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*Review Article*

# Engineering Exosomes for Ischemic Heart Disease Therapy

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**Abstract**

Ischemic heart disease is a leading cause of heart failure, with current treatments limited in promoting myocardial repair. Engineered exosomes have emerged as promising therapeutic carriers due to their low immunogenicity, biocompatibility and barrier-crossing capacity. This review highlights two core strategies: membrane modification to enhance targeting to ischemic myocardium and loading of therapeutic cargo to improve cardiac repair through angiogenesis, anti-apoptosis, immunomodulation and anti-fibrosis. We also discuss ongoing challenges and future directions for engineered exosomes as precision tools in cardiac regeneration.

**Keywords:** Heart Disease; Immunogenicity; Cardiac Regeneration

## Introduction

Ischemic Heart Disease (IHD) is a major health threat to humanity [1]. While Mesenchymal Stem Cell (MSC) transplantation has shown promise due to its paracrine effects, limitations such as poor cell survival and embolic risk have spurred interest in cell-free therapies [2]. Exosomes, nanoscale extracellular vesicles secreted by cells, have emerged as attractive therapeutic carriers. These vesicles transport bioactive cargo such as proteins, lipids and miRNAs and offer advantages including low toxicity, stability, excellent biocompatibility and low immunogenicity [3]. Notably, exosomal miRNAs can promote cardiomyocyte proliferation and regeneration while inhibiting apoptosis [4]. However, natural exosomes present several limitations for cardiac repair: First, the miRNA profiles are heterogeneous and often low in abundance; Furthermore, natural exosomes lack cardiac targeting specificity and are rapidly cleared by the mononuclear phagocytic system. Therefore, engineering exosomes to carry cardioprotective miRNAs and enhancing their targeting specificity represent key strategies for improving therapeutic efficacy against Ischemic Heart Disease (IHD).

## Optimization of the Contents of the Exosome

Engineered exosomes allow precise manipulation of cargo, including endogenous bioactive molecules from homologous cells and exogenous drugs, proteins or miRNAs.

### *Exosomal Vesicles Carry Drugs*

Drug loading employs passive and active techniques [5]. Passive loading is generally accomplished by co-incubating exosomes with drugs, gene-carrying plasmids or viruses, thereby producing engineered exosomes loaded with therapeutic cargo. Small molecule drugs, particularly those used to treat arrhythmias and systolic dysfunction, can be encapsulated into exosomes to enable targeted delivery to cardiac tissue. In contrast, active loading techniques allow more efficient incorporation of small molecules and nucleic acids. These methods include electroporation, mechanical extrusion, sonication and freeze-thaw cycling. Among them, electroporation is widely employed for loading proteins and miRNAs. This approach allows the target drug to be loaded through transient pores formed under acoustic waves, while preserving the intrinsic properties of the exosomal membrane [6].

*Exosomal Vesicles Loaded with miRNA*

Modulating therapeutic miRNAs within exosomes has emerged as a promising strategy for disease treatment, particularly in oncology and cardiovascular medicine [7]. Double-stranded miRNA mimics can restore or enhance the activity of endogenous mature miRNAs, whereas single-stranded antisense oligonucleotides (anti-miRNAs) are employed to inhibit specific miRNAs. Preclinical studies in small and large animal models of heart failure have demonstrated that anti-miRNAs can effectively regulate cardiac miRNA levels and exert therapeutic benefits [8]. Pharmacological investigations in rodents and pigs have shown that antisense inhibitors targeting miR-132, miR-21 and miR-34 confer cardioprotective, anti-fibrotic and immunomodulatory effects, while inhibition of miR-125b reduces cellular apoptosis [8,9]. Conversely, studies utilizing miRNA mimics have revealed that delivery of exosomes loaded with miR-486 to H9C2 cardiomyocytes attenuates apoptosis induced by hypoxia/reoxygenation injury and reduces myocardial infarct size. A clinical trial is currently underway to evaluate the administration of allogeneic MSC-derived exosomes enriched with miR-124 in patients with acute ischemic stroke.

**Membrane Surface Modification**

Exosomal surface engineering employs genetic or chemical strategies to display targeting peptides, enhancing tissue specificity based on the peptide's properties.

*Installing Different Targeting Peptides*

Exosomal surface engineering via genetic or chemical methods conjugates targeting peptides like Cardiomyocyte-Specific Binding Peptide (CMP), Ischemic Myocardium-Targeting Peptide (IMTP) and Cardiac Targeting Peptide (CTP) to enhance cardiac tropism. CMP improves cardiomyocyte uptake and retention while reducing apoptosis [10,11]. IMTP demonstrates high affinity, specificity and low immunogenicity, enabling targeted delivery to ischemic myocardium [2,12]. CTP enables targeted cardiac delivery, achieving preferential transduction in the endocardial and epicardial layers within 15-30 minutes [13].

*Genetic Engineering*

The genetic engineering approach involves fusing the gene encoding a targeting peptide with that of a transmembrane protein (LAMP-2B, CD63, CD9 or CD81), followed by transfection into donor cells [14]. Among these, LAMP-2B is the most widely used exosomal surface protein, characterized by a large N-terminal luminal domain, a C-terminal transmembrane region and a short cytoplasmic tail. Consequently, targeting peptides can be fused to the N-terminal luminal domain of LAMP-2B to achieve directed delivery [15]. Kim, et al., transfected HEK 293 cells with a plasmid encoding a CTP-Lamp2B fusion protein, generating exosomes that displayed CTP-Lamp2B on their membrane [16]. Stable expression was facilitated by incorporating a Glycosylation Sequence (GNSTM). *In-vivo*, exosomes displaying CTP-Lamp2B showed a 15% increase in cardiac delivery in mice.

*Chemical Modification*

Chemical surface modification of exosomes is primarily achieved through two strategies: click chemistry and lipid assembly. The click chemistry approach typically relies on the conversion of surface-exposed amine groups to alkynes [17]. First, Dibenzocyclooctyne-sulfo-N-hydroxysuccinimide ester (DBCO-sulfo-NHS) is conjugated to phosphatidylethanolamine on the exosomal membrane, anchoring the DBCO moiety to the vesicle surface. Subsequently, a terminal azide group is introduced to the CTP, enabling its covalent linkage to the surface-bound Dibenzocyclooctyne (DBCO) via copper-free click chemistry. This approach enables the covalent conjugation of CTP to the exosomal surface [2]. Lipid assembly represents another established chemical modification strategies, wherein amphiphilic molecules are directly inserted into the exosomal lipid bilayer [17]. For instance, incorporating an IMTP-FAM peptide complex linked to PEG-cholesterol into the membrane enables stable surface functionalization and confers targeting specificity to the exosome [18].

**Hydrogel-Exosome Combinations**

Hydrogels, 3D crosslinked polymers with hydrophilic porous structures, serve as biocompatible carriers that regulate exosome release via hydrolytic or enzymatic degradation [19,20]. Encapsulation in hydrogels provides a stable extracellular matrix-mimicking environment, prolonging local retention. Han, et al., encapsulated human umbilical cord MSC-derived exosomes in PGN peptide hydrogel, achieving sustained release for 21 days, improving cardiac function and reducing fibrosis and inflammation [21,22]. Laponite-gelatin hydrogels maintain mechanical stability for 21 days, minimizing exosome leakage. Injectable hydrogel patches delivering induced pluripotent stem cell-derived exosomes restored cardiomyocyte function and

reduced infarct size in rats [23,24]. Some hydrogels (STG) exert inherent therapeutic effects via hyaluronic acid, promoting angiogenesis through CD44 signaling [25].

**Delivery Approaches**

*Surgical Delivery*

Although surgical intervention inevitably causes myocardial injury, it offers distinct advantages over exosome-based delivery, which relies on inherent targeting and results in slow distribution. Surgery enables direct cardiac access, significantly improving delivery efficiency. Moreover, it allows precise control over the delivery process and possesses the capacity to deliver large-scale materials, making it an attractive option for patients already scheduled for open-chest surgery [26].

*Atrial Painting*

Atrial painting represents a unique surgical approach developed specifically for gene delivery. In this technique, as demonstrated by Kikuchi, et al., an adenoviral solution is applied directly to the atrial surface [27]. Transmural gene expression was achieved when trypsin was co-administered with the viral vector.

**Minimally Invasive Transcatheter Delivery**

*Coronary Artery Intervention*

Coronary artery catheter-based drug delivery is generally less invasive than surgical approaches and can be utilized in patients with advanced cardiac dysfunction. Compared with intramyocardial injection, which typically results in focal distribution, intracoronary catheter infusion achieves more uniform myocardial coverage [28]. For patients with severe coronary stenosis or occlusion in whom antegrade myocardial blood flow is limited, retrograde perfusion via the coronary sinus has been proposed as an alternative route to deliver vectors or cells [29]. Using this retrograde approach, delivered agents exhibit greater expression in the basal and epicardial regions of the heart [30].

*Endocardial Catheter*

Endocardial catheterization, guided by NOGA systems to detect scar tissue via low electrical signals, allows percutaneous targeted injection into septal regions, outperforming intramyocardial and intracoronary delivery for MSC targeting [31,32].

*Microbubble Destruction*

The microbubble destruction method enhances cardiac-targeted delivery by employing ultrasound to disrupt drug-loaded microbubbles. The transient, localized injury induced by this disruption promotes the absorption of therapeutic agents [33].

**Conclusion and Future Directions**

Engineered exosomes hold great potential for IHD therapy, but critical challenges remain: unclear mechanisms of exosome-cell interaction and uptake, undefined cardiac binding sites for targeting peptides and limited data on whether targeted exosomes compensate for myocardial injury from direct delivery. Ensuring long-term retention without phagocytic clearance and exploring viral protein incorporation for enhanced targeting require further investigation. Future research should focus on optimizing cargo selection, refining targeting strategies and developing personalized delivery systems to maximize therapeutic efficacy. Despite current limitations, the integration of engineered exosomes with hydrogels and advanced delivery techniques offers a promising avenue for revolutionizing IHD treatment.

**Conflict of Interest**

The authors declare no conflicts of interest.

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None.

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