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Exosomes Induce Crosstalk Between Multiple Types of Cells and Cardiac Fibroblasts: Therapeutic Potential for Remodeling After Myocardial Infarction

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Abstract: Recanalization therapy can significantly improve the prognosis of patients with acute myocardial infarction (AMI). However, infarction or reperfusion-induced cardiomyocyte death, immune cell infiltration, fibroblast proliferation, and scarring formation lead to cardiac remodeling and gradually progress to heart failure or arrhythmia, resulting in a high mortality rate. Due to the inability of cardiomyocytes to regenerate, the healing of infarcted myocardium mainly relies on the formation of scars. Cardiac fibroblasts, as the main effector cells involved in repair and scar formation, play a crucial role in maintaining the structural integrity of the heart after MI. Recent studies have revealed that exosome-mediated intercellular communication plays a huge role in myocardial repair and signaling transduction after myocardial infarction (MI). Exosomes can regulate the biological behavior of fibroblasts by activating or inhibiting the intracellular signaling pathways through their contents, which are derived from cardiomyocytes, immune cells, endothelial cells, mesenchymal cells, and others. Understanding the interactions between fibroblasts and other cell types during cardiac remodeling will be the key to breakthrough therapies. This review examines the role of exosomes from different sources in the repair process after MI injury, especially the impacts on fibroblasts during myocardial remodeling, and explores the use of exosomes in the treatment of myocardial remodeling after MI.

Keywords: exosomes, myocardial infarction, myocardial fibrosis, cardiac fibroblasts

Introduction

Myocardial infarction (MI) is the most serious manifestation of coronary artery disease and a major cause of related deaths.[1] The main clinical treatment for MI aims to unblock the coronary artery, restore blood flow, and minimize post-infarction myocardial remodeling.[2] Adult myocardial cells cannot regenerate after necrosis, so the maintenance of normal cardiac structure after MI mainly relies on the proliferation of fibroblasts.[3] However, cardiac fibrosis and remodeling caused by continuous fibroblast activation[4] still requires the further search for new therapeutic strategies. Studies on extracellular vesicles have exponentially increased in the past decade, from basic researches to clinical translational applications. Due to the endogenous, biocompatible and multifunctional properties, the extracellular vesicles may become a novel treatment for various cardiac diseases in the future.[5,6]

Exosomes being paracrine is a key pathway for intercellular information exchange, transporting critical proteins[7] and genetic material (such as miRNA,[8] mRNA,[9] and DNA[10]), mediating the transfer of various biomolecules between cells,

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which is an important component of various physiological and pathological processes.[11] Recent studies have shown that various types of cells, including myocardial cells,[12,13] endothelial cells (ECs),[14] immune cells,[15] and stem cells,[16] can secrete extracellular vesicles to participate in the process of myocardial remodeling. Certain extracellular vesicles exhibit significant advantages in myocardial remodeling after heart attack, while others aggravate the progression of myocardial remodeling. Although there are literature reviews on the effects of exosomes on cardiovascular diseases, as well as how the contents of exosomes (microRNA (miRNA), non-coding RNAs (ncRNA), long non-coding RNAs (lncRNA) et al) affect cardiac fibrosis or myocardial remodeling processes after MI,[17–19] there is currently no literature that specifically explains how exosomes and their contents derived from different cell sources act on fibroblasts and their mechanisms after MI. This would provide a detailed understanding of the role of fibroblasts in the myocardial remodeling process following MI.

Thus, this review focuses on the dual role of fibroblasts in the pathological process of myocardial repair, and provides an overview of the role of exosome-mediated intercellular crosstalk from various cell types targeting fibroblasts in post-MI fibrosis. This review aims to illustrate the potential therapeutic significance of exosomes in the treatment of myocardial remodeling after MI.

Myocardial Remodeling After MI

The pathological manifestations of MI primarily encompass the apoptosis and necrosis of cardiomyocytes, the activation of inflammatory factors, the phagocytosis and elimination of macrophages, the activation of fibroblasts, the secretion of extracellular matrix (ECM), and the process of angiogenesis.[20–22]

Cardiac fibroblasts (CFs) serve as the main effector cells in the repair process. After the clearance of dead and damaged tissues by phagocytes, the inflammatory response diminishes. At this stage, pro-fibrotic factors, including transforming growth factor-b (TGF-β), endothelin-1, reactive oxygen species (ROS), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF),[23–26] work in conjunction with neuroendocrine signals and mechanical stress to activate CF proliferation and transformation into myofibroblasts.[27] A variety of signaling pathways have been demonstrated to be involved in the repair process, among which the main pathways including the TGF-β1/Smad-2/3 pathway,[28] and other pathways such as matrix metalloproteinases (MMPs), tissue inhibitor of matrix metalloproteinases (TIMPs), and nuclear factor κB (NF-κB),[29,30] which regulate the intensity and duration of pro-fibrotic signals, and induce myofibroblasts to secret collagen and ECM to repair the areas loss of cardiomyocytes. These processes play a protective role in the early stage of MI, maintaining the structural integrity of the injured myocardium,[31] which is called substitute fibrosis. At the same time, myofibroblasts express actin and myosin, which are required for contraction, and compensate for part of the contractile function.[32] In the late stage of injury repair, the gradual decrease of pro-fibrotic factors, collagen cross-linking, and apoptosis of myofibroblasts indicates the cessation of the repair process. However, if the stimulus persists, the activation of myofibroblasts will lead to excessive deposition of ECM, which triggers diffuse interstitial fibrosis and perivascular fibrosis, thus leading to cardiac stiffness and severely affecting the systolic and diastolic functions.[33,34] Excessive myocardial fibrosis will also lead to electrophysiological remodeling of the heart, which will induce ventricular arrhythmias.[35] Therefore, controlling the proliferation and activation of fibroblasts to achieve a dynamic balance between pro-fibrosis and anti-fibrosis is important for post-MI repair.

Exosomes

Exosomes (Exos) are extracellular vesicular bodies that are characterized by their bilayer membrane structure and range in diameter 30–150 nm.[36] These Exos can be secreted by a variety of cells. They are structurally stable and small in size, containing RNAs, proteins, and other molecules involved in metabolic and growth processes.[37] Additionally, they express a variety of antigens and antibodies in their membrane structures, which can mediate the interaction and communications between different cells.[38] Exosomogenesis encompasses the process of plasma membrane invagination, the encapsulation of components in close proximity to the membrane, and the subsequent formation of early endosomes (Figure 1). Early endosomes undergo a gradual maturation process, leading to formation of late endosomes. Late endosomes emerge through budding from the endosome membrane, leading to subsequent formation of polyvesicles.[39,40] The formation of intracellular vesicles can be accomplished via the endosomal sorting complex required for transport (ESCRT)-dependent pathway for the

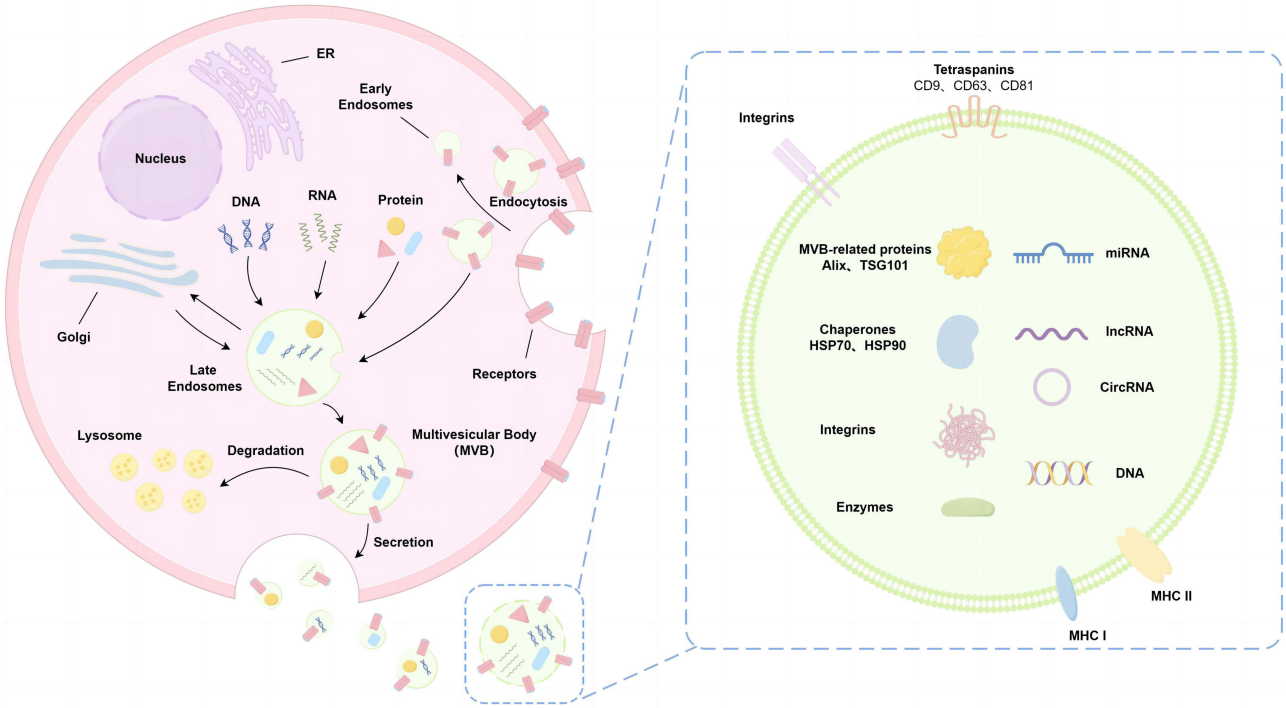

Figure 1 Production and characterization of exosomes. Exosomes are originated from the endocytosis pathway and are initially formed as early endosomes through the process of endocytosis from the plasma membrane. Late endosomes transport various cellular components such as DNA, RNA, proteins, and lipids by intercalating with other organelles (such as the nucleus, endoplasmic reticulum (ER), Golgi apparatus, and others). Upon fusion with the plasma membrane, exosomes are released (double-membraned structures, vesicle-like vesicles with a diameter of 30–150 nm). The cargo carried by exosomes can elicit distinct biological reactions due to the diverse array of molecules they transport, and the unique compositions of these exosomal cargoes underscore the wide range of biological functions that exosomes can mediate.

sorting and transporting of ubiquitin proteins,[41] and ceramide enrichment induced budding is another route.[42] The precise mechanism underlying the transport and fusion of intracellular polyvesicles to the plasma membrane is still unclear, potentially implicating the involvement of the small Rab GTPases protein family.[43] Currently, researchers posit that exosomes represent a novel mechanism of intercellular communication, and potentially a new therapeutic target capable of modulating the occurrence and development of diseases. Exos are released in both physiological and pathological conditions.[44] The substances in exosomes depend on the cell state, and the identification of different exosomes is achieved through the analysis of their surface markers.[45] Presently, there are several confirmed markers of exosomes: four transmembrane family proteins (CD9, CD63, CD81, CD82, CD89, etc.),[46] heat shock proteins (HSP27, HSC70, HSP90, etc.),[47] proteins related to membrane vesicles formation (Alix, TSG101, etc.),[48,49] integrins, major histocompatibility complex (MHC) class I/II molecules,[50] and some biological enzymes.[51] When exosomes are released into the extracellular environment, they not only act on neighboring cells through parasecretion, but also play a remote regulatory role via the circulation of body fluids. Intercellular communication can be realized through various ways. For example, recipient cells can internalize Exos cargo through uptake pathways of endocytosis and membrane fusion, thus obtaining information substances from the donor cells.[52] Exos in the plasma of patients with coronary heart disease contain circular RNA circ_0001785, which "sponges" the expression of miR-513a-5p in the endothelial cells. This interaction leads to increased downstream expression of TGFBR3, which promotes endothelial cell proliferation and migration while inhibiting apoptosis, thereby delaying the onset of atherosclerosis.[53] Secondly, Exos mediate intercellular communication and molecular transport by facilitating the transfer of various bioactive molecules, including nucleic acids, proteins, and lipids from donor cells to recipient cells.[54] Macrophage-derived Exos can penetrate the blood–brain barrier and deliver a cargo protein (BDNF, brain-derived neurotrophic factor) to the brain to play a therapeutic role in central nervous system diseases.[55] In addition, Exos can also be in the form of receptor-ligand (receptor membrane protein-exosome membrane protein), which directly regulates the signaling pathways in the recipient cells. Exos can also be used as drug delivery systems for disease treatment.[56,57]

Effect of Exosomes from Different Cell Sources on Injury Repair After MI

Exos, serving as the "mailman" for exchanging biological information between cells, have great potential and value in the treatment of various diseases, including cancer, kidney diseases, inflammatory diseases, and neurodegenerative diseases.[22,58–61]At the same time, more and more cardiovascular studies are focusing on the contribution of exosomes, especially in various stages after MI.[62] The repair response post-MI is necessary for the injured myocardium, and CFs are the major bearers of myocardial remodeling. When activated, CFs transform into functional myofibroblasts, and this transformation is regulated by a variety of factors.[63] After being captured by CFs, exosomes derived from different cells can regulate the repair and fibrosis after MI by acting on the phenotype, secretion, proliferation, activation and other processes of CFs.[64] Understanding the mechanisms is important for the development of new methods for targeted treatment of adverse remodeling caused by excessive fibrosis after MI. The effects of exosomes from different sources on cardiac remodeling will be discussed in detail.

Cardiomyocyte-Derived Exosomes

Cardiomyocytes (CMs) are the most abundant cells of the heart which cannot regenerate,[65] and CMs in the region of infarction are in a state of ischemia and hypoxia due to reduced blood supply. In recent years, researchers have demonstrated that CMs can release exosomes containing a variety of cytokines to enhance information transfer with other cells, reduce vascular endothelial damage, attenuate fibrosis and play a certain cardioprotective role in repair after MI.[66,67] Recently, exosomes released in cardiospheres by CMs and progenitor cells are referred to as cardiosomes, which mediate cell-cell/matrix communications at the infarct zone. Cardiosomes cargo transfers cardiomyocyte-specific miR-195 to fibroblasts, promoting the activation of myofibroblasts.[68] Research has demonstrated that the expression of miR-222 has been shown a significant increase in exosomes secreted by ischemic CMs, which positively affects angiogenesis after MI by stimulating cellular tubulogenesis and outgrowth, promoting endothelial cell growth and proliferation, as well as angiogenesis.[69] Simultaneously, the interaction between CMs and fibroblasts becomes increasingly pronounced. The miR-92a in cardiosomes stimulates the transformation of fibroblast into myofibroblast by downregulating Smad7-mediated transcriptional repression of α-smooth muscle actin (α-SMA).[70] The exosomal miR-217 secreted by CMs enhances the fibroblast proliferation by regulating phosphatase and tensin homologue (PTEN).[71] The aforementioned studies indicate that cardiosomes have some positive effects during the pathophysiological process of MI by promoting vascular regeneration and activating fibroblasts involved in cardiac repair.

However, CMs also secrete exosomes containing factors that negatively regulate myocardial remodeling. The exosomal miR-19a-3p in cardiosomes inhibits the proliferation of endothelial cells and decreases angiogenesis after MI by targeting hypoxia inducible factor-1α (HIF-1α).[72] Exosoma lncRNA AK139128, secreted by hypoxic CMs, obviously suppresses fibroblast growth and accelerates fibroblast apoptosis when co-cultured with fibroblasts, thereby playing an important role in slowing down the procession of myocardial fibrosis.[73]

Fibroblast-Derived Exosomes

As a part of non-myocardial cells in the normal cardiac architecture, CFs play an important role in myocardial remodeling.[74] After MI, fibroblasts migrate to the damaged area under the regulation of a series of bioactive factors. They transform and proliferate, secrete large amounts of collagen, and participate in the repair of injury heart.[75] However, myofibroblasts play a dual role in ventricular remodeling. On one hand, they contribute to the formation of scar tissue and the maintenance of cardiac integrity by regulating the levels of extracellular matrix and various proteins. On the other hand, when a substantial number of myofibroblasts are activated, excessive deposition of extracellular matrix and proteins can disrupt cardiac rhythm and lead to arrhythmia.[76] Previous studies have displayed some cardioprotective effects of exosomes partially derived from CFs. A study has shown that cardiac fibroblasts secreted exosomes (CFs-Exo) can enhance ventricular conductivity and reduce the risk of RA after cold ischemia/reperfusion (I/R). At the same time, cardiac fibroblasts containing sevoflurane increase the relative expression of Cx43 and enhance the activity of myocardial cells after hypoxia/reoxygenation (H/R). Sevoflurane-treated cardiac fibroblasts exosomes (Sev-CFs-Exo) increase the expression of Cx43, reduce it and improve the area of myocardial infarction.[77] H/R-induced

exosomal secretion from fibroblasts confers protection to H9C2 cells against H/R injury and enhances cell survival rates. Following ischemic post-treatment, the secretion of fibroblast-derived exosomal miR-423-3p is elevated, and the targeted modulation of Ras-related protein Rap-2c (RAP2C) can mitigate cellular apoptosis and ameliorate myocardial injury.[78] MiR-133a, derived from CF exosomes under H/R conditions, regulates the expression of embryonic lethal abnormal vision like 1 (ELAVL1), thereby inhibiting cardiomyocyte apoptosis, reducing cardiac injury, and promoting tissue repair and fibrosis.[79] Furthermore, exosomes containing miR-133a also facilitate the differentiation of fibroblasts into CM-like cells.[80] However, some studies have indicated that not all exosomes secreted by fibroblasts exert a positive inhibitory effect on cardiac fibrosis following MI.[81] For instance, Exos containing miR-223 act as potent pro-fibrotic factors, promoting the proliferation, migration, and differentiation of CFs. Consequently, inhibiting miR-223 after MI may prevent malignant cardiac fibrosis and arrhythmias.[82] Fibroblasts also secrete miR-21-3p, which can induce cardiomyocyte hypertrophy and accelerate ventricular remodeling.[83] In conclusion, exosomes derived from fibroblasts not only act on cardiomyocytes but also affect the signaling pathways of the fibroblasts themselves, thereby influencing myocardial remodeling after MI. Targeted regulation of exosomes derived from fibroblasts can help to maintain ventricular stability, reduce myocardial fibrosis and alleviate myocardial remodeling after MI.

Endotheliocyte-Derived Exosomes

Endotheliocytes (ECs) serve as the communication link between blood and matrix. After MI, blood flow occlusion and tissue ischemia cause damage to endothelial cells, driving them to synthesize and secrete exosomes containing biologically active substances.[84] Carter et al demonstrated that exosomes derived from ECs promoted angiogenesis, thereby attenuating repair adverse effects.[85] Additionally, inhibition of miRNA-126 also reduced area of MI and preserved cardiac function.[86]

Endothelial progenitor cells (EPCs) are the precursors of vascular ECs. Under the stimulation of various factors, EPCs can be mobilized from the bone marrow to the peripheral blood to participate in injury repair, which play a paracrine role through the release of various cytokines.[87] Accumulating data have proved that exosomes derived from endothelial progenitor cells (EPCs-Exos) can promote mesenchymal to endothelial transition (MEndoT) engaging them in angiogenesis in cardiac injury areas, thus reversing fibrosis. CFs treated with EPCs-Exos shows up-regulated expression of EC-specific markers, such as vascular endothelial growth factor receptor-2, and down-regulated expression of fibrosis-related markers, such as α-SMA, collagen I, TGF-β, and high mobility group box 1 (HMGB1). These results suggest that EPCs-Exos can promote the CF proliferation and angiogenesis by increasing MEndoT and inhibiting HMGB1 expression.[88] Upregulation of miR-218-5p or miR-363-3p in EPC-Exos after MI inhibits myocardial fibrosis through MEndoT elevation mediated by targeting the p53/JMY signaling pathway.[89] In addition, enrichment of miR-1246 or miR-1290 in EPC-Exos induces upregulation of E74-like factor-5 (ELF5) and specificity protein-1 (SP1), which also achieves the same effect of improving myocardial fibrosis after MI.[90] Similarly, YBX-1-mediated miR-133 sorting into H/R-induced EPCs-Exos promotes angiogenesis and MEndoT of CFs and inhibits fibrosis in vitro.[91] All these results indicate that EPC-Exos have the potential roles for promoting MEndoT and improving myocardial fibrosis.

Immune Cell-Derived Exosomes

Although CFs are the executor of cardiac repair after MI, the importance of the immune system as the initiator of this process is undeniable.[92] Following the occurrence of MI, resident and infiltrating immune cells are rapidly recruited and activated, initiating a complex immune response.[93] When the inflammatory stage gradually transitions to the repair stage, it is necessary to timely inhibit the inflammatory process and activate the repair response through the transformation of immunosuppressive lymphocytes and pro-inflammatory/anti-inflammatory immune cells.[94–96] Exos secreted by immune cells, play an important role in mediating intercellular crosstalk with CFs and participating in the repair of injured myocardium.[97] M1-macrophages-derived exosomes (M1-Exos) inhibit cardiac repair. Previous studies have investigated the upregulation of miR-155 in exosomes secreted by M1 macrophages after MI, which can down-regulate multiple target genes of ECs, including the small GTPase rac1 (RAC1), p21-activated kinase 2 (PAK2), Sirtuin 1 (Sirt1) and Adenosine5'-monophosphate-activated protein kinase α 2 (AMPKα 2), thereby reducing the angiogenesis and inhibiting cardiac healing.[98] M2 macrophages promote cardiac repair. A long non-coding RNA (lncRNA-ASLNCS5088) is

enriched in M2 macrophage-derived exosomes (M2-Exos) treated with TGF-β1. This lncRNA could be transferred to fibroblasts with high efficiency and act as an endogenous sponge to absorb miR-200c-3p, resulting in increased activation of CF and synthesis of collagen I, collagen III, glutaminase, and α-SMA.[99] Moreover, upregulation of HuR (human antigen R) in M-Exos, exposed to high glucose, could also mediate intercellular crosstalk with CFs, significantly increasing the fibrotic response both in vitro and in vivo.[100] Some M2-Exos promote cardiac repair by inhibiting CM apoptosis. Some studies have shown that M2-Exos carry miR-1271-5p in the acute myocardial infarction (AMI) mouse model, which reduces cardiomyocyte apoptosis and promotes cardiac repair by down-regulating SOX6.[101] M2-Exos containing circUbe3a promote the proliferation, migration, and phenotypic transformation of CFs by targeting the miR-138-5p/RhoC axis, which may exacerbate myocardial fibrosis following AMI.[102] In addition, dendritic cells (DCs) were also involved, that MI-induced DCS-derived exosomes (DCS-Exos) were found to directly activate CD4+ cells in the spleen. Activated CD4+ T cells could then migrate to the infarcted myocardium and play a crucial role in improving myocardial healing.[103] The activated CD4+ T cell-derived exosomes (CD4-Exos) enriched with miR-142-3p, which activate the WNT signaling, induce pro-fibrotic effects of CFs, mediate the proliferation, migration and differentiation of CFs, promote cardiac fibrosis, and accelerate cardiac remodeling after ischemia.[104] It can be seen from the above that, due to the complexity of the inflammatory process and the diversity of immune cell types after MI, the regulatory mechanisms of the Exos crosstalk with fibroblasts are also completely different. It is also confirmed that intervening the immune response in the course of MI to control the fibrosis process and make the injured myocardium reach the appropriate repair state can be a promising treatment in the future.

Adipose Tissue-Derived Exosomes

Adipose tissue mainly consists of adipocytes (ADs) and adipose stem cells (ADSCs), which are considered to be an endocrine organ of the body. Both ADs and ADSCs can release exosomes into the circulating plasma under stress to regulate cell behavior and metabolism, in which exosome cargo acts as an important mediator.[105,106] Exosomes derived from adipose tissue (Ads-Exos) primarily play a role in mediating local inflammatory responses and regulating metabolic processes. Ads-Exos produced under palmitate stress protects the heart from I/R injury, demonstrating a significant reduction in fibrosis following I/R. However, the study did not determine whether the most pronounced effects of Ads-Exos are on the initial infarct size or on subsequent remodeling.[107] In addition, the secretion of inducible nitric oxide synthase (iNOS) in the exosomes is also increased, thus promoting cardiac fibrosis and dysfunction.[108] These publications imply the existence of a likely adipose-to-fibroblastic paracrine mechanism.

Numerous studies have demonstrated exosomes derived from ADSCs participate in the activation of CFs and promote repair through a variety of pathways, such as Wnt/β-catenin, p-Akt/Akt and TGF-β1.[109–111] It have beneficial effects on adverse remodeling after MI. Down-regulation of miR-196a-5p in ADSCs-Exos effectively reverses myofibroblast activation and reduces collagen expression after MI in rats.[112] ADSCs-Exos carrying miRNA-671 reduces myocardial fibrosis and inflammation by targeting TGFBR2/Smad2 axis, thereby alleviating MI injury in vivo and in vitro.[113] In addition, miR-126 enrichment in ADSCs-Exos also reduces the expression of fibrosis-related proteins in H9c2 cells under hypoxic conditions.[114]

Cardiac Progenitor Cell-Derived Exosomes

Anversa et al first proposed cardiac progenitor cells (CPCs) in 1998,[115] including cardiac sphere-derived cells (CDCs).[116] CPCs are a special class of cardiac progenitor cells capable of forming clusters in suspension that can differentiate into CMs and some mesenchymal cells under certain conditions.[117] CPCs implantation in the ischemic heart promotes the recovery of cardiac function and ameliorates arrhythmia in AMI/DCM models in rats, dogs and pigs, suggesting that CPCs exhibit a strong protective effect in the process of chronic ischemic myocardial remodeling.[118–121] Exosomes derived from CPCs (CPCs-Exos) play a key role in this process. Human cardiac progenitor cell-derived exosomes (hCDC-Exos) can not only inhibit the proliferation of fibroblasts but also reprogram them to undergo phenotypic transformation.[122] Hypoxia-induced CPCs-Exos reduce TGF-β-mediated profibrotic gene expression in fibroblasts and enhance endothelial tube formation. Microarray analysis identifies 11 up-regulated miRNAs that are relative to normoxic conditions, suggesting their potential involvement.[123] Another study demonstrated that cardiac sphere cell-derived

exosomes (CDCs-Exos) altered the CF phenotype and secretome in a beneficial positive feedback loop both in vivo and in vitro. This alteration included the secretion of higher levels of stromal cell-derived factor 1 (SDF-1) and vascular endothelial growth factor (VEGF).[124] In addition, miR-146a-5p is enriched in CDCs-Exos, which may alleviate myocardial fibrosis in dilated cardiomyopathy.[125] Apart from exosomes, certain proteins secreted by CPCs also decrease the degree of cardiac remodeling after MI. Soluble endothelial glycoprotein secreted by cardiac spheres injected into the infarct area reduces scar formation and collagen density, and enhances ventricular function by inhibiting the TGF-β1/Smad signaling pathway.[126] These results indicate that CPCs-Exos have significant potential in the treatment of myocardial remodeling after infarction.

Despite the beneficial effects of CDC-Exos on the injured heart, clinical application of exosomes is facing great challenges. CDC-Exos with cardiac homing peptide (CHP) modification (exosomes bind to CHP via Doxorubicin-N-hydroxysuccinimide (DOX-NHS) linker) preferentially target the heart, and reduces the degree of fibrosis and scar area, increases cell proliferation and angiogenesis, and significantly improves its therapeutic effect on MI.[127]

Exosomes Derived from Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs), a kind of pluripotent stem cells with multi-directional differentiation potential, have been utilized in the replacement therapy of infarcted myocardium.[128] However, the retention and survival rate of MSCs in the infarcted myocardium after transplantation are very low, which poses challenges for their clinical application.[129] While MSCs-derived exosomes (MSCs-Exos) provide the possible opportunity and play an important role in ameliorating excessive fibrosis after MI.

It is well known that bone marrow mesenchymal stem cells (BMSCs) can promote myocardial repair. Numerous studies have shown that exosomes secreted by BMSCs (BMSCs-EXos) can exert therapeutic effects by promoting angiogenesis and M2 macrophage transformation to reduce inflammation and promote anti-apoptosis in CMs.[130,131] Meanwhile, BMSCs-Exos also have great potential in anti-myocardial fibrosis. MiR-24 and miR-29 are key players in a variety of fibrotic diseases and are highly expressed in BMSCs-Exos, which are internalized by local fibroblasts, reducing fibroblast proliferation and transformation through reprogramming.[132] MiR-29b-3p, as a member of the miR-29 family, is down-regulated in the myocardium of rats with MI. However, upregulated miR-29b-3p delivered by BMSC-Exos improves myocardial angiogenesis and ventricular remodeling, and reduces myocardial fibrosis by targeting a disintegrin and metalloproteinase with thrombospondin 16 (ADAMTS16).[133] Interestingly, the expression of miR-212-5p is low in the clinicopathological samples and animal models of cardiac fibrosis caused by MI, while its expression is abundant in BMSCs-Exos. MiR-212-5p from BMSCs-Exos has the potential to alleviate myocardial fibrosis by inhibiting the NLRC5/VEGF/TGF-β1/Smad axis after MI.[134] Furthermore, miR-129-5p of BMSCs-Exos also alleviates fibrosis by inhibiting inflammation in MI mice through the targeting of HMGB1.[135]

Compared to other MSC-Exos, exosomes derived from human umbilical cord mesenchymal stem cells (hucMSC-Exos) are widely used in the treatment of various diseases due to their non-invasive collection method and higher proliferation rate. And there are two-sided effects in the role of hucMSC-Exos in cardiac remodeling after MI. On the one hand, hucMSC-Exos can be used as an effective carrier for specific miRNAs and proteins to reduce myocardial fibrosis. HucMSC-Exos loaded with miR-29b mimics are internalized by CFs in vitro and down-regulate the expression of fibrosis-related proteins. After implantation into the infarcted hearts of mice, hucMSC-Exos reduce fibrosis and improve cardiac function in vivo.[136] In addition, overexpressing TIMP2 in hucMSC-Exos reduces ECM (eg, MMP2, MMP9 and α-SMA) and collagen deposition, and inhibits TGFβ-induced secretion of CFs, thereby reducing MI-induced cardiac remodeling. The potential mechanism may be mediated through the Akt/Sfrp2 pathway.[137] On the other hand, hucMSC-Exos can also repair the damaged myocardium by promoting fibrosis. Hypoxia leads to the down-regulation of Smad7 and up-regulation of miRNA-125b-5p both in vitro and in vivo, which are reversed after treatment with hucMSC-EXO. The results show that hucMSC-exosomes may promote the expression of Smad7 by downregulating miR-125b-5p, thereby enhancing myocardial fibrosis.[138] Intraoperative injection of hucMSC-Exos in rats with MI increases the density of myofibroblasts and decreases the apoptosis of myocardial cells in the inflammatory stage of the infarction area after operation. This indicates that hucMSC-Exos promotes the differentiation of fibroblasts into myofibroblasts in the inflammatory environment, thereby promoting cardiac repair.[139]

Human Induced Pluripotent Stem Cell-Derived Exosomes

Human induced pluripotent stem cells (hiPSCs) can be obtained by transforming certain differentiated human cells into hiPSCs through genetic reprogramming technology.[140] They also possess totipotency, do no present ethical concerns, and have abundant sources, making them a common choice in regenerative medicine. Currently, numerous of studies have confirmed the application value of hiPSCs in MI,[141] and clinical trials are gradually carried out.[142] HiPSCs-derived exosomes (hiPSCs-Exos) have complex components and maintain the glycan characteristics of hiPSCs-Exos.[143] Systematic proteomics and miRNA profiling of hipSCs-Exos show that the unique miRNAs of hiPSCs-Exos regulate mTOR signaling, cell senescence, retinol metabolism, and tumor necrosis factor (TNF) signaling.[144] Meanwhile, the abundant cargo of hiPSCs-Exos mediates therapeutic effects in myocardial repair after MI. Recent studies have shown that large myocardial patches designed from hiPSCs-derived CMs can improve the recovery of infarcted myocardium in pigs.[145] HiPSCs-Exos can improve the survival rate of CMs and reduce fibrosis by regulating the production and autophagic flux of hypoxic CMs.[146] Furthermore, exosomes isolated from hiPSCs-EC containing miR-199b-5p also alleviate ischemic injury by promoting angiogenesis.[147] However, it should be noted that hiPSCs-Exos induced by special treatments may actually promote fibrosis. For example, hiPSCs can differentiate into MSCs after being stimulated by Ang II or TGF-β1, which promotes the secretion and mRNA expression of collagen I, collagen III and elastin in fibroblasts.[148]

Cortical Bone Stem Cell-Derived Exosomes

Cortical bone stem cell-derived exosomes (CBSCs-Exos) can also mediate the crosstalk with fibroblasts, thereby playing a protective role in the remodeling stage of infarct-related myocardium. The reduction in scar size and improvement in cardiac function are observed after CBSCs-Exos treatment in both MI and I/R models. Further studies suggest that CBSsC-Exos alter fibroblast activation through the hereto-unknown mechanism of decreasing small nucleolar RNA (snoRNA) signaling within CFs. Those findings demonstrate that CBSCs-Exos induce alterations in cardiac remodeling via decreasing fibroblast activation, leading to long-term reductions in cardiac scarring, and improvements in cardiac repair and function.[149]

Circulating Exosomes in Plasma

Circulating exosomes are released by almost all cells. After MI, the cargo and quantity of circulating exosomes are significantly changed,[150] while free miRNAs can also be packaged in exosomes, stably exist in the blood circulation, and reach target cells through the blood circulation to rapidly regulate intracellular signals.[151] Some circulating exosomes are anti-myocardial fibrosis, such as those rich in miR-133, miR-135, and miR-29.[152] Up-regulating miR-29a in the plasma significantly reduces interstitial fibrosis in the left ventricle border region in MI.[153] Up-regulation of miR-133a in the blood of patients with AMI inhibits myocardial fibrosis.[154,155] Conversely, circulating Exos can also promote fibrosis. miR-21 mimic-loaded Exos resulted in the down-regulation of phosphatase and tensin homologue (PTEN), increased expression levels of Smad7 and MMP2, and increased myocardial fibrosis in MI mice.[156] Down-regulation of miR-425 and miR-744 in plasma Exos of patients with heart failure (HF) attenuates the inhibitory effects on TGF-β1, resulting in the overexpression of collagen I and α-SMA to promote fibrosis.[157] In addition, it is interesting to note that the isolation and detection of different subtypes of circulating exosomes can reflect the pathophysiological changes of heart diseases and can be used as a diagnostic tool for cardiovascular disease in the future.[158,159]

The mechanisms of action of exosomes from all these sources on post-MI fibrosis or fibroblasts are summarized in Table 1 and Figure 2

The Use of Exosomal Therapy

Exosome therapy represents an innovative therapeutic strategy that has attracted considerable attention and application within the cardiovascular disease in recent years.[160]

It has been proved in animal models that minimally invasive gel injections, gelatin microneedles, microneedle patches,[102,136,161] and various exosome treatments effectively modulate cellular functions and facilitate tissue repair.

Table 1 Specifies the Biological Effects, Acting Factors and Mechanisms of Exosomes from Different Cell Sources in the Model

Biological Effects	Origin	Effector	Experimental Model	Mechanism	References
Anti-fibrosis	CMs	miR-19a-3p	MI	Targeting HIF-1α, Promotes angiogenesis	[72]
	CMs	lncRNA AK139128	Hypoxia	Inhibit fibroblast proliferation	[73]
	CFs	miR-133	CFs culture in vitro	Promote the differentiation of fibroblasts into CM-like cells.	[80]
	CFs	unknown	I/R	Cx43, Inhibit cardiomyocyte apoptosis	[77]
	CFs	miR-423-3p	I/R	Reduce apoptosis	[78]
	CFs	miR-133a	I/R	ELAVL1, Inhibit CM apoptosis	[79]
	M1	miR-155	MI	Sirt1/AMPKα2-eNOS, RAC1-PAK2	[98]
	ADSCs	miR-196a-5p	MI	Reverses myofibroblast activation	[112]
	ADSCs	miR-671	MI	TGFBR2/Smad2	[113]
	ADSCs	miR-126	Hypoxia	Decreased fibrosis-related protein expression	[114]
	hCDCs	unknown	TGF-β	Inhibit fibroblast proliferation	[122]
	CPCs	miR-17, miR-199a, miR-210, miR-292	Hypoxia	Promote fibroblast transformation	[123]
	CDCs	Soluble endothelial glycoprotein	MI	TGF-β1/ Smad	[126]
	CDCs	unknown	MI	Promote fibroblast transformation	[124]
	EPCs	unknown		MendoT, HMGB1	[88]
	EPCs	miR-218-5p, miR-363-3p	MI	p53/JMY, MEndoT	[89]
	EPCs	miR-1246, miR-1290	MI	ELF5, SP1	[90]
	EPCs	miR-133	H/R	Angiogenesis, MEndoT	[91]
	MSCs	miR-24, miR-29	MI	Reduced proliferation and activation of fibroblasts	[132]
	BMSCs	miR-29b-3p	MI	ADAMTS16	[133]
	BMSCs	miR-212-5p	MI	NLRC5/VEGF/TGF-β1/Smad	[134]
	BMSCs	miR-129-5p	MI	HMGB1	[135]
	hucMSCs	Simulant of miR-29b	MI	Decreased fibrosis-related protein expression	[136]
	hucMSCs	TIMP2	MI	Akt / Sfrp2	[137]
	hiPSCs	unknown	MI	Autophagy promotion	[146]
	mCBSCs	snoRNA	MI, I/R	Inhibition of fibroblast activation	[149]
	Circulating	miR-133, miR-135 and miR-29	MI		[152]
	Circulating	miR-29a	MI		[153]

(*Continued*)

Table 1 (Continued).

Biological Effects	Origin	Effector	Experimental Model	Mechanism	References
Pro-fibrosis	CMs	miR-222	Ischemic	Promotes angiogenesis	[69]
	CMs	miR-92a	MI	Smad7, Promotes fibroblast activation	[70]
	CMs	miR-21-5p	MI	Promotes angiogenesis	[67]
	M	HuR	Diabetes		[100]
	M2	lncRNA-ASLNCS5088	TGF-β1	miR-200c-3p, GLS, α-SMA	[99]
	M2	miR-1271-5p	AMI	SOX6	[101]
	$CD4^+$ T	miR-142-3p	MI	APC/Wnt	[103]
	hucMSCs	miRNA-125b-5p	Ischemia	Smad7	[138]
	hucMSCs	Unknown	MI	Inhibition of fibroblast activation	[139]
	hiPSCs	Unknown		Collagen I, Collagen III, elastin	[148]
	Circulating	Simulant of miR-21	MI	Phosphatase, PTEN, Smad7, MMP2	[156]

Abbreviations: CMs, cardiomyocytes; miRNA, microRNA; MI, myocardial infarction; HIF-1α, hypoxia inducible factor-1α; lncRNA, long non-coding RNAs; CFs, cardiac fibroblasts; I/R, ischemia/reperfusion; Cx43, connexin-43; ELAVL1, embryonic lethal abnormal vision like 1; M1, M1-macrophage; Sirt1, silent mating type information regulation 2 homolog 1; AMPKα2, 5'-AMP-activated protein kinase catalytic subunit alpha-2; eNOS, endothelial nitric oxide synthase; RAC1, Ras related C3 botulinum toxin substrate 1; PAK2, p21 protein activated kinase 2; ADSCs, adipose-derived mesenchymal stem cells; TGFBR2, transforming growth Factor beta receptor 2; Smad2, mothers against decapentaplegic homolog2; hCDCs, human cardiac sphere-derived cells; TGF-β, transforming growth factor beta; CDCs, cardiac sphere-derived cells; EPCs, endothelial progenitor cells; MEndoT, mesenchymal–endothelial transition; HMGB1, high mobility group protein 1; p53, Tumor Suppressor Protein p53; ELF5, ETS-related transcription factor Elf-5; SP1, specificity protein 1; H/R, hypoxia/reoxygenation; MSCs, mesenchymal stem cells; BMSCs, bone marrow mesenchymal stem cells; ADAMTS16, a disintegrin and metalloproteinase with thrombospondin 16; NLRC5, nucleotide oligomerization domain-like receptor subfamily C5; VEGF, vascular endothelial growth factor; HMGB1, high mobility group protein 1; hucMSCs, human umbilical cord mesenchymal stem cells; TIMP2, tissue inhibitor of matrix metalloproteinases 2; Akt, protein kinase B; Sfrp2, secreted frizzled related protein 2; CBSCs, cortical bone stem cells; snoRNA, small nucleolar RNA; Smad7, mothers against decapentaplegic homolog 7; M, macrophages; HuR, human antigen R; M2, M2-macrophages; GLS, glutaminase; α-SMA, α-smooth muscle actin; AMI, acute myocardial infarction; CD4+ T, CD4+ T cells; APC, adenomatous polyposis coli; Wnt, wingless; SOX6, Transcription factor SOX6; hiPSCs, Human induced pluripotent stem cells; PTEN, phosphatase and tensin homolog; MMP2, matrix metalloproteinase 2.

For example, bioengineered CPCs-Exos transfected with the pro-angiogenic miR-322 (CPCexo-322), can enhance therapeutic efficacy in a mouse model of MI. The engineering of CPCs-Exos through miRNA programming can promote angiogenesis, making it a potentially effective therapy for ischemic cardiovascular diseases.[162] The delivery system (GelMA-MN@3D-Exo) was constructed using microneedles topical delivery technology, MSC exosomes (3D-MSC-Exo) 3D culture, and biocompatible gelatin methacryloyl (GelMA) employed used to construct for the delivery of for (GelMA-MN@3D-Exo). The (GelMA-MN@3D-Exo) microneedles microneedle can mitigate attenuated ischemia-reperfusion cell damage in the middle cerebral artery occlusion (MCAO) model.[161] A gelatin-based biocompatible microneedles (MN) patch loaded with exosomes containing microRNA-29b (miR-29b) mimics was fabricated, which possessed anti-fibrotic activity and prevented excessive cardiac fibrosis after MI.[136] These results show that Exos involved in cardiac repair by activating signal transduction that promotes cell survival, regulating autophagy, reducing cardiac oxidative stress levels, regulating immune cell polarization, and cytokine secretion.[79,132,163] Although these experiments have confirmed the therapeutic efficacy of Exos and cargos, the specific application of Exos in humans as a treatment for MI or cardiovascular diseases needs to be further verified. Several studies involving patients with acute coronary artery disease have observed changes in exosomal load; however, the application of exosomal therapy in patients with heart disease has not yet been implemented.[164] Consequently, the future efficacy of Exos application in the treatment of cardiovascular diseases remains to be determined.

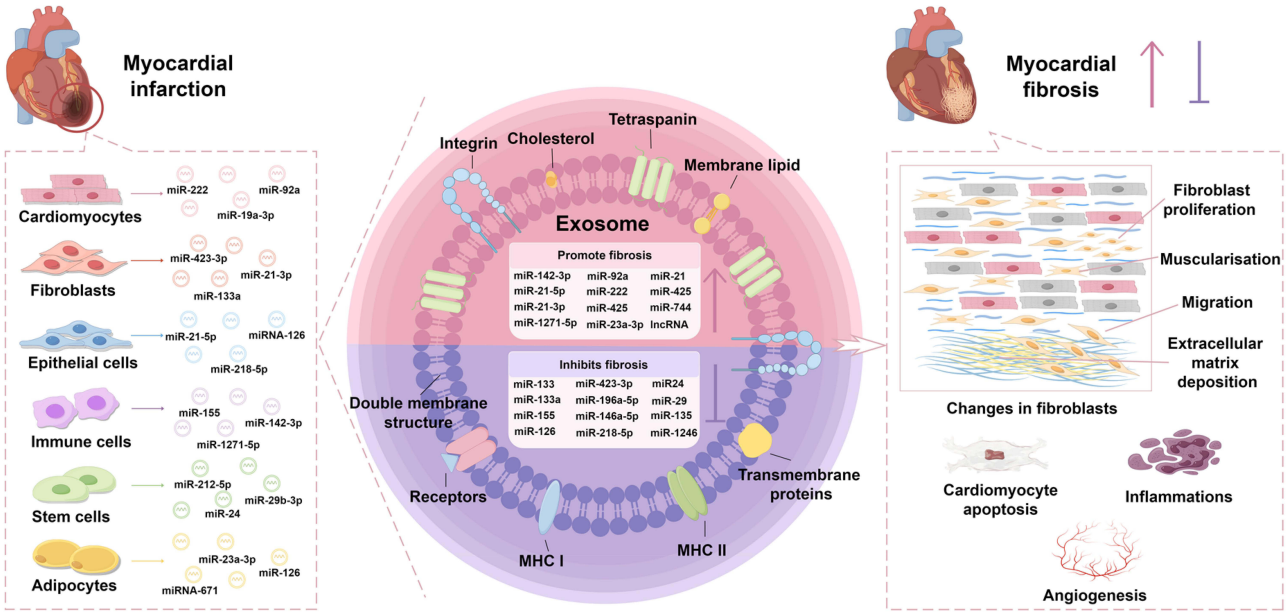

Figure 2 Active participation of exosomes from different cellular sources in cardiac repair after myocardial infarction. In instances of myocardial injury, various cells originating from cardiac tissue produce distinct varieties of exosomes in response to inflammatory factors or signaling molecules. Exosomes derived from different cell types consist of a diverse array of constituents such as miRNA, snoRNA, lncRNA, proteins, and other bioactive molecules. These exosomal cargos mainly regulate the proliferation, migration, muscularisation, and extracellular matrix deposition of fibroblasts, and also regulate the process of angiogenesis, inflammations, and cardiomyocyte apoptosis. Therefore, exosomes play a dual role in regulating myocardial fibrosis and modulate cardiac function through cell-to-cell transmission of particular signaling molecules.

Conclusions and Prospects

The damage of the heart caused by MI varies depending on the degree of repair, but the permanent loss of CMs and the formation of scar tissue are common features. Fibroblasts are major contributors to scar tissue, and there is increasing evidence that exosomes play an important regulatory role in them. The corresponding pathophysiological changes in both in situ and distal cells lead to variations in the exosome-carrying cargoes they produce, and the intercellular exosome crosstalk with CFs has a dual effect on myocardial remodeling after MI. On the one hand, the proliferation and activation of CFs are inhibited, the expression of fibrosis-related proteins is down-regulated, and the phenotype and secretion of CFs are changed, thus achieving anti-fibrosis. On the contrary, it promotes fibrosis by activation of CFs. In-depth study of exosome cargo and signaling pathways of different cellular origin not only helps to provide molecular mechanisms for complex damage repair after MI, but also guides the delivery of effective exosome cargo through the carrier for targeted therapy of infarcted myocardium. At present, there have been relevant studies, but they have not been used in clinical treatment of heart disease, which will become a new direction of clinical research on exosomes in cardiovascular diseases. Despite this, much is still unknown and more research is needed to fully understand the mechanisms of cell crosstalk in cardiac repair to optimize cell-free therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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