Review

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Exosomes-mediated drug delivery for the treatment of myocardial injury

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Abstract

Cardiovascular disease has become a major cause of death worldwide. Myocardial injury (MI) caused by myocardial infarction, myocarditis, and drug overdose can lead to impaired cardiac function, culminating in serious consequences such as angina pectoris, arrhythmias, and heart failure. Exosomes exhibit high biocompatibility and target specificity, rendering them an important non-cellular therapy for improving MI. Exosomes are diminutive vesicles that encapsulate nucleic acids and proteins. Exosomes derived from cardiac stem cells themselves have therapeutic effects, and they can also serve as carriers to deliver therapeutic drugs to recipient cells, thereby exerting a therapeutic effect. The molecules within exosomes are encapsulated in a lipid bilayer, allowing them to stably exist in body fluids without being affected by nucleases. Therefore, the utilization of exosomes as drug delivery systems (DDS) for disease treatment has been extensively investigated and is currently undergoing clinical trials. This review summarizes the therapeutic effects of exosomes on MI and provides an overview of current research progress on their use as DDS in MI.

Key words: drug delivery systems, exosomes, heart disease, myocardial injury

Introduction

Despite advocating lifestyle changes such as smoking cessation, healthy eating habits, moderate exercise, and the management of weight and blood pressure to prevent and alleviate cardiovascular diseases, myocardial infarction and myocarditis have remained the leading causes of death worldwide for over 20 years[1]. While endoscopic catheter intervention and drug treatment have been reported to improve prognosis, they do not provide a curative treatments. Early studies have reported the potential of embryonic stem cells and induced pluripotent stem cells in cardiac regeneration, as they can effectively repair and replace damaged blood vessels and heart tissue, ultimately leading to improved heart function[2,3]. These stem cell-based therapies are expected to become a new curative option for heart transplantation. However, cell-based therapy has some problems such as causing natural and adaptive immune responses, which may lead to low survival rates of transplanted cells[3,4]. Therefore, cell-free therapy based on exosomes has attracted widespread attention due to its high biological compatibility and targeted specificity[5].

Exosomes are lipid bilayer biological nanovesicles containing various proteins, lipids, mRNA, microRNA, etc. All major cardiac cell types can regulate receptor cell function through the release of exosomes[6,7]. Initially, exosomes were thought of as 'garbage' secreted by cells as a means of waste elimination. However, there is increasing evidence that cardiac cells secrete exosomes as an important means of intercellular communication between cardiac cells under both physiological and pathological conditions[8,9]. Exosomes carry biological information from parent cells to target cells, thereby regulating the latter's biological functions. This intercellular communication, mediated by exosomes, plays an important regulatory role in cancer, autoimmune diseases, inflammation, infection, metabolism, and cardiovascular diseases[10]. In recent years, there has been rapid development in exosomes research for disease diagnosis and treatment, making them a highly anticipated new type of biopharmaceutical product[11]. Exosomes possess multiple biological functions, with diameters ranging from 40 to 100 nm. In some ways, they may be more suitable for drug delivery compared to synthetic nanoparticles[12]. Compared with synthetic nanoparticles, exosomes as carriers exhibit good stability, low immunogenicity, and excellent biocompatibility[13]. They also possess the ability to deliver molecules to specific cells located in distant organs and tissues[14]. Additionally, exosomes possess several advantages, including evasion monocyte phagocytosis, ability to migrate beyond blood vessels, passive accumulation in tissues, and permeation through existing barriers within the body such as the blood-brain barrier[1,15]. Currently, research is being conducted to use exsomes as carriers for delivering nucleic acid drugs (such as siRNA), protein drugs, and small molecule drugs, taking advantage of their characteristics[16–18].

In this review, we briefly introduce the biological properties of exosomes and their potential as carriers for drug delivery, and

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hope that they can serve as drug delivery carriers in the field of heart disease treatment. We focus on the therapeutic effects of exosomes in MI and the recent evidence that supports their efficacy as carriers for drug delivery.

Formation of exosomes

Exosomes are small vesicles surrounded by a double-layered lipid membrane, which include exosomes, microvesicles, and apoptotic bodies. Exosomes are a typical subclass of extracellular vesicles, with diameters ranging from 40 to 100 nm[12]. During the initial stage of exosome formation, transmembrane proteins are internalized and transported to early endosomes. Early endosomes produce intraluminal vesicles by changing their protein composition and budding into the lumen of cells, gradually maturing into multivesicular bodies (MVBs). MVBs can be degraded by fusing with lysosomes or released into the extracellular space as exosomes after fusion with the plasma membrane[10,19]. The process of exosome formation is illustrated in Fig. 1. Secreted exosomes do not interact with every cell they encounter. Exosomes have specific target cells depending on their origin. The currently proposed interaction mode between exosomes and target cells mainly involves receptor-ligand interactions, binding to the cell surface, and then endocytosis, fusing the exosome membrane with the target cell membrane, releasing its contents into the recipient cells[7]. The contents of exosomes depend on both the cell type and the functional status of the cells that produce them. They contain lipids, metabolites, proteins, miRNAs, mRNAs, long non-coding RNAs, DNA, and more[20,21]. To date, most studies have focused on the functions of different miRNAs within exosomes.

The biological functions of exosomes in MI repair

In recent years, stem cell therapy has shown a beneficial trend in repairing MI and improving cardiac function. This is not only due to the targeted differentiation ability of transplanted stem cells and their regulation through direct cell-to-cell contact, but also benefits from the paracrine effect of stem cells. Among them, exosomes derived from stem cells mediate intercellular communication to regulate the biological functions of recipient cells[22,23]. Due to their unique biological functions, exosomes are currently being widely studied and applied as an alternative therapy for cardiovascular diseases in place of stem cells[24,25]. The biological role of exosomes in the repair of MI is illustrated in Fig. 2.

Anti-inflammatory activity

Damaged myocardial tissue results in a large number of necrotic myocardial cells, which triggers an inflammatory response, activates the innate immune response, induces the expression of cytokines and chemokines, as well as the synthesis and release of a large amount of inflammatory factors such as TNF-α and IL-1β[26]. These inflammatory factors can stimulate fibroblasts to present a pro-inflammatory phenotype, thereby inducing the secretion of additional inflammatory factors that further promote an inflammatory response[27]. Currently, numerous studies have demonstrated that extracellular vesicles derived from mesenchymal stem cells (MSCs) can regulate the inflammatory response after MI by promoting macrophage polarization[28,29]. Exosomes derived from MSCs (MSCs-exo) can exert anti-inflammatory effects both *in vitro* and *in vivo* by converting M1-type pro-inflammatory macrophages into M2-type anti-inflammatory macrophages[30]. When miR-182 is reduced in MSCs-exo, the regulatory effect of exosomes on macrophage polarization weakens. Therefore, MSCs-exo can effectively alleviate the inflammatory response after MI in mice by transferring miR-182 to change the polarization state of macrophages[31].

Anti-apoptotic effect

Following MI, a significant number of functional myocardial cells are progressively lost, leading to irreversible cardiac remodeling

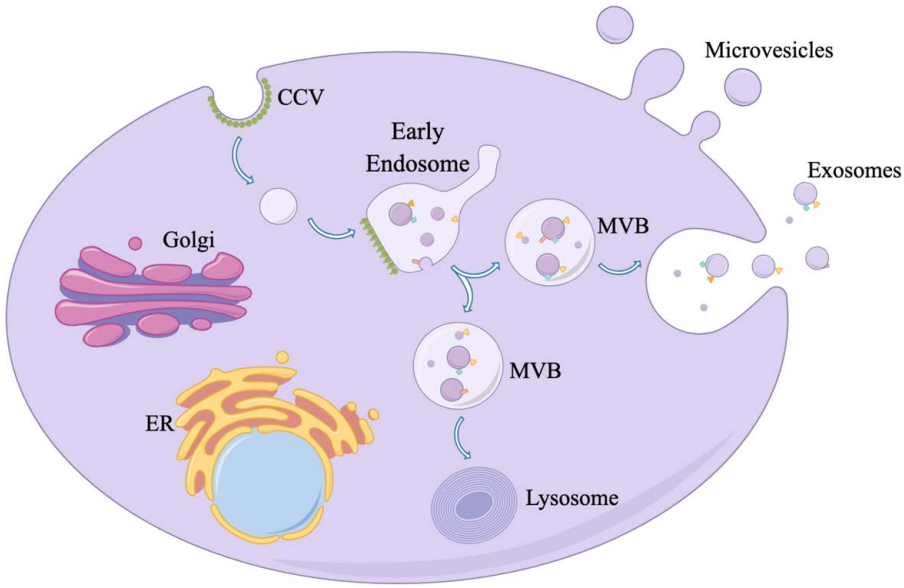

Figure 1. Cell-derived exosome formation pathway. CCV, Clathrin-coated vesicles; MVB, multivesicular body. Image created by Figdraw.

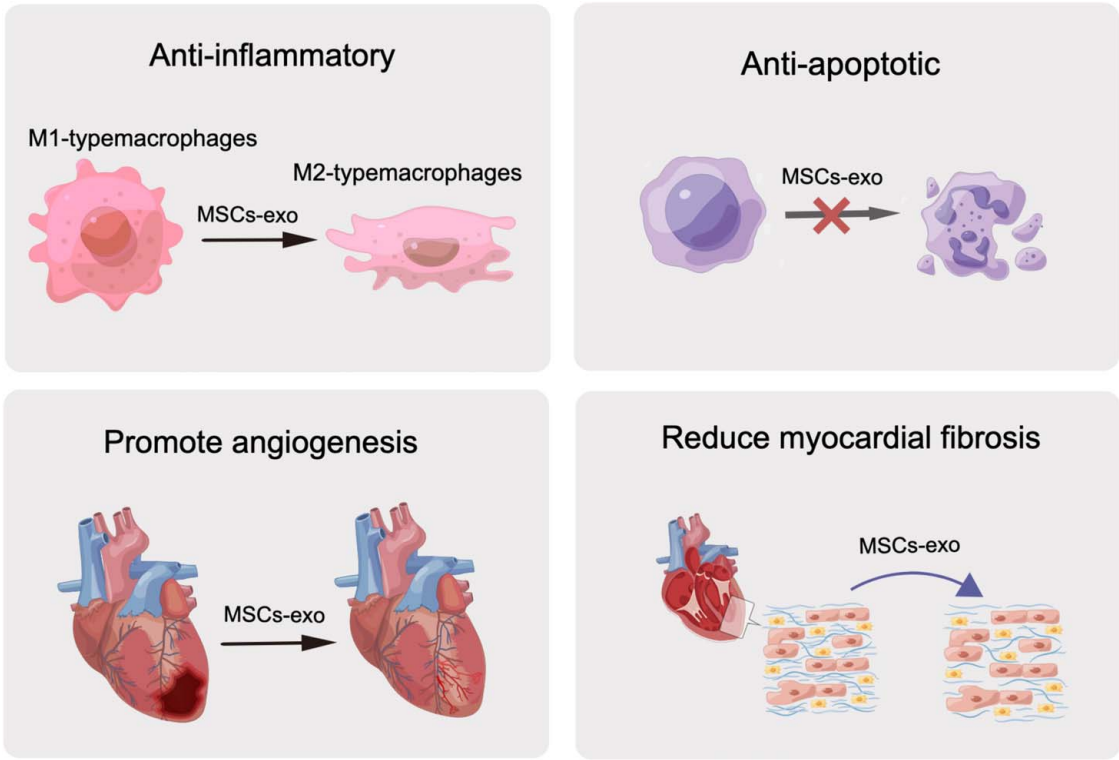

Figure 2. The reparative effects of exosomes on myocardial injury. MSC, mesenchymal stem cell. Image created by Figdraw.

and decreased heart function. Treating this condition remains a challenging clinical problem due to the non-regenerative nature of myocardial cells. MSCs transplantation provides a new approach to treat MI, as they can differentiate directly into myocardial cells and secrete abundant exosomes and growth factors that exert anti-apoptotic effects on myocardial cells[32]. MSCs-exo increase ATP levels, reduce oxidative stress, activate the PI3K/Akt pathway to enhance myocardial activity, thereby exerting anti-apoptotic effects[33]. MSCs-exo can induce autophagy in myocardial cells through the AMPK/mTOR and Akt/

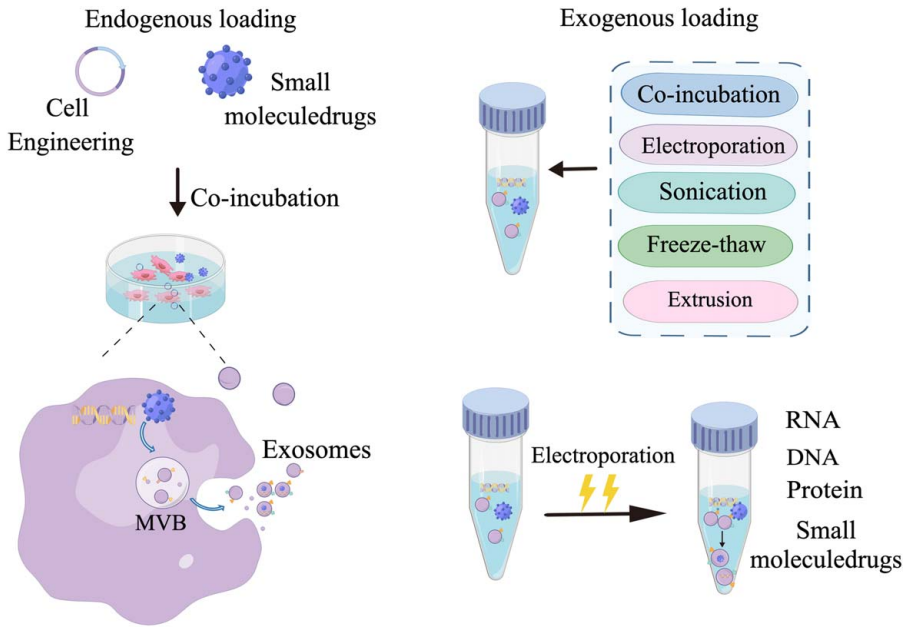

Figure 3. Loading methods for drug delivery using exosomes. MVB, multivesicular body. Image created by Figdraw.

mTOR signalling pathways, thereby alleviating MI after ischaemia/reperfusion[34]. Furthermore, exosomes derived from various types of stem cells have been shown to exert protective effects on myocardial cells after ischaemia. Exosomes derived from human adipose-derived stem cells (ADSCs) can protect myocardial cells against oxidative stress and decrease apoptosis in them[35]. In addition, exosomes derived from induced pluripotent stem cells (iPSCs) can deliver cardioprotective miRNAs, such as miR-21 and miR-210, to inhibit apoptosis in ischaemic myocardial cells[36].

Promote angiogenesis

Angiogenesis is an important process in cardiac repair after injury. MSCs-exo have the potential to enhance neovascularization after myocardial infarction and facilitate recovery of cardiac function[37,38]. *In vitro*, MSCs-exo can be taken up and internalized by human umbilical vein endothelial cells (HUVECs) in a dose-dependent manner, thereby promoting their proliferation, migration, and angiogenesis. In an acute myocardial infarction rat model, intramyocardial injection of MSCs-exo significantly promoted blood flow restoration, reduced the size of the infarct, preserved cardiac contractile and diastolic function mainly by promoting angiogenesis to protect the heart tissue from ischaemic injury[39]. In-vitro cell experiments have shown that MSCs-exo under ischaemic conditions are rich in key factors promoting angiogenesis, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and fibroblast growth factor (FGF)[40]. Another study suggested that the pro-angiogenic effect of MSCs-exo is mainly mediated by extracellular matrix metalloproteinase inducer within the exosome[41]. Further exploration is needed to determine which substances in MSCs-exo promote angiogenesis.

Reduce myocardial fibrosis

Due to the limited ability of myocardial regeneration, ischaemia, hypoxia, and inflammatory stimuli cause fibroblasts to compensate by producing a large amount of collagen fibres after injury, leading to scar tissue formation that plays a dominate role in the healing response to cardiac injury[42]. In adult mammalian hearts, the endogenous repair mechanism after MI relies more on the supplementation of cardiac progenitor cells than on the proliferation of resident myocardial cells[43]. The inhibitory effects of exosomes on inflammation and fibrosis mainly reside in their unique miRNAs, which can be taken up and internalized by macrophages, fibroblasts, and myocardial cells. Reprogramming of fibroblasts through these specific miRNAs fundamentally changes their phenotype by inhibiting the TGF-b pathway, increasing collagen degradation via matrix metalloproteinases, reducing collagen production, and thereby decreasing scar content[44].

Although exosomes possess favourable biological properties for MI repair and treatment of other diseases, their therapeutic efficacy remains limited[3,10]. A large body of research indicates that the inherent properties of exosomes make them an ideal DDS for nucleic acid, protein and small molecule drugs, thereby improving therapeutic efficacy against diseases[12].

Exosome-based drug delivery system

Advantages of using exosomes as carriers

Exosomes exhibit several advantages over other nanoparticle systems. (1) Limited immunogenicity and cellular toxicity[45]. Currently, liposomes are the main method for delivering nucleic acid and small molecule drugs. However, they often induce toxic immune reactions *in vivo* and mainly accumulate in the liver, resulting in suboptimal therapeutic effects. In contrast, exosomes are derived from organisms themselves and have high biological compatibility, making them less susceptible to immune clearance[46]. (2) Circulatory stability. Exosomes are synthesized endogenously by biology, which ensures their high stability *in vivo*[47]. However, some reports have shown that the half-life of exosomes is only 2–20 min, which is much shorter than that of liposomes[48,49]. Surface modification can enhance the stability of exosomes[46,50,51]. (3) Cell-specific targeting. The properties of exosomes vary depending on the cells that produce them and the conditions under which they are produced. Exosomes from different cell sources may also be found in specific tissues. For instance, exosomes derived from hypoxic tumour cells are often taken up by other hypoxic tumour cells[52], and those derived from the central nervous system can cross the blood-brain barrier, serving as a unique delivery system for specific groups of neurons[53]. As a result, exosomes are considered targeted carriers with minimal side effects and maximum drug activity, which has generated great interest in the field of drug delivery.

Exosome loading strategies for drug delivery

Loading therapeutic drugs into exosomes can further enhance their therapeutic value. However, one of the biggest challenges in this field is the efficiently loading therapeutic drugs. Currently, various methods have been developed for loading exosomes, but they mainly fall into two categories. One method involves directly modifying purified exosomes[54]. Co-culturing therapeutic drugs with the source cells of exosomes enables the naturally secreted vesicles to the incorporation of these drugs[55]. For example, when MSCs or tumour cells are co-cultured with chemotherapeutic drugs such as paclitaxel or 5-fluorouracil, they can package and release these substances into their exosomes, which gives the drug-loaded exosomes the ability to inhibit tumours[56]. The other method involves modifying the parent cells of exosomes to secrete specific molecules into the vesicles, and it is primarily used for gene therapy[57]. Shtam *et al.*[58] successfully loaded siRNA into exosomes derived from HeLa cells using this method, and they also loaded miR-130b into exosomes derived from Hela-229 cells using the same method.

Loading therapeutic drugs directly into purified exosomes has become a more prevalent strategy due to the low efficiency of drug loading during exosome formation[59]. The simplest method is to co-culture purified exosomes with therapeutic molecules, such as loading paclitaxel into exosomes derived from prostate cancer cells for the treatment of prostate cancer[60]. In order to enhance loading efficiency, active loading strategies such as electroporation have been developed. Electroporation applies voltage pulses to create transient pores in the lipid bilayer membrane of exosomes, facilitating the transport of target molecules across the vesicle membrane[61]. Tian *et al.*[62] utilized electroporation to load doxorubicin into exosomes for cancer treatment. Additionally, this technique can be used to load siRNA. For example, siRNA

targeting β-secretase 1 or mRNA targeting α-Syn can be loaded into dendritic cell-derived exosomes (DC-exo) to treat Alzheimer's disease (AD) and Parkinson's disease (PD) in mice, respectively[63]. It has been demonstrated that electroporation can preserve the integrity and function of extracellular vesicles.

There are other loading strategies, such as detergent permeabilization, repeated freeze-thaw cycles, sonication, and extrusion. These methods have varying levels of loading efficiency. Sonication, extrusion, and detergent permeabilization are the methods that exhibit higher loading efficiencies[64]. Each loading method has its own advantages and disadvantages, and the choice of loading method is usually determined by the therapeutic component that needs to be loaded[65]. These active loading strategies can preserve the integrity of exosomes while enhancing their therapeutic effectiveness[66]. The drug delivery strategies of exosomes is illustrated in Fig. 3.

Types of drugs loaded into exosomes

Exosomes can serve as carriers for various types of drugs, including nucleic acids (siRNA and miRNA), proteins, and small molecule drugs[67].

Small molecule drugs

Exosomes-based DDS can overcome biological barriers, particularly the blood-brain barrier, to treat various brain diseases such as glioblastoma, autoimmune encephalomyelitis, and other central nervous system diseases[68]. By utilizing exosomes secreted by M2 macrophages and loading berberine into the vesicles using ultrasound, researchers were able to overcome the blood-brain barrier and effectively target the injured spinal cord, thereby exerting a therapeutic effect[69]. Furthermore, extensive research has been conducted on the use of exosomes loaded with chemotherapy drugs for tumour treatment. Wei *et al.*[70] loaded doxorubicin into MSCs-exo for the treatment of osteosarcoma and found that it not only inhibited tumour growth but also effectively reduced doxorubicin-induced cardiotoxicity. Loading paclitaxel into tumour-derived exosomes enables targeted uptake by tumour cells through endocytosis, followed by release into the cytoplasm and induction of cell death[60].

Protein

There are two ways to transfer proteins through exosomes. One is to directly package proteins into exosomes for delivery, which currently serves as the primary method of protein transportation. Cheng *et al.*[71] efficiently encapsulated protein molecules in biomimetic metal-organic coordination polymer nanoparticles through aqueous self-assembly, and further wrapped them with a layer of homologous tumour-derived exosome membrane to construct a biomimetic nanocarrier that achieves immune escape, tumour targeting, and intracellular transport of the protein for inhibiting tumour growth. Datta *et al.*[72] combined a pH-sensitive membrane fusion peptide (GALA) with cationic liposomes and exosomes, which successfully induce cell toxicity.

Another method involves packaging the genetic material that expresses the protein into exosomes, which release the genetic material upon reaching recipient cells and subsequently produce the corresponding protein in those cells. Various active loading methods can be used to internalize hydrogen peroxide into exosomes, which can exert neuroprotective effects in a PD model[64]. What we want to introduce here are macrophages transfected with the plasmid encoding the hydrogen peroxide enzyme, which can produce exosomes carrying the necessary genetic material for generating the hydrogen peroxide enzyme. This genetic material can be internalized by neurons via exosomes and exert antioxidant effects[73]. Zhang *et al.* induced MSCs with IFN-γ and used the secreted exosomes to treat myocardial infarction in mice, resulting in reduced fibrosis, decreased cardiac cell apoptosis, and improved heart function[74].

Nucleic acid

Extracellular vesicles, which can carry nucleic acids and participate in intercellular communication, have attracted the interest of many researchers. Currently, research on gene-loaded drugs carried by exosomes is more common, mainly using exosomes loaded with siRNA, miRNA, and mRNA for gene therapy. Exosomes carry different types of nucleic acids depending on the specific needs for treating diseases. In Kamerkar and colleagues' study, genetically modified exosomes were able to specifically target pancreatic cancer cells and deliver siRNA. Furthermore, the presence of CD47 on the surface of exosomes enables them to evade phagocytosis by circulating monocytes, resulting in effective treatment of pancreatic cancer in mice and increased overall survival rate[46]. Munoz *et al.*[75] developed exosomes containing anti-miR-9 to facilitate their transmission to resistant glioblastoma cells, thereby blocking miR-9 in the cells and increasing their sensitivity to temozolomide, thus improving treatment efficacy. Effective delivery of miR-132 may offer hope for ischaemic diseases. Ma *et al.*[76] used electroporation to load MSCs-exo with miR-132, which regulated endothelial cell behaviour in the process of angiogenesis and significantly promoted the generation of blood vessels around myocardial infarction in mice, resulting in a significant increase in left ventricular ejection fraction.

Exosomes as drug carriers in MI application

Considering the biological functions of exosomes in MI repair and the inherent advantages of utilizing exosomes as DDS, it is suggested that delivering drugs through exosomes can enhance their reparative effect on injured myocardium.

Targeting specificity

Exosomes have many surface proteins that are similar to those of the donor cells, which suggests they may have specific targeting abilities towards their donor cells[77]. However, studies have shown that targeted exosomes need to compete with natural exosomes in body fluids, accumulate in the liver and spleen like most ordinary liposomes, and are ultimately cleared by macrophages in these organs[78,79]. Therefore, effective methods are needed to further enhance the targeting ability of exosomes in order to deliver them to target tissues. Nakase *et al.*[80] modified exosomes with arginine-rich cell-penetrating peptides to actively induce macropinocytosis and enhance cellular uptake of the exosomes. Vandergriff *et al.*[81] targeted myocardial infarction tissue by inserting a cardiac homing peptide into the exosomes membrane, resulting in reduced fibrosis and scar size, as well as increased cell proliferation and angiogenesis. Hu *et al.*[82] hybridized exosomes with platelet membranes to enhance their targeting ability towards injured hearts and reduce macrophage

uptake, resulting in increased therapeutic efficacy against myocardial infarction damage.

Cycle time

The delivery of drugs via exosomes can harness the reparative effects of both the exosomes and drugs on damaged myocardium, resulting in superior therapeutic outcomes compared to their individual use. However, injected exosomes may be rapidly eliminated by the body[44]. To prevent rapid elimination, exosomes are encapsulated in functional hydrogels and injected into the border zone of rat myocardial infarction. The results indicate that functional hydrogel encapsulation prolongs the retention time of exosome, reduces cell apoptosis, inflammation, and fibrosis, and improved heart function[83]. ISLET-1 promotes angiogenesis. Hu *et al.*[84] utilize genetically engineered exosomes containing ISLET-1 and combine them with vasculogenic peptide-1 hydrogel, thus increasing the circulation time of exosomes and significantly improves the survival of endothelial cells as well as angiogenesis, thereby promoting myocardial repair. Cheng and colleagues embedded MSCs-exo in a hyaluronic acid hydrogel to create an injectable gel, which was injected into the pericardium of mice with heart failure. This hydrogel prolongs the circulation time of exosome, reduces the size of left ventricular, and prevents thickening of the left ventricular wall[85].

Drug delivery

Various cardiac patches have been used to repair myocardial infarction-induced damage, but their delivery often requires invasive surgery, which limits their clinical applition. The effective utilization of fibrous protein-sealed exosomes enhances cardiac function, reduces infarct size, increases left ventricular wall thickness and smooth muscle generation, and preserves surviving cardiac tissue in the at-risk area[86]. Yao and colleagues used mesoporous silica nanoparticles to load miRNA, which were then encapsulated in exosomes. This nanocomposite exhibited a high capacity for loading miRNA, protected it from degradation in body fluids, evaded immune system clearance, targeted ischaemia-injured cardiac cells, inhibited translation of apoptosis-related proteins, and promoted proliferation of cardiac cells[87].

Exosomes not only deliver miRNAs to repair damaged hearts, but also include various natural compounds, transcription factors, cytokines, and many other substances. Curcumin is a natural compound that has anti-inflammatory and anti-fibrotic effects[88,89]. Mixing curcumin with exosomes can improve its water solubility and stability, prevent curcumin degradation, and enhance its bioavailability by facilitating self-assembly into the lipid bilayer of the exosomes. Treatment of lipopolysaccharide-induced septic shock mice with these curcumin-loaded exosomes can effectively deliver curcumin to inflammatory cells, significantly reduce inflammation levels, and promote recovery of the damaged heart[90].

Conclusion

Exosomes have important implications in drug delivery. These endogenous vesicles have advantages such as low immunogenicity and inherent cell targeting, which make them a promising next-generation nanomaterial with enormous potential in the biomedical field. This paper mainly introduces the role of exosomes in cardiac protection, both as a protective agent themselves and as a delivery vehicle for other cardioprotective agents. Exosomes have more advantages compared to stem cell therapy, which may benefit us through cell-free therapy. Although some achievements have been made, research on exosomes is still in its early stage, and there are many problems to be solved, such as the lack of standardized isolation and purification processes. As a result, exosomes may exhibit slight variations in size, surface proteins, and composition of their enveloped bodies[15]. In addition, the majority of exosomes reported for heart disease treatment are administered via direct injection into either the myocardium or pericardial cavity, which presents a level of invasiveness that is unsuitable for clinical application. To achieve the therapeutic effect of venous injection of exosomes for heart disease, it is necessary to enhance the cardiac targeting and prolong the retention time of exosomes[91–93]. Furthermore, the drug loading capacity of exosomes as drug carriers is limited[94]. Without overcoming these problems, the utilization of exosomes as delivery vehicles for MI treatment in clinical practice will not be feasible. We hope that this review will help to understand the research on exosomes in the field of MI repair and anticipate further improvements in therapeutic efficacy, as well as facilitate its clinical application.

Ethical approval

This article does not involve patients and therefore does not require ethical approval.

Consent

This article does not involve patients and therefore does not require ethical approval.

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Author contribution

Study concept or design: J.L., R.J., Y.H. Data collection and analysis: J.L., P.C., A.L., C.X. Writing the paper: J.L.,Y.Hou.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

We confirm that any datasets generated during and/or analyzed during the current study are publicly available.

Provenance and peer review

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