EXCLI Journal 2024;23:401-420 – ISSN 1611-2156
Received: September 01, 2023, accepted: January 05, 2024, published: March 25, 2024

Review article:

DETAILED ROLE OF MESENCHYMAL STEM CELL (MSC)-DERIVED EXOSOME THERAPY IN CARDIAC DISEASES

Ali Hassanzadeh[1], Navid Shomali[2,3], Amin Kamrani[2,3], Hadi Nasiri[3], Javad Ahmadian Heris[4], Maryam Pashaiasl[5,6], Mohammadreza Sadeghi[7], Shahram Sadeghvand[8], Zahra Valedkarimi[3], Morteza Akbari[3,9*]

1 Department of Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
2 Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
3 Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
4 Department of Allergy and Clinical Immunology, Pediatric Hospital, Tabriz University of Medical Sciences, Tabriz, Iran
5 Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
6 Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, P.O. Box 51376563833, Tabriz, Iran
7 Department of Molecular Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
8 Pediatrics Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
9 Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

* **Corresponding author:** Morteza Akbari, Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran; E-mail: akbarimo@tbzmed.ac.ir

https://dx.doi.org/10.17179/excli2023-6538

ABSTRACT

Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality. There are numerous therapeutic reperfusion methods, including thrombolytic therapy, primary percutaneous coronary intervention, and anti-remodeling drugs like angiotensin-converting enzyme inhibitors and beta-blockers. Despite this, there is no pharmacological treatment that can effectively stop cardiomyocyte death brought on by myocardial ischemia/reperfusion (I/R) injury. For the purpose of regenerating cardiac tissue, mesenchymal stem cell (MSC) therapy has recently gained more attention. The pleiotropic effects of MSCs are instead arbitrated by the secretion of soluble paracrine factors and are unrelated to their capacity for differentiation. One of these paracrine mediators is the extracellular vesicle known as an exosome. Exosomes deliver useful cargo to recipient cells from MSCs, including peptides, proteins, cytokines, lipids, miRNA, and mRNA molecules. Exosomes take part in intercellular communication processes and help tissues and organs that have been injured or are ill heal. Exosomes alone were found to be the cause of MSCs' therapeutic effects in a variety of animal models, according to studies. Here, we have focused on the recent development in the therapeutic capabilities of exosomal MSCs in cardiac diseases.

Keywords: Mesenchymal stem cell (MSC), exosome, cardiac diseases, treatment, regeneration

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide, particularly coronary heart disease (CHD) (CDC, 2011). Acute myocardial infarction (MI) is the main reason for death in all CHDs. A substantial medical, social, and financial burden results from subsequent complications like heart failure (HF) (Reddy et al., 2015). In addition to anti-remodeling drugs like angiotensin-converting enzyme inhibitors and beta-blockers, a wide range of curative reperfusion plans are accessible, including thrombolytic therapy and primary percutaneous coronary intervention (Rich, 2006). However, no pharmacological treatment can effectively stop cardiomyocyte destruction brought on by myocardial ischemia/reperfusion (I/R) (Kalogeris et al., 2016).

Additionally, cardiac fibrosis, myocardial remodeling, cardiac arrhythmia, and ultimately heart failure could all be influenced by this I/R injury. Heart transplantation or ongoing left ventricular (LV) support are the only therapies for treating heart failure at its most advanced stage (Mangini et al., 2015). Therefore, there is great interest in and demand for novel remedies for post-MI LV remodeling and dysfunction.

Due to their involvement in numerous facets of cardiac biology and disease, exosomes significantly impact cardiac health (Yao et al., 2021). The importance of exosomes in cardiac health is highlighted in the following key points. Exosomes help the heart's intercellular communication by carrying biological information between cells. Cells can communicate and coordinate their functions thanks to the molecules they transfer, which also have proteins, genetic material (like RNA), and other molecules (Harrell et al., 2020: Lu et al., 2018). Exosomes are essential for heart tissue regeneration and repair. They may contain regenerative substances that encourage cardiac progenitor cells to multiply and differentiate, aiding in repairing damaged cardiac tissue after trauma or illness (Liu et al., 2022). Numerous cell types, including stem cells and cardiomyocytes, have been shown to produce exosomes that have cardioprotective properties (Vrijsen et al., 2010). They can lower heart-related oxidative stress, inflammatory response, and cell death, maintaining cardiac function and enhancing recovery from cardiac conditions (Cosme et al., 2013). Importantly, exosomes from mesenchymal stromal cells (MSCs) have a promising future in regenerative medicine (Lai et al., 2011; Nasser et al., 2021). They are a strong candidate for cardiac regeneration and repair due to their potential trophic and immunomodulatory effects (Han et al., 2019). Exosomes produced by MSCs are considered a viable alternative to cell-based therapies because numerous studies have shown that they mimic their parent cells' anti-inflammatory, anti-apoptotic, pro-angiogenic, and anti-fibrotic possessions (Deng et al., 2019; Yue et al., 2022). They are desirable in regenerative medicine due to their superior immune tolerance, stability, and lower tumorigenic risk than their parent stem cells (Ahmed and Al-Massri, 2022). Therefore, the potential for using MSC-derived exosomes for cardiac renewal and repair has been assessed.

This article offers an organized framework for compiling and presenting data on the therapeutic capability of MSCs-exosomes in cardiac diseases.

OVERVIEW OF CARDIAC CONDITIONS

Heart failure and myocardial infarction are common cardiac conditions that seriously impact people's health and well-being. A compromised heart's ability to pump blood efficiently may result in heart failure (HF) (Groenewegen et al., 2020). Several underlying conditions, including coronary artery disease, hypertension, or damaged heart valves, may bring it on. Breathing difficulty, exhaustion, fluid retention, and a decreased capacity for exercise are all signs of heart failure (Bader et al., 2021, Lopaschuk et al., 2021). It is known as a MI when the blood supply to a portion of the heart muscle is cut off, typically due to a blood clot in the coronary arteries (Reed et al., 2017). The heart muscle cells die

EXCLI Journal 2024;23:401-420 – ISSN 1611-2156
Received: September 01, 2023, accepted: January 05, 2024, published: March 25, 2024

from this blockage, causing chest pain, breathlessness, and potentially fatal complications. In addition, these symptoms characterize coronary artery disease (CAD), which restricts or blocks the arteries that carry blood to the heart muscle (Frangogiannis, 2011; Saleh and Ambrose, 2018). It is typically brought on by plaque development in the artery walls, which comprises cholesterol, fat, and other substances (Okrainec et al., 2004). Heart attack, heart failure, or angina are all possible CAD outcomes. Arrhythmias, abnormal heartbeats, can also impair the heart's typical ability to pump blood (Libby and Theroux, 2005). They might show up as tachycardia, bradycardia, or an irregular heartbeat. Symptoms of arrhythmias include palpitations, lightheadedness, fainting, and, in extreme cases, cardiac arrest (Malakar et al., 2019). Also, valvular heart disease describes illnesses that affect the heart valves and compromise their ability to control blood flow properly. Fatigue, breathlessness, chest pain, and fluid retention are signs and symptoms of valvular heart disease (Aluru et al., 2022).

Additionally, a group of cardiomyopathies affects the heart muscle, resulting in structural and functional abnormalities (Crisafulli et al., 2020). The heart may enlarge, thicken, or stiffen due to these conditions, which can be genetic or acquired (Tesson et al., 2019). Cardiomyopathies can bring on heart failure, arrhythmias, and other complications. For the best possible patient outcomes, these disorders must be appropriately assessed, diagnosed, and managed medically (Neisius et al., 2019).

MESENCHYMAL STEM CELL IN CARDIAC REGENERATION

Based on *in vivo* reports, MSCs therapy has attracted increasing attention in cardiac regeneration, more importantly, MI (Table 1). MSCs can be differentiated into cardiomyocytes, endothelial cells, and vascular smooth muscle cells by the contribution of various paracrine effectors, finally promoting cardiac repair and regeneration (Taylor and Robertson, 2009). MSCs can arouse the production of manifold growth factors, replace injured cells, and create an environment to favor endogenous cardiac rehabilitation. 5-Azacytidine (5-AZA), a well-known inhibitor of DNA methylation, is a chemical ingredient that can induce BM-MSCs differentiation into cardiomyocytes, as shown in rodents (Jia et al., 2020; Makino et al., 1999). Moreover, the supportive impacts of the miR-1a overexpressing on BM-MSCs differentiation into cardiac cells has recently been suggested (Zhao et al., 2016). Other studies have demonstrated that IL-1β contributes to the pathogenesis, development, and function of cardiomyocytes in the injured heart and can induce neovascularization post-MI (Guo et al., 2018). Recently, BM-MSCs therapy improved cardiac function in rodents with MI by stimulating cardiac endothelial cell (CEC) migration to the infarcted border area primarily through CXCL12/CXCR4 axis (Lu et al., 2019a). Recently, in patients with compensated HF, intravenous (IV) administration of allogeneic UC-MSCs and BM-MSCs led to a remarkable increase in the expression of hepatocyte growth factor (HGF), finally causing myogenesis and suppression of inflammation (Bartolucci et al., 2017). Also, IV administration of UC-MSCs promoted left ventricular function and life quality in HF patients (Bartolucci et al., 2017). In 6 patients with MI, autologous MSCs therapy also caused concordant amelioration in regional activity, tissue perfusion, and, eventually, fibrotic burden (Karantalis et al., 2014).

EXOSOMES IN CARDIAC REGENERATION

Explanation of exosome function in tissue repair

Exosomes are essential for intercellular communication and the delivery of vital biological signals to recipient cells engaged in the healing process, which is critical for tissue repair (Huang et al., 2021). Exosomes carry a cargo of proteins, nucleic acids (like RNA), lipids, and other molecules necessary for cellular contact and tissue repair (Bjørge et al., 2018). Growth factors, cytokines, enzymes,

EXCLI Journal 2024;23:401-420 – ISSN 1611-2156
Received: September 01, 2023, accepted: January 05, 2024, published: March 25, 2024

Table 1: MSCs therapy in cardiac regeneration

Condition	Animal	Dose	Route	Result	Reference
AMI	Mice	0.5–5 × 10^5	IM	Decrease in infarct size and fibrosis	Kudo et al., 2003
AMI	Mice	3 × 10^5	IM	Increase in cardiac function	Fazel et al., 2005
AMI	Mice	5 × 10^5	IM	Decrease in infarct size and increase in cardiac function	Noiseux et al., 2006
AMI	Mice	1 × 10^6	IM	Increase in LVEF	Nakamura et al., 2007
AMI	Mice	1× 10^6	IM	Increase in cardiac function	Shiota et al., 2007
AMI	Mice	2 × 10^5	IM	Increase in LVEF and LV function	Grauss et al., 2008
AMI	Rat	5 × 10^6	IM	Decrease in cardiac remodeling and increase in cardiac performance	Mangi et al., 2003
AMI	Rat	5 × 10^6	IV	Increase in cardiac function and decrease in infarct size	Nagaya et al., 2004
AMI	Rat	2 × 10^6	IM	Increase in LV function	Dai et al., 2005
AMI	Rat	2 × 10^6	IM	Decrease in fibrosis and increase in cardiac function	Berry et al., 2006
AMI	Rat	6 × 10^6	IM	Increase in LVEF and decrease in infarct size	Li et al., 2007
AMI	Rat	1 × 10^6	IM	Increase in LVEF and decrease in infarct size	de Macedo Braga et al., 2008
AMI	Rat	5 × 10^6	IM	Increase in LVFS and decrease in fibrosis	Imanishi et al., 2008
Subacute MI	Swine	6 × 10^7	IM	Decrease in wall thinning in the scar area and improvemen in cardiac function	Shake et al., 2002
Chronic MI	Swine	2 × 10^8	IM	Preserving LVEF	Makkar et al., 2005
Acute MI	Swine	3.2 × 10^8	IV	Increase in LVEF and decrease in hypertrophy	Price et al., 2006
Subacute MI	Swine	6.3 × 10^5	IM	Decrease in scar size and EDV and increase in LVEF	Gyöngyösi et al., 2008
Chronic MI	Swine	2 × 10^8	Transendocardial	Decrease in scar size, increase in EF and regional contractility	Quevedo et al., 2009
Chronic MI	Swine	0.2–2 × 10^8	IM	Decrease in scar size, increase in EF and regional contractility	Schuleri et al., 2009
Chronic ischemia	Canine	1 × 10^8	IM	Decrease in fibrosis and increase in LVEF	Silva et al., 2005
Subacute MI	Canine	1 × 10^8	Transendocardial Intracoronary	Increase in EF, decrease in myocardial ischemia and reduction in EDV and ESV	Perin et al., 2008

and genetic material that control various cellular processes can all be found in these cargos. Different cell types, including stem cells, immune cells, and damaged or injured cells, secrete exosomes (Newton et al., 2017). These cells produce exosomes reacting to cellular stress, injury, or particular signaling cues that target unique bioactive molecules. Depending on the specific mechanisms, exosomes can be selectively taken up by around or distant cells (Fan et al., 2022; Lai et al., 2010). The transfer of their cargo into the recipient cells is made possible by their ability to either fuse with or bind to the cell membrane of the target cells.

Exosomes carry molecules that activate regenerative signaling pathways in recipient cells as part of their cargo (Fang et al., 2019). Exosomes, for example, can stimulate signaling pathways that promote cell migration, proliferation, and differentiation. Exosomes can control inflammation in harmed tissue by modifying immune reactions (Su et al., 2021; Toh et al., 2018). They may transport molecules that control excessive inflammation and encourage a tissue's ability to regenerate. Exosomes can also promote angiogenesis, the growth of new blood vessels, in the injured tissue (Qin et al., 2016). Transferring pro-angiogenic components to endothelial cells can encourage their growth, migration, and the development of new blood vessels, which are essential for furnishing the regenerating tissue with oxygen and nutrients (Manuel et al., 2017).

Additionally, they affect the remodeling of the extracellular matrix (ECM), the framework that supports cells and thus aids in tissue repair. Exosomes can transport enzymes that break down or alter the ECM, making eliminating harmed matrix elements easier and depositing fresh ECM proteins needed for tissue regeneration (Chen et al., 2019; Wen et al., 2021). Exosomes play various roles in tissue repair, including transporting bioactive molecules, delivering those molecules to recipient cells, activating regenerative signaling pathways, reducing the inflammatory response, promoting angiogenesis, and participating in ECM remodeling (Moghadasi et al., 2021). These procedures help damaged tissues heal and regenerate in various situations, such as wound healing, cardiac repair, and tissue regeneration following disease or injury.

Detailed role of exosomes in cardiac regeneration

Exosomes produced by different cell types, including stem cells, cardiac progenitor cells, and mesenchymal stem cells, function as paracrine signaling messengers. They deliver bioactive molecules, such as growth factors, cytokines, and miRNAs, to recipient cells in the damaged cardiac tissue. Exosomes have the potential to aid in the injured heart's angiogenesis and feed endothelial cells pro-angiogenic substances like vascular endothelial growth factor (VEGF), which encourages the growth of new blood vessels (Wang et al., 2016). Improved blood flow makes reaching the regenerating tissue easier for nutrients and oxygen. Cardiomyocytes, the muscle cells liable for the heart's contraction, can survive and increase with the help of exosomes (Garcia et al., 2015). They distribute substances that promote the proliferation of cardiomyocytes and prevent cell death (apoptosis). MiRNAs like miR-133 and miR-210, which have been demonstrated to improve cardiomyocyte survival and proliferation, can be one of these factors (Cervio et al., 2015; Ma et al., 2018b). Exosomes can modify cardiac fibrosis, a condition marked by excessive creation of extracellular matrix proteins that results in scar tissue formation (Ranjan et al., 2019). They can transfer molecules that control the fibroblast's activity, which broadly participate in ECM generation and performance (Tikhomirov et al., 2020). Exosomes can attenuate fibrosis and encourage tissue regeneration by altering the equilibrium between collagen synthesis and degradation. Exosomes support the injured cardiac tissue's immune system to be modulated. They may contain anti-inflammatory substances like transforming growth factor-beta (TGF-β) or interleukin-10 (IL-10), which reduce extravagant inflammation and encourage regener-

ation (Wen et al., 2021). This immunomodulatory impact contributes to developing an advantageous microenvironment for cardiac regeneration. There is growing evidence that exosomes play a role in ECM remodeling, essential for the structural integrity and practical restoration of the injured cardiac tissue (Cao et al., 2021). They deliver enzymes and matrix remodeling elements that aid in breaking down harmed ECM elements and synthesizing fresh ECM proteins, promoting tissue remodeling and regeneration. Exosomes can also influence several cellular functions, including cell migration, differentiation, and metabolism, which are crucial for cardiac regeneration (Ranjan et al., 2019). They have the ability to transfer regulatory molecules, such as proteins and miRNAs, to control these processes in recipient cells and enhance their capacity for regeneration (Emanueli et al., 2016; Nasser et al., 2021). The role of exosomes in cardiac regeneration highlights their potential as therapeutic agents for heart diseases. To improve outcomes in conditions like myocardial infarction, heart failure, and other cardiac pathologies, scientists are working to develop exosome-based therapies that increase cardiac tissue repair (Figure 1).

THERAPEUTIC APPLICATION OF MSC-DERIVED EXOSOME

Due to their inherent capacity to transport biomolecules between cells, exosomes have drawn considerable interest as a potential means of delivering therapeutic cargo. Exosomes are helpful delivery agents because of their small size, stability, biocompatibility, and capacity to target particular cell types (Table 2) (Xiao et al., 2018; Zhu et al., 2018).

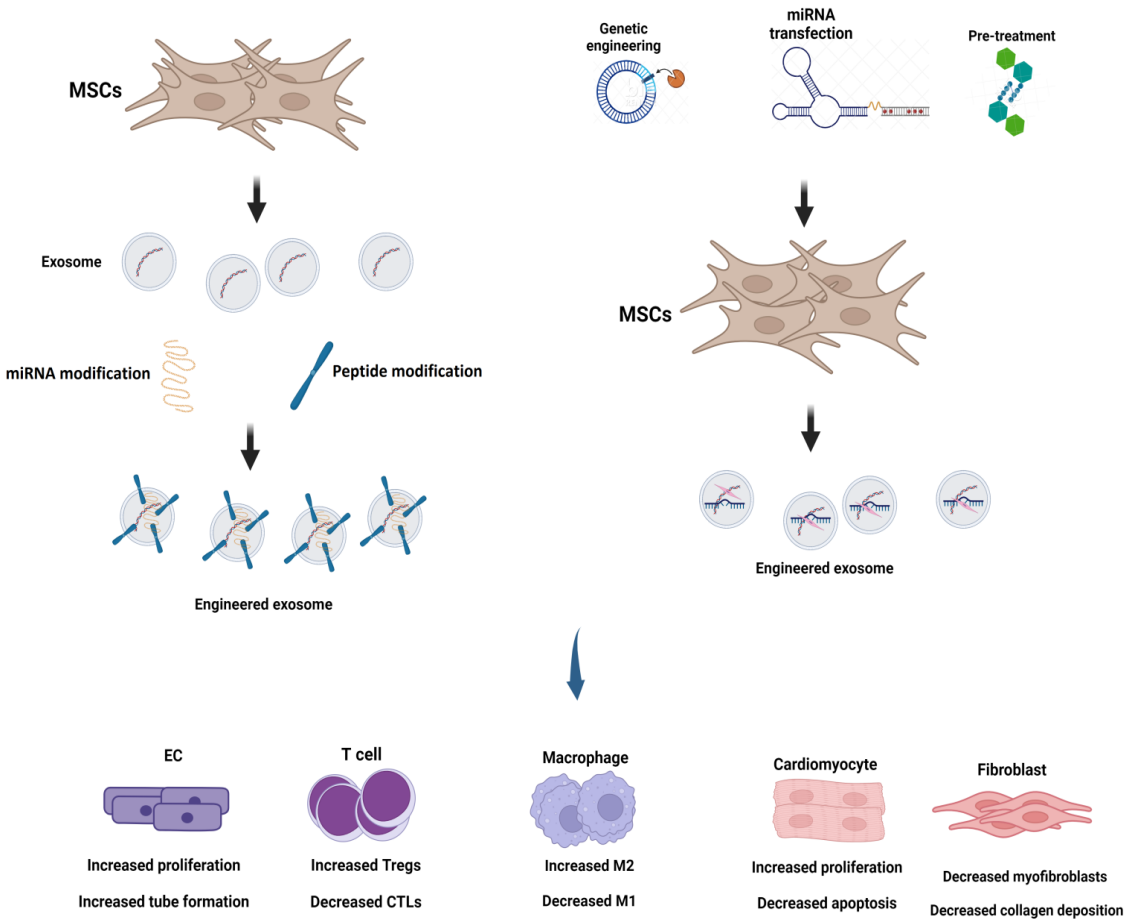

Figure 1: Engineered mesenchymal stem cell (MSC)-derived exosome in cardiac regeneration (created by BioRender).

Table 2: The advantages of MSC-derived exosomes over their parent cells (Hassanzadeh et al., 2021; Moghadasi et al., 2021)

Item	MSCs	MSCs-exosome
Risk of tumorigenicity	low	no
Immune rejection	low	no
Stability	low	high
Production cost	high	low
Therapeutic efficacy after systemic delivery	low	high

Exosomes can be created artificially or loaded with therapeutic cargo (Das et al., 2018). Drugs, growth factors, siRNA, miRNA, and gene-editing tools are examples of the cargo that may be present (Peng et al., 2020). Incubation, electroporation, sonication, genetic modification of the parent cells that make exosomes, and other techniques can all be used to load (Lai et al., 2020). Exosomes can be altered to improve their targeted abilities. Specific targeting ligands can be added, enabling exosomes to connect to receptors on target cells selectively; this can be accomplished by altering the surface proteins of exosomes or their membrane structure. This targeting strategy permits the precise delivery of therapeutic cargo to particular cell types, increasing efficacy and reducing off-target possessions (Feng et al., 2014). Exosomes interact with other cells within the body and deliver therapeutic cargo directly to recipient cells (Luo et al., 2017). Beyond the therapeutic benefits of the transferred cargo itself, the transmitted cargo can modify the recipient cells' gene expression, signaling pathways, or cellular behavior. In addition to promoting tissue repair and improving therapeutic results, this communication can aid in controlling cellular processes.

MSC-exosome in HF

MSCs-exosomes have cardioprotective properties. Interleukin (IL)-1, IL-4, IL-6, tumor necrosis factor (TNF), and brain natriuretic peptide (BNP) levels were decreased by exosome therapy in animal models of heart failure (HF) (Ren et al., 2023).

In a mouse model of pressure-overload heart failure, Nakamura et al. examined the cardioprotective effects of intravenously injected adiponectin-induced MSCs-exosome (Nakamura et al., 2020). Exosomes, extracellular vesicles with endosome origins produced by the injected MSCs, are responsible for their function. Because T-cadherin is a special glycosylphosphatidylinositol-anchored cadherin on MSCs, adiponectin stimulated exosome biogenesis and secretion by binding to it (Nakamura et al., 2020). Promising findings were achieved from a study on the prevention of heart failure (HF) in MI rats using BMMSCs-exosomes expressing microRNA-30e (miR-30e) (Pu et al., 2021). Exosome overexpressing miR-30e was administered to rats to treat the pathological injury, cardiomyocyte apoptosis, and fibrosis in rat myocardial tissues.

Additionally, miR-30e negatively regulated LOX1 expression, which was overexpressed in the MI rats, but additional exosome treatment restrained LOX1 expression. Further, exosome overexpressing miR-30e reduced NF-κB p65/Caspase-9 signaling in the myocardial tissues of MI rats, reducing cardiomyocyte apoptosis and fibrosis (Pu et al., 2021). By blocking the NF-κB signaling pathway, the miR-129-5p enriched MSC-Exos injection reduced ventricular dysfunction and reduced oxidative stress, apoptosis, inflammation, and fibrosis in cardiomyocytes in mice with HF (Yan et al., 2022) - exosomal

miR-129-5p from MSCs guards against heart failure by focusing on TRAF3 and the subsequent NF-κB signaling. This regulatory axis could be a potential therapeutic target for HF (Yan et al., 2022). Similarly, exosomal miR-1246 released from human UCMSCs reduced hypoxia-induced myocardial tissue damage by targeting PRSS23 and preventing the activation of the Snail/alpha-smooth muscle actin signaling. By targeting PRSS23 and encouraging angiogenesis, exosomal miR-1246 from hucMSCs does guard the heart against failure (Wang et al., 2021).

MSC-exosome in MI

MSCs-exosomes have a cardioprotective effect in rats with I/R injury, as shown by a significant reduction in I/R-induced myocardial infarction and a drop in the serum levels of cardiac troponin I (cTnI), lactate dehydrogenase, and creatine kinase-myocardial band. In addition to up-regulating Bcl-2 and down-regulating Bax, and inhibiting Caspase 3 activity in the rat myocardium, ADMSCs-ex concurrently significantly reduced I/R-induced myocardial apoptosis. In addition, Wnt3a, p-GSK-3β (Ser9), and -catenin expression were not as strongly inhibited by I/R and H/R, which allowed ADMSCs-ex to induce the activation of Wnt/β-catenin signaling (72) more clearly. *In vitro*, exosomes from MSCs were able to reduce the production of ROS and cell apoptosis in H9C2s (Liu et al., 2017). Similarly, *in vivo*, exosome injections significantly decreased apoptosis and the size of the myocardial infarct, increased myocardial LC3B expression, and improved heart function in rats that had undergone I/R injury. In fact, by triggering cardiomyocyte autophagy via the AMPK/mTOR and Akt/mTOR pathways, MSC-derived exosomes could lower MI (Liu et al., 2017).

Given that microRNA-132 (miR-132) controls endothelial cell behavior during angiogenesis and that delivering microRNAs safely and effectively *in vivo* is uncommon, ischemic diseases may benefit from developing an ideal vehicle for miR-132 delivery (Ma et al., 2018a). MiR-132 can be shown through exosomes made from MSCs to treat myocardial ischemia. In HUVECs pretreated with exosomes, the expression of the miR-132 target gene RASA1 was inversely correlated with that of miR-132, demonstrating that RASA1 was a direct target of miR-132. Endothelial cells formed more tubes when exosomes carrying miR-132 were used as a method of miRNA transfer (Ma et al., 2018a). Additionally, subcutaneous injection of HUVECs pretreated with miR-132 exosomes in nude mice significantly improved their *in vivo* angiogenesis capacity. Furthermore, the transplantation of miR-132 exosomes in mice with ischemic hearts significantly increased the neovascularization in the peri-infarct zone while maintaining heart functions (Ma et al., 2018a). The miR-210-enriched MSCs-exosome induces both *in vitro* and *in vivo* pro-angiogenic effects. In HUVECs, MSC-exosome treatment decreased the expression of the miR-210 target gene Efna3, which prevents angiogenesis (Wang et al., 2017b). MSC-exosomes are satisfactory in enhancing angiogenesis and exert therapeutic effects on MI; their pro-angiogenic effect may be related to a miR-210-Efna3-reliant mechanism (Wang et al., 2017b). Additional studies have shown that exosomes from ADSCs overexpressing SIRT1 (ADSCs-SIRT1-Exos) increased the expression of C-X-C motif chemokine 12 (CXCL12) and nuclear factor E2 related factor 2 (Nrf2) in AMI-EPCs, which promoted migration and tube formation of AMI-EPCs (Huang et al., 2020a). ADSCs-SIRT1-exosome treatment increased survival, aided myocardial function recovery, decreased infarct size, and prevented post-AMI left ventricular remodeling. It also inspired vasculogenesis and reduced AMI-related myocardial inflammation. Thus, ADSCs-SIRT1-exosome may attract EPCs to the repair site, and this attraction may be aided by Nrf2/CXCL12/CXCR7 signaling (Huang et al., 2020a).

It has been demonstrated that MSC-derived exosomes play a role in macrophage immunomodulation following myocardial ischemia/reperfusion (I/R) and promoting angiogenesis. The polarization of M1 macrophages

to M2 macrophages in animal models of MI was altered by MSC-Exo administration (Zhao et al., 2019). MiR-182 was identified as a potential candidate mediator of macrophage polarization by miRNA sequencing of MSC-exosome and bioinformatics analysis, with toll-like receptor 4 (TLR4) identified as a downstream target. MiR-182's influence on macrophage polarization was somewhat attenuated in MSC-Exo when it was reduced. In a mouse model of myocardial I/R, knockdown of TLR4 also provided cardioprotective efficacy and decreased inflammation level (Zhao et al., 2019).

Similarly, LPS preconditioning BMSC-derived exosomes may be a fruitful cell-free treatment plan for managing MI. Exosomes from BMSCs increased M2 macrophage polarization while decreasing M1 macrophage polarization in response to LPS stimulation (Xu et al., 2019), inhibiting the LPS-dependent NF-κB signaling pathway and partially activating the AKT1/AKT2 signaling pathway (Xu et al., 2019). Further, intramyocardial injection of MSC-EXO enriched in miRNA-181a in a mouse model of myocardial I/R injury resulted in significant protection against various immune-related genes via the miRNA-mRNA network. MiRNA-181a delivery by MSC-exosome combined the immune-suppressing properties of miRNA-181a and the cell targeting capabilities of MSC-exosome to have a more substantial therapeutic effect on myocardium I/R injury (Wei et al., 2019). Another study used ADSC-exosome therapy to lessen the severity of MI-induced cardiac damage by preventing cardiac dysfunction, cardiac apoptosis, cardiac fibrosis, and inflammatory responses both *in vitro* and *in vivo*. The ADSC-exosome treatment additionally supported macrophage M2 polarization (Deng et al., 2019). Further research revealed that the ADSC-exosome-mediated myocardial repair was mediated by S1P/SK1/S1PR1 signaling. The downregulation of S1PR1 under hypoxic conditions, which increased the expression of NF-κB and TGF-1, and reduced the fibrosis and inflammatory response brought on by MI, also reversed the ADSC-exosome-induced macrophage M2 polarization (Deng et al., 2019). A study of the effectiveness of MSC exosomes in a porcine model of myocardial infarction (MI) showed apparent effects of systemic exosomes administered over 7 days to decrease infarct size with largely unaltered cardiac function (Charles et al., 2020). The infarct size is significantly reduced (30–40 %) after 7 days of IV exosome administration, as measured at 7 and 28 days after MI. Additionally, exosome therapy decreased transmural and weakened wall thinning in the infarct zone. Pigs treated with exosomes demonstrated a largely sustained level of LV function and marked improvement in falls in fractional wall thickening (Charles et al., 2020). Additionally, MSCs-Exo-treated with IFN have more substantial cardioprotective effects in MI. IFNγ-exosome accelerated H9c2 migration and the development of tube-like structures while halting OGD-induced apoptosis (Zhang et al., 2022). Comparatively to Ctrl-exosome treatment, IFNγ-Exo treatment decreased cardiomyocyte apoptosis, reduced fibrosis, and enhanced cardiac function. In IFNγ-primed MSCs, MiR-21 was markedly up-regulated and suppressed the expression of BTG anti-proliferation factor 2 (BTG2). Under OGD conditions, BTG2 induced apoptosis in H9c2 cells and blocked the protective effects of miR-21 (Zhang et al., 2022). In line with this, miR-25-3p levels in cardiomyocytes significantly increased due to exosome uptake (Zhang et al., 2022). Exosomal miR-25-3p from MSCs ameliorated MI by targeting pro-apoptotic proteins, as demonstrated by the mechanistically demonstrated direct targeting of the pro-apoptotic genes FASL and PTEN and subsequent reduction in their protein levels (Zhang et al., 2022).

Furthermore, Exo secreted by MSCs undergoing hypoxia conditioning was discovered to have anti-ischemic properties. Significant enrichment of miR-125b-5p was found in Hypo-Exo, according to the miRNA array (Zhu et al., 2018). This study provides evidence for a novel mechanism whereby the miR125b-5p produced by Hypo-Exo pro-

motes cardiomyocyte apoptosis and ischemic cardiac repair. Exosomes from HIF-1-modified MSCs also restored the impaired angiogenic capacity, migratory function, and proliferation of hypoxia-damaged HUVECs (Sun et al., 2020). In the rat MI model, HIF-1-overexpressed exosomes simultaneously preserved heart function by encouraging neovessel development and preventing fibrosis (Sun et al., 2020). Exosomes produced by MSCs that overexpress SDF1 (Gong et al., 2019) and CXCR4 (Kang et al., 2015) also helped to improve cardiac remodeling, reduce infarct size, and promote angiogenesis, all of which helped to restore cardiac function; this was accomplished primarily by activating the PI3K/AKT axis and preventing autophagy in ischemic myocardial cells.

Table 3: MSCs-exosome therapy in MI

Animal	Cell source	Cargo	Result	Reference
Mouse	BMSCs	125b-5p	Facilitating cardiac repair by down-regulation of the expression of the pro-apoptotic genes p53 and BAK1	Zhu et al., 2018
Mouse	BMSCs	miR-125b	Reduction of infarct size, and promotion of cardiac performance by miR-125b-mediated p53-Bnip3 signaling	Xiao et al., 2018
Mouse	BMSCs	miR-22	Reduction of cardiomyocyte apoptosis by targeting Mecp2 and reducing cardiac fibrosis	Feng et al., 2014
Mouse	BMSCs	miR-25-3p	Confers cardioprotective effects and targeting inflammation	Peng et al., 2020
Mouse	ADSCs	miR-221/miR-222	Reduction of cardiac damage by miR-221/miR-222/PUMA/ETS-1 pathway	Lai et al., 2020
Rat	hUC-MSCs	miR-19a	Decreas in cell apoptosis by miR-19a/SOX6-mediated AKT activation and also targeting JNK3/caspase-3	Huang et al., 2020b
Rat	ADSCs	miR-126	Prevention of myocardial damage by suppressing apoptosis, inflammation, and fibrosis and potentiating angiogenesis	Luo et al., 2017
Rat	ADSCs	miR-146a	Decrease in cell apoptosis, inflammatory response, and fibrosis by targeting EGR1	Pan et al., 2019
Rat	BMSCs	miR-210	Prevention of myocyte apoptosis, decrease in infarct size and promotion of heart function	Cheng et al., 2020
Rat	BMSCs	miR-19a	Increase in cell survival by targeting PTEN to induce the Akt and ERK signaling	Yu et al., 2015
Rat	BMSCs	miR-338	Reduction of cell apoptosis, and promotion of cardiac function by governing the MAP3K2/JNK signaling pathway	
Rat	BMSCs	miR-133	Decrease in inflammation and infarct size by targeting snail 1	Chen et al., 2017
Rat	BMSCs	miR-29 and miR-24	Promotion of cardiac repair by increasing cardiomyocyte proliferation, and inhibiting fibrosis of fibroblast cell	Shao et al., 2017
Rat	EnMSCs	miR-21	Induction of cardioprotective effects by enhancing cell survival via the miR-21/PTEN/Akt pathway	Wang et al., 2017a
Rat	hUC-MSCs	Circular RNA 0001273	Inhibition of cell apoptosis and promoteion of cardiac repair	Li et al., 2020
Rat	MSCs	lncRNA KLF3-AS1	Decrease in MI progression by the lncRNA KLF3-AS1/miR-138-5p/Sirt1 pathway	Mao et al., 2019

Table 3 (cont.): MSCs-exosome therapy in MI

Animal	Cell source	Cargo	Result	Reference
Rat	Sfrp2	hUC-MSCs	Inhibition of cell apoptosis and attenuation of MI-mediated oxidative stress	Ni et al., 2019
Mouse	BMSCs	miR-132	Enhancement of the neovascularization in the peri-infarct zone	Ma et al., 2018a
Mouse	BMSCs	miR-210	Increase in angiogenesis and promotion of cardiac protection	Wang et al., 2017b
Mouse	ADSCs	Nrf2, CXCL12	Improvement of cell migration by Nrf2/CXCL12/CXCR7 signaling	Huang et al., 2020a
Rat	EnMSCs	miR-21	Promotion of angiogenic effects by the PTEN/Akt pathway	Wang et al., 2017a
Rat	hUC-MSCs	miR-133a-3p	Promotion of proliferation, migration, and angiogenesis	Zhu et al., 2021
Rat	BMSCs	lncRNA H19	Promotion of the activation of VEGF and intercellular adhesion molecule-1 to induce angiogenesis finally	Huang et al., 2020c
Rat	hUC-MSCs	Sfrp2	Promotion of cell proliferation and migration, and stimulation of angiogenesis	Ni et al., 2019
Rat	hUC-MSCs	PDGF-D	Triggering of angiogenesis by PDGF-D secretion	Ma et al., 2017
Mouse	hUCB-MSCs	miRNA-181a	Inhibition of inflammatory response and increase in Treg cell polarization by affecting c-Fos	Wei et al., 2019
Mouse	BMSCs	miR-182	Targeting macrophage polarization by affecting toll-like receptor 4	Zhao et al., 2019
Rat	BMSCs	miR-29 and miR-24	Increase in cardiac repair by transporting miR-29 and miR-24 to fibroblasts	Shao et al., 2017
Rat	hUC-MSCs	Sfrp2	Decrease in TGF-β-induced MMP2, MMP9, and α-SMA secretion in cardiac fibroblast and suppression of ECM remodeling	Ni et al., 2019

DETECTION OF CARDIAC BIOMARKERS IN EXOSOMES

Specific cardiac biomarkers may be present in exosomes derived from cardiac cells or found in the bloodstream, and these biomarkers can reveal important details about cardiac health and disease (Emanueli et al., 2016). Identifying cardiac biomarkers in exosomes may provide information about the pathological processes in the heart and even function as a non-invasive diagnostic or prognostic tool (Lu et al., 2019b).

Troponins are proteins that control the contraction of the cardiac muscle. Cardiovascular troponins with elevated levels, notably troponin T (cTnT) and troponin I (cTnI), are used to diagnose myocardial infarction and are diagnostic markers for myocardial injury (Liu et al., 2023). Exosomes made from damaged cardiomyocytes can be found to contain cardiac troponins. The heart responds to increased pressure or volume overload by secreting natriuretic peptides like B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Cao et al., 2019). They act as biomarkers for identifying and tracking heart failure. Exosomes derived from cardiac cells and circulating exosomes have both been found to contain natriuretic peptides and their receptors. Additionally, myosin-binding protein C (cMyBP-C) plays a crucial regulatory role in cardiac muscle contraction (Harris, 2019). Hypertrophic cardiomyopathy is connected to mutations in the MYBPC3 gene that codes for cMyBP-C. Exosomes from patients with hypertrophic cardiomyopathy have been found to contain cMyBP-C, indicating the possibility that this molecule could serve as a biomarker for the condition (Gao et al., 2022).

Small non-coding RNA molecules called microRNAs (miRNAs) control the expression

of genes. Numerous miRNAs are biomarkers for cardiac disorders, and exosomes can contain them. Myocardial infarction and heart failure are linked, for instance, to miR-208a, miR-133a, and miR-1 (Bostjancic et al., 2010). The identification of these miRNAs in exosomes may shed light on cardiac pathologies. Exosomes may contain biomarkers linked to cardiac ischemic circumstances. Exosomes from ischemic myocardium, for example, may include the miRNAs miR-1, miR-133a, and miR-208a, which are linked to ischemic injury and cardiac damage (Bostjancic et al., 2010). These exosome biomarkers can indicate the degree and scope of cardiac ischemia. Exosomes can also carry inflammatory markers linked to cardiac inflammation. Inflammatory biomarkers have been found in the exosomes of cardiac patients, including C-reactive protein (CRP), interleukins (like IL-6), and tumor necrosis factor-alpha (TNF-α) (Albar et al., 2022; Soeki and Sata, 2016). These markers can help diagnose and follow up inflammatory cardiac conditions because they show the presence of cardiac inflammation.

CLINICAL TRIALS EXPLORING MSC-EXOSOME THERAPIES FOR CARDIAC CONDITIONS

The potential of exosome therapies for different cardiac conditions is currently being studied in several clinical trials. The use of MSCs-exosome for treating patients with heart failure with preserved ejection fraction (HFpEF) is being investigated as part of the DREAM-HF phase II clinical trial (Bolli and Tang, 2022). The trial's objectives are to evaluate the safety and effectiveness of MSC-exosome in enhancing exercise capacity, cardiac function, and quality of life (Bolli and Tang, 2022). Exosomes derived from allogeneic BM-MSCs are being investigated for treating ST-elevation myocardial infarction (STEMI) patients in the PRECISE phase I/II clinical trial (Sanz-Ruiz et al., 2010).

Exosomes derived from MSCs will be tested to see how they affect tissue repair and cardiac function. Similarly, the safety and effectiveness of delivering exosomes from BM-MNCs intracoronary to patients with AMI are being studied in the EVOMEND phase I/II clinical trial (Attar et al., 2021). Exosomes made from autologous adipose tissue-derived (AD)-MSCs are also being administered intravenously to patients with acute AMI as part of the EXOSOMA phase I clinical trial, which evaluates their safety and viability (Attar et al., 2021; Fan et al., 2010). The trial assesses how AD-MSC exosomes affect cardiac function and tissue repair.

These are just a few active clinical trials examining exosome therapies for cardiac conditions. These studies seek to shed light on the efficacy, safety, and viability of exosome-based treatments in enhancing cardiac function, fostering tissue regeneration, and possibly revolutionizing the management of various cardiac diseases. It is significant to note that the results of clinical trials are still pending, and additional study is required to determine the efficacy and long-term effects of exosome therapies in cardiac patients (Chou et al., 2014).

CHALLENGES AND CONCERNS

There is still a need for reliable exosome isolation and characterization techniques. Standard protocols must be established to guarantee isolated exosomes' reproducibility, purity, and quality (Rezaie et al., 2022). Achieving high loading efficiency of therapeutic cargo into exosomes is still technically challenging. The best therapeutic results depend on the development of effective and dependable procedures for therapeutic agent loading into exosomes while maintaining their stability and functionality (Yamashita et al., 2018). Exosome delivery and precisely targeting the desired cardiac cell types or tissues are difficult. It is necessary to conduct more research to strengthen targeting tactics, increase the specificity of exosome-cell interactions, and get past potential obstacles like the blood-brain barrier or the development of scar tissue. Exosome production at a larger scale for medical uses presents a challenge (Mehryab et al., 2020). Scalable manufact-

uring processes must be created to produce therapeutic-grade exosomes in sufficient quantities and with reliable quality and effectiveness.

Further research is needed to determine the durability and safety of exosome-based therapies over the long term (Adamiak and Sahoo, 2018). It is crucial to comprehend potential adverse effects, immune responses, and the determination of therapeutic possessions over time to guarantee the long-term advantages and security of exosome-based treatments (Ahmadi and Rezaie, 2021; Ludwig et al., 2019). Exosome-based therapies are still in their infancy, and regulatory frameworks for their clinical translation and approval are changing. Exosome-based therapies must be successfully translated into clinical practice, which will require overcoming regulatory obstacles and establishing suitable guidelines and standards (Cheng et al., 2017).

Exosome therapies can be expensive, so it's essential to consider their accessibility to all patients, including those from low socioeconomic statuses. Fair resource allocation, prioritizing patients based on clinical need, and preventing disparities in entrance to potentially helpful treatments are all ethical considerations (Ayala-Mar et al., 2019). Careful thought must be given to exosome therapy's security and long-term effects. While exosomes derived from autologous sources may have less immunogenicity, potential risks, such as immune reactions, off-target effects, or unexpected long-term consequences, must be carefully evaluated through rigorous preclinical and clinical studies (Ding et al., 2021). Monitoring patients receiving exosome therapy and long-term follow-up is crucial to assess the safety and guarantee patient well-being. Exosome therapies develop, and regulatory oversight ethics become increasingly important. Exosome-based treatments must be developed, produced, and used in clinical settings following ethical standards, maintaining patient safety, and adhering to pertinent legal and regulatory frameworks, requiring adequate regulation and oversight (Rezaie et al., 2022).

CONCLUSION

Exosomes have the potential to significantly improve cardiac patient outcomes and play a substantial role in cardiac health. Exosomes can promote the growth and differentiation of cardiac progenitor cells, which produces new, functional cardiomyocytes. Exosomes are a promising therapeutic option for treating the adult heart's constrained capacity for regeneration because of their regenerative potential. Specific molecules, such as proteins, RNA, and miRNA, are found in exosomes derived from cardiac cells and can be used as diagnostic biomarkers for cardiac diseases. Exosomal biomarker analysis enables non-invasive detection, monitoring, and risk stratification of cardiac conditions, offering important visions into disease progression and treatment response. Exosomes can be used as organic nanocarriers for the delivery of specific drugs. They can transport various therapeutic molecules to particular cardiac cells or tissues by encasing and delivering them as proteins, nucleic acids, small molecules, or gene-editing agents. This targeted delivery method increases treatment effectiveness while reducing systemic toxicity and off-target effects.

Cardiologists can practice personalized medicine using autologous exosomes from a patient's cells. Exosome therapies can be customized to each patient, maximizing treatment efficacy and lowering immunogenicity by utilizing the patient's biological characteristics. Exosome therapies can open new avenues for cardiac regeneration, non-invasive diagnosis, targeted drug delivery, cardioprotection, and personalized medicine. Researchers and clinicians can address current therapies' shortcomings and potentially enhance patient outcomes by utilizing the therapeutic potential of exosomes. More research, clinical trials, and technological developments are required to understand the impact of exosome therapies in cardiology fully.

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable.

Competing interests
There is no conflict of interest.

Funding
No funders.

REFERENCES

Adamiak M, Sahoo S. Exosomes in myocardial repair: advances and challenges in the development of next-generation therapeutics. Mol Ther. 2018;26:1635-43.

Ahmadi M, Rezaie J. Ageing and mesenchymal stem cells derived exosomes: molecular insight and challenges. Cell Biochem Funct. 2021;39(1):60-6.

Ahmed L, Al-Massri K. New approaches for enhancement of the efficacy of mesenchymal stem cell-derived exosomes in cardiovascular diseases. Tissue Engin Regener Med. 2022;19:1129-46.

Albar Z, Albakri M, Hajjari J, Karnib M, Janus SE, Al-Kindi SG. Inflammatory markers and risk of heart failure with reduced to preserved ejection fraction. Am J Cardiol. 2022;167:68-75.

Aluru JS, Barsouk A, Saginala K, Rawla P, Barsouk A. Valvular heart disease epidemiology. Med Sci. 2022;10(2):32.

Attar A, Bahmanzadegan Jahromi F, Kavousi S, Monabati A, Kazemi A. Mesenchymal stem cell transplantation after acute myocardial infarction: a meta-analysis of clinical trials. Stem Cell Res Ther. 2021;12 (1):600.

Ayala-Mar S, Donoso-Quezada J, Gallo-Villanueva RC, Perez-Gonzalez VH, González-Valdez J. Recent advances and challenges in the recovery and purification of cellular exosomes. Electrophoresis. 2019;40: 3036-49.

Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. Heart Fail Rev. 2021;26(1):1-10.

Bartolucci J, Verdugo FJ, Gonzalez PL, Larrea RE, Abarzua E, Goset C, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: a phase 1/2 randomized controlled trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). Circ Res. 2017;121:1192-204.

Berry MF, Engler AJ, Woo YJ, Pirolli TJ, Bish LT, Jayasankar V, et al. Mesenchymal stem cell injection after myocardial infarction improves myocardial compliance. Am J Physiol Heart Circ Physiol. 2006;290: H2196-203.

Bjørge I, Kim S, Mano J, Kalionis B, Chrzanowski W. Extracellular vesicles, exosomes and shedding vesicles in regenerative medicine–a new paradigm for tissue repair. Biomaterials Sci. 2018;6:60-78.

Bolli R, Tang X-L. Clinical trials of cell therapy for heart failure: recent results warrant continued research. Curr Opin Cardiol. 2022;37:193-200.

Bostjancic E, Zidar N, Stajer D, Glavac D. MicroRNAs miR-1, miR-133a, miR-133b and miR-208 are dysregulated in human myocardial infarction. Cardiology. 2010;115:163-9.

Cao F, Li Z, Ding W, Yan L, Zhao Q. Angiotensin II-treated cardiac myocytes regulate M1 macrophage polarization via transferring exosomal PVT1. J Immunol Res. 2021;2021:1994328.

Cao Z, Jia Y, Zhu B. BNP and NT-proBNP as diagnostic biomarkers for cardiac dysfunction in both clinical and forensic medicine. Int J Mol Sci. 2019;20(8):1820.

Cervio E, Barile L, Moccetti T, Vassalli G. Exosomes for intramyocardial intercellular communication. Stem Cells Int. 2015;2015:482171.

Charles CJ, Li RR, Yeung T, Mazlan SMI, Lai RC, de Kleijn DPV, et al. Systemic mesenchymal stem cell-derived exosomes reduce myocardial infarct size: characterization with MRI in a porcine model. Front Cardiovasc Med. 2020;7:601990.

Chen P, Zheng L, Wang Y, Tao M, Xie Z, Xia C, et al. Desktop-stereolithography 3D printing of a radially oriented extracellular matrix/mesenchymal stem cell exosome bioink for osteochondral defect regeneration. Theranostics. 2019;9:2439-59.

Chen Y, Zhao Y, Chen W, Xie L, Zhao ZA, Yang J, et al. MicroRNA-133 overexpression promotes the therapeutic efficacy of mesenchymal stem cells on acute myocardial infarction. Stem Cell Res Ther. 2017;8(1): 268.

Cheng H, Chang S, Xu R, Chen L, Song X, Wu J, et al. Hypoxia-challenged MSC-derived exosomes deliver miR-210 to attenuate post-infarction cardiac apoptosis. Stem Cell Res Ther. 2020;11(1):224.

Cheng L, Zhang K, Wu S, Cui M, Xu T. Focus on mesenchymal stem cell-derived exosomes: opportunities and challenges in cell-free therapy. Stem Cells Int. 2017;2017:6305295.

Chou S-H, Lin S-Z, Kuo W-W, Pai P, Lin J-Y, Lai C-H, et al. Mesenchymal stem cell insights: prospects in cardiovascular therapy. Cell Transplant. 2014;23:513-29.

CDC, Centers for Disease Control and Prevention. Prevalence of coronary heart disease - United States, 2006-2010. Morbidity and Mortality Weekly Report (MMWR). 2011;60:1377-81.

Cosme J, Liu PP, Gramolini AO. The cardiovascular exosome: current perspectives and potential. Proteomics. 2013;13:1654-9.

Crisafulli A, Pagliaro P, Roberto S, Cugusi L, Mercuro G, Lazou A, et al. Diabetic cardiomyopathy and ischemic heart disease: prevention and therapy by exercise and conditioning. Int J Mol Sci. 2020;21(8):2896.

Dai W, Hale SL, Martin BJ, Kuang J-Q, Dow JS, Wold LE, et al. Allogeneic mesenchymal stem cell transplantation in postinfarcted rat myocardium: short-and long-term effects. Circulation. 2005;112:214-23.

Das CK, Jena BC, Banerjee I, Das S, Parekh A, Bhutia SK, et al. Exosome as a novel shuttle for delivery of therapeutics across biological barriers. Mol Pharm. 2018;16(1):24-40.

de Macedo Braga LMG, Lacchini S, Schaan BDA, Rodrigues B, Rosa K, De Angelis K, et al. In situ delivery of bone marrow cells and mesenchymal stem cells improves cardiovascular function in hypertensive rats submitted to myocardial infarction. J Biomed Sci. 2008;15:365-74.

Deng S, Ge Z, Song Y, Wang H, Liu X, Zhang D. Exosomes from adipose-derived mesenchymal stem cells ameliorate cardiac damage after myocardial infarction by activating S1P/SK1/S1PR1 signaling and promoting macrophage M2 polarization. Int J Biochem Cell Biol. 2019;114:105564.

Ding L, Yang X, Gao Z, Effah CY, Zhang X, Wu Y, et al. A holistic review of the state‐of‐the‐art microfluidics for exosome separation: an overview of the current status, existing obstacles, and future outlook. Small. 2021;17(29):2007174.

Emanueli C, Shearn AI, Laftah A, Fiorentino F, Reeves BC, Beltrami C, et al. Coronary artery-bypass-graft surgery increases the plasma concentration of exosomes carrying a cargo of cardiac microRNAs: an example of exosome trafficking out of the human heart with potential for cardiac biomarker discovery. PloS One. 2016;11(4):e0154274.

Fan L, Liu C, Chen X, Zheng L, Zou Y, Wen H, et al. Exosomes‐loaded electroconductive hydrogel synergistically promotes tissue repair after spinal cord injury via Immunoregulation and enhancement of myelinated axon growth. Adv Sci. 2022;9(13):2105586.

Fan M, Chen W, Liu W, Du G-Q, Jiang S-L, Tian W-C, et al. The effect of age on the efficacy of human mesenchymal stem cell transplantation after a myocardial infarction. Rejuvenation Res. 2010;13:429-38.

Fang Y, Zhang Y, Zhou J, Cao K. Adipose-derived mesenchymal stem cell exosomes: a novel pathway for tissues repair. Cell Tissue Bank. 2019;20:153-61.

Fazel S, Chen L, Weisel RD, Angoulvant D, Seneviratne C, Fazel A, et al. Cell transplantation preserves cardiac function after infarction by infarct stabilization: augmentation by stem cell factor. J Thorac Cardiovasc Surg. 2005;130(5):1310.

Feng Y, Huang W, Wani M, Yu X, Ashraf M. Ischemic preconditioning potentiates the protective effect of stem cells through secretion of exosomes by targeting Mecp2 via miR-22. PloS One. 2014;9(2):e88685.

Frangogiannis NG. Pathophysiology of myocardial infarction. Compr Physiol. 2011;5:1841-75.

Gao H, Zhang L, Wang Z, Yan K, Zhao L, Xiao W. Research progress on transorgan regulation of the cardiovascular and motor system through cardiogenic exosomes. Int J Mol Sci. 2022;23(10):5765.

Garcia NA, Ontoria-Oviedo I, González-King H, Diez-Juan A, Sepúlveda P. Glucose starvation in cardiomyocytes enhances exosome secretion and promotes angiogenesis in endothelial cells. PloS One. 2015;10(9): e0138849.

Gong XH, Liu H, Wang SJ, Liang SW, Wang GG. Exosomes derived from SDF1-overexpressing mesenchymal stem cells inhibit ischemic myocardial cell apoptosis and promote cardiac endothelial microvascular regeneration in mice with myocardial infarction. J Cell Physiol. 2019;234:13878-93.

Grauss RW, van Tuyn J, Steendijk P, Winter EM, Pijnappels DA, Hogers B, et al. Forced myocardin expression enhances the therapeutic effect of human mesenchymal stem cells after transplantation in ischemic mouse hearts. Stem Cells. 2008;26:1083-93.

Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020; 22:1342-56.

Guo X, Bai Y, Zhang L, Zhang B, Zagidullin N, Carvalho K, et al. Cardiomyocyte differentiation of mesenchymal stem cells from bone marrow: new regulators and its implications. Stem Cell Res Ther. 2018; 9(1):44.

Gyöngyösi M, Blanco J, Marian T, Trón L, Petneházy O, Petrasi Z, et al. Serial noninvasive in vivo positron emission tomographic tracking of percutaneously intramyocardially injected autologous porcine mesenchymal stem cells modified for transgene reporter gene expression. Circ Cardiovasc Imaging. 2008;1:94-103.

Han C, Zhou J, Liang C, Liu B, Pan X, Zhang Y, et al. Human umbilical cord mesenchymal stem cell derived exosomes encapsulated in functional peptide hydrogels promote cardiac repair. Biomaterials Sci. 2019;7:2920-33.

Harrell CR, Jovicic N, Djonov V, Volarevic V. Therapeutic use of mesenchymal stem cell-derived exosomes: from basic science to clinics. Pharmaceutics. 2020;12(5):474.

Harris SP. Acute loss of cMyBP-C induces auto-oscillatory contractions in permeabilized cardiomyocytes: implications for reverse EC coupling? Biophys J. 2019; 116:461a-2a.

Hassanzadeh A, Rahman HS, Markov A, Endjun JJ, Zekiy AO, Chartrand MS, et al. Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities. Stem Cell Res Ther. 2021; 12:297.

Huang H, Xu Z, Qi Y, Zhang W, Zhang C, Jiang M, et al. Exosomes from SIRT1-overexpressing ADSCs restore cardiac function by improving angiogenic function of EPCs. Mol Ther Nucleic Acids. 2020a;21:737-50.

Huang J, Xiong J, Yang L, Zhang J, Sun S, Liang Y. Cell-free exosome-laden scaffolds for tissue repair. Nanoscale. 2021;13:8740-50.

Huang L, Yang L, Ding Y, Jiang X, Xia Z, You Z. Human umbilical cord mesenchymal stem cells-derived exosomes transfers microRNA-19a to protect cardiomyocytes from acute myocardial infarction by targeting SOX6. Cell Cycle. 2020b;19:339-53.

Huang P, Wang L, Li Q, Tian X, Xu J, Xu J, et al. Atorvastatin enhances the therapeutic efficacy of mesenchymal stem cells-derived exosomes in acute myocardial infarction via up-regulating long non-coding RNA H19. Cardiovasc Res. 2020c;116:353-67.

Imanishi Y, Saito A, Komoda H, Kitagawa-Sakakida S, Miyagawa S, Kondoh H, et al. Allogenic mesenchymal stem cell transplantation has a therapeutic effect in acute myocardial infarction in rats. J Mol Cell Cardiol. 2008;44:662-71.

Jia Y, Chang Y, Sun P, Li H, Guo Z. Inhibition of profibrotic signalling enhances the 5-azacytidine-induced reprogramming of fibroblasts into cardiomyocytes. Int J Biochem Cell Biol. 2020:122:105733.

Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/reperfusion. Compr Physiol. 2016;7(1):113.

Kang K, Ma R, Cai W, Huang W, Paul C, Liang J, et al. Exosomes secreted from CXCR4 overexpressing mesenchymal stem cells promote cardioprotection via Akt signaling pathway following myocardial infarction. Stem Cells Int. 2015;2015:659890.

Karantalis V, DiFede DL, Gerstenblith G, Pham S, Symes J, Zambrano JP, et al. Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting. Circ Res. 2014;114:1302-10.

Kudo M, Wang Y, Wani MA, Xu M, Ayub A, Ashraf M. Implantation of bone marrow stem cells reduces the infarction and fibrosis in ischemic mouse heart. J Mol Cell Cardiol. 2003;35:1113-9.

Lai RC, Arslan F, Lee MM, Sze NSK, Choo A, Chen TS, et al. Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. Stem Cell Res. 2010; 4:214-22.

Lai RC, Chen TS, Lim SK. Mesenchymal stem cell exosome: a novel stem cell-based therapy for cardiovascular disease. Regener Med. 2011;6:481-92.

Lai TC, Lee TL, Chang YC, Chen YC, Lin SR, Lin SW, 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.

Li CX, Song J, Li X, Zhang T, Li ZM. Circular RNA 0001273 in exosomes derived from human umbilical cord mesenchymal stem cells (UMSCs) in myocardial infarction. Eur Rev Med Pharmacol Sci. 2020;24: 10086-95.

Li W, Ma N, Ong L-L, Nesselmann C, Klopsch C, Ladilov Y, et al. Bcl-2 engineered MSCs inhibited apoptosis and improved heart function. Stem Cells. 2007; 25:2118-27.

Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111:3481-8.

Liu H, Deng S, Han L, Ren Y, Gu J, He L, et al. Mesenchymal stem cells, exosomes and exosome-mimics as smart drug carriers for targeted cancer therapy. Colloids Surf B Biointerfaces. 2022;209:112163.

Liu L, Jin X, Hu C-F, Li R, Zhou Ze, Shen C-X. Exosomes derived from mesenchymal stem cells rescue myocardial ischaemia/reperfusion injury by inducing cardiomyocyte autophagy via AMPK and Akt pathways. Cell Physiol Biochem. 2017;43:52-68.

Liu P, Wang S, Li K, Yang Y, Man Y, Du F, et al. Exosomal microRNA-4516, microRNA-203 and SFRP1 are potential biomarkers of acute myocardial infarction. Mol Med Rep. 2023;27(6):124.

Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res. 2021;128:1487-513.

Lu D, Liao Y, Zhu S-H, Chen Q-C, Xie D-M, Liao J-J, et al. Bone-derived Nestin-positive mesenchymal stem cells improve cardiac function via recruiting cardiac endothelial cells after myocardial infarction. Stem Cell Res Ther. 2019a;10(1):127.

Lu J, Wu J, Tian J, Wang S. Role of T cell-derived exosomes in immunoregulation. Immunol Res. 2018;66: 313-22.

Lu M, Yuan S, Li S, Li L, Liu M, Wan S. The exosome-derived biomarker in atherosclerosis and its clinical application. J Cardiovasc Transl Res. 2019b;12:68-74.

Ludwig N, Whiteside TL, Reichert TE. Challenges in exosome isolation and analysis in health and disease. Int J Mol Sci. 2019;20(19):4684.

Luo Q, Guo D, Liu G, Chen G, Hang M, Jin M. Exosomes from MiR-126-overexpressing Adscs are therapeutic in relieving acute myocardial ischaemic injury. Cell Physiol Biochem. 2017;44:2105-16.

Ma J, Zhao Y, Sun L, Sun X, Zhao X, Sun X, et al. Exosomes derived from Akt-modified human umbilical cord mesenchymal stem cells improve cardiac regeneration and promote angiogenesis via activating platelet-derived growth factor D. Stem Cells Transl Med. 2017;6(1):51-9.

Ma T, Chen Y, Chen Y, Meng Q, Sun J, Shao L, et al. MicroRNA-132, delivered by mesenchymal stem cell-derived exosomes, promote angiogenesis in myocardial infarction. Stem Cells Int. 2018a;2018:3290372.

=2018aMa X, Wang J, Li J, Ma C, Chen S, Lei W, et al. Loading MiR-210 in endothelial progenitor cells derived exosomes boosts their beneficial effects on hypoxia/ reoxygeneation-injured human endothelial cells via protecting mitochondrial function. Cell Physiol Biochem. 2018b;46:664-75.

Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, et al. Cardiomyocytes can be generated from marrow stromal cells in vitro. J Clin Invest. 1999;103: 697-705.

Makkar RR, Price MJ, Lill M, Frantzen M, Takizawa K, Kleisli T, et al. Intramyocardial injection of allogenic bone marrow-derived mesenchymal stem cells without immunosuppression preserves cardiac function in a porcine model of myocardial infarction. J Cardiovasc Pharmacol Ther. 2005;10:225-33.

Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019; 234:16812-23.

Mangi AA, Noiseux N, Kong D, He H, Rezvani M, Ingwall JS, et al. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. Nat Med. 2003;9:1195-201.

Mangini S, Alves BR, Silvestre OM, Pires PV, Pires LJT, Curiati MNC, et al. Heart transplantation. Einstein (Sao Paulo). 2015;13:310-8.

Manuel GE, Johnson T, Liu D. Therapeutic angiogenesis of exosomes for ischemic stroke. Int J Physiol Pathophysiol Pharmacol. 2017;9:188-91.

Mao Q, Liang XL, Zhang CL, Pang YH, Lu YX. LncRNA KLF3-AS1 in human mesenchymal stem cell-derived exosomes ameliorates pyroptosis of cardiomyocytes and myocardial infarction through miR-138-5p/Sirt1 axis. Stem Cell Res Ther. 2019;10(1): 393.

Mehryab F, Rabbani S, Shahhosseini S, Shekari F, Fatahi Y, Baharvand H, et al. Exosomes as a next-generation drug delivery system: An update on drug loading approaches, characterization, and clinical application challenges. Acta Biomater. 2020;113:42-62.

Moghadasi S, Elveny M, Rahman HS, Suksatan W, Jalil AT, Abdelbasset WK, et al. A paradigm shift in cell-free approach: the emerging role of MSCs-derived exosomes in regenerative medicine. J Transl Med. 2021;19:302.

Nagaya N, Fujii T, Iwase T, Ohgushi H, Itoh T, Uematsu M, et al. Intravenous administration of mesenchymal stem cells improves cardiac function in rats with acute myocardial infarction through angiogenesis and myogenesis. Am J Physiol Heart Circ Physiol. 2004;287:H2670-6.

Nakamura Y, Kita S, Tanaka Y, Fukuda S, Obata Y, Okita T, et al. Adiponectin stimulates exosome release to enhance mesenchymal stem-cell-driven therapy of heart failure in mice. Mol Ther. 2020;28:2203-19.

Nakamura Y, Wang X, Xu C, Asakura A, Yoshiyama M, From AH, et al. Xenotransplantation of long-term-cultured swine bone marrow-derived mesenchymal stem cells. Stem Cells. 2007;25:612-20.

Nasser M, Masood M, Adlat S, Gang D, Zhu S, Li G, et al. Mesenchymal stem cell-derived exosome microRNA as therapy for cardiac ischemic injury. Biomed Pharmacother. 2021;143:112118.

Neisius U, Myerson L, Fahmy AS, Nakamori S, El-Rewaidy H, Joshi G, et al. Cardiovascular magnetic resonance feature tracking strain analysis for discrimination between hypertensive heart disease and hypertrophic cardiomyopathy. PloS One. 2019;14(8): e0221061.

Newton WC, Kim JW, Luo JZ, Luo L. Stem cell-derived exosomes: a novel vector for tissue repair and diabetic therapy. J Mol Endocrinol. 2017;59:R155-65.

Ni J, Liu X, Yin Y, Zhang P, Xu YW, Liu Z. Exosomes derived from TIMP2-modified human umbilical cord mesenchymal stem cells enhance the repair effect in rat model with myocardial infarction possibly by the Akt/Sfrp2 pathway. Oxid Med Cell Longev. 2019; 2019:1958941.

Noiseux N, Gnecchi M, Lopez-Ilasaca M, Zhang L, Solomon SD, Deb A, et al. Mesenchymal stem cells overexpressing Akt dramatically repair infarcted myocardium and improve cardiac function despite infrequent cellular fusion or differentiation. Mol Ther. 2006;14:840-50.

Okrainec K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. Am Heart J. 2004;148(1):7-15.

Pan J, Alimujiang M, Chen Q, Shi H, Luo X. Exosomes derived from miR-146a-modified adipose-derived stem cells attenuate acute myocardial infarction-induced myocardial damage via downregulation of early growth response factor 1. J Cell Biochem. 2019;120: 4433-43.

Peng Y, Zhao JL, Peng ZY, Xu WF, Yu GL. Exosomal miR-25-3p from mesenchymal stem cells alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2. Cell Death Dis. 2020;11(5):317.

Perin EC, Silva GV, Assad JA, Vela D, Buja LM, Sousa AL, et al. Comparison of intracoronary and transendocardial delivery of allogeneic mesenchymal cells in a canine model of acute myocardial infarction. J Mol Cell Cardiol. 2008;44:486-95.

Price MJ, Chou C-C, Frantzen M, Miyamoto T, Kar S, Lee S, et al. Intravenous mesenchymal stem cell therapy early after reperfused acute myocardial infarction improves left ventricular function and alters electrophysiologic properties. Int J Cardiol. 2006;111:231-9.

Pu L, Kong X, Li H, He X. Exosomes released from mesenchymal stem cells overexpressing microRNA-30e ameliorate heart failure in rats with myocardial infarction. Am J Transl Res. 2021;13(5):4007.

Qin Y, Sun R, Wu C, Wang L, Zhang C. Exosome: a novel approach to stimulate bone regeneration through regulation of osteogenesis and angiogenesis. Int J Mol Sci. 2016;17(5):712.

Quevedo HC, Hatzistergos KE, Oskouei BN, Feigenbaum GS, Rodriguez JE, Valdes D, et al. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. Proc Natl Acad Sci U S A. 2009; 106:14022-7.

Ranjan P, Kumari R, Verma SK. Cardiac fibroblasts and cardiac fibrosis: precise role of exosomes. Front Cell Dev Biol. 2019;7:318.

Reddy K, Khaliq A, Henning RJ. Recent advances in the diagnosis and treatment of acute myocardial infarction. World J Cardiol. 2015;7:243-76.

Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017;389(10065):197-210.

Ren Y, Wu Y, He W, Tian Y, Zhao X. Exosomes secreted from bone marrow mesenchymal stem cells suppress cardiomyocyte hypertrophy through Hippo-YAP pathway in heart failure. Genet Mol Biol. 2023;46: e20220221.

Rezaie J, Feghhi M, Etemadi T. A review on exosomes application in clinical trials: Perspective, questions, and challenges. Cell Commun Signal. 2022;20(1):145.

Rich MW. Epidemiology, clinical features, and prognosis of acute myocardial infarction in the elderly. Am J Geriatric Cardiol. 2006;15(1):7-13.

Saleh M, Ambrose JA. Understanding myocardial infarction. F1000Res. 2018;7:F1000 Faculty Rev-1378.

Sanz-Ruiz R, Gutierrez Ibanes E, Arranz AV, Fernandez Santos ME, Fernández PLS, Fernández-Avilés F. Phases I–III clinical trials using adult stem cells. Stem Cells Int. 2010;2010:579142.

Schuleri KH, Feigenbaum GS, Centola M, Weiss ES, Zimmet JM, Turney J, et al. Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. Eur Heart J. 2009;30:2722-32.

Shake JG, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, Redmond JM, et al. Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. Ann Thorac Surg. 2002;73:1919-26.

Shao L, Zhang Y, Lan B, Wang J, Zhang Z, Zhang L, et al. MiRNA-sequence indicates that mesenchymal stem cells and exosomes have similar mechanism to enhance cardiac repair. BioMed Res Int. 2017;2017: 4150705.

Shiota M, Heike T, Haruyama M, Baba S, Tsuchiya A, Fujino H, et al. Isolation and characterization of bone marrow-derived mesenchymal progenitor cells with myogenic and neuronal properties. Exp Cell Res. 2007; 313:1008-23.

Silva GV, Litovsky S, Assad JA, Sousa AL, Martin BJ, Vela D, et al. Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model. Circulation. 2005;111:150-6.

Soeki T, Sata M. Inflammatory biomarkers and atherosclerosis. Int Heart J. 2016;57:134-9.

Su N, Hao Y, Wang F, Hou W, Chen H, Luo Y. Mesenchymal stromal exosome–functionalized scaffolds induce innate and adaptive immunomodulatory responses toward tissue repair. Sci Adv. 2021;7(20): eabf7207.

Sun J, Shen H, Shao L, Teng X, Chen Y, Liu X, et al. HIF-1α overexpression in mesenchymal stem cell-derived exosomes mediates cardioprotection in myocardial infarction by enhanced angiogenesis. Stem Cell Res Ther. 2020;11(1):373.

Taylor DA, Robertson MJ. The basics of cell therapy to treat cardiovascular disease: one cell does not fit all. Rev Española Cardiol. 2009;62:1032-44.

Tesson S, Butow PN, Sholler GF, Sharpe L, Kovacs AH, Kasparian NA. Psychological interventions for people affected by childhood-onset heart disease: A systematic review. Health Psychol. 2019;38:151-61.

Tikhomirov R, Reilly-O'Donnell B, Catapano F, Faggian G, Gorelik J, Martelli F, et al. Exosomes: from potential culprits to new therapeutic promise in the setting of cardiac fibrosis. Cells. 2020;9(3):592.

Toh WS, Zhang B, Lai RC, Lim SK. Immune regulatory targets of mesenchymal stromal cell exosomes/small extracellular vesicles in tissue regeneration. Cytotherapy. 2018;20:1419-26.

Vrijsen K, Sluijter J, Schuchardt M, Van Balkom B, Noort W, Chamuleau S, et al. Cardiomyocyte progenitor cell-derived exosomes stimulate migration of endothelial cells. J Cell Mol Med. 2010;14: 1064-70.

Wang K, Jiang Z, Webster KA, Chen J, Hu H, Zhou Y, et al. Enhanced cardioprotection by human endometrium mesenchymal stem cells driven by exosomal microRNA-21. Stem Cells Transl Med. 2017a;6(1): 209-22.

Wang N, Chen C, Yang D, Liao Q, Luo H, Wang X, et al. Mesenchymal stem cells-derived extracellular vesicles, via miR-210, improve infarcted cardiac function by promotion of angiogenesis. Biochim Biophys Acta. 2017b;1863:2085-92.

Wang X, Gu H, Huang W, Peng J, Li Y, Yang L, et al. Hsp20-mediated activation of exosome biogenesis in cardiomyocytes improves cardiac function and angiogenesis in diabetic mice. Diabetes. 2016;65:3111-28.

Wang Z, Gao D, Wang S, Lin H, Wang Y, Xu W. Exosomal microRNA-1246 from human umbilical cord mesenchymal stem cells potentiates myocardial angiogenesis in chronic heart failure. Cell Biol Int. 2021;45: 2211-25.

Wei Z, Qiao S, Zhao J, Liu Y, Li Q, Wei Z, 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.

Wen H, Peng L, Chen Y. The effect of immune cell-derived exosomes in the cardiac tissue repair after myocardial infarction: Molecular mechanisms and preclinical evidence. J Cell Mol Med. 2021;25:6500-10.

Xiao C, Wang K, Xu Y, Hu H, Zhang N, Wang Y, et al. Transplanted mesenchymal stem cells reduce autophagic flux in infarcted hearts via the exosomal transfer of miR-125b. Circ Res. 2018;123:564-78.

Xu R, Zhang F, Chai R, Zhou W, Hu M, Liu B, et al. Exosomes derived from pro-inflammatory bone marrow-derived mesenchymal stem cells reduce inflammation and myocardial injury via mediating macrophage polarization. J Cell Mol Med. 2019;23:7617-31.

Yamashita T, Takahashi Y, Takakura Y. Possibility of exosome-based therapeutics and challenges in production of exosomes eligible for therapeutic application. Biol Pharm Bull. 2018;41:835-42.

Yan F, Cui W, Chen Z. Mesenchymal stem cell-derived exosome-loaded microRNA-129-5p inhibits TRAF3 expression to alleviate apoptosis and oxidative stress in heart failure. Cardiovasc Toxicol 2022;22: 631-45.

Yao J, Huang K, Zhu D, Chen T, Jiang Y, Zhang J, et al. A minimally invasive exosome spray repairs heart after myocardial infarction. ACS Nano. 2021;15: 11099-111.

Yu B, Kim HW, Gong M, Wang J, Millard RW, Wang Y, et al. Exosomes secreted from GATA-4 overexpressing mesenchymal stem cells serve as a reservoir of anti-apoptotic microRNAs for cardioprotection. Int J Cardiol. 2015;182:349-60.

Yue R, Lu S, Luo Y, Zeng J, Liang H, Qin D, 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(1):202.

Zhang J, Lu Y, Mao Y, Yu Y, Wu T, Zhao W, et al. IFN-γ enhances the efficacy of mesenchymal stromal cell-derived exosomes via miR-21 in myocardial infarction rats. Stem Cell Res Ther. 2022;13(1):333.

Zhao J, Li X, Hu J, Chen F, Qiao S, Sun X, et al. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. Cardiovasc Res. 2019;115:1205-16.

Zhao X-L, Yang B, Ma L-N, Dong Y-H. MicroRNA-1 effectively induces differentiation of myocardial cells from mouse bone marrow mesenchymal stem cells. Artif Cells Nanomed Biotechnol. 2016;44:1665-70.

Zhu L-P, Tian T, Wang J-Y, He J-N, Chen T, Pan M, et al. Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction. Theranostics. 2018;8:6163-77.

Zhu W, Sun L, Zhao P, Liu Y, Zhang J, Zhang Y, et al. Macrophage migration inhibitory factor facilitates the therapeutic efficacy of mesenchymal stem cells derived exosomes in acute myocardial infarction through up-regulating miR-133a-3p. J Nanobiotechnol. 2021;19 (1):61.