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Review Article

Stem Cells and Exosomes in Myocardial Ischemia-Reperfusion Injury: A Comprehensive Review of the Literature

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Abstract
Ischemia-reperfusion injury (IRI) remains a global public health problem, with increasing incidence which is associated with significant morbidity and mortality. The duration of blood flow deprivation is a critical risk factor in conditions such as myocardial infarction (MI), stroke, solid organ transplantation, and hemorrhagic shock. From a pathophysiological perspective, IRI leads to numerous architectural, cellular, and metabolic changes in tissues. Moreover, local and systemic inflammation occurs after reperfusion of ischemic tissue. Clinically, the treatment of cases with IRI is frequently restricted to supportive maneuvers, with no exact target-oriented therapies validated so far. Recent research reveals the efficacy of stem cells as a promising therapeutic approach. Additionally, exosomes have been suggested to exert a significant impact on the stimulation of useful signaling pathways in different cardiovascular diseases. This review provided an overview of the new treatment strategies such as stem cell therapy (SCT) and exosome-based treatments for improving myocardial IRI.
Keywords: Myocardial ischemia/reperfusion injury, Stem cell, Exosome, Inflammation

Introduction

Ischemia-reperfusion injury (IRI) is a complex pathophysiological process that inaugurates cellular injury in various vascular complications such as myocardial infarction (MI), stroke, and even organ transplantation.[1] Myocardial reperfusion is inevitable due to prevalent MI treatments such as thrombolysis, angioplasty, and coronary bypass.[2] While the re-establishment of blood flow to ischaemic myocardial tissue has a critical effect in life-saving therapies, its paradoxical harmful results may decrease the beneficial effects of myocardial reperfusion.[3] It has been demonstrated that reperfusion can affect left ventricle function more significantly than infarction. Consequently, IRI may independently contribute to cardiac remodeling.[4]

Stem cells (SCs) increase the opportunity to develop effective and safer therapies for various diseases with the potential to generate or replace damaged tissue.[5-7] SC therapy can provide a promising treatment strategy for patients with ischemic heart disease. Recent research on this therapeutic approach has yielded contradictory and heterogeneous results.[8] Different types of SCs have been identified, each with various regenerative and improvement effects on cardiac tissues.[9] During myocardial ischemic attacks, adult heart SCs can regenerate vascular smooth muscle cells and vascular endothelial cells. However, SC regeneration capacity is limited, and myocardial tissue improvement is associated with scar formation. In addition, the microenvironment surrounding the infracted region is not a suitable substrate for SC survival, and SCs in the infarcted area of the heart are destroyed by apoptosis.[10] Therefore, there is an urgent need to develop new therapies for the treatment of ischemic heart damage. Recent evidence suggests that the therapeutic properties of SCs are mediated by paracrine agents released by these cells.

Exosomes, small extracellular vesicles, with 30 to 150 nm in diameter, are released from most cells, including dendritic cells, lymphocytes, platelets, and mast cells, under both physiological and pathological conditions.[11,12] These extracellular vesicles spread throughout the body and are abundant in blood, saliva, urine, and breast milk.[12] Exosomes have a fluid lipid bilayer membrane and contain proteins, nucleic acids, and lipids.[13] Exosomes exist in two sizes: large exosomes (90 to 120 nm in diameter) and small exosomes (60 to 80 nm in diameter).[14]

These extracellular vesicles mediate various biological processes such as cell-to-cell communication, autophagy, lysosomal exocytosis,[15] organ crosstalk, intercellular signaling, inhibition of apoptosis,[16] cell waste product clearance, maintenance of cell homeostasis in an optimal level, modulation of the immune and inflammatory systems, and angiogenesis.[17]. Furthermore, microRNAs (miRNAs) carried by exosomes can activate restorative and protective pathways in recipient cells by inducing genetic instructions.[18-20] Notably, exosomes, as one of the paracrine factors released by SCs, play a prominent role in improving myocardial IRI.[10,20-22] In this study, we summarized the applications, possible mechanisms, and functions of SCs and exosomes in myocardial IRI and highlighted the latest research progress.

Pathophysiology of Ischemia-Reperfusion Injury

To date, the precise underlying mechanisms of IRI pathogenesis have not been elucidated. IRI arises from ischemia and is further exacerbated during tissue reoxygenation. Oxygen is a critical molecule in cellular respiration through oxidative phosphorylation for adenosine triphosphate (ATP) production.[23] Tissue deprivation of oxygen during ischemia induces the degradation of cellular ATP resources due to the sudden cessation of oxidative phosphorylation. Free radicals are highly reactive molecules formed primarily during cellular respiration and normal myocardial metabolism. Unbalanced production of free radicals and the cell's ability to scavenge them may cause tissue damage.[24] Furthermore, the restoration of blood flow triggers some pathologic pathways involved in tissue injuries such as disruption of calcium (Ca^{+}) homeostasis, reduced level of ATP production, induction of toxic lipid metabolites by phospholipase, endonucleases, proteases enzymes, and overproduction of tissue-damaging reactive oxygen species (ROS) in the area, which may cause oxidative injury to cellular structures, activation of inflammatory processes, and the opening of mitochondrial permeability transition pore (MPTP), resulting in cell death by apoptosis and necrosis.[25] Mitochondria are the primary reservoir of intracellular ROS. MPTP pores may be opened by elevated levels of ROS, which also have extra-mitochondrial targets. The tetrahydrobiopterin–e nitric oxide synthase (NOS) complex is theoretically a crucial target of ROS, which may be reduced by oxidation, leading to peroxynitrite formation and reduced NO production. Programmed cell death via receptor-interacting protein 3 (RIP3) plays a significant role in myocardial reperfusion damage through Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the MPTP.[26]

Furthermore, the opening of pores results in the release of mitochondrial DNA fragments, ATP, calcium, and high mobility group box 1 protein (HMBGB1), which amplifies the NLRP3-inflammasome and TLR9. This activation leads to the expression of the myeloid differentiation primary response gene 88 (MyD88) and nuclear factor-κB (NF-κB) pathways, ultimately causing the overproduction of inflammatory mediators such as monocyte-chemoattractant protein 1 (MCP1), interleukin-1β (IL-1β), IL-6, tumor-necrosis factor-α (TNF-α), and IL-18.[27] IL-1β and IL-18 levels in cardiac fibroblast are exacerbated by inflammasome activity, inducing pyroptosis in surrounding cardiac cells via caspase-1.[27] Additionally, B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), Bcl-2-associated death promoter (Bad), and glycogen synthase kinase 3 β (GSK-3β) may regulate MPTP. The opening of the pore results in cell death by releasing pro-apoptotic agents such as cytochrome c along with ROS.[28]

Stem Cell Therapy in Cardiac Ischemia-Reperfusion Injury

SCs are considered valuable candidates in the vast majority of biological and medical applications due to their unique characteristics.[29,30] Acute myocardial infarction (AMI) is one of the most devastating cardiovascular events and a common phenomenon that results in cardiac ischemia damage and increased mortality through the induction of apoptosis, inflammatory responses, and tissue necrosis.[31] Ischemic heart damage results in a change in myocardial contractility, scar formation, and problematic ventricular stiffness.[31,32] In recent years, stem cell therapy (SCT) has emerged as a valuable promising therapeutic method for overcoming AMI-induced defaults.[31-34] Large-scale studies have proposed that SCT improves left ventricular ejection fraction and exercise capacity and decreases the rate of rehospitalization followed by death, thereby improving the quality of life in these patients.[32] Various cell types from different resources have been identified and used for the repair and regeneration of cardiac tissues such as cardiac SCs,[35] skeletal myoblasts, bone marrow mononuclear cells (BMMNCs), mesenchymal SCs, endothelial progenitor cells, and hematopoietic SCs.[32,36]

Among the SCs with different resources, mesenchymal stem cells (MSCs) showed the most beneficial impacts in the cardiac infarct model in terms of mechanical and regenerative activity, and even clinical outcomes.[37] When comparing the therapeutic effects of MSCs and bone marrow-derived mesenchymal stem cells (BMMSCs) in chronic cardiac ischemic diseases, it is strongly approved that MSCs are more effective in improving heart function. MSC therapy has biological efficacy for several reasons. First, MSCs have the capability to differentiate into cardiomyocytes and other cell types. Secondly, they can form new networks of blood vessels following MI. Thirdly, they stimulate the endogenous cardiac precursors to repair and regenerate faulted tissues, and finally, these cells are involved in paracrine mediators' secretions.[37]

In cases of IRI, MSC administration was significantly associated with reduced cell death markers and improved cell viability.[38] However, previous studies have demonstrated that the transplantation of MSCs into hearts after AMI or IRI leads to improvements in infarct size and

cardiac function, accompanied by a significant reduction in cardiomyocyte death,[39] and these cardioprotective effects are attributed to paracrine factors.[40,41] Furthermore, numerous in vitro and in vivo studies on cardiac IRI have reported the pleiotropic effects of MSCs, including proangiogenic, immunomodulatory, anti-apoptotic, and antifibrotic characteristics, as well as modulation of inflammation and cytokine expression. In addition, MSCs can affect the homing process, including endothelial cell adhesion, chemokine-chemokine receptor interactions, invasion via the extracellular matrix, and transendothelial migration.[42]

Several previous studies have started MSC injection a few hours post-reperfusion. In such situations, activation of lethal reperfusion injury and the deterioration of endothelial cells can be observed within the first minutes of reflow, underscoring the importance of MSC injection in cardiac injuries at the onset of reperfusion.[38] Heldman et al showed the regenerative and antifibrotic effects of mesenchymal adult stromal cells on the myocardium, which were associated with improved functional capacity and quality of life.[43]

In a study, Cho et al used human thymus adipose tissue-derived mesenchymal stem cell (TAT-MSC) to treat a rat model of heart ischemia-reperfusion. Histopathological studies revealed a significant reduction in the infarcted area in the TAT-MSC group compared to the control group.[44] Cortical bone-derived stem cell (CBSC) therapy in a swine model of AMI exhibited a reduction in apoptosis and scar size, an elevation in the number of macrophages and T cells, and an improvement in cardiac pump function after seven days of treatment.[5] Previous studies have suggested that the cortical bone, compared to bone marrow, might be a source of primitive SCs.[46,47] Some beneficial features of CBSCs include routine bone biopsy procedures for obtaining cells, expression of cell surface markers distinct from MSCs, and finally a lack of hematopoietic markers.[48] A research team recently documented that in a mouse MI model, autologous CBSCs delivery can improve heart structure by inducing the differentiation of CBSCs into new cardiovascular cells. These findings suggest that the ability of CBSCs to secret paracrine factors is involved in healing wounds after ischemic injury.[49]

It was previously believed that the mammalian heart is a terminally differentiated post-mitotic organ with no regenerative potential.[50] Nevertheless, Beltrami et al for the first time isolated and expanded cardiac SCs (CSCs) from the hearts of adult rats, which could differentiate into the myogenic cell lineage, including endothelial cells, cardiomyocytes, and vascular smooth muscle cells, both in vivo and in vitro. In addition, CSCs were found to improve infarcted hearts.[51] Some studies have claimed the superior effects of CSCs compared to other SCs such as MSCs and BMMNCs.[52] Systematic research has documented the improvement effects of CSC therapy on ejection fraction in animal models of MI compared to the placebo group. However, due to overlapping culture characteristics in different CSC types, significant differences were reported in their effects in post-MI animal research.[53] Several studies have reported the potential of CSCs in cardiac repair, along with their effectiveness, safety, and feasibility in therapeutic approaches involving cell transplantation.[50] For example, in an animal study by Dawn et al, the transplantation of CSCs after reperfusion in rats resulted in a 20% reduction in infarction size and induced myocardial regeneration.[54] These results were approved by other researchers working on larger laboratory animals such as pigs. Johnston et al showed that intracoronary infusion of cardiosphere-derived CSCs leads to a reduction in infarcted size, adverse cardiac remodeling, and the generation of new myocardial tissue, followed by improved hemodynamics.[55]

As a result of the original European Society of Cardiology (ESC) Task Force consensus document, autologous bone marrow cell therapy in AMI was designed as the first Phase III controlled clinical trial with autologous BMCS injection as part of standard treatment for AMI, with the main goal of finishing recruitment by October 2017.[56] The results of Mathur and colleagues' study on AMI showed that this treatment approach provides a new therapeutic strategy for future clinical trials for treatment in AMI treatment.[57]

Despite the positive findings of clinical trials in improving myocardial function after using CSCs in infarcted patients, some disappointing results were observed due to the engraftment of the transplanted cells.[50,58] To overcome this issue, researchers have focused on using biomaterials (e.g., cell sheets), hydrogels, and notably, porous scaffolds to improve the engraftment and survival rates of CSCs.[59]

Another promised SC that is effective in improving heart function and directly impacts myocardial remodeling post-MI is human embryonic stem cell-derived cardiomyocytes (ESC-CMs).[60] Nevertheless, the efficacy of ESC-CMs in treating and repairing cardiac faults remains controversial. It is assumed that different ischemia models might lead to different heart repair and cell retention outcomes.[61] However, cardiomyocyte renewal, as comprehensively defined by Eschenhagen et al, provides new insight into the improvement and treatment of injured hearts in different animal models and future clinical trials.[62]

Exosome Therapy in Cardiac Ischemia-Reperfusion Injury

Several studies demonstrated that exosomes have a protective effect on myocardial IRI.[11,20,63] miRNAs are the most important exosomal cargos involved in controlling pathological damage caused by AMI.[64] The results of a study indicated that exosomes from macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine with survival and proliferative effects, engineered umbilical cord MSCs,[65] have a cardioprotective effect in AMI and significantly reduce fibrosis area while

Table 1. Summary of Effects of Exosomes in Heart IRI

Exosome	miRNA	Effect	Signaling Pathway	Reference
MSC-derived exosome	miR-133a-3p	Inhibits apoptosis, reduces fibrosis, and preserves heart function in vitro and in vivo	AKT signaling pathway	16
Ischemic preconditioning-induced serum exosomes	-	Improves cardiac function and reduces inflammatory factor production, cardiomyocyte apoptosis, and myocardial infarct size	PI3K/AKT signaling pathway	11
MSC-derived exosome	miR-338	Inhibits cardiomyocyte apoptosis and improves cardiac function in rats with MI	MAP3K2/JNK signaling pathway	20
MSC-derived exosome	-	Reduces myocardial IRI by inducing cardiomyocyte autophagy	AMPK/mTOR and AKT/mTOR pathways	20
Adipose-derived SC-derived exosomes	miR-126	Protects myocardial cells from apoptosis, inflammation, and fibrosis and increases angiogenesis	MAPK, PI3K, and VEGF signaling pathways	75
Human umbilical cord MSC-derived exosome	-	Protects myocardial cells from apoptosis, promotes tube formation, migration of EA hy926 cells, and angiogenesis and regulates expression of Bcl-2 family	PI3K/AKT pathway	80
Coronary serum of patients with MI-derived exosome	miRNA-143	Enhances angiogenesis in cardiac endothelial cells	IGF-IR/NO signaling pathway	81
MSC-derived exosome	miRNA-144	Inhibits cell apoptosis in hypoxic conditions	PTEN/AKT pathway	82
BM-MSC-derived exosomes.	miR-149/let-7c/ Faslg Axis	Protects rat cardiomyoblasts from H/R injury	w/β-catenin signaling pathway	83
MSC-derived exosome	miRNA-301	Inhibits myocardial cell autophagy	LC3-II/LC3-I and P62 pathway	84
MSC-derived exosome	miRNA-181a	Provides protection against a host of immune-related genes by the miRNA-mRNA network	A/PI3K → ERK → c-Fos pathway	85
TIMP2-modified human umbilical cord MSC-derived exosome	-	Ameliorates cardiac function by improving MI-induced oxidative stress and ECM remodeling, suppresses cardiomyocyte apoptosis, and increases angiogenesis	AKT/Sfrp2 pathway	86
Adipose-derived MSC-derived exosome	-	Protects the heart by reducing inflammatory oxidative stress and apoptosis in IRI conditions	TLR4/NF-kB/PI3K/AKT pathway	87
MSC- derived exosome	miR-182	Polarizes inflammatory macrophage towards the anti-inflammatory macrophage in the heart	TLR4/NFkB/PI3K/AKT pathway	88
MSC-derived exosome	-	Increases angiogenesis in cardiac cells, enhances proliferation in cardiomyocytes, and improves heart function	ERK1/2 pathway	89
MSC-derived exosome	miR-21a-5p	Provides cardioprotecting by inducing cell proliferation and angiogenesis	PI3K/AKT pathway. Peli1, PDCD4, FasL, and PTEN	90
Adipose-derived MSC-derived exosome	-	Prevents apoptosis in cardiomyocytes by inhibiting oxidative stress	AMPK/mTOR and Akt/mTOR pathways and Hsp70–TLR4–Hsp27 axis	91
BM-MSC-derived exosome	-	Reduces anoxia-induced cardiomyocyte apoptosis and ameliorates myocardial function after infarction by regulating GATA-4 expression	AKT and ERK pathways	92
BM-MSC-derived exosome	miR-486-5p	Suppresses apoptosis in cardiomyocyte induced by I/R injury and protects cardiomyocytes against ischemic injury in vitro and in vivo	PTEN/ PI3K/AKT signaling pathway	93
Hypoxia-elicited MSC-derived exosomes	miR-125b	Facilitates ischemic heart repair by anti-apoptotic effect	VEGF, FGF, and PDGF pathways	94
Engineered exosomes with ischemic myocardium	-	Promotes therapeutic effects in acute MI condition	Intracellular protein kinase B and extracellular signal-regulated kinase 1/ 2 pathway	95
Transplanted MSC-derived exosome	mir-125b	Diminishes infarct size and improves cardiac function by reducing autophagic flux in infarcted hearts	mTOR and AMPK pathways	96

Note. IRI: Ischemia-reperfusion injury; miRNAs: MicroRNAs; MSC: Mesenchymal stem cell; AKT: Protein kinase β; MI: Myocardial infarction; BM-MSC: Bone marrow mesenchymal stem cells; MAPK: Mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; VEGF: Vascular endothelial growth factor; PI3K: Phosphatidylinositol 3-kinase; ECM: Extracellular matrix.

increasing capillary formation. Interestingly, the overexpression of miR-133a-3p in exosomes derived from MIF, to some extent, mediates the cardioprotective effects of these exosomes in the ischemic heart through protein kinase β (AKT) signaling pathway and by increasing AKT phosphorylation in cardiomyocytes and endothelial cells.[16] The AKT signaling pathway is a prominent target for cardioprotection.[66,67] This pathway is an effective factor for cell growth, migration, proliferation, differentiation, adhesion, survival, cytoskeletal organization, protein production, and metabolism and prevents IRI by reducing inflammatory factors, oxidative stress, and apoptosis.[68-70] However, these cardioprotective effects are reduced by suppressing miR-133a-3p.[16] Additionally, another animal study showed that ischemic preconditioning-induced serum exosomes, through activating the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway, ameliorate cardiac function, decrease the formation of inflammatory cytokines, reduce cardiomyocyte apoptosis, and have a protective effect against myocardial IRI.[11] Moreover, the results of a study showed that microRNA-338 in MSCs-derived exosomes can suppress apoptosis in myocardial cells during MI by regulating mitogen-activated protein 3 kinase/c-Jun N-terminal kinases signaling pathway.[20] Excessive ROS generation during myocardial IRI leads to autophagy dysfunction and cell death.[63] However, moderate myocardial autophagy decreases the apoptosis rate and increases survival in myocardial cells, whereas excessive autophagy exacerbates myocardial injury.[71,72] Injection of MSC-derived exosomes into an in vivo myocardial IRI rat model increased moderate autophagy by regulating the AMPK/mechanistic target of rapamycin (mTOR) and AKT/mTOR signaling pathways, leading reduced apoptosis, increased MI size, and improved heart function.[63] It is recognized that the PI3K/AKT pathway is involved in the autophagy signaling pathway,[73] and probably AMPK/mTOR and AKT/mTOR pathways are actively involved in autophagy processes. Exosomes can interfere with these processes, mediated by their miRNA content.[74] Furthermore, it has been demonstrated that exosomes from miR-126-overexpressing adipose-derived SCs protect myocardial cells against acute myocardial ischemic injury by inhibiting apoptosis, inflammation, and fibrosis and by increasing angiogenesis.[75] Thus, exosomes represent a promising new therapeutic approach for treating myocardial IRI by transferring their miRNAs and modulating different signaling pathways in recipient cells.

Remote ischemic preconditioning (RIPC) can reduce myocardial IRI.[76] RIPC in MI models inhibits the release of anti-inflammatory exosomes,[77] blocks NF-κB related cytokine release through TLR4 receptor pathways, inhibits inflammatory-induced fibrosis and cardiac dysfunction, and limits myocardial apoptosis.[77,78] The concentration of extracellular vesicles increases during RIPC, and extracellular vesicles containing miRNAs are likely involved in cardioprotection.[76] Moreover, exosomes containing miRNA allow distant intercellular communication and cellular cross-talk, playing a prominent role in myocardial protection.[76,77]

After MI, proinflammatory M1-like macrophages release exosomes. A recent study demonstrated that M1-like macrophage-derived exosomes carry high levels of proinflammatory miRNA-155 to endothelial cells. These exosomes target Rac family genes, protein kinase AMP-activated catalytic subunit alpha 2 (AMPKα2), Sirt1/AMPKα2–endothelial NOS, and RAC1–PAK2 signaling pathways, thereby inhibiting angiogenesis and aggravating cardiac dysfunction. Therefore, preventing the secretion of M1-like macrophage-derived exosomes may be a potential therapeutic target for facilitating cardiac repair after MI.[79] The effects of exosomes in myocardial IRI are summarized in Table 1.

Conclusion

Despite major advances in the treatment and management of ischemic heart disease, it remains a main cause of morbidity and mortality worldwide. Treatment of IRI cases is still restricted, and exact target-oriented therapies have not been confirmed yet. SCT is a promising approach for improving damaged myocardial tissue, with various types of SCs being beneficial for ischemic heart disease treatment. Additionally, exosomes which are released by SCs as paracrine factors, play a critical role in improving myocardial IRI. Therefore, there is hope for the progress of these therapies as remarkable therapeutic strategies.

Authors' Contribution

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Competing Interests

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