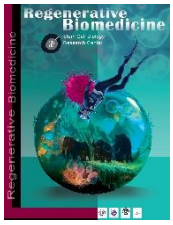

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Mini-Review Article

Stromal/stem Cell-derived Exosomes: Therapeutic Approach for Heart Failure

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Abstract

Heart failure remains a notable clinical and public health challenge worldwide. Current treatment modalities have shown limited success in reducing morbidity and mortality rates, highlighting the urgent need for alternative and novel therapeutic approaches. Growing evidence suggests that stem cell-derived exosomes, membrane-bound extracellular vesicles, are emerging as promising candidates for treating heart failure. Exosome released from mesenchymal stem cells and induced pluripotent stem cells (iPSCs) have demonstrated cardioprotective, immunomodulatory, and reparative effects. key advantages include targeted delivery, reduced immunogenicity, decreased tumor formation risk, and improvement storage and transportation feasibility. Despite their promise, challenges such as low production yield, stability concerns, and efficient delivery methods remain. standard methods for exosome isolation and characterization is needed. This mini-review summarizes stem cell-derived exosomes with potential applications in heart failure. Modifying exosome contents by regulating specific microRNA (miRNAs) can modulate communication between cardiac cells, often resulting in improved cardioprotection through various signaling pathways. The underling mechanism of these pathways encompasses enhancing angiogenesis, apoptosis inhibition, and fibrosis reduction.

Keywords: Cardiac Repair, Embryonic Stem Cells (ESCs), Exosome, Mesenchymal Stem Cells (MSCs), Pluripotent Stem Cells (PSCs)

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Introduction

Heart failure continues to be a significant public health issue and ranks among the leading causes of hospitalization and death worldwide (1). As conventional treatments often fall short of reversing damage, interest has grown in regenerative medicine as a way to restore heart function by repairing injured tissue (2). Several strategies including the use of stem cells, gene-based interventions, and engineered tissue have shown promise in research and early clinical settings (3).

Of particular interest are pluripotent stem cells (PSCs), which include embryonic stem cells (ESCs) (2, 4) and induced pluripotent stem cells (iPSCs) (5, 6). These cells can differentiate into various types of cardiovascular cells such as cardiomyocytes, smooth muscle cells, and endothelial cells making them attractive candidates for heart regeneration due to their versatility and renewable nature.

However, translating PSC-based therapies into clinical practice has proven challenging. Concerns such as tumor formation, low engraftment rates, immune rejection, and complications like embolism and graft-versus-host disease have made researchers cautious. As a result, attention has shifted toward safer, non-cellular alternatives.

In this context, exosomes (small vesicles released by cells), including PSCs have become an exciting area of investigation (4,7). These nano-sized carriers contain biologically active substances like proteins, lipids, and RNAs that can influence neighboring or distant cells. By modulating immune responses, encouraging blood vessel formation, and supporting cell survival, exosomes seem to offer many of the benefits associated with stem cell therapies, yet without the same safety concerns (4, 8). Their stability, scalability, and lower risk profile position them as a promising tool in cardiac regenerative medicine.

This mini-review highlights current findings on exosomes derived from both mesenchymal stem cells (MSCs) and pluripotent stem cells (PSCs), with a focus on their therapeutic potential in heart failure. It also compares their mechanisms of action and discusses their advantages and future clinical relevance.

Therapeutic effects of stem cells in cardiac disease

Stem cells contribute to treatment of cardiovascular diseases by modulating inflammation, stimulating angiogenesis, and supporting cellular survival and tissue regeneration. Both MSCs and PSCs have demonstrated reparative effects in preclinical models of heart failure (6).

However, challenges such as poor cell engraftment, immune rejection, and risks of tumor formation have restricted their widespread clinical use. These limitations have encouraged the exploration of their secreted products—particularly exosomes—as safer, more controllable alternatives (9).

Mesenchymal stem cell (MSC)-derived exosomes

MSCs can be isolated from various tissues, including bone marrow, adipose tissue, and umbilical cord (10). MSC-derived exosomes contain abundant microRNAs, proteins, and lipids contributing to their cardioprotective potential. They have been shown to reduce

apoptosis, modulate immune responses, and promote angiogenesis and tissue regeneration. Experimental studies have demonstrated that MSC exosomes can improve cardiac function, reduce fibrosis, and enhance vascularization in models of myocardial infarction and heart failure. Their low immunogenicity and minimal risk of tumor formation make them attractive candidates for clinical translation (11).

Pluripotent stem cell (PSC)-derived exosomes

Exosomes derived from ESCs and iPSCs also exhibit potent regenerative properties. These vesicles carry functional molecules that can influence cell survival, differentiation, and tissue remodeling. Exosomes originating from PSCs have been shown to promote cardiomyocyte proliferation, inhibit apoptotic pathways, and modulate the cardiac microenvironment (12). Unlike MSCs, PSCs offer an unlimited capacity for expansion and scalability, which could facilitate large-scale production of therapeutic exosomes. Safety and standardization issues surrounding PSC sources, especially ESCs, continue to raise regulatory and ethical concern (10).

Exosomes and their mechanisms of action in heart failure

Exosomes are small (30-160 nm) extracellular vesicles found in bodily fluids secreted by various cell types, including mesenchymal stem cells (MSCs). These vesicles serve as key mediators of intercellular communication. Exosome formation occurs through the inward budding of multivesicular bodies (MVBs) (13, 14). Through fusion with the plasma membrane, MVBs release exosomes into the surrounding extracellular environment. They transport diverse bioactive molecules, including proteins, lipids, mRNAs, microRNAs (miRNAs), DNA, cytoplasmic proteins, cytokines, and lipids (7, 15). This molecular cargo allows exosomes to modulate the function of recipient cells and play essential roles in immune regulation. Due to these unique characteristics, exosomes hold significant potential in disease diagnosis and prognosis, particularly through liquid biopsies and the development of novel treatment strategy. as a result, research is increasingly focused on using exosomes as biomarkers and therapeutic tools (16). MSC-derived exosomes contribute to cardiac repair and regeneration in heart failure through various mechanisms (Fig. 1):

A) Anti-inflammatory effects: MSC exosomes modulate the inflammatory response by reducing pro-inflammatory cytokines and promoting anti-inflammatory cytokines (17) (14). They polarise macrophages from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotype. Both intramyocardial and intravenous transplantation of exosomes derived from mesenchymal stem cells (MSCs) can reduce the infiltration of pro-inflammatory immune cells in the infarcted heart (17-19).

B) Angiogenesis: Exosomes promote the formation of new blood vessels by delivering pro-angiogenic microRNAs (e.g., miR-126, miR-132) and growth factors (e.g., VEGF) (20, 21). increased angiogenesis improves oxygen and nutrient supply to the compromised myocardium (20).

C) Anti-apoptotic effect: Exosomes can minimize cardiomyocyte apoptosis by suppressing pro-apoptotic pathways via transfer of specific molecular cargos such as

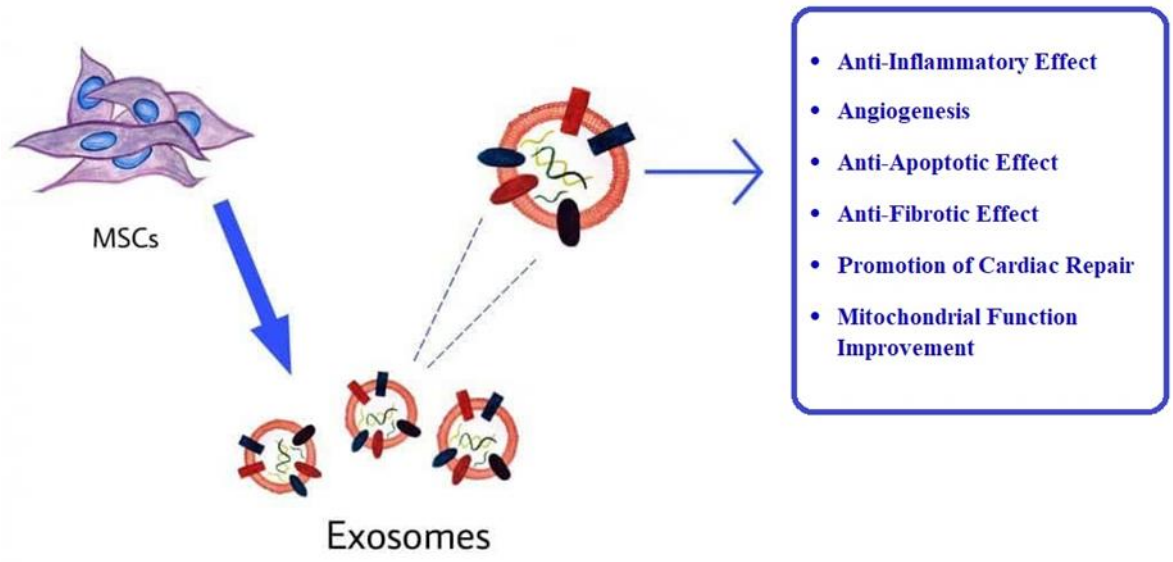

Figure 1. MSC-derived exosomes contribute to cardiac repair and regeneration in heart failure. MSCs: Mesenchymal stem cells. Figure with permission from Yassaman Tahmasebi Birgani, Cardiologist, Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences.

microRNAs (miRNAs), proteins, and lipids (21). Exosomes derived from MSCs overexpressing GATA4 demonstrated both anti-apoptotic and cardioprotective effect by delivering anti-apoptotic microRNAs, such as miR-19a (24n). Previous studies have shown that intramyocardial, intravenous, intracoronary, or intrapericardial transplantation of MSC-derived exosomes can effectively reduce apoptosis in endogenous cardiomyocytes (11, 22, 23).

D) Anti-fibrotic effect: Exosomes also attenuate cardiac fibrosis by regulating fibroblast activation and extracellular matrix deposition (24). MiR-29 is a well-known microRNA involved in regulating cardiac fibrosis. Reduced expression of miR-29 increases extracellular matrix deposition, ultimately contributing to cardiac fibrosis (25).Therefore, exosomes having anti-inflammatory and anti-apoptotic properties contribute to cardiac regeneration during the pro-inflammatory phase, while pro-angiogenic and anti-fibrotic exosomes support vascularization and cardiac repair during the healing phase (24, 25).

E) Promotion of cardiac repair : MSC exosomes activate endogenous cardiac progenitor cells and stimulate myocardial regeneration (26, 27). Certain exosomal contents, such as miR-21 and miR-19a, are involved in reducing scar formation and improving cardiac contractility (28).

F) Mitochondrial function improvement: Extracellular vesicles derived from cardiac cells enhance mitochondrial function, protecting the heart from ischemia/reperfusion injury. They achieve this by delivering mitochondrial components, such as ATP5a1, which boost the bioenergetics and resilience of stressed cardiac cells. Targeting ATP5a1 presents significant therapeutic potential as an effective strategy for managing myocardial damage caused by MI injury (29).

Table 1. Summary of selected studies investigating the therapeutic effects of exosomes in cardiac repair

Study	Source of exosomes	Disease Model	Mechanism	Outcome
Lai et al., 2010 (30)	MSC(Human)	MI (Rat)	Anti-apoptotic, angiogenic	enhanced myocardial viability, prevention of active remodeling
Khan et al., 2015 (12)	CDC-derived exosomes	Ischemic HF (Mouse)	Anti-fibrotic, regenerative	Reduced fibrosis, improved function
Sujitha Thavapalachandran et al., 2021 (31)	iPSC-MSCs	MI (Mouse)	Anti apoptosis, fibrose reduction, angiogenic	Reduced infarct size, increased vascular density
Wang, Zicheng, et al., 2021 (32)	Umbilical cord MSC	HF (Rat)	miR-1246 targets PRSS23 and inhibits the Snail/α-SMA	Increased angiogenesis, reduced apoptosis

Comparative studies on exosome-based cardiac therapy

Several experimental and preclinical studies have investigated the cardioprotective potential of exosomes derived from different stem cell sources. Summarizes key findings from selected studies, highlighting the source of exosomes, experimental models, mechanisms of action, and therapeutic outcomes (Table 1).

Key advantages of exosome-based therapy

Exosome therapy is a cell-free approach, which minimizes the safety concerns associated with live cell management and reduces the risk of tumorigenicity, graft-versus-host reaction, or immune rejection (2, 4, 6). Exosomes can be selectively absorbed by target cells, offering tissue—and cell-specific targeting opportunities (3, 5, 7). They contain proteins with binding affinities to specific receptors on recipient cells, enabling targeted delivery to desired cell types (8). Exosomes are less immunogenic than cells, reducing the likelihood of triggering an immune response (3, 13, 14). Allogeneic iPSC-Exosomes did not elicit lymphocyte infiltration, suggesting their suitability as "off-the-shelf" iPS cell-free products (7). Compared to stem cells, exosomes have a negligible risk of tumor development (3, 4, 13). Macaque iPSC-exosomes contained low level of pluripotent mRNAs and did not deliver pluripotency to host cells, suggesting no risk of forming teratomas (7). Exosomes can be delivered through various methods, which enhances their therapeutic potential (13). Due to their smaller size and simpler structures exosomes exabit greater stability and are easier to manipulate, produce, and store than cells (3, 13). They can also be preserved for long-term storage and transport (13). Trehalose can prevent exosome aggregation and cryodamage, and lyophilization preserves exosomes at room temperature (15). Exosomes deliver various bioactive components, including RNAs, peptides, and small molecules, facilitating intercellular communication (9, 16, 33). A bilayer lipid coat protects their cargo from degradation (5). Exosomes are capable of crossing the blood-brain barrier, allowing them to transport their contents to target

cells located either nearby or at distant sites (4). Exosomes offer the potential for personalized medicine and gene therapy due to their ability to manipulate molecular components through miRNA cargo and selectively target cell types of interest (8). Exosomes inherit key therapeutic properties from their parent cells, such as anti-inflammation, immunomodulation, and tissue regeneration. In some instances, they have demonstrated similar or superior therapeutic effects to the cells from which they are derived (9).

Challenges and Future Directions

Exosomes derived from iPSCs face challenges and present future directions for therapeutic applications in various diseases. one of the primary obstacles is the low yield of exosome production. Exosomes have stability and half-life limitations. Delivering exosomes to target cells efficiently is another challenge. A major challenge remains the absence of standardized protocols for the exosome isolation, storage, characterization, and analysis. The exosome subpopulation origin is complex, encompassing various cell types such as cardiomyocytes, endothelial cells, smooth muscle cells, and immune cells. In terms of factors operating at the intracellular level, delivery into the correct cellular compartments while maintaining stability, integrity, and biological potency remains challenging and costly.

Conclusion

Exosomes from pluripotent stem cells offer a promising cell-free therapy for heart failure. Their ability to enhance cardiac repair through paracrine signaling, combined with low immunogenicity and non-tumorigenic properties, makes exosomes an attractive alternative to traditional treatments. MSC-derived exosomes hold immense promise for heart failure therapy due to their ability to mediate multi-faceted repair mechanisms without complications associated with stem cell transplantation. However, further research is needed to fully realise their potential in clinical settings. Future research should optimize the production and delivery of exosomes to maximize their regenerative potential.

Conflict of interest

All authors declare no conflict of interest.

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