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Exosome-Based Therapy in Cardiovascular Diseases: A New Frontier in Cardiovascular Disease Treatment

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AUTHOR'S SUMMARY

This review paper highlights the potential of exosome-based therapeutics in addressing unmet needs in cardiovascular disease (CVD) treatment. Despite advances in medical interventions, CVD remains a leading cause of mortality worldwide, underscoring the necessity for innovative approaches. Exosomes, as natural nanocarriers, exhibit unique properties such as biocompatibility, targeted delivery, and the ability to mediate intercellular communication. By leveraging these advantages, our review paper explores their therapeutic applications in repairing damaged cardiovascular tissues and modulating pathological processes. This work holds significant scientific and clinical implications, paving the way for transformative strategies in CVD management and personalized medicine.

ABSTRACT

Exosomes, small extracellular vesicles ranging from 30 to 150 nanometers in diameter, have emerged as pivotal mediators of intercellular communication. These vesicles, originally perceived as cellular debris, are now recognized for their intricate roles in transporting bioactive molecules, including proteins, lipids, and nucleic acids, between cells. Exosomes have received considerable attention due to their roles in diverse physiological and pathological processes, especially in relation to cardiovascular diseases (CVDs). CVDs are intricately linked, sharing common risk factors and pathological mechanisms, such as inflammation, oxidative stress, and endothelial dysfunction. Exosomes have been implicated in either directly or indirectly influencing these phenomena. They are secreted by virtually all cell types, including endothelial cells, cardiomyocytes, and stem cells, play critical roles in maintaining vascular homeostasis and responding to pathological stimuli. Their capacity to traverse biological barriers, maintain stability in circulation, and effectively encapsulate and deliver a variety of molecular cargos makes them promising candidates for both biomarkers and therapeutic agents. This review aims to explore the multifaceted roles of exosomes

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Conflict of Interest

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in CVDs. And we will discuss the mechanisms of exosome biogenesis and release, their molecular composition, and the ways in which they contribute to disease pathophysiology. Additionally, we will emphasize the potential of exosomes as diagnostic biomarkers and their therapeutic uses, highlighting their significance in the advancement of innovative treatment strategies. This review explores recent findings and advancements in exosome research, emphasizing their significance in CVD and paving the way for future studies and clinical applications.

Keywords: Exosomes; Cardiovascular diseases; Treatment strategies; MicroRNA; Long non-coding RNA

INTRODUCTION

Exosomes, small extracellular vesicles (EVs) ranging from 30 to 150 nanometers in diameter, have emerged as pivotal mediators of intercellular communication.[1] These vesicles, originally perceived as cellular debris, are now recognized for their intricate roles in transporting bioactive molecules, including proteins, lipids, and nucleic acids, between cells.[2] Exosomes have received considerable attention due to their roles in diverse physiological and pathological processes, especially in relation to cardiovascular diseases (CVDs). Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, encompassing a spectrum of disorders such as atherosclerosis (AS), myocardial infarction (MI), and heart failure.[2] CVDs are intricately linked, sharing common risk factors and pathological mechanisms, such as inflammation, oxidative stress, and endothelial dysfunction.[2] Exosomes have been implicated in either directly or indirectly influencing these phenomena. They are secreted by virtually all cell types, including endothelial cells, cardiomyocytes, and stem cells, play critical roles in maintaining vascular homeostasis and responding to pathological stimuli. Their capacity to traverse biological barriers, maintain stability in circulation, and effectively encapsulate and deliver a variety of molecular cargos makes them promising candidates for both biomarkers and therapeutic agents.

This review aims to explore the multifaceted roles of exosomes in CVDs. And we will discuss the mechanisms of exosome biogenesis and release, their molecular composition, and the ways in which they contribute to disease pathophysiology. Additionally, we will emphasize the potential of exosomes as diagnostic biomarkers and their therapeutic uses, highlighting their significance in the advancement of innovative treatment strategies. This review explores recent findings and advancements in exosome research, emphasizing their significance in CVD and paving the way for future studies and clinical applications.

ROLE OF EXOSOMES IN CARDIOVASCULAR DISEASES

Molecular mechanisms of exosomes in cardiovascular diseases

Exosomes, tiny EVs released by almost all types of cells, have become a focal point due to their role in cell-to-cell communication, especially in CVDs.[2] These vesicles contain a rich mix of bioactive compounds such as proteins, lipids, and various RNA forms, and play a key role in numerous processes of CVDs.

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Biogenesis of exosome starts with the inner budding of the endosomal membrane to create multivesicular bodies (MVBs).[3] These MVBs merge with the plasma membrane, subsequently releasing exosomes into the extracellular environment.[3] This process is controlled through various mechanisms, including both endosomal sorting complexes required for transport-dependent and -independent pathways that involve tetraspanins and lipid rafts.[4] Exosomes carry diverse molecules that are crucial for CVDs. Specifically, the microRNAs (miRNAs) within exosomes have been found to alter gene expression in cells that receive them and it affect key processes such as angiogenesis, inflammation, and cell death.[4] Notable miRNAs like miR-21, miR-126, and miR-146a are particularly influential in regulating endothelial function and the development of AS.[5][6] Here, we present the role of exosomes in various heart diseases (**Figure 1**).

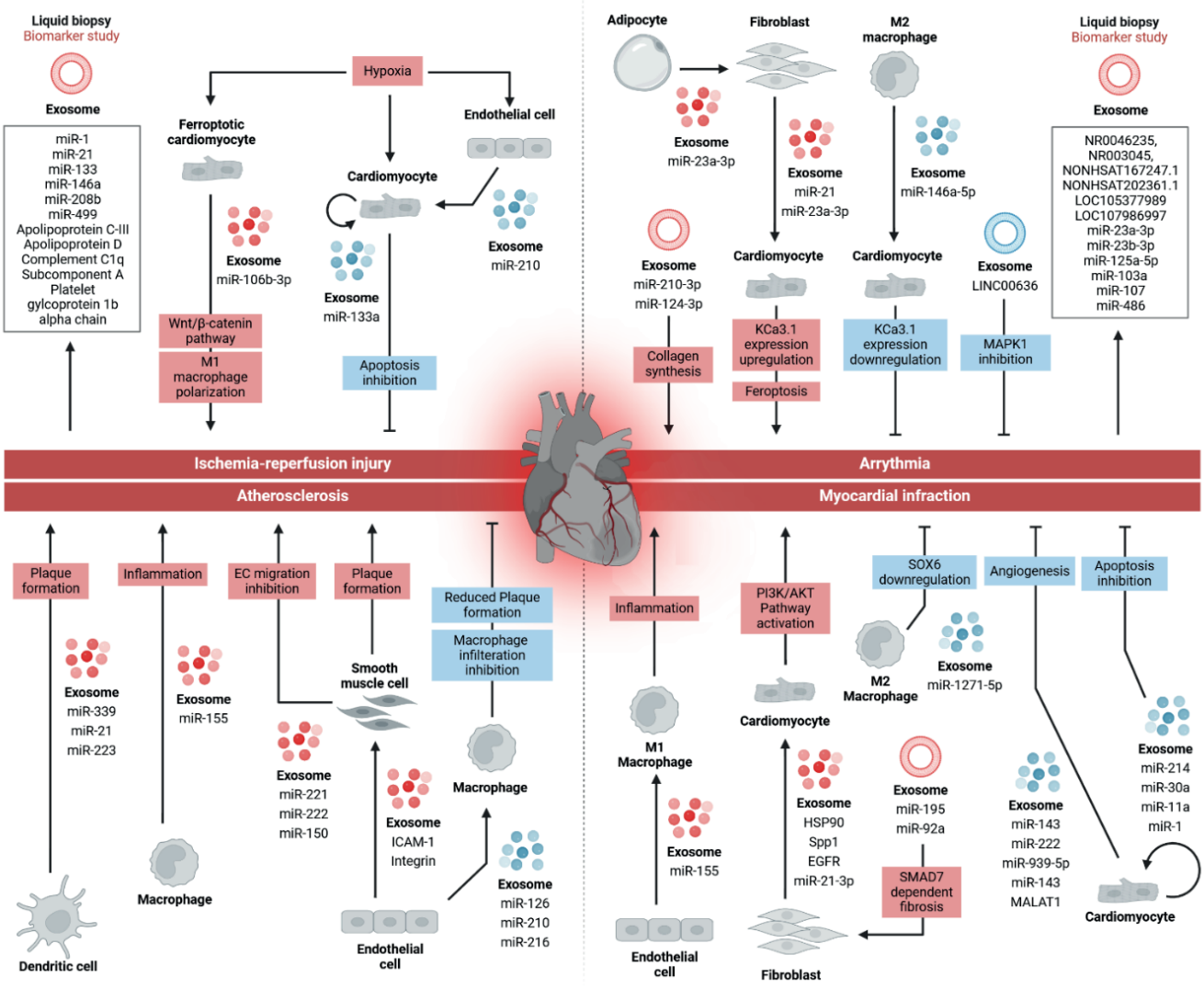

Figure 1. Exosomes and their role in the pathogenesis and repair mechanisms of CVDs.
CVD = cardiovascular disease; EC = endothelial cell; ICAM-1 = intercellular adhesion molecule-1; MAPK1 = mitogen-activated protein kinase 1; PI3K = phosphatidylinositol 3-kinase; SOX6 = SRY-box transcription factor 6.

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Ischemia-reperfusion injury

Ischemia-reperfusion (I/R) injury refers to tissue damage caused by the restoration of blood flow (reperfusion) following a period of insufficient blood supply (ischemia).[7] This paradoxical process involves complex cellular and molecular mechanisms, including oxidative stress, inflammatory responses, calcium overload, and mitochondrial dysfunction.[8] While reperfusion is essential to restore oxygen and nutrients to ischemic tissues, it can exacerbate injury through the generation of reactive oxygen species and the activation of immune pathways.[9] Therefore, reperfusion therapy is essential for mitigating ischemic damage, but paradoxically, it can exacerbate injury through a process known as I/R injury.[9] This phenomenon affects multiple organs and may result in severe complications, including disability and death. I/R injury involves a range of pathological processes, such as cell death (via apoptosis, necrosis, and ferroptosis), oxidative stress, inflammation, disruption of the blood-brain barrier (BBB), remodeling of the extracellular matrix (ECM), angiogenesis, cardiac hypertrophy, and fibrosis.[10]

Recent studies have highlighted the role of exosomes—small EVs—in modulating the pathological and reparative processes of I/R injury.[7] Exosomes released by injured cells can carry bioactive molecules, including miRNAs, proteins, and lipids, which mediate intercellular communication and influence inflammation, oxidative stress, and apoptosis.[11] Exosomes can modulate immune responses by regulating macrophage polarization and suppressing excessive inflammation.[10] However, exosomes released during I/R injury may also propagate damage by spreading pro-inflammatory signals. Therapeutically, engineered exosomes offer a novel approach for targeted delivery of drugs or RNA therapeutics to ischemic tissues, presenting a promising avenue for reducing I/R injury. Additionally, exosomes derived from mesenchymal stem cells (MSCs) have been shown to attenuate I/R injury by delivering protective factors such as miR-21 and miR-126, which inhibit apoptosis and promote angiogenesis.[12] Understanding the dual roles of exosomes in I/R injury is critical for optimizing their use in regenerative medicine and precision therapies.[12] However, further research is required to improve exosome isolation techniques and to clarify the mechanisms driving their effects across various tissues.

Arrhythmia

Arrhythmias are disorders of cardiac rhythm resulting from abnormalities in the generation or conduction of electrical impulses in the heart.[13] They arise due to a combination of structural, molecular, and electrophysiological alterations, which can be broadly categorized into three primary mechanisms: abnormal automaticity, triggered activity, and reentry.[14]

Exosomes play a critical role in the pathogenesis of atrial fibrillation (AF) by mediating intercellular communication and influencing pathological processes.[15] Atrial fibroblast-derived exosomal miR-21 has been shown to upregulate KCa3.1 (the intermediate-conductance calcium-activated potassium channel) expression in atrial myocytes, contributing to arrhythmogenesis.[15] Conversely, exosomes from M2 macrophages,[16] enriched with miR-146a-5p, have been reported to downregulate KCa3.1 expression, suggesting an opposing regulatory role.[16][17] Epicardial fat-derived exosomes have been implicated in promoting AF by influencing the cardiac microenvironment.[18] Additionally, exosomal miR-23a-3p from cardiac fibroblasts has been found to induce ferroptosis in cardiomyocytes, further facilitating AF in a canine model.[17] On the other hand, certain exosomal components, such as LINC00636, have shown therapeutic potential by preventing cardiac fibrosis via mitogen-activated protein kinase 1 (MAPK1) inhibition.[19] And exosomes derived from human

atrial appendage cells exhibit anti-inflammatory properties and reduce atrial fibrosis, thereby lowering the likelihood of AF.[19]

In AF patients, specific exosomal long non-coding RNA (lncRNA) profiles have been observed: NR0046235, NR003045, NONHSAT167247.1, and NONHSAT202361.1 are upregulated,[19] while NONHSAT205820.1 and NONHSAT200958.1 are downregulated. All of these lncRNAs are linked to pro-inflammatory effects.[19] Additionally, exosomal lncRNAs LOC105377989 and LOC107986997 have been suggested as potential biomarkers for AF.[20][21] Exosomal miRNA profiling has also revealed significant changes: some miRNAs (e.g., miR-23a-3p, miR-23b-3p, and miR-125a-5p) were increased and some miRNAs (e.g., miR-16-2-3p and miR-22-3p) decreased in AF patients.[6][17] Of the upregulated miRNA, miR-210-3p and miR-124-3p, have been linked to enhanced atrial remodeling by promoting collagen synthesis and fibroblast activation, respectively.[22][23]

Persistent AF patients exhibit elevated levels of several exosomal miRNAs, including miR-103a, miR-107, and miR-486.[24] However, the role of miR-320d remains controversial. Some studies suggest miR-320d as a biomarker of AF,[25] while others report its cardioprotective effects by inhibiting Stat3.[24] In non-valvular AF patients, upregulated exosomal miRNAs (e.g., miR-106b-3p and miR-590-5p) has potential as diagnostic markers.[26] Exosomes have also been recognized for their role in reducing inflammation. As one example, intramyocardial injection of exosomes from cardiac explant-derived cells decreased pro-inflammatory cytokines, inflammatory cell infiltration, and oxidative stress with decreased NLR family pyrin domain containing 3 (NLRP3) inflammasome in rat AF model.[27][28] In addition, nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that plays an important role in antioxidant and cytoprotective responses. Intravenous injection of Nrf2-overexpressing BM-MSC derived exosome alleviated AF in rat model by reducing cardiac fibrosis.[29][30]

Taken together, exosomes not only mediate the pathological processes of AF but also hold significant promise as biomarkers and therapeutic targets for its treatment.

Atherosclerosis

AS, a major contributor to CVD, involves the buildup of lipids and inflammatory cells in the arterial wall.[1][18] The primary pathological features of AS include inflammatory cell infiltration, lipid accumulation, cell proliferation, and apoptosis, which collectively contribute to complications such as MI and stroke.[9] Exosomes secreted by endothelial cells, smooth muscle cells, and macrophages are key players in promoting AS progression.[18] For example, endothelial cell-derived exosomes can transport adhesion molecules like intercellular adhesion molecule-1 to smooth muscle cells, enhancing their migratory capabilities and contributing to plaque formation.[31] Consequently, investigating the underlying mechanisms of exosomes in AS and identifying their contents as biomarkers associated with onset and progression are crucial for advancing early detection and therapeutic interventions, potentially reducing side effects.[31] It has been demonstrated that exosomes act as critical mediators of intercellular communication, facilitating the release of inflammatory cytokines and the over-activation of inflammatory pathways. Additionally, exosomes transfer genetic information between cells. These vesicles are abundant in body fluids and maintain remarkable stability, enabling them to selectively encapsulate RNA, proteins, and active factors from their source cells and deliver them to specific target cells.[32][33] Recent studies have revealed that exosomes with these functions plays 2 major roles in the bloodstream: facilitating the formation of microcalcifications within atheromatous

plaques and mediating communication between blood cells and vascular walls.[33][34] And the cargo of exosomes can serve as biomarkers for the diagnosis and prognosis of AS and as potential delivery vehicles for targeted therapies. Taken together, these findings therefore further clarify the link between exosomes and the mechanisms that promote the formation and progression of AS, highlighting the pivotal role of exosomes.

In addition to these CVDs, exosomes are a double-edged sword in MI, one of the representative CVDs.[35] They can worsen the cardiac muscle injury by delivering pro-apoptotic signals and also supporting recovery by promoting angiogenesis and tissue regeneration.[35] In heart failure, exosomal signaling is implicated in the pathological restructuring of the heart muscle. Exosomes from stressed cardiomyocytes may lead to fibrosis by transferring fibrotic agents such as transforming growth factor (TGF)-β to cardiac fibroblasts. Additionally, exosomes found in the circulation of heart failure patients frequently contain high levels of inflammatory cytokines, indicating the systemic inflammation that accompanies disease progression.[35]

Therapeutic potential of exosomes

Myocardial infarction

While treatments for MI are still not fully effective, exosome-based therapies show promising potential.[36] Exosomes can deliver therapeutic molecules or genes to damaged heart tissue, contributing to reduced inflammation, increased cardiac cell survival, and enhanced angiogenesis. Various studies are exploring approaches to promote the repair of injured heart tissue using exosomes, with stem cell-derived exosomes in particular demonstrating regenerative effects on the heart.[36][37] Here, we describe the application of exosomes derived from various cell types for the treatment of MI (**Figure 1**).

Adipose derived stem cell (ADSC)-derived exosomes have emerged as a promising therapeutic strategy for MI due to their capacity to modulate cellular processes essential for cardiac repair.[38] Upon systemic or local administration, ADSC-derived exosomes are internalized by recipient cardiomyocytes, endothelial cells, and immune cells, mediating their therapeutic effects through bioactive cargo such as miRNAs, proteins, and lipids. One critical mechanism involves the inhibition of cardiomyocyte apoptosis via miR-21 and miR-146a, which suppress pro-apoptotic pathways and reduce oxidative stress.[39][40] Additionally, exosomal cargo promotes angiogenesis by enhancing vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1α signaling, leading to increased capillary density in ischemic myocardium.[41][42] These exosomes also modulate immune responses by polarizing macrophages toward an anti-inflammatory M2 phenotype, reducing inflammation and fibrosis.[43] Furthermore, they activate phosphatidylinositol 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) 1/2 pathways, facilitating cardiomyocyte survival and proliferation.[44] Exosomal proteins such as HSP70 and TGF-β contribute to ECM remodeling and scar size reduction.[42] By regulating endothelial function, they restore vascular integrity and improve myocardial perfusion. Moreover, exosomal lncRNAs fine-tune gene expression networks involved in cardiac regeneration.[45] Collectively, these mechanisms work synergistically to enhance myocardial repair, restore cardiac function, and reduce post-MI adverse remodeling.

Bone marrow-derived mesenchymal stem cell (BM-MSC) is one of the preferred sources of exosomes for MI treatment.[46] BM-MSC-derived exosomes have garnered significant attention as a potential therapeutic approach for MI due to their ability to modulate multiple reparative processes in the injured heart.[47] Upon systemic or local administration, BM-

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MSC-derived exosomes are internalized by cardiomyocytes, endothelial cells, fibroblasts, and immune cells, delivering a diverse array of bioactive molecules, including miRNAs, lncRNAs, proteins, and lipids.[47] A key cardioprotective mechanism involves the inhibition of apoptosis in ischemic cardiomyocytes, primarily mediated by exosomal miR-21, miR-126, and miR-19a, which suppress pro-apoptotic pathways such as PTEN and Bcl-2-associated pathways.[48][49] These exosomes also enhance angiogenesis through the activation of VEGF, HIF-1α, and endothelial nitric oxide synthase signaling, leading to increased capillary density and improved myocardial perfusion. Additionally, they modulate the inflammatory response by promoting macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, reducing excessive inflammation and mitigating fibrosis.[43] BM-MSC exosomes also facilitate ECM remodeling by regulating TGF-β and matrix metalloproteinases (MMPs), thereby limiting adverse cardiac remodeling and scar formation.[50] Furthermore, activation of the PI3K/Akt and ERK1/2 signaling pathways enhances cardiomyocyte proliferation and survival under ischemic conditions.[50] Exosomal HSP70 and interleukin (IL)-10 contribute to the attenuation of oxidative stress and immune activation, protecting cardiac tissue from secondary injury.[51] By preserving endothelial function, these exosomes help maintain vascular integrity and reduce microvascular obstruction.[52] They also promote endogenous cardiac progenitor cell activation, enhancing the heart's intrinsic regenerative capacity.[52] Notably, exosomal Wnt and Notch signaling modulators aid in restoring cardiac homeostasis by regulating cell-cell communication.[52] Through these multifaceted mechanisms, BM-MSC-derived exosomes significantly improve myocardial repair, restore left ventricular function, and reduce post-MI complications, making them a promising candidate for regenerative therapy in ischemic heart disease.

Myocardial ischemia/reperfusion injury

Myocardial ischemia/reperfusion injury (MIRI) is the leading cause of mortality related to CVDs. Therapeutic approaches using exosomes have also been reported for MIRI.[53] Administration of BM-MSC originated exosomes was reported to improve cardiac function and suppress myocardial apoptosis and inflammatory response by increasing the expression of Ki67 and Yap through miR-302.[22][53] BM-MSC exosomes also exhibited improved regional systolic function and diastolic relaxation by recovering cardiomyocyte mitochondrial respiration and reducing myocardial inflammation.[54] Besides BM-MSC exosomes, cardiac MSC is also used as the source of exosome treatment as it improves angiogenesis and preserves ejection fraction.[55] And exosomal sphingosylphosphoryl choline from vascular endothelial cells showed an elevated level of mitophagy within IR-affected myocardium by activating NR4A2-OPTN pathway.[55] Additionally, the oral dose of miR-146a enriched exosome from bovine milk improved cardiac function through the nuclear factor-κB signaling pathway in the rat myocardial ischemia model.[56]

Other cardiovascular diseases

Although studies that use exosomes as therapeutics in CVDs are mainly focused on MI and MIRI, other CVDs are also actively investigated with promising outcomes.

For thrombosis, ADSC-derived exosomal miR-483-5p reduced thrombus weight with decreased expression of tissue factor protein, inhibiting the influx of inflammatory cells into the vein by suppressing MAPK1 thereby reducing NLRP3 inflammasomes.[27] Also, miR-25-3p enriched exosomes from human umbilical cord MSC alleviated thrombosis in portal veins by modulating PTEN, KLF4, AKT, and ERK1/2.[57] To prevent postsurgical pericardial adhesions, exosomes from human induced pluripotent stem cell-derived cardiomyocytes were treated,

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resulting in attenuation of oxidative stress in cardiomyocytes by activating NRF2.[57] H9C2 cell line, a murine myoblast cell line, was also used as the source of exosomal therapy in myocardial injury, hindering inflammatory cell infiltration, apoptosis, and promoting angiogenesis via AMP-activated protein kinase signaling with upregulated telomerase reverse transcriptase messenger RNA expression.[58]

Intramyocardial injection of exosomes from cardiac explant-derived cells decreased pro-inflammatory cytokines, inflammatory cell infiltration, and oxidative stress with decreased NLRP3 inflammasome in rat AF model.[28] Additionally, intravenous injection of exosomes from human cardiosphere-derived cells (CDCs) improved cardiac function by inhibiting β-MHC, BNP, GP130, p-STAT3, p-ERK1/2, and p-AKT via miR-148a in mouse cardiac hypertrophy model.[28][59] In the mouse viral myocarditis model, M2 macrophage derived exosomes were used as a therapeutic, promoted M2 polarization of macrophage via lncRNA AK083884 which inhibits the activation of pyruvate kinase M2 (PKM2), and suppressing GLUT1, ENO1, LDHA, PDK1, and glycolysis by inhibiting the binding of PKM2 and HIF-1α, thus facilitate myocardial protection.[59]

Endothelial progenitor cells (EPCs) have been used in the treatment of CVDs through direct transplantation.[59] In recent studies, exosomes derived from EPCs have been shown to promote angiogenesis and protect against ischemia/reperfusion injury in animal models of heart failure.[41] EPC-derived exosomes carry miRNAs and other bioactive molecules that modulate inflammation, apoptosis, and oxidative stress, contributing to their cardioprotective effects.[41] CDC exosomes are another type of exosome that has been widely studied in preclinical models. It reduced fibrosis, promoting the regeneration of cardiomyocytes, and improving vascular density in the infarcted tissue.[60]

In preclinical studies, exosome therapy has demonstrated significant promise in treating CVDs, particularly in models of MI and ischemic heart disease. In addition to their direct effects on cardiac cells, exosomes have been shown to modulate the immune response and reduce inflammation in the cardiovascular system. This anti-inflammatory effect is particularly relevant in conditions such as heart failure and AS, where chronic inflammation plays a critical role in disease progression.[61] While preclinical studies provide strong evidence for the therapeutic potential of exosome-based therapies, it is essential to recognize that translating these findings to clinical practice is not without challenges. Further research is needed to optimize exosome isolation techniques, dosing regimens, and administration routes to maximize their therapeutic potential in human patients.

ROLE OF EXOSOMES DERIVED VARIOUS TYPE OF CELLS

Exosomes derived from various types of cells play diverse roles in physiological and pathological processes (**Figure 1**).

Cardiomyocyte-derived exosomes

Exosomes derived from cardiomyocytes are crucial EVs that significantly influence intercellular communication in the heart, impacting both its physiology and pathology. As previously described, these vesicles transport a wide range of biomolecules, such as proteins, lipids, and nucleic acids, which can alter the behavior of recipient cells. A key role of these cardiomyocyte-derived exosomes is to support the repair and regeneration of cardiac tissue,

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especially following ischemic events like MI. They achieve this by promoting angiogenesis, reducing apoptosis, and modulating the immune response, which are critical processes for cardiac tissue recovery and remodeling.[62] The mechanisms by which these exosomes exert their effects involve the transfer of specific miRNAs, mRNAs, and proteins that can influence gene expression and signaling pathways in recipient cells. For example, miRNAs such as miR-1, miR-21, and miR-133a present in cardiomyocyte-derived exosomes have been shown to regulate key pathways involved in cell survival, proliferation, and differentiation.[39] miR-21, in particular, has been demonstrated to reduce apoptosis and fibrosis in cardiac fibroblasts, thus mitigating adverse cardiac remodeling.[39] Additionally, the uptake of these exosomes by target cells can activate receptor-mediated pathways, such as the PI3K/Akt signaling pathway, which promotes cell survival and growth.[47] These findings suggest that cardiomyocyte-derived exosomes are not only crucial for normal heart function but also hold therapeutic potential for treating CVDs by enhancing endogenous repair mechanisms.[47]

Endothelial cell-derived exosomes

Endothelial cell-derived exosomes are small EVs that are vital to vascular biology, affecting both normal and abnormal vascular functions. These vesicles also contain a variety of molecules that can influence the behavior of target cells. A major function of these exosomes from endothelial cells is to control angiogenesis, which is essential for processes like wound healing, tissue regeneration, and tumor development. Depending on the circumstances, they can either enhance or suppress the formation of new blood vessels, thus playing a versatile role in both health and disease. For instance, they can enhance angiogenesis by delivering pro-angiogenic factors like VEGF and miRNAs such as miR-126, which are known to stimulate endothelial cell proliferation and migration.[49][63]

The mechanisms through which endothelial cell-derived exosomes exert their effects involve complex interactions with recipient cells. These exosomes can fuse with or be internalized by target cells, releasing their cargo and modulating signaling pathways. Key miRNAs within these exosomes, such as miR-214 and miR-222, have been shown to regulate apoptosis, cell cycle progression, and inflammation, thereby influencing vascular function and pathology. For example, miR-214 can suppress the expression of ataxia-telangiectasia mutated, a protein involved in DNA repair and cell cycle control, thereby promoting endothelial cell survival under stress conditions.[64] Additionally, these exosomes can affect the immune response by altering the behavior of immune cells, such as macrophages and T-cells, which can lead to either pro-inflammatory or anti-inflammatory effects depending on the cargo and context.[56] This immunomodulatory capacity highlights the potential therapeutic applications of endothelial cell-derived exosomes in treating various vascular and inflammatory diseases.[61]

Cardiac perivascular cell-derived exosomes

Cardiac perivascular cells, including pericytes and smooth muscle cells, are integral components of the heart's vascular niche, playing essential roles in maintaining vascular stability and homeostasis. Recent studies have highlighted the significant contributions of exosomes derived from these cells to cardiac health and disease. Cardiac perivascular cell-derived exosomes are involved in several key processes, including angiogenesis, vascular remodeling, and fibrosis. They are particularly important in the context of CVDs, where they can influence both pathological and reparative responses. For instance, these exosomes have been shown to carry pro-angiogenic factors such as VEGF and angiopoietin, as well as miRNAs like miR-126 and miR-132, which promote endothelial cell proliferation and migration.[38][49] This angiogenic potential is critical for tissue repair following MI, where

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enhancing blood supply to the damaged myocardium can significantly improve recovery outcomes. The mechanisms by which cardiac perivascular cell-derived exosomes exert their effects involve the transfer of bioactive cargo to recipient cells, modulating their behavior and function. For example, the miRNA content within these exosomes can regulate gene expression in endothelial cells, fibroblasts, and cardiomyocytes. miR-126 targets negative regulators of the PI3K/Akt signaling pathway, thereby enhancing endothelial cell survival and angiogenesis.[14] Similarly, miR-132 can modulate the endothelial response to vascular injury by promoting the expression of growth factors and inhibiting anti-angiogenic factors.[38] Additionally, these exosomes can influence the immune response by affecting macrophage polarization, thereby alleviating inflammation in the cardiac tissue.[14)44] The ability of these exosomes to alter the inflammatory environment and promote angiogenesis makes them promising candidates for therapeutic strategies aimed at mitigating damage and promoting repair in CVDs.[14)44]

Cardiac macrophage and leukocyte-derived exosomes

Exosomes derived from immune cells, including cardiac macrophages and leukocytes, play critical roles in the immune response and tissue remodeling within the heart. These exosomes are acting as key mediators of intercellular communication that can influence both inflammation and repair processes in cardiac tissues. Cardiac macrophage-derived exosomes are pivotal in modulating the immune response during heart injury and disease. They can either promote inflammation or facilitate tissue repair, depending on their molecular cargo and the microenvironmental context. For instance, macrophage-derived exosomes can carry pro-inflammatory cytokines like IL-1β and tumor necrosis factor-α, which can exacerbate inflammatory responses in cardiac tissues.[36] Conversely, these exosomes may also contain anti-inflammatory mediators such as IL-10 and TGF-β, which promote resolution of inflammation and healing.[63] In the context of MI, these exosomes have been shown to facilitate the clearance of apoptotic cells and debris, a process crucial for proper healing and regeneration. Leukocyte-derived exosomes, including those from T-cells, B-cells, and neutrophils, are also involved in the regulation of immune responses within the heart. These exosomes can carry molecules that modulate the activity of other immune cells, thus influencing the overall immune milieu. For example, T-cell-derived exosomes can contain miRNAs like miR-155, which has been implicated in promoting inflammatory responses.[65] Moreover, neutrophil-derived exosomes can help resolve inflammation by delivering miRNAs that inhibit pro-inflammatory pathways, thereby supporting tissue repair after injury. The mechanisms through which macrophage and leukocyte-derived exosomes exert their effects involve the delivery of specific signaling molecules and regulatory RNAs to target cells. For instance, exosomal miRNAs such as miR-21 and miR-146a,[39)66] commonly found in macrophage-derived exosomes, can modulate the expression of inflammatory mediators and signaling pathways in recipient cells.[39)65] miR-21, for example, has been shown to regulate the MAP kinase signaling pathway, thereby influencing macrophage polarization towards a more reparative phenotype.[43] Similarly, miR-146a is known to act as a negative regulator of pro-inflammatory signaling, helping to resolve inflammation and promote tissue healing.[67] Leukocyte-derived exosomes also play a role in modulating adaptive immune responses. For instance, exosomes derived from B-cells can present antigens and regulate T-cell responses, thereby affecting the immune reaction to cardiac antigens after a MI [65]. Additionally, neutrophil-derived exosomes can interact with endothelial cells, influencing vascular permeability and leukocyte transmigration during inflammatory responses.

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Mesenchymal stem cell-derived exosomes

MSCs are multipotent stromal cells with the ability to differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes. MSC-derived exosomes have gained attention for their therapeutic potential in regenerative medicine due to their ability to modulate immune responses, promote tissue repair, and facilitate cell-cell communication. These nano-sized EVs are making them potent mediators of MSCs' paracrine effects. MSC-derived exosomes play a crucial role in enhancing tissue repair and regeneration. They exert anti-inflammatory, anti-apoptotic, and pro-angiogenic effects, which are particularly beneficial in the case of cardiac injuries such as MI. These exosomes contain a variety of growth factors and cytokines, including hepatocyte growth factor (HGF), VEGF, and IL-10,[68] which contribute to the regenerative processes.[69] The therapeutic effects of MSC-derived exosomes are primarily mediated through the transfer of bioactive molecules, particularly miRNAs and proteins, which can influence gene expression and cellular pathways in recipient cells.[35] For example, miR-21, miR-23a, miR-126, and miR-146a present in MSC-derived exosomes are known to regulate apoptosis, inflammation, and angiogenesis.[67] miR-21 has been shown to inhibit apoptosis by targeting programmed cell death protein 4[66] and miR-126 promotes angiogenesis by activating the PI3K/Akt pathway and enhancing endothelial cell proliferation.[49] Additionally, MSC-derived exosomes can enhance the regenerative potential of injured tissues by modulating the ECM remodeling, promoting angiogenesis, and reducing fibrosis. They achieve this by transferring ECM-modulating proteins and miRNAs that regulate the expression of MMPs and tissue inhibitors of metalloproteinases, which are critical in maintaining ECM homeostasis.[42] MSC-derived exosomes can modulate the immune response by promoting a shift from a pro-inflammatory (M1) to an anti-inflammatory (M2) macrophage phenotype, thereby aiding in the resolution of inflammation and facilitating tissue repair.[49] Furthermore, MSC-derived exosomes have been shown to play a role in immune modulation by transferring anti-inflammatory cytokines and miRNAs that downregulate the expression of inflammatory cytokines and chemokines. This immune-modulatory function is crucial in creating a favorable microenvironment for tissue repair and regeneration.

EXOSOME CLINICAL TRIALS IN CARDIOVASCULAR DISEASES

As previously described, exosomes play a crucial role in cell-to-cell communication, and thus have demonstrated considerable potential in both diagnosing and treating CVDs. Their function as transporters of bioactive substances such as proteins, lipids, and nucleic acids has paved the way for innovative therapeutic approaches. Here, we describe the clinical trials applying exosomes in CVDs and offer an update on the present research status and potential future developments.

Clinical trials applying exosomes in CVDs have focused on their diagnostic and therapeutic potentials.[70] These trials range from early-phase studies assessing safety and feasibility to more advanced trials evaluating efficacy and clinical outcomes. The primary sources of exosomes in these trials include MSCs, CDCs, and other progenitor cells known for their regenerative capabilities.[70]

The therapeutic potential of exosomes in CVDs is being explored through various clinical trials. Exosomes derived from MSCs and CDCs are of particular interest due to their regenerative properties. These exosomes have been shown to promote angiogenesis, reduce

inflammation, and enhance cardiac repair in preclinical studies.[55] Clinical trials are now translating these findings into human studies. There are primarily 2 types of exosome therapies. MSC-Derived exosomes used in early-phase clinical trials are assessing the safety and efficacy of MSC-derived exosomes in patients with MI and chronic heart failure.[70] These trials aim to evaluate the ability of exosomal therapy to reduce infarct size, improve left ventricular function, and enhance overall cardiac function. Preliminary results have shown promising safety profiles and potential therapeutic benefits.[70] CDC-derived exosomes are evaluated for their cardioprotective effects. In particular, the CADUCEUS trial explored the use of CDCs in patients with MI, demonstrating significant reductions in scar size and improvements in viable myocardium.[71] Follow-up studies are investigating the isolated exosomes from CDCs to determine their direct effects and potential as a cell-free therapeutic option. This randomized, controlled phase I study investigated the safety and efficacy of intracoronary infusion of autologous CDCs in patients with left ventricular dysfunction following MI.[71] The trial demonstrated that CDC therapy was feasible and safe, with no significant adverse events reported. Magnetic resonance imaging assessments revealed a significant reduction in scar mass and an increase in viable heart mass in CDC-treated patients compared to controls.[71] These findings suggest that CDC-derived exosomes may contribute to myocardial regeneration by reducing scar tissue and promoting the growth of healthy myocardial tissue.[71] The observed improvements in regional contractility and systolic wall thickening further support the therapeutic potential of exosome-based interventions in cardiac repair.[71] While these results are promising, further research is necessary to elucidate the precise mechanisms by which exosomes exert their effects and to determine their long-term efficacy and safety in larger, more diverse patient populations.[60][71]

Clinical trials of cell therapy and paracrine effect of exosome therapy in cardiovascular diseases

Cell-based therapies, particularly MSC therapy, have been investigated in numerous clinical trials as potential treatments for CVDs, specifically for MI and heart failure.[72] For example, the BAMI trial (NCT01569178), a phase III clinical trial, aimed to determine the efficacy of autologous bone marrow-derived stem cells in MI patients.[72] While MSC therapy has shown promise in improving cardiac function and reducing scar size, it was limited by several factors such as low cell retention in the target tissue, potential immune rejection, and concerns over long-term safety, including the risk of tumorigenesis. Exosome therapy, however, presents an attractive alternative by addressing these limitations. Exosomes are small vesicles that can deliver bioactive molecules such as proteins, lipids, and nucleic acids, effectively mediating cellular repair without the need for intact cells. Because exosomes are acellular, they carry a lower risk of immune rejection, unlike live cell-based therapies. Furthermore, their small size allows exosomes to penetrate tissues more efficiently, cross biological barriers like the BBB, and potentially reach damaged heart tissues more effectively than MSCs.[69] In preclinical studies, MSC-derived exosomes have been shown to significantly reduce MI damage by promoting angiogenesis, decreasing inflammation, and preventing cardiomyocyte apoptosis.[69] Another advantage of exosome therapy is its scalability and ease of administration. Unlike stem cell transplantation, which requires the expansion of cells in vitro, exosomes can be mass-produced and stored for long periods without losing functionality. This simplifies the logistics of therapy delivery, making it more practical for widespread clinical use.[69] In conclusion, while traditional MSC therapies have shown some success, exosome therapy offers several advantages that may make it a more viable option for cardiovascular repair. Its cell-free nature, scalability, and potential to deliver therapeutic agents with fewer risks provide a compelling case for further investigation in clinical trials (**Figure 2**).

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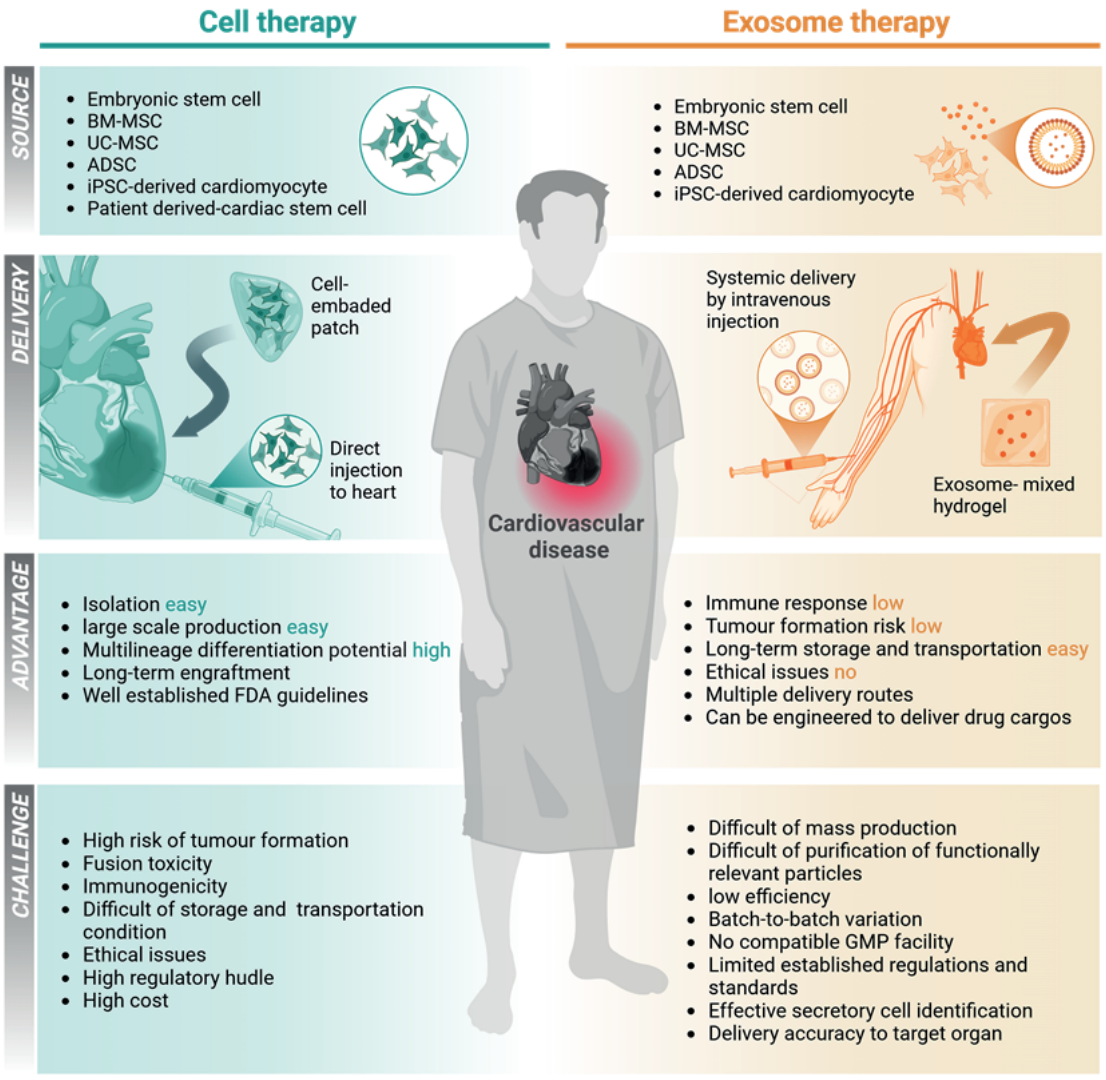

Figure 2. Scheme of cell therapy and exosome therapy.
ADSC = adipose derived stem cell; BM-MSC = bone marrow-derived mesenchymal stem cell; FDA = Food and Drug Administration; GMP = good manufacturing practices; iPSC = induced pluripotent stem cell; UC-MSC = umbilical cord-derived mesenchymal stem cell.

Clinical trials of exosome therapy and its limitations

Exosome-based therapies, despite their significant potential, are still in their infancy when it comes to clinical applications. While there are numerous preclinical studies exploring the use of exosomes as therapeutic approaches for various CVDs with exosomes derived from a variety of sources, there are only a limited number of clinical trials investigating their application in treating CVDs. In some cases, including NCT03384433, patient enrollment has begun, but it remains uncertain whether the study will continue. The clinical trials currently being conducted are in the early stages (phase I and II), with a primary focus on evaluating the safety, feasibility, and preliminary efficacy of exosome products.[73]

There are 2 ongoing clinical trials in total (**Table 1**): a phase I study (NCT06138210) and a Phase I/II study (NCT05669144). Specifically, NCT06138210 targets acute ischemic stroke through intravenous injection of exosomes derived from human iPSCs. Since this is a phase I study, its primary focus is on safety and delivery efficacy rather than the therapeutic effects of

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Table 1. Clinical trials in exosome therapy

ID	Disease	Trial detail	EV score	Administration dosage	Mode of administration	Study aim
NCT06138210	Acute ischemic stroke	· Phase 1 · Update posted: 05/29/2024 · Trial status: Recruiting · Enrollment: 29	hiPSC	2–8×10^9 (particles/kg)	Intravenous	Assessing the safety and initial efficacy of intravenous exosomes derived from human-induced pluripotent stem cells (GD-iEx003) in patients with acute ischemic stroke.
NCT03384433	Acute ischemic stroke	· Phase 1/2 · Update posted: 01/15/2021 · Trial status: Unknown · Enrollment: 5	MSC	Not provided	Intravenous	Evaluating the effects of administering MSC-derived exosomes on reducing disability in patients with acute ischemic stroke.
NCT05669144	Myocardial infraction	· Phase 1/2 · Update posted: 12/30/2022 · Trial status: Recruiting · Enrollment: 20	MSC	100 μg	Intracoronary intra-myocardial	Reducing damage through mitochondrial transplantation and MSC-derived exosome administration.

EV = extracellular vesicle; hiPSC = human induced pluripotent stem cell; MSC = mesenchymal stem cell.

exosomes. The other trial, NCT05669144, targets MI. Based on results that intramyocardial injection of mitochondria-rich exosomes in a mouse MI model has shown improved cardiac function and restored bioenergetics,[74] this trial integrates two therapeutic concepts for MI treatment: mitochondrial transplantation and MSC-derived exosome therapy. Neither mitochondrial transplantation therapy nor MSC-derived exosome therapy has been clinically validated for MI, so this trial aims to compare the 2 treatments and evaluate their potential synergistic effects. Intracoronary and intramyocardial administration of autologous mitochondria-rich exosomes and MSC-derived exosomes is performed, with an additional focus on sustaining therapeutic efficacy while minimizing inflammatory damage caused by allogeneic MSC-derived exosomes and oxidative stress induced by autologous mitochondria-rich exosomes. If the results of this trial are positive, it is expected to significantly advance the development of CVD therapies using exosomes.

However, none of trials have progressed to later phases, such as phase III or IV, which is primarily due to the regulatory, manufacturing, and scalability challenges associated with exosome therapy.[70] One of the major reasons for the scarcity of exosome clinical trials is the difficulty in standardizing exosome production. Current isolation methods, such as ultracentrifugation or size-exclusion chromatography, result in heterogeneous exosome preparations, which can affect the consistency and potency of the therapeutic product. The lack of standardized protocols for exosome isolation and characterization creates variability in clinical outcomes, making it difficult to advance these therapies to later-phase trials.[73] Additionally, regulatory agencies like the Food and Drug Administration are still in the process of developing guidelines for exosome-based therapies, which has slowed down their progression into large-scale clinical studies.[63] Another significant challenge is determining the optimal dosing and administration route for exosome therapy. Unlike cell-based therapies, where the dosage is relatively easy to quantify, exosome dosing is less straightforward. The bioactive cargo carried by exosomes can vary significantly depending on the cell of origin, and this variability adds another layer of complexity to clinical trials.[63][70] In conclusion, while exosome therapy holds considerable promise, its clinical application is still limited due to issues related to production standardization, regulatory hurdles, and dosing. Overcoming these challenges is essential for the future success of exosome-based treatments in CVD.

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CHALLENGES AND FUTURE DIRECTIONS

While initial clinical trial results for exosome-based therapies are promising, significant challenges remain in their clinical translation.[70] These include the need for standardized methods for exosome isolation, characterization, and storage to ensure batch-to-batch consistency and therapeutic efficacy. Additionally, the mechanisms through which exosomes promote cardiac repair require further investigation.[70] Efficient targeting and delivery to damaged cardiac tissue remain major obstacles, necessitating advancements in biomaterials and delivery systems. Furthermore, the potential immunogenicity and off-target effects of exosome therapies require thorough evaluation, with long-term studies essential for establishing their safety profiles. The regulatory framework for exosome-based therapies is still developing, and clear guidelines are needed to support their clinical application. Future research is expected to focus on large-scale, multicenter trials to confirm the therapeutic efficacy of exosomes across diverse patient populations, while advances in bioengineering and exosome modification may enhance their targeting and functional outcomes. Combining exosome therapy with existing treatment modalities could further improve outcomes for patients with CVDs. Exosome-based therapies have emerged as a promising strategy for CVD treatment,[68] but several hurdles and safety concerns must be addressed before their widespread clinical application.[70]

One major challenge is the scalability and standardization of exosome production, as current isolation and purification techniques, such as ultracentrifugation and size-exclusion chromatography, are labor-intensive and yield heterogeneous populations of exosomes.[70] Ensuring batch-to-batch consistency in exosome composition and bioactivity is crucial for maintaining therapeutic efficacy and minimizing variability in clinical outcomes. Another significant concern is the potential immunogenicity of exosomes, particularly when derived from allogeneic or genetically modified cells, which could elicit unwanted immune responses or adverse effects. Additionally, the possibility of off-target effects remains a critical issue, as exosomes can be taken up by multiple cell types, potentially leading to unintended biological consequences.[70]

From a safety perspective, the long-term fate of administered exosomes is not yet fully understood, raising concerns about their biodistribution, clearance, and potential accumulation in non-target organs such as the liver, spleen, and lungs.[75] Moreover, the potential for horizontal gene transfer via exosomal RNA raises concerns about oncogenic transformation or epigenetic alterations that could have unforeseen consequences.[75] The lack of standardized dosing regimens and optimal administration routes further complicates the clinical translation of exosome-based therapies, as different dosages and delivery methods may significantly impact therapeutic outcomes and safety profiles.[75]

Another challenge is the difficulty in fully characterizing the cargo of exosomes, as they contain a complex mixture of proteins, lipids, and nucleic acids that can vary depending on the cell source, culture conditions, and isolation methods.[76] This complexity makes it challenging to pinpoint the exact bioactive components responsible for their therapeutic effects, complicating regulatory approval.[76] Additionally, exosome stability and storage conditions must be optimized to preserve their bioactivity over time, as degradation or aggregation of exosomes could reduce efficacy or trigger adverse immune responses. Regulatory challenges also pose a significant hurdle, as exosomes fall into a gray area between biologics and cell-based therapies, making it difficult to establish clear guidelines

for their approval and commercialization. Ensuring the absence of contaminants such as endotoxins, residual cellular debris, and unwanted vesicle subtypes is essential for clinical safety. Finally, large-scale, well-designed clinical trials with long-term follow-up are needed to assess the true therapeutic potential and risks associated with exosome-based therapies for CVDs. Addressing these challenges through advancements in isolation techniques, rigorous safety testing, and comprehensive clinical evaluation will be essential for translating exosome-based therapies into a viable treatment option for heart disease.

Nevertheless, exosome-based therapy has the potential to bring revolutionary changes not only in the treatment of CVDs but also in various intractable diseases. Compared to conventional stem cell therapy, exosomes have the advantage of inducing therapeutic effects without the need for direct cell transplantation, while also exhibiting lower immune rejection. This makes them a promising tool for ushering in a new paradigm of personalized medicine.

Furthermore, various nanotechnology and bioengineering advancements are actively being explored to enhance the biocompatibility of exosomes and improve their targeted delivery to specific tissues. For instance, researchers are investigating the combination of exosomes with gene-editing technologies such as CRISPR-Cas9, as well as the loading of specific proteins to maximize their delivery efficiency to damaged cardiac tissue.

Additionally, as new technologies for large-scale production and quality control continue to emerge, exosome-based therapies are expected to become more cost-effective and efficient. The use of microfluidics and artificial intelligence (AI)-based analytical techniques can enable precise control over exosome properties, thereby accelerating the development of standardized treatment protocols.

In the future, strategies that combine exosomes with existing drugs are also likely to be developed. For example, exosomes loaded with anti-inflammatory or antioxidant agents could enhance the therapeutic efficacy for CVDs. Moreover, AI and data-driven approaches could facilitate the development of personalized exosome therapies based on patient-specific biomarkers.

In conclusion, while exosome-based therapy faces numerous challenges and hurdles, continuous research and technological advancements are expected to establish its role not only in CVD treatment but also in neurodegenerative disorders, cancer, immune diseases, and other medical fields. With standardized manufacturing processes, improved targeting technologies, and thorough safety validation, exosome therapy has the potential to become a groundbreaking medical innovation that transforms modern healthcare.

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