New Hope for Myocardial Infarction Therapy: Mechanisms of Mesenchymal Stem Cell–Derived Exosomes and Optimization Strategies

Linrui Zhu *

School of Biomedical, Nutritional, and Sport Sciences, Newcastle University, Newcastle upon Tyne, NE1 7RU, United Kingdom

* Corresponding Author Email: c4029297@newcastle.ac.uk

Abstract. Myocardial infarction (MI) constitutes a significant cause of heart failure and mortality. Mesenchymal stem cells (MSCs), because of their anti-inflammatory, anti-apoptotic, and pro-angiogenic properties, have been extensively employed in myocardial repair research. However, their low survival rate and limited colonization efficiency within the ischemic microenvironment continue to constrain clinical efficacy. In recent years, MSC-derived exosomes (MSC-Exo), acting as key paracrine effectors, have demonstrated potential in animal studies to reduce infarct dimension, suppress inflammatory responses, and improve cardiac function using the measurement of carrying multiple bioactive molecules. They are considered a safer and more controllable alternative strategy, which provide a critical microenvironment for cell retention and survival. However, clinical research remains in its infancy, such as possible weak clinical effects and variability in outcomes which link to multiple factors such as MSCs infusion routes, time of transplantation, cell sources, and injection dosages. To overcome these limitations, optimization strategies including improved delivery routes, application of biomaterial and pre-treatment or genetic modification of MSCs have shown promising prospects.

Keywords: Myocardial infarction, mesenchymal stem cells, microRNA, optimization strategies.

1. Introduction

One of the primary clinical manifestations of ischemic heart disease is myocardial infarction (MI), which ranks among the world's deadliest diseases. MI is mainly caused by the rupture of atherosclerotic plaques followed by thrombus formation which results in localized interruption of myocardial blood flow and irreversible damage. Drug therapy, thrombolytic therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) have improved acute MI management in recent years. However, traditional treatments mainly enhance outcomes through reperfusion and prevent further ischemic injury. Their limitation is that they cannot effectively promote myocardial regeneration, leaving some patients still facing risks of left ventricular remodeling, heart failure, and recurrence [1]. Therefore, repairing damaged myocardium and improving cardiac function have become the core challenges in cardiovascular disease research. Recently, stem cell therapy and cell-free therapy have emerged as promising new approaches to promote myocardial repair after MI. Among these, mesenchymal stem cells (MSCs), due to their wide availability, are considered ideal candidate cells, while their derived exosomes (MSC-Exo) are extensively studied as cell-free therapy.

2. Mesenchymal Stem Cells and Exosomes

MSCs are a widely source multipotent cell type that can be acquired from various tissues including bone marrow, adipose tissue, umbilical cord, and fetal membranes. They possess multiple functions such as pro-angiogenesis, anti-inflammation, and anti-apoptosis. Initially, stem cell therapy for MI was hoped to repair myocardial damage by differentiating MSCs into cardiac progenitor cells and cardiomyocytes. However, subsequent studies revealed that the main effects of MSCs rely more on paracrine effects than direct differentiation. Besides, MSCs exhibit low survival rates and limited

colonization efficiency in the microenvironment of ischemic myocardial necrosis, and the existence of immune responses further limits their efficacy [1]. Thus, it is becoming increasingly important to focus on cell-free therapies based on their secreted products.

In the secreted products of MSCs, exosomes are considered the key carriers for the core effects. MSC-Exo carry abundant bioactive molecules, including microRNAs (miRNAs), mRNAs, proteins, and lipids, which can mediate intercellular communication, regulate inflammatory responses, inhibit cardiomyocyte apoptosis, and promote angiogenesis. It is considered a safer and more controllable cell-free therapy compared to MSCs due to its wider in vivo distribution, almost no risk in immune rejection aspects, and safety concerns related to cell transplantation [1]. This article will discuss the mechanisms underlying MSC-Exo therapy for MI and explore future clinical application directions with a view to providing possible pathways for treatment optimization.

3. Mechanism of Action of MSC-Exo in Treating Myocardial Infarction

The key function of MSC-Exo primarily relies on the miRNAs they carry. Exosomes selectively enrich specific miRNAs, enabling them to bind complementarily with target mRNAs upon entering recipient cells, thereby inhibiting or degrading transcription products and regulating signaling pathways and protein expression. Additionally, certain miRNAs exert multifaceted effects on cell growth, differentiation, immune regulation, and apoptosis control by influencing protein function, receptor activation, or mitochondrial metabolism through non-classical mechanisms. During MI repair, MSC-Exo primarily exert effects through three pathways: promoting vascular regeneration, suppressing inflammatory responses, and inhibiting cardiomyocyte apoptosis. The following sections, as shown in Table 1, will elaborate on these three mechanisms with illustrative examples.

Table 1. Summary of MSC-Exo miRNAs and their mechanisms in experimental models

miRNA	Experimental model	Main mechanism	Reference
miR-132	Mouse MI model	Targets RASA1 → activates Ras-MAPK signaling → promotes angiogenesis, increases capillary density, and improves cardiac function	[2]
miR-126	Mouse skin wound model (HUVECs)	Targets PIK3R2 → activates PI3K/Akt pathway → upregulates VEGF and Ang-1 → enhances migration and angiogenesis, accelerates repair	[3]
miR-543	Rat MI model	Upregulates miR-543, suppresses COL4A1 → enhances cardiomyocyte survival and angiogenesis, reduces infarct size, improves LVEF	[4]
miR-181a	Mouse MI/I/R model	Targets c-Fos → suppresses AP-1 activity → enhances Treg polarization (↑$CD4^+CD25^+Foxp3^+$, ↑IL-10, ↓TNF-α, ↓IL-6) → attenuates inflammation, preserves function	[5]
miR-182	Mouse I/R model	Targets TLR4 → inhibits TLR4/NF-κB pathway, activates PI3K/Akt → promotes macrophage polarization (↓M1, ↑M2) → alleviates inflammation	[6]
miR-212-5p	Mouse MI model	Targets NLRC5 → inhibits VEGF/TGF-β1/SMAD signaling → reduces fibrosis, improves EF and FS	[7]
miR-125b-5p	Mouse permanent MI model, hypoxia-injured H9C2 cells	Suppresses p53 and BAK1 → reduces apoptosis and infarct size, improves cardiac function	[8]
miR-182-5p	Mouse I/R model	Inhibits GSDMD, ASC, caspase-1 → reduces pyroptosis, inflammation, oxidative stress, MI size → improves LVEF/LVFS	[9]
miR-221-3p	Rat MI model	Targets PTEN → activates Akt → ↓apoptosis (↓caspase-3), ↑angiogenesis and proliferation (↑VEGF, ↑Bcl-2) → reduces fibrosis	[10]
miR-183-5p	Rat MI/R model	Targets FOXO1 → inhibits oxidative stress and apoptosis → enhances cardiomyocyte survival, reduce infarct size, improve LVEF/LVFS	[11]

3.1. Angiogenesis

Following MI, impaired local blood flow leads to myocardial hypoxia and necrosis. Angiogenesis is essential for restoring regional perfusion and enhancing the function of the heart. MSC-Exo enhances endothelial cell proliferation and migration, significantly promoting angiogenesis to improve local blood supply and cardiac function.

For instance, miR-132 enhances endothelial angiogenesis by downregulating the target gene RASA1, thereby releasing inhibition on the Ras/MAPK pathway [2]. Additionally, miR-126 directly targets and suppresses PIK3R2, activating the PI3K/Akt signaling pathway to upregulate VEGF and Ang-1 expression, thus promoting endothelial cell migration, proliferation, and lumen formation [12]. This indicates that MSC-Exo effectively promote angiogenesis in various models by carrying miRNAs, offering novel therapeutic approaches for ischemic tissue repair.

Beyond regulating recipient cell signaling pathways through abundant miRNAs, MSC-Exo can also directly load pro-angiogenic factors. For example, proteins such as HIF-1α, VEGF and Ang-1 detectable in MSC-Exo are transported to endothelial cells, where they promote proliferation, migration, and lumen formation to speed up new vessel generation [12]. This direct delivery mechanism with indirect activation mediated by miRNAs enhances the pro-angiogenic effect of MSC-Exo in ischemic repair.

3.2. Anti-Inflammatory

During MI, massive necrosis of myocardial cells rapidly activates the innate immune system. Immune cells such as T cells and macrophages are attracted to the injury site, secreting pro-inflammatory cytokines. Moderate inflammation aids in clearing necrotic tissue, but an ongoing excessive response causes additional myocardial damage and increased ventricular remodeling. MSC-Exo suppresses this harmful immune overreaction by regulating immune cells and inflammatory mediators.

MSC-Exo also performs anti-inflammatory and immunomodulatory functions by balancing T lymphocyte activity. Under normal conditions, regulatory T cells (Tregs) limit excessive activation of effector T cells, maintaining immune tolerance. However, following MI, the proportion of Tregs decreases, leading to excessive release of pro-inflammatory T cell factors such as IL-6 and TNF-α, which exacerbate inflammation and accelerate ventricular remodeling. Research indicates that miR-181a in MSC-Exo suppresses c-Fos protein expression, driving $CD4^+$ T cells toward Treg polarization. Upon Treg upregulation, IL-10 and TGF-β secretion inhibit proinflammatory responses in effector T cells and macrophages, reducing TNF-α and IL-6 levels to achieve local inflammatory suppression and myocardial protection [6]. In macrophages, MSC-Exo deliver miR-182 to inhibit TLR4/NF-κB signaling while activating PI3K/Akt signaling, inducing polarization from M1 (pro-inflammatory) to M2 (anti-inflammatory) macrophages. M2 macrophages release anti-inflammatory factors such as IL-10, further reducing inflammatory responses, decreasing infarct size and promoting cardiac function [13].

3.3. Anti-apoptotic

Cardiomyocyte apoptosis is a major cause of cardiac dysfunction following MI. MSC-Exo not only deliver miRNAs to regulate key pathways but also provide multifaceted protection by modulating cardiomyocyte bioenergetics and stress responses. miR-125b-5p directly targets and suppresses p53 and BAK1 expression, thereby blocking mitochondrial pathway-mediated apoptotic signals. This results in reduced cardiomyocyte apoptosis and enhances survival rates [13].

MI-induced ischemia rapidly causes depletion of ATP and NADH, accompanied by massive accumulation of reactive oxygen species (ROS). At normal levels, ROS participate in cellular signaling. However, excessive ROS attack cell membranes, proteins, and DNA, impairing mitochondrial energy metabolism. Mitochondrial damage further reduces ATP production and releases ROS, creating a vicious cycle [13]. MSC-Exo can enhance ATP and NADH levels, reduce

ROS accumulation, and protect mitochondrial homeostasis, thereby inhibiting cardiomyocyte apoptosis.

4. Current Status and Future Directions

In recent years, although numerous animal studies have demonstrated that MSCs and their exosomes exert significant cardioprotective effects following MI, clinical experiments results remain relatively limited. Most randomized controlled experiments indicate that MSCs transplantation performs well in terms of safety, with some suggesting it can improve LVEF, reduce infarct size, or lessen ventricular remodeling. Existing research on exosomes is still in its infancy, and their translational application faces significant shortcomings, such as generally weak clinical benefits and considerable variability in outcomes. This variability may be related to multiple factors including MSCs infusion routes, transplantation timing, cell sources, and dosages. Additionally, patient individual differences and comorbidities can influence efficacy. Therefore, enhancing the effectiveness of MSCs therapy and reducing the gap between basic research and clinical practice have become key challenges for future studies. To address these limitations and improve efficacy, researchers have proposed various optimization strategies. Among these, the following three representative approaches are commonly employed.

4.1. Route of Administration

In clinical practice, intravenous injection is widely adopted due to its minimally invasive nature. However, it exhibits limited cardiac homing efficiency and may cause cellular obstruction in peripheral organs. To address these limitations, multiple optimization strategies have been proposed: First, enhancing homing signals, such as modulating the S1P-S1PR2 or CSF2/CSF2RB axis to promote MSCs migration to ischemic myocardium [14]; Second, selecting optimal timing for administration, as both animal and clinical studies indicate peak efficacy when MSCs are delivered during the acute inflammatory phase (2–14 days post-injury [15]); Third, employing multiple intravenous injections to compensate for insufficient cell survival in single-dose transplantation [14].

In addition to the intravenous route, comparisons of different injection methods have revealed therapeutic efficacy differences. Studies indicate that in porcine MI models, coronary artery injection yields the highest retention of MSCs in the infarct zone, followed by endocardial and intravenous injection. However, coronary artery injections may increase the risk of coronary blood flow reduction. Recent research suggests that endocardial injections slightly surpass the coronary artery route in improving LVEF and reducing infarct size [16]. Therefore, future studies need to further clarify the advantages and disadvantages of different routes and their appropriate patient populations.

4.2. Biomaterials

Direct injection of exosomes rapidly dilutes in the bloodstream and is cleared by organs such as the liver and spleen, causing diminished therapeutic efficacy. Biomaterials are used to enhance the retention time and release efficiency of MSCs or exosomes within the damaged cardiac region. Hydrogels represent one of the most widely applied materials. Their highly hydrated three-dimensional networks not only shield transplanted cells from mechanical injury but also provide a stable local microenvironment, significantly enhancing the retention rate and survival of both cells and exosomes [17]. In recent years, various functionalized hydrogels have been developed, and minimally invasive thoracoscopic injection of MSC-Exo-loaded hyaluronic acid hydrogels [18], both enhance retention rates and minimize injury from traditional needle injection or open-heart surgery through localized delivery and sustained release of exosomes. Consequently, they promote angiogenesis, reduce fibrosis, and improve cardiac function in MI models.

4.3. Pretreatment of MSCs

The biological properties of MSCs are highly dependent on their microenvironment, and specific pretreatment methods can significantly increase their survival capacity and paracrine functions. For example, hypoxia pretreatment upregulates myocardial protection-related factors, enabling MSC-Exo to superiorly inhibit cardiomyocyte apoptosis and improve left ventricular function compared to exosomes derived under normal conditions. Pretreatment with growth factors (e.g., FGF-2, IGF-1, BMP-2) or inflammatory factors (e.g., IFN-γ) has also been shown to enhance MSCs anti-apoptotic and anti-inflammatory effects by regulating signaling pathways such as STAT1/miR-21 [19]. Besides physical methods, pharmacological pretreatment is also widely used to enhance MSCs survival and function in ischemic myocardium. For example, statins (e.g., atorvastatin, rosuvastatin) can upregulate eNOS expression, improve NO bioavailability, and enhance MSCs survival and myocardial repair capacity through signaling pathways such as PI3K/Akt, AMPK, and MEK/ERK1/2 [20].

5. Discussion

Based on the above three optimization strategies, it is evident that each of them has distinct characteristics in terms of mechanism of action and application prospects, while also exhibiting certain complementarity. Modification of the delivery route can enhance the distribution and targeting of MSCs and their exosomes in the cardiac region, but the feasibility and safety in clinical practice still require careful consideration. Biomaterials significantly improve cell retention and survival by providing a three-dimensional microenvironment, while also enabling controlled release of factors. However, their long-term biocompatibility requires further validation. Cell pretreatment and genetic modification directly enhance the functional properties of MSCs, demonstrating stronger anti-inflammatory, anti-apoptotic, and pro-angiogenic effects in animal models. Nevertheless, standardization and safety issues must be resolved before clinical application. Overall, these three strategies are not mutually exclusive in optimizing MSCs therapeutic outcomes. Future combination approaches—such as minimally invasive delivery of pretreated MSCs or their exosomes supported by biomaterials—may achieve more ideal myocardial repair effects.

6. Conclusion

In conclusion, MSCs and their exosomes have shown significant potential in post-MI repair, exerting cardioprotective effects through multiple mechanisms including promoting angiogenesis, anti-inflammation, and anti-apoptosis. Preclinical studies have provided promising results, but clinical trials have demonstrated relatively limited efficacy, primarily constrained by factors such as administration routes, low cell retention rates, and adverse transplantation environments. To enhance therapeutic outcomes, researchers have proposed various optimization strategies, including MSCs pretreatment, improved delivery methods, and bioengineering approaches such as hydrogels and cardiac patches. These measures not only improve the survival and function of MSCs and their exosomes but also enhance their retention and targeting within ischemic myocardium. Moving forward, high-quality, large-scale clinical experiments must integrate these latest optimization strategies to advance MSCs and exosome therapies toward clinical application.

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