trans-differentiation. The smaller size, less complex nature, and potential to nullify stem cell-associated regulatory issues make exosomes an ideal candidate in the heart repair and regeneration process.

According to research, exosomes made from MSCs possibly have unique components depending on the growth conditions. For instance, MSCs cultured with stroke serum, generated from the blood of mice with middle cerebral artery blockage, showed considerably higher cellular proliferation

when compared to MSCs produced in fetal bovine serum or normal serum [58]. Additionally, research indicates that the size of the exosome, the route of administration, the techniques used for its separation and purification, and the origin of its parental cells all play a significant role in the therapeutic effects of MSC-Exos. The most effective method of distributing exosomes produced from MSCs remains under investigation. Although intramyocardial and intravenous transplantation are the two administration techniques used the most frequently, transendocardial transplantation is perhaps the most effective technique [59, 60]. It has been reported that intravenous delivery of MSC-Exos in the rat model uses 40–400 µg, while intramyocardial injection uses 20–80 µg. In contrast, intravenous delivery of MSC-Exos in mice requires 20–50 µg, whereas intramyocardial injection needs between 1–600 µg [61].

It has been reported that genetic alterations in the parental cells is an effective method for increasing the therapeutic benefits of exosomes. By enhancing or suppressing the expression of particular genes or proteins, this approach has been validated in various studies. Ma et al. [62] in 2017 reported that the recombinant adenovirus with the Akt gene sequence was able to genetically modify MSCs and cause the expression of platelet-derived growth factor-D (PDGF-D) in its associated exosomes. These genetically modified MSCs and their exosomes promote neovascularization, cardiomyocyte repair, and regeneration. The majority of studies show that MSC-Exos has cardioprotective effects when administered immediately after a MI, but preservative effects have been reported when MSC-Exos was administered 30 min, 48 h, or even 1 week after a MI. Therefore, the timing of MSC-Exos administration after MI is crucial [61]. Pre-clinical trials using MSC-Exos to treat cardiovascular disorders are still in their early stages. However, investigations have shown that MSC-Exos have cardioprotective and regenerative benefits following myocardial damage.

MSC-derived exosomes are considered an important regulator in the processes of angiogenesis, survival, and immune response modulation [63]. A large set of data demonstrate the potential of exosomes in improving the functioning of the damaged heart [64–68]. These studies from the last decades contribute to confirming the hypothesis about exosomes being a persuasive factor that may aid in the treatment of heart injury. Yet, the details about the underlying mechanisms and the effecting molecules needed some thorough investigations.

### MSC-Derived Exosomes Promote Heart Regeneration via Angiogenesis

Multiple scientific studies support the narration that exosomes implement their therapeutic effects by upregulating

angiogenesis, which is a process that restores blood supply to the injured heart through stimulation of the process of new blood vessel growth [69]. The exosomes being involved in upregulating angiogenesis have been confirmed by the considerable increase of vascular endothelial growth factor (VEGF), a key element to maintain vascular homeostasis and angiogenic cascade, in MSC-Exo-treated endothelial cells (ECs) in multiple *in vitro* investigations [70–74]. In 2014, Bian et al. [68] reported that the combination of MSC-derived EVs and exosomes promotes angiogenesis and improves cardiac functions. The authors have isolated the EVs (mixture of microvesicles and exosomes) from hypoxia-induced MSCs and injected them into the rat model of myocardial infarction (MI) and have observed an enhanced blood circulation, improved systolic and diastolic performance of the heart, and reduced infarct size. However, the exact mechanism stayed unclear how EVs show their functionality when it comes to their therapeutic use. Similar results have also been validated by a few other *in vitro* studies, in which the MSC-derived exosomes (MSCs-Exos) significantly upregulated the vascular tube formation in human umbilical vein endothelial cell (HUVEC), thus promoting the angiogenesis [75, 76]. According to these results, it can be assumed that ischemic MSCs can induce an angiogenic environment by secreting exosomes which aid *in situ* tissue repair. Furthermore, the possible inductive effects of hypoxic condition on the process of angiogenesis are also not negligible. Similar angiogenic effects of MSCs-Exos have been reported in *in vivo* study of 2020, by Xu et al. [74], who stated that exosomes derived from multiple sources (i.e., bone marrow, adipose, and umbilical cord blood-derived MSCs) improve cardiac cell survival and angiogenesis, thus improve heart function and protect the myocardium. The enhanced angiogenesis has been confirmed by the upregulation of specific growth factors such as VEGF, bFGF (basic fibroblast growth factor), and HGF (hepatocyte growth factor). Additionally, the authors have provided a comparative analysis of exosomes derived from MSCs of different sources, thus contributing to evaluate the idea that exosomes derived from different MSCs sources may have different therapeutic efficiencies.

As we are already familiar with the fact that exosomes perform the intracellular signaling mechanism by releasing the cargo of active chemicals, the modern era of growing research is focusing on different biochemical molecules in this aspect, such as mRNAs, proteins, and miRNAs, that may be the root elements causing the angiogenic effects of EVs. The cargo-dependent functionality of MSCs-Exos in angiogenesis has been briefly reviewed recently [16, 77]. VEGF, epidermal growth factors (EGF), platelet-derived growth factors (PDGF), fibroblast-derived growth factors (FGF), transforming growth factors (TGF), nuclear factor κB (NF-κB)

interleukins, galectin-1, ezrin, cadherin, inducers of extracellular matrix metalloprotease, transcription factors, and miRNAs are some of the studied molecules involved in angiogenesis by cargo-dependent role of MSCs-Exos. Collino et al. in 2017 [78] have also reported a variety of pro-angiogenic and pro-migratory molecules (i.e., VEGF, PDGF, TGF, and IL-8) in the fractions of EVs, separated on the basis of density, along with a cluster of proteins and miRNAs which are crucially involved in different pathways of cell protection. A detailed proteomic analysis of MSC-Exos has been carried out by Anderson et al. [79]; the authors have reported the presence of putative paracrine effector proteins of angiogenesis (i.e., PDGF, EGF, FGF, NF- $\kappa$ B), besides other clusters of proteins. The expression of these angiogenic proteins was enhanced when exposed to ischemic tissue-simulated conditions. In addition, the authors have deliberately discussed the NF- $\kappa$ B signaling pathway proteins as a key mediator of angiogenesis. This provides us with an explicit direction for future research, which may lead us toward the treatment of ischemic tissue-related diseases. A further investigation by Vrijssen et al. [80] described that the stimulation of VEGF expression in ECs ultimately activates the protein kinase cAMP-dependent (PKA) signaling pathway which synergistically controls the expression of angiopoietin-1 (Ang1) and fetal liver kinase-1 (Flk1), and stops the expression of vasohibin-1 (Vash1), a negative regulator of angiogenesis. Suppression of Vash1 in endothelial cells was also reported in 2016 by Liang et al. [81]. Another proteomic investigation revealed that MSC-Exos participate in angiogenesis and cellular proliferation through cell adhesion proteins (galectin-1, ezrin, and p195) [82]. Angiopoietin network (ANGPT1, ANGPT4, and ANGPTL4) and other crucial angiogenesis mediators including ephrin type-B receptor-2 (EPHB2) and neuropilin-2 (NRP2) that were involved in angiogenesis were increased in ECs treated with MSC-Exos. Moreover, numerous genes that influence the expression of VEGF such as semaphoring-5B (SEMA5B), nuclear receptor coactivator-1 (NCOA1), and MYC-associated zinc finger protein (MAZ) were also markedly elevated. Whereas ECs in response to MSCs-Exo-treatment dramatically reduce the expression of anti-angiogenic genes such as serine protease inhibitor Kazal-type 5 (SPINK5), arachidonate 5-Lipoxygenase (ALOX5), and protein phosphatase-1A (PPM1A) [83]. Hence, it has therefore been suggested that the potentiality of MSC-Exos therapeutic effects in cardiac injury somewhat rely on the culture parameters and sources of MSC. As the multiple *in vitro* and *in vivo* studies recommend that MSCs-Exos show their strongly convincing therapeutic effects in cardiac regeneration, there is still a large gap needed to be filled with thorough investigations until it becomes a main treatment option for cardiac injuries with a high percentile of recovery. With this account, it is crucial to understand the underlying mechanisms of MSCs-Exos in angiogenesis.

### MSC-Derived Exosomes Promote Heart Regeneration via Anti-inflammatory Effects

The therapeutic effect of MSC-Exos in the case of ischemic heart diseases does not only limit to their angiogenic properties, but MSC-Exos also holds strong immunosuppressive anti-inflammatory effects [16]. As it has been acknowledged that myocardial infarction (MI)-induced inflammation stimulates the reactive oxygen species (ROS) level and increases cardiac injury [84, 85]. Briefly, inflammation induced by MI increases fibrosis, protease activity, and pro-inflammatory cytokine production and alters the morphological configuration of the left ventricle which develops serious clinical complications [86–90]. Previous research declares that anti-inflammatory effects are developed by the exosome release from MSCs [55, 91, 92]. Cargo of MSC-Exos restricts MI-induced inflammation in cardiac tissues by limiting the invasion and proliferation of immune cells [75]. *In vitro*, MSC-derived exosome releases IL-10 which reduces T cell activation, multiplication, and differentiation [93]. Moreover, in 2012 Mokarizadeh et al. [94] reported that MSC-Exos through membrane-bound transforming growth factor- $\beta$  (TGF- $\beta$ ) and programmed death-ligand-1 (PD-L1) convert the pro-inflammatory response of acute MI to a tolerogenic immune response which ultimately inhibits tissue damage and stimulates repairing mechanisms. It has been hypothesized that MSC-derived exosome's anti-inflammatory properties originate from their parental cell. According to the prior studies, MSCs have distinct anti-inflammatory activities that include deactivating T effector cells, reducing the generation of B cells, and controlling the polarization of macrophages [95–97]. Numerous studies show that MSC-Exo has anti-inflammatory properties that enable it to produce cardioprotective benefits by intramyocardial and intravenous transplantation [69, 98–103]. A recent study demonstrated that exosomes made from MSCs successfully mimicked the immunosuppressive effects attributed to MSCs. This was demonstrated by their capacity to control B cell proliferation and immunoglobulin production [104].

### MSC-Derived Exosomes Promote Heart Regeneration via Anti-apoptotic Effects

Therapeutic effects of MSC-derived exosomes in heart diseases arbitrated by the alteration of biomolecules such as ATP, NADH, and ROS expression in cardiac cells. These biomolecules participate in the phosphorylation of c-Jun N-terminal kinase (JNK) followed by the activation of multiple proteins including mitogen-activated protein kinase-7 (MKK7), MKK4, and MAP2Ks that regulate apoptosis, oxidative stress, and cellular regeneration [105]. MI resulted in the accumulation of infiltrated inflammatory cells that

produce ROS and ultimately lead to apoptosis. ROS generation is reduced and the apoptotic response is controlled by the MSC-Exo transplantation [61]. Another study demonstrated that cargo of MSC-Exos induces the expression of protein kinase B or phosphoinositide 3-kinase (PI3K), ATP, and NADH in the ischemic reperfused murine model, which activates the signaling cascade of cell survival and cellular metabolism [64]. Numerous studies demonstrated the anti-apoptotic role of MSC-Exos in cardiac injury, when administered through intravenous [99, 101, 106, 107], intramyocardial [71, 74, 98, 102, 108–112], intrapericardial sac [113], and intracoronary [64].

### MSC-Derived Exosomes Promote Heart Regeneration by Reducing Fibrosis

Most myocardial injuries result in reactive fibrosis, which is followed by the loss of cardiomyocytes, and thus contributes to the remodeling of post-myocardial damage [114, 115]. Notably, Collagen I has been identified as a promoter of myocardial fibrosis during myocardial injuries [116]. It has been reported that MSC-Exos efficiently reduce myocardial fibrosis and cardiac dysfunctions comparable with cellular therapy of MSCs [66, 117–119]. During the process of cardiac regeneration and repair, MSC-derived exosomes can mitigate cardiac fibrosis when transplanted intramyocardially [68, 98, 110, 117] or intravenously [101]. The precise mechanism by which MSC-Exos mediate the reduction in fibrosis after MI is not fully understood yet. However, in response to MSC-Exos, the zeste homolog 2 (EZH2) and group AT-Hook 2 (HMGA2) levels change, delaying the epithelial-mesenchymal transition (EMT) and fibrosis in cardiac tissues. As a result, cardiac function is generally improved and the left ventricle's end-diastolic and end-systolic internal diameters increase [118]. Additionally, it has been reported that MSC-Exos limit TGF- $\beta$ /Smad2 signaling by decreasing the production of TGF and Smad2 proteins. As a result, patients had less heart fibrosis and damage [120].

### MSC-Derived Exosomes Promote Heart Regeneration via Modulation of Energy Metabolism

Heart regeneration is mediated by various mechanisms in which modulation of cellular metabolic energy is also included. Therefore, abnormalities in myocardial energy metabolism may contribute to contractile dysfunction and the progressive decline in left ventricular (LV) function following a MI. MSCs are believed to have the capacity to effectively correct severe bioenergetic deficiencies in perinfarcted myocardial regions following MI [121]. There is evidence of significant intracellular ATP depletion following ischemic injury, and research has shown that exosomes from adipose-derived stem cells (ADSCs) are capable of

restoring ATP and NADH levels [122]. Moreover, exosome therapy has been shown to successfully restore cellular bioenergy by increasing levels of ATP and NADH, decreasing oxidative stress, and increasing phosphorylated-Akt and phosphorylated-GSK-3 pathways [64]. However, it is important to note that just a small number of research have investigated how MSCs, specifically MSC-Exos, alter cardiac metabolism.

To conclude, MSC-Exos have emerged as a highly promising cell free entity that confers greatly in ischemic heart condition by means of angiogenesis, protection against apoptosis, fibrosis reduction, and immune and energy metabolism modulation, but there is still much to be investigated about the nature, effects, and types of exosomes and their underlying mechanisms of repairing. However, MSC-Exos-based therapy gets hampered due to poor purification and uncharacterized off-target. Moreover, heterogeneous components of exosomes can also arise the risk of tumors and immune reactions. To avoid such unfavorable circumstances, it is crucial to harness the natural abilities (cargo-dependent paracrine effects) of exosomes to transfer the therapeutic payloads into the target cells. According to recent research, MSC and Exos have the ability to release multiple chemical components that can have a variety of therapeutic effects in different microenvironments. A vast number of research studies have explicitly considered the miRNAs as a potential candidate due to their comparatively high proportion, short size, and pleiotropic effects. Moreover, exosomal miRNAs regulate cell fate decisions, communication, cell division, and cell death. Therefore, it is now important to discuss the miRNAs and their reported beneficial effects in the process of cardiac regeneration. So that MSC-Exos-based cell free therapy can be practically applied in the medicinal field with high proficiency.

### MicroRNA

miRNAs are single short-stranded (15–27 nucleotides) and non-coding RNA sequences which play an important role in gene regulation. The biosynthesis of miRNA takes place by canonical and multiple non-canonical pathways; both pathways have already been reviewed elsewhere [123]. The mechanism of action of miRNA relies on the site where miRNA interacts with the mRNA (i.e., 3'-UTR, 5'-UTR, promoter region, coding region) [124, 125]. This mechanism is mediated by epigenetic modifiers or blocking of repressor molecules which modify chromatin structure and facilitate transcriptional activation [126]. The interaction of miRNA with mRNA depends upon multiple factors such as the abundance of miRNA and mRNA, the affinity between them, and subcellular localization of miRNAs [123]. Furthermore, miRNA participates in cell–cell communication via exosome

[127]. A specific set of miRNAs that are present in various tissues and abnormal alterations in the miRNA levels have been correlated with organ dysfunction and embryonic malformation. The miRNA is one of the main regulators of cardiac development and dysregulation. The loss-of-function studies emphasize the role of functional miRNA in heart development [128–130]. As it has been already discussed that MSC-Exos perform its function by releasing a cargo of molecules with different natures and every entity of the exosomal cargo has its definite role in cardiac development and regeneration. However, miRNAs have attracted the most attention because of their regulatory role in gene expression. miRNAs are not supposed to be randomly selected by the exosomes but they have been preferentially picked up by specific mechanisms. Additionally, it has also been stated that miRNAs are more in excess in exosomes rather than in the parent cell itself, thus suggesting that the cells have their sorting mechanism that guides specific intracellular miRNAs to load into the exosomes and signifying its importance in heart regeneration [131].

## Role of Mesenchymal Stem Cell-Derived Exosomal miRNAs in Heart Regeneration

### MSC-Derived Exosomal miRNAs Promote Angiogenesis

Exosomal miRNAs are considered key regulators in various biological processes such as cell signaling, proliferation, differentiation, and immunomodulation. There has been an increasing amount of data that confirmed the role of MSC-Exos carrying miRNAs in heart regeneration. It has been reported that MSC-Exos transmit pro-angiogenic signals directly by miRNA transfer. A study performed in 2018 by Ferguson et al. [83] stated that MSC-Exos have an excess amount of the pro-angiogenic miRNAs such as miRNA-199a, miRNA-21, miRNA-1246, miRNA-23a-3p, and miRNA-23. In 2018, Zhu et al. [132] found that in comparison to normally occurring MSC-Exos, hypoxia-induced MSC-Exos are considerably enriched in pro-angiogenic miR-125b-5p. In 2018 Mayourian et al. [133] further confirmed that miR-21-5p induces pro-angiogenic VEGF- $\alpha$ , ANGPT-1, and TGF- $\beta$  signaling pathway and produces hypertrophic atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP). Likewise, other miRNAs derived from MSC-Exos including miRNA-19a, miR-132, and miR-210 also promote angiogenesis for repairing injury [71, 134–139].

### MSC-Derived Exosomal miRNAs Improve Immunomodulatory Effects

MSC-derived exosomal miRNAs have been shown to provide an immunomodulatory effect in heart disease [117]. A study declared that miRNA-181a binds with the c-Fos

protein and limits the activity of dendritic cells [140]. Another study stated that adipose tissue-derived exosomal miRNA (ADMSCs-Exos), miRNA-34a-5p, and miRNA-146a-5p exert immunomodulatory effects by targeting neurogenic locus notch homolog protein 1 (Notch 1) and nuclear factor kappa-light-chain-enhancer of activated B cell (NF- $\kappa$ B) signaling cascades, respectively. Moreover, miRNA-21 participates in macrophage polarization by suppressing MEK/ERK and activates the signal transducer and activator of transcription 3 (STAT3) signaling cascade [141]. Evidence suggests that miRNAs such as miRNA-126, miRNA-25-3p, miRNA-182, and miR-21-5p derived from MSC-Exos also exert immunomodulatory effects in cardiovascular diseases [139, 142, 143]. Furthermore, miRNA-133 and miRNA-22 limit fibrotic activity and improve cardiac regeneration [144].

### MSC-Derived Exosomal miRNAs Reduce Apoptosis

MSC-derived exosomal miRNAs have shown a crucial anti-apoptotic role in heart repair and regeneration [108]. In 2020, Wen et al. found that miRNA-144 secreted from bone marrow-derived MSC-Exos regulate apoptotic activity by inducing the PI3K-Akt pathway in a hypoxic environment [145]. Additionally, in 2019, Sun et al. [146] reported that miRNA-486-5p-enriched MSC-Exos reduce apoptosis inducer protein, i.e., phosphatase and tensin homolog (PTEN), and promote the Akt signaling cascade. Likewise, in an in vitro study anti-apoptotic effect was also observed by regulating the Wnt/ $\beta$ -catenin pathway when cardiomyocytes were treated with adipose tissue-derived MSC exosome [147]. Another study demonstrated that MSC-Exos enriched with miRNA-22 interact with methyl CpG binding protein-2 (Mecp2) and restrict apoptotic activity [108]. Moreover, it is also reported that miRNA-21 derived from MSCs-Exos reduces apoptotic activity [70, 148]. BM-derived MSC-Exos expressed miRNA-24 which reduces the apoptotic activity of cardiac cells in the murine model by suppressing the expression of the apoptotic protein, Bax, and caspase 3 [149]. Additionally, GATA-4 expressing MSC-derived exosome (MSCGATA-4-DEs) reduce cardiac injury and apoptosis by releasing anti-apoptotic RNAs, e.g., miRNA-19a in hypoxic conditions. miRNA-19a reduces the expression of apoptosis inducer protein B cell lymphoma-2 (Bcl2) interacting mediator of cell death (BIM) and phosphatase and tensin homolog (PTEN) [150]. Moreover, miRNA-19a activates cell survival by Akt and ERK signaling and suppresses JNK/caspase-3 cascade by interacting with SRY-box transcription factor-6 (SOX-6). A large set of data demonstrated that the MSC-Exos miRNAs such as miRNA133a-3p, miRNA 125b-5p, miRNA-221, miRNA-338, miR-150-5p, miR-21a-5p, miR-486-5p, miR-22, and miR-214 show anti-apoptotic activity and thus produce cardioprotective effects [111–113, 151–153].

## MSC-Derived Exosomal miRNAs Reduce Fibrosis

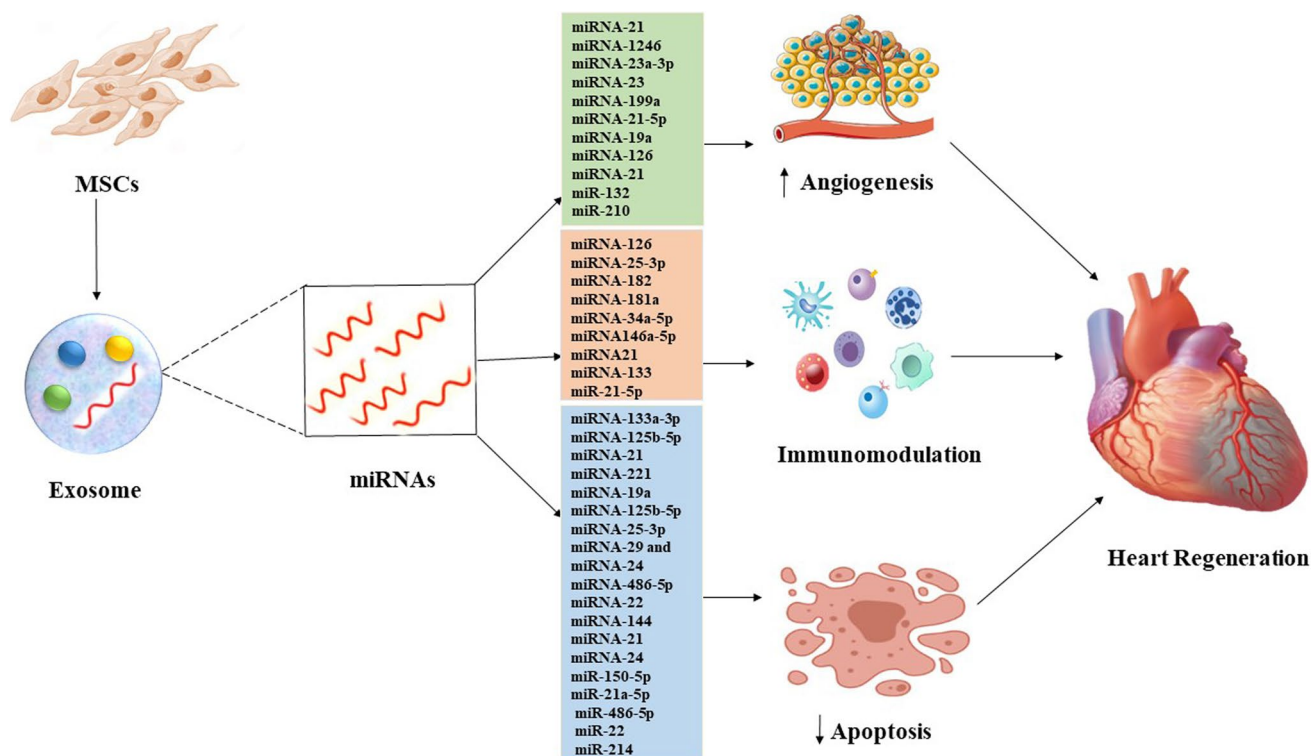
MSCs are reported to regulate endogenous tissue inhibitor of matrix metalloproteinases (TIMPs), the matrix metalloproteases (MMPs), and anti-fibrotic factors, thus lessening the remodeling of cardiomyocytes after MI [121]. Numerous studies have shown that the presence of miRNAs in MSC-derived exosomes contributed to the reduction of collagen accumulation during cardiac remodeling and lessen post-MI-induced fibrosis [61, 66]. For example, thrombospondin-1 and connective tissue growth factor (CTGF) were regulated by miR-19a, among other extracellular matrix proteins [61]. According to Chen et al. (2017), overexpression of miR-133 from MSCs-Exos downregulate the expression of *Snail1* which exhibited cardioprotective effects [144]. Additionally, it has been reported that ischemic preconditioned MSC-derived exosomal miR-22 control the post-fibrotic effects of cardiac damage by reducing *Mecp2* gene [108].

Like exosomes, miRNAs also demonstrate very important roles in cardiac regeneration by means of angiogenesis, immunomodulation, anti-apoptotic, and anti-fibrotic molecular mechanisms (Fig. 1 and Table 1). This suggest that most of the exosomal functions in cardiac regeneration greatly depend upon its miRNA content, which needs further investigations. A significant number of researchers

have put their efforts into genetically modifying the MSCs to reprogram their miRNA content so that the properties of miRNAs can be enhanced and be used for the treatment of ischemic diseases for each patient.

## Role of miRNA Reprogrammed MSCs in Heart Regeneration

miRNAs have been considered a major factor that helps in the lineage commitment of MSCs through positive or negative regulation thus providing a better understanding of the underlying mechanisms of stem cell differentiation [154]. The various sources of MSCs show a specific set of miRNAs that maintain the proliferation, differentiation, and self-renewal properties of mesenchymal stem cells [155, 156]. Few studies have examined the effect of various miRNAs in cardiac differentiation of MSCs that have undergone chemical treatment. As in 2007 Shan et al. [157] identified a set of heart specific miRNAs such as miRNA-143, miRNA-181, miRNA-206, and miRNA-208 in MSCs treated with 5-azacytidine or by an indirect co-culture with rat myocyte. Interestingly, miRNA-181 has been reported to downregulate the homeobox protein Hox-A11, a repressor of the differentiation process [158, 159]. In 2010, Rongrong et al. [160] reported that the overexpressed miRNA-145 has



**Fig. 1** Mesenchymal stem cell-derived exosomal microRNAs promote heart regeneration: exosomes secreted from MSCs show specific set of miRNAs that regulate various biological functions such as

angiogenesis, immunomodulation, and apoptosis. This results in an improvement in heart repair/ regeneration



**Table 1** MSC-derived exosomal microRNAs promote heart regeneration

Source of MSCs	MicroRNA	Major finding	Pathways	Cells	Reference
<b>Angiogenesis</b>					
BM-MSCs	miRNA-21, miRNA-1246, miRNA-23a-3p, miRNA-23, miRNA-199a	↑ Angiogenesis and cardiomyocyte proliferation	miRNA-21: Akt, and ERK miRNA1246: Smad 2/3 and 1/5/8 miRNA23: Sprouty2 and Sema6A miRNA199a: <i>Crim 1</i>	DU145 cells HUVECs Endothelial cells CMs	[83]
BM-MSCs	miRNA-21-5p	↑ Angiogenesis and contractility of cardiac tissue	VEGF- $\alpha$ , angiopoietin 1, ANP, and BNP	hECTs	[133]
NMCMs	miRNA-19a	↑ Angiogenesis	HIF-1 $\alpha$	Endothelial cells	[137]
AT-MSCs	miRNA-126	↑ Angiogenesis	-	H9c2	[139]
Endometrium-derived MSCs (EnMSCs)	miRNA-21	↑ Angiogenesis	-	CMs and HUVECs	[71]
BM-MSCs	miR-132	↑ Angiogenesis	-	HUVECs	[134]
BM-MSCs	miR-210	↑ Angiogenesis	Efn3	HUVECs	[138]
<b>Immunomodulatory effects</b>					
AT-MSCs	miRNA-126	↓ Inflammation fibrosis	-	H9c2	[139]
BM-MSCs	miRNA-25-3p	↓ Inflammation	SOCS3	CMs	[142]
BM-MSCs	miRNA-182	↑ Immunomodulatory activities	TLR4/NF- $\kappa$ B	Myocardium	[103]
UC blood-MSCs	miRNA-181a	↓ Inflammatory response	c-Fos protein	Myocardium	[140]
AT-MSCs	miRNA-34a-5p miRNA146a-5p miRNA21	↓ Inflammation, polarize	miR-34: Notch 1 miR-146: NF- $\kappa$ B miR-21: Sirp- $\beta$ 1	Monocytes	[141]
BM-MSCs	miRNA-133	↓ Inflammatory reactions and fibrosis	Snail 1	Myocardium	[144]
MSCs	miR-21-5p	↓ Inflammatory response	-	Myocardial cells	[143]
<b>Anti-apoptotic effects</b>					
UC-MSCs	miRNA-133a-3p	↓ Apoptosis ↓ Fibrotic activity	Akt	HUVECs and H9C2	[151]
BM-MSCs	miRNA-125b-5p	↓ Apoptosis	p53 and Bnip3	CMs	[111]
BM-MSCs	miRNA-21	↓ Oxidative stress induced apoptosis	PTEN, Akt	CSCs	[148]
BM-MSCs	miRNA-221	↓ Apoptosis	p53 and Bcl-2	CMs	[112]
BM-MSCs	miRNA-19a	↑ Anti-apoptotic effects	PTEN, BIM, Akt, and ERK	CMs	[150]
BM-MSCs	miRNA-125b-5p	↑ Anti-apoptotic effects ↓ Infarction size	BAK1 and p53	Myocardium	[132]
BM-MSCs	miRNA-25-3p	↓ Apoptosis	FASL, PTEN, and EZH2	CMs	[142]
BM-MSCs	miRNA-29 and miRNA-24	↓ Apoptosis ↓ Fibrotic activity	Collagen	Myocardium	[117]
BM-MSCs	miRNA-486-5p	↓ Apoptosis	PTEN, Akt, and PI3k	H9C2	[146]
BM-MSCs	miRNA-22	↓ Apoptosis	Methyl CpG binding protein 2 (Mecp2)	Myocardium	[108]
BM-MSCs	miRNA-144	↓ Apoptosis in hypoxic condition	PTEN and Akt	H9C2	[145]
EnMSCs	miRNA-21	↑ Anti-apoptotic and angiogenic effects	PTEN and Akt	Myocardium	[71]
BM-MSCs	miRNA-24	↓ Apoptotic	-	Myocardium	[149]
BM-MSCs	miR-150-5p	↓ Apoptotic effects	-	CMs	[153]
BM-MSCs	miR-21a-5p, miR-486-5p, miR-22, and miR-214	↓ Apoptosis	Peli1, PTEN, Fas1, PDCD4	H9c2	[113]
<b>Anti-fibrotic effects</b>					
BM-MSCs	miR-19a	↓ Fibrosis	-	CMs	[61]

**Table 1** (continued)

Source of MSCs	MicroRNA	Major finding	Pathways	Cells	Reference
BM-MSCs	miR-133	↓ Fibrosis	<i>Snail1</i>	CMs	[144]
BM-MSCs	miRNA-22	↓ Fibrotic activity	<i>Mecp2</i>	CMs	[108]

the ability to enhance the cardiac differentiation of 5-azacytidine-treated BM-MSCs.

While some research use miRNA reprogrammed MSCs to thoroughly investigate the process of heart regeneration. As in 2013 Lee et al. [161] describe the useful effects of miRNA-133a in the cardiac differentiation of MSCs. miRNA-133a reprogrammed MSCs improve the survival of MSCs in the MI model via downregulation of pro-apoptotic genes, i.e., apoptotic protease activating factor-1 (Apaf-1), caspase-3, and caspase-9. Similarly, miRNA-133 overexpressed BM-MSCs improve cardiac activity with enhanced expression of total poly ADP-ribose polymerase protein, reduced hypoxia-induced apoptosis, and expression of snail-1, which mediate the cardiac fibrosis after MI via connective tissue growth factor (CTGF) [145, 163]. It has been documented that miRNA-1 regulates various genes that are essential for cardiac function, such as histone deacetylase-4 (HDAC4), hand transcription factor-2 (Hand), connexin-43 or Gap junction alpha-1 protein (GJA1), and K<sup>+</sup> channel subunit Kir2.1 (KCNJ2) [164]. In 2013, Huang et al. [165] reported that MSCs transduced with miRNA-1 could promote the regeneration of the injured heart. Similarly, miRNA-1 overexpressed in MSCs improves heart function via downregulation of the transcriptional repressor of cardiac specific gene Delta-like 1 (Dll-1) [166]. In a study in 2018, Lu et al. [167] demonstrated that MSCs overexpressing miRNA-149 enhance cardiac specific gene expression by Wnt/ $\beta$ -catenin-dependent disabled homolog-2 (Dab2) targeted mechanism. Dab2 is a scaffold protein that plays a role in cell growth, cell interactions, and signal transduction [168]. In addition, Dab2 improves the healing ability

of transplanted MSCs. A number of studies have confirmed the role of miRNA-126 in heart regeneration [169]. miR-126 overexpressed MSCs improve angiogenesis and heart function by AKT/ERK related pathways [170]. Moreover, in 2013, Huang et al. [171] also reported that overexpressing miRNA-126 MSCs improved the release of angiogenic factors and resistance toward hypoxia, promoting tubulogenesis by controlling Notch ligand Delta-like 4 expressions in MSCs. The upregulation of miRNA-34 resulted in cell death and poor pro-angiogenic activity of pro-angiogenic cells. The BM-MSC downregulation of miRNA-34a via insulin like growth factor-1 (IGF1) thus inhibits cardiomyocyte apoptosis and exceeds the limits of cell survival [172]. The chemokine receptor type 4 (CXCR4) gene participates in stem cell migration and mobilization in injured tissue via its ligand, i.e., stromal cell-derived factor (SDF)-1. In 2011, Tano et al. [173] reported that ischemic conditions repress miRNA-150 in MSCs which in turn activate the CXCR4 gene, which resulted in enhanced migration and mobilization of transplanted MSCs thus improving heart function in terms of neovascularization. The overexpression of miRNA-19a/19b enhances the therapeutic potential of MSCs in heart regeneration. Moreover, it improves the functional recovery of injured heart in diabetic MI mouse model, possibly through the repression of apoptotic genes [174]. MicroRNAs reprogrammed MSCs promote heart regeneration via various mechanisms, which are presented in Table 2.

Various clinical studies give us convincing pieces of evidence about miRNAs as the targets of improving cell-based therapies and the endogenous repair process of the heart. However, regardless of all the encouraging data, the

**Table 2** miRNAs reprogrammed MSCs in heart regeneration

Name of miRNA	Source of miRNA	Targets	Cells	Biological functions	References
miRNA-133a	hBM-MSCs	EGFR	Myocardium	↑ Cardiac differentiation	[161]
miRNA-133a	BM-MSCs	Apaf-1, caspase-3, and caspase-9	Myocardium	↑ Cardiomyocyte survival	[162]
miRNA-133a	BM-MSCs	Snail 1	Myocardium	↓ Inflammation and infarct size	[144]
miRNA-1	BM-MSCs	-	Myocardium	↑ Cardiomyocyte survival and differentiation	[165]
miRNA-1	BM-MSCs	Delta-like 1 (Dll)-1	-	↑ Cardiac differentiation	[166]
miRNA-149	BM-MSCs	Dab2	-	↑ Cardiac differentiation	[167]
miRNA-126	BM-MSCs	AKT and ERK	Myocardium	↑ Angiogenesis	[170]
miRNA-126	BM-MSCs	Notch ligand Delta-like (Dll)-4	Myocardium	↑ Cardiomyocyte survival	[171]
miRNA19a/19b	BM-MSCs	-	Myocardium	↑ Cardiomyocyte survival ↓ Inflammation	[174]

miRNA-based cell regenerative therapies face a lot of challenges due to the poor knowledge of biological processes and the absence of a streamlined purification method that creates obstacles in ongoing research of exosomes. As the miRNAs have different patterns on their different targets, some miRNAs target genes with similar biological functions, while others target genes with antagonistic functions. So, it becomes more crucial to have a system biology approach to completely understand the possible outcome of miRNAs in CVDs.

## Conclusion

In the current review, we highlighted the therapeutic potential of MSC-derived exosomes and their miRNAs in heart regeneration while covering biological functions involved in the regeneration of heart. Exosomes are tiny vesicles secreted by numerous cells including mesenchymal stem cells. It plays an important role in intercellular communication by releasing bioactive molecules, such as proteins, lipids, nucleic acids, and miRNA. Among these molecules, exosomal miRNA has gained considerable attention in recent years. MSC-exosome-derived miRNAs have the potential to regulate biological processes related to heart regeneration such as blood vessel formation, cell propagation, survival, and immunomodulation, and therefore possess an enormous regenerative capability in the treatment of heart diseases. As highlighted in this review, MSC-derived exosomes and their miRNA play a crucial role in the pathophysiology of heart diseases, and their therapeutic potential in heart repair and regeneration is an area of active research. However, many studies examined the expression of related miRNA in MSC-Exos without studying their detailed mechanism. Therefore, further research is still needed to determine how related genes exert their therapeutic effects. Furthermore, MSC-Exos require standardized isolation protocols since the instability of miRNA content in MSC-Exos will directly affect its clinical application value. In addition to the above approaches, the model miRNA combination needs to be identified for the treatment of ischemic heart diseases.

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## Declarations

**Human and Animal Rights and Informed Consent** Not applicable.

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