Biomimetic nanomaterials in myocardial infarction treatment: Harnessing bionic strategies for advanced therapeutics

Tingting Yu [a,b,1], Qiaxin Xu [a,b,1], Xu Chen [c,1], Xiujiao Deng [a,b], Nenghua Chen [a,b], Man Teng Kou [a,b], Yanyu Huang [f], Jun Guo [b,d,**], Zeyu Xiao [b,e,*], Jinghao Wang [a,b,***]

[a] Department of Pharmacy, The First Affiliated Hospital of Jinan University, Guangzhou, 510630, China
[b] The Guangzhou Key Laboratory of Basic and Translational Research on Chronic Diseases, Jinan University, Guangzhou, 510630, China
[c] Department of Clinical Pharmacy, Daqing Oilfield General Hospital, Daqing, 163000, China
[d] Department of Cardiology, The First Affiliated Hospital of Jinan University, Guangzhou, 510630, China
[e] The Guangzhou Key Laboratory of Molecular and Functional Imaging for Clinical Translation, Jinan University, Guangzhou, 510630, China
[f] Department of Biochemistry and Molecular Medicine, University of California Davis, Sacramento, CA, 95817, USA

ARTICLE INFO

ABSTRACT

Myocardial infarction (MI) and its associated poor prognosis pose significant risks to human health. Nano-materials hold great potential for the treatment of MI due to their targeted and controlled release properties, particularly biomimetic nanomaterials. The utilization of biomimetic strategies based on extracellular vesicles (EVs) and cell membranes will serve as the guiding principle for the development of nanomaterial therapy in the future. In this review, we present an overview of research progress on various exosomes derived from mesenchymal stem cells, cardiomyocytes, or induced pluripotent stem cells in the context of myocardial infarction (MI) therapy. These exosomes, utilized as cell-free therapies, have demonstrated the ability to enhance the efficacy of reducing the size of the infarcted area and preventing ischaemic reperfusion through mechanisms such as oxidative stress reduction, polarization modulation, fibrosis inhibition, and angiogenesis promotion. Moreover, EVs can exert cardioprotective effects by encapsulating therapeutic agents and can be engineered to specifically target the infarcted myocardium. Furthermore, we discuss the use of cell membranes derived from erythrocytes, stem cells, immune cells and platelets to encapsulate nanomaterials. This approach allows the nanomaterials to camouflage themselves as endogenous substances targeting the region affected by MI, thereby minimizing toxicity and improving biocompatibility. In conclusion, biomimetic nano-delivery systems hold promise as a potentially beneficial technology for MI treatment. This review serves as a valuable reference for the application of biomimetic nanomaterials in MI therapy and aims to expedite the translation of NPs-based MI therapeutic strategies into practical clinical applications.

1. Introduction

Cardiovascular diseases (CVD) encompass a group of hemorrhagic or ischemic conditions affecting the heart, brain and blood vessels of the body, posing a significant public health concern due to their escalating burden [1]. The World Health Organization reports that CVD is responsible for claiming the lives of approximately 18 million individuals annually [2]. Among CVD, myocardial infarction (MI) stands as the most prevalent and leading cause of global mortality [3]. Thus far,

numerous optimization strategies have been explored, with nano-materials emerging as a promising avenue for MI treatment [4]. Nano-materials can be serve as effective drug delivery systems (DDS), offering advantages in precise drug targeting and controlled release capabilities [5]. Additionally, nanomaterials possess the ability to incorporate multiple surface moieties, enabling selective therapeutic effects such as anti-inflammatory, anti-apoptotic and immunomodulatory actions [6].

In recent years, the application of synthetic conventional nano-materials, including liposomes, polymers and inorganic/metal

* Corresponding author. The Guangzhou Key Laboratory of Basic and Translational Research on Chronic Diseases, Jinan University, 510630, China.
** Corresponding author. The Guangzhou Key Laboratory of Basic and Translational Research on Chronic Diseases, Jinan University, 510630, China.
*** Corresponding author. The Guangzhou Key Laboratory of Basic and Translational Research on Chronic Diseases, Jinan University, 510630, China.
E-mail addresses: dr.guojun@163.com (J. Guo), zeyuxiao@jnu.edu.cn (Z. Xiao), wangjinghao@jnu.edu.cn (J. Wang).
[1] These authors should be considered joint first author.

Table 1
Summary of the biomimetic nanomaterials for the treatment of MI.

Category	Sources	Model	Administration route	Mechanism	Results	Ref.
Stem cells	hESC-MSCs derived EVs	Acute I/R mice	Tail vein injection	Not mentioned	Reduced the size of myocardial infarcts and improved repair of cardiac function	[7]
	hESC-MSCs derived EVs	Acute I/R mice	Tail vein injection	PI3K/Akt, inhibit c-JNK	Reduced the infarct size of I/R injured mice and reduced inflammatory response	[8]
	BM-MSCs derived EVs	MI rats	2 site injections in the injured region	Enhanced autophagy to AMPK/mTOR	Reduced the extent of infarction	[9]
	BM-MSCs derived EVs	Acute MI rats	4 site injections in the infarct margins	Enhanced the tube formation of HUVEC and inhibited T cell function	Improved blood flow to stimulate vascular neogenesis and reduced infarct size	[10]
	BM-MSCs, ADMSCs and UCBMSCs derived EVs	MI rats	5 site injections in the infarct margins	Increased levels of VEGF, bFGF and HGF	Promoted angiogenesis and inhibited the CMs apoptosis	[11]
	BM-MSCs derived EVs	Acute I/R mice	3 site injections in the infarct margins	Delivered miR-182 targeting TLR4	Regulated the polarization state of macrophages to reduce myocardial I/R injury	[12]
	Telomerase Anti transcriptase modification Immortalized MSCs derived EVs	MI rats	2 site injections in the infarct margins	Enriched miR-4732-3p to reduce scar tissue and fibrosis	Exerted cardioprotective effects under hypoxic conditions	[13]
	MSC with hypoxia in sEVs (HP-sEVs)	MI mice and Non-human primate (NHP)	Intramyocardial injection	Suppressed MMP19 cleavage signaling to VEGFA through miR-486-5p overexpression	Enhanced angiogenesis and promoted cardiac repair	[14]
	MSC with Atorvastatin pretreatment (MSC^{ATV}-EV)	MI rats	Intramyocardial injection	Generation of miR-139-3p that mediates macrophage polarization and upregulated long lncRNA H19	Improved cardiac function and increase the survival of CMs	[15]
	IONP-NVs	MI rats	4 site injections in the infarct margins	Improved the therapeutic efficacy by magnetic guidance	Reduced apoptosis and fibrosis	[16]
	CPCs derived EVs	Acute I/R mice	Intramyocardial injection	Inhibited caspase 3/7 activation	Protected CMs from oxidative stress and inhibited apoptosis	[17]
	CPCs derived EVs	MI rats	3 site injections in the infarct margins	Enriched miR-210, miR-132 and miR-146a-3p to down-regulated specific targets	Inhibited apoptosis in CMs while promoting angiogenesis to increase left ventricular ejection fraction	[18]
	CDCs derived EVs	MI mice	2 site injections in the infarct margins	Promoted tubular formation of HUVEC due to the enrichment of miR-146a	Inhibited apoptosis and promoted angiogenesis	[19]
	CDCs derived EVs	Acute I/R rat and pig model	Intramyocardial injection	Transferred miR-181b from extracellular to macrophages and regulated macrophage polarization	Exerted cardioprotective effects	[20]
	Mouse ESC derived exosomes (mES Ex)	MI mice	2 site injections in the infarct margins	Delivered microRNA-290 family	Reduced cardiac fibrosis by improving CMs survival and angiogenesis	[21]
	iPSC derived EVs	Acute I/R mice	Intramyocardial injection	Not mentioned	Prevented left ventricular from remodeling and hypertrophy and interstitial fibrosis	[22]
	hiPSC-CMs, hiPSC-ECs and hiPSC-SMC derived EVs	MI swine	5 site injections in the infarct margins	Promoted EC tube formation and microvessel sprouting, maintaining intracellular calcium homeostasis, and increasing ATP	Protected hiPSC-CMs by reducing apoptosis	[23]
	Shh-modified CD34$^+$ HSCs derived exosomes	MI mice	2 site injections in the infarct margins	Modified Shh protein	Prevented AMI-related ventricular dilation and improved cardiac function	[24]
Cardiac Cells	EPCs derived EVs	MI mice	3 site injections in the infarct margins	The ability of IL-10 to reduce the enrichment of ILK in CMs	Improves cardiac function and reduces scar area	[25]
	CTs derived EVs	MI mice	3 site injections in the infarct margins	Containing miRNA-21-5p can target and silence the Cdip1 gene	Inhibited apoptosis in cardiac microvascular ECs	[26]
Other cells	DEX derived EVs	MI mice	5 site injections in the infarct margins	Upregulating miR-494-3p to promote tubular formation	Improved cardiac function	[27]
	M2 macrophage-derived EVs	MI mice	Tail vein injection	Carrying miR-1271-5p to down-regulate SOX6 expression	Protected CMs from hypoxia-induced apoptosis	[28]
Platelets membrame	PNV-CSCs	MI rats and porcine	Intracoronary injection	Increased CSCs retention	Reduced infarct size	[29]
	CsA@PPTK	MI mice	Tail vein injection	Scavenged ROS and regulated the protein expression of MMP-9 as well as Cx43	Reversed left ventricular remodeling and improved cardiac function	[30]
	PINCs	I/R mice	Intravenous injection	Combined PGE2-modified platelet membranes and factors secreted by cardiac stromal cells target damaged hearts	Achieved targeting of I/R-injured myocardium and participated in myocardial tissue repair and pro-angiogenesis	[31]
Macrophage membrane	MMNPs loaded with miR-199a-3p	MI mice	Tail vein injection	Binding to IL-1β, IL-6 and TNF-α inflammatory factors and their receptors	Improved left ventricular remodeling and protected the heart by inhibiting inflammatory responses and myocardial fibrosis	[32]

Table 1 (*continued*)

Category	Sources	Model	Administration route	Mechanism	Results	Ref.
Neutrophil membrane	NM-NPIL-5	MI mice	Intravenous injection	Promoted post-MI EOS accumulation and angiogenesis	Protected CMs from excessive inflammation-induced apoptosis, thereby inhibiting unfavorable cardiac remodeling	[33]
Monocyte membrane	Monocyte mimics through membrane fusion	MI/RI mice	Intravenous injection	By imitating the interaction between adhesion molecules on monocyte mimics and endothelium after MI	Enhanced targeting efficiency to injured myocardium	[34]
Stem cell membrane	nanocomposite for stem cell membrane camouflage	MI mice	Tail vein injection	Achieved targeted delivery of miRNA and inhibited the translation of apoptosis-related proteins	Promoted CMs proliferation	[35]

nanoparticles (NPs), has demonstrated success in the treatment of CVD [54,55]. However, it should be noted that synthetic NPs have limitations in replicating the full functionality of biological systems and encounter challenges in terms of biocompatibility and biosafety [56]. For example, polyethylene glycol (PEG) has been widely employed as a surface modification for nano-delivery systems because of its advantage of evading immune recognition and clearance [57]. However, it has been also reported that the immune system response to polymers lead to the production of anti-PEG antibodies in vivo, potentially leading to toxic effects or compromising long-term efficacy [58,59]. In addition, traditional passive and active targeting approaches using NPs also face several obstacles in the treatment of MI, such as off-targeting effects arising from biomarker expression in normal tissue or reduced binding because of limited ligand modifications [60,61].

In recent years, an increasing number of researchers have embraced bionic strategies as a guiding principle for the design of next-generation nanoplatforms [62]. The utilization of bionics-based DDS holds significant promise for the treatment of MI due to their notable biocompatibility, immunogenicity, and low toxicity [63]. Biomimetic nanomaterials primarily consist of bionic substances and nanomaterials. The biomimetic substances encompass cells, cellular components (such as cell membranes, lipoproteins, etc.) as well as exosomes [64]. Among these, biomimetic strategies based on cell membranes and extracellular vesicles (EVs) are particularly prevalent in biomimetic approaches [65]. Nanomaterials derived from biomimetic strategies can act as natural carriers, resembling EVs, or cell membranes in living organisms. These materials can be further combined with synthetic NPs to develop nanoparticles encapsulated within cell membranes. This approach enables the drug carrier to mimic endogenous substances, allowing it to directly evade the immune system in the body [66].

EVs have demonstrated their role as significant mediators of cardioprotection by facilitating intercellular signaling. Various types of stem cell-derived EVs and cardiac cell-derived EVs have been shown to reduce myocardial infarct zones through diverse mechanisms [67]. Moreover, stem cell-derived EVs exhibit favorable characteristics as vehicles for delivering therapeutic drugs and nucleic acids to the heart [68]. To enhance bioavailability and improve cardioprotective efficacy, cardiac homing or targeting peptides can be engineered onto the EVs, allowing for specific targeting to the ischemic heart. Notably, some researchers have outlined distinct strategies for engineering EVs and their application in CVD [69], while others have focused on the isolation of EVs and their diagnostic applications in MI [70]. In addition, the development of biofilm-coated NPs as biomimetic delivery systems, which combine various cell membrane characteristics through engineering strategies, has garnered attention in the field of disease treatment [71,72]. Consequently, this review aims to provide an overview of
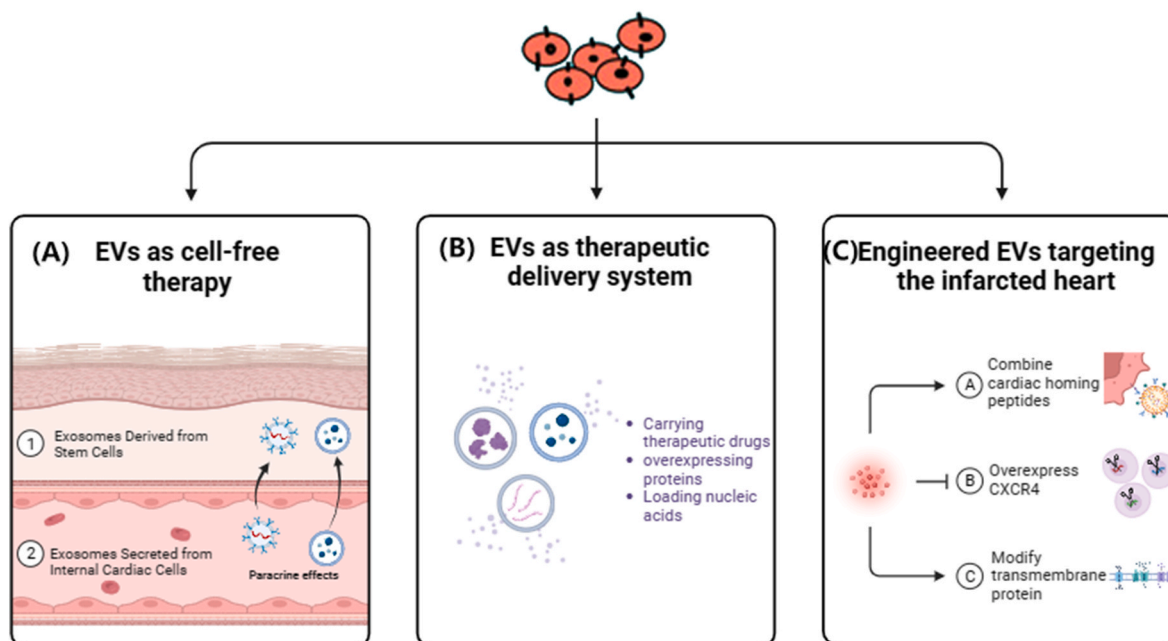

Fig. 1. Main ideas for treating MI with EVs. (A) As cell-free treatment strategy. (B) As good delivery vehicles for therapeutics. (C) Engineering EVs to target the heart. Created with BioRender.com.
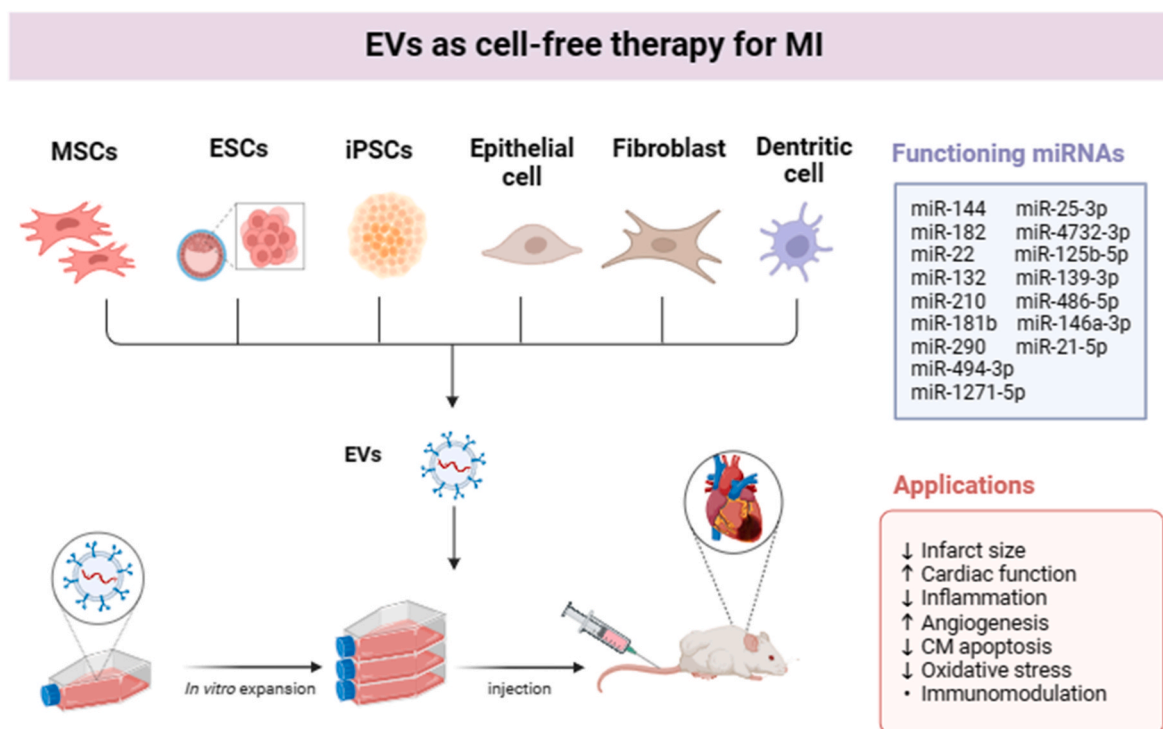
Fig. 2. Overview diagram of EVs as cell-free therapy for MI. Created with BioRender.com.

the latest advancements in bionanomaterials for therapeutic MI, with a particular focus on the application of cell membrane and extracellular vesicle-based bionanocarriers in myocardial infarction therapy. The following two aspects will dicuss two main aspects: (1) endogenous bionanomaterials, specifically cell-derived extracellular vesicles that act as direct therapeutic agents by mediating signal transduction through paracrine action or can be artificially modified and loaded with therapeutic agents to serve as carriers or target directly damaged myocardium; (2) biomimetic nanodrug delivery systems prepared using cell membranes, which encapsulate the therapeutic agents or nanoparticles, and are designed to mimic endogenous substances for targeted to the damaged myocardium (see Table 1).

2. Cell-derived extracellular vehicles

In recent years, extracellular vehicles (EVs), which were once considered as cellular fragments, are receiving increasing attention as new mediators of intercellular signaling. EVs are naturally occurring vesicles with a lipid bilayer structure secreted by cells, released by most cell types and found in body fluids including blood, urine and saliva [73]. They are classified according to biogenesis and molecular size into exosomes (30–100 nm), microvesicles (100–1000 nm) and apoptotic vesicles (>800 nm), but there is no strict consensus on the exact cut-off point for these classfications [74]. Of particularly interest are exosomes, which are enriched with biomolecules such as proteins, nucleic acids and lipids, especially miRNAs [75]. The presence of numerous key proteins and miRNAs within EVs derived from cardiac tissue has been closely linked to the development of MI [67]. Additionally, some surface proteins have been identified that are exclusive to certain cell types [76, 77]. CMs can readily utilize exosomes to transport the above-mentioned bioactive molecules to regulate the function of neighboring cells. In particular, they can be released into body fluids where they play a vital role in facilitating intercellular communication between proximal and distal cells [78]. Studies have also shown that exosomes released from cardiac tissue exhibit targeted properties, allowing for targeted therapy delivery to the infarcted area by leveraging the differences in type,

quantity and functionality of exosomes produced by infarcted and normal myocardium [79].

EVs, particularly exosomes, have garnered significant interest as potential cardioprotective mediators following MI [80]. They have emerged as promising candidates for cell-free strategies for the treatment of CVD or as good carriers for the delivery of therapeutics [81]. This is attributed to their advantageous characteristics, such as high cargo capacity, low immunogenicity, good biocompatibility and ability to traverse biological barriers. As a result, the primary concepts driving the utilization of EVs for promoting myocardial repair include: (1) the direct use of endocardial or stem cell-derived EVs as therapeutic agents; (2) employing EVs as DDS by loading exogenous bioactive molecules, including drugs; and (3) engineered modifications to facilitate targeted delivery to the heart. The main ideas is as shown in Fig. 1.

2.1. EVs as cell-free therapy for MI

2.1.1. Exosomes derived from stem cells

Although stem cell therapy for the treatment of AMI shows promise, current research is shifting focus towards investigating the paracrine effects mediated by exosomes secreted from stem cells. In recent years, compelling evidence has emerged indicating that exosome derived from ESCs, CPCs and MSCs have the ability to induce CMs proliferation, promote angiogenesis, reduce apoptosis and inhibit fibrosis for myocardial protection [82] (see Fig. 2).

Amongst the various stem cell types used in post-MI cell therapy, mesenchymal stromal cells (MSCs) have gained attention due to their cardioprotective effects mediated by their secretion [83]. In 2010, Lai et al. provided the first demonstration that MSC-derived EVs could reduce myocardial infarct sizes after 24 h in acute I/R mice model, confirming the improved repair effect of exosomes on cardiac function [7]. Furthermore, an early meta-analysis supported the beneficial effect of MSC-derived exosomes in improving cardiac function in I/R injury [84].

The improvement in CMs survival mediated by MSC-derived EVs is primarily attributed to the regulation of autophagy, activation of the
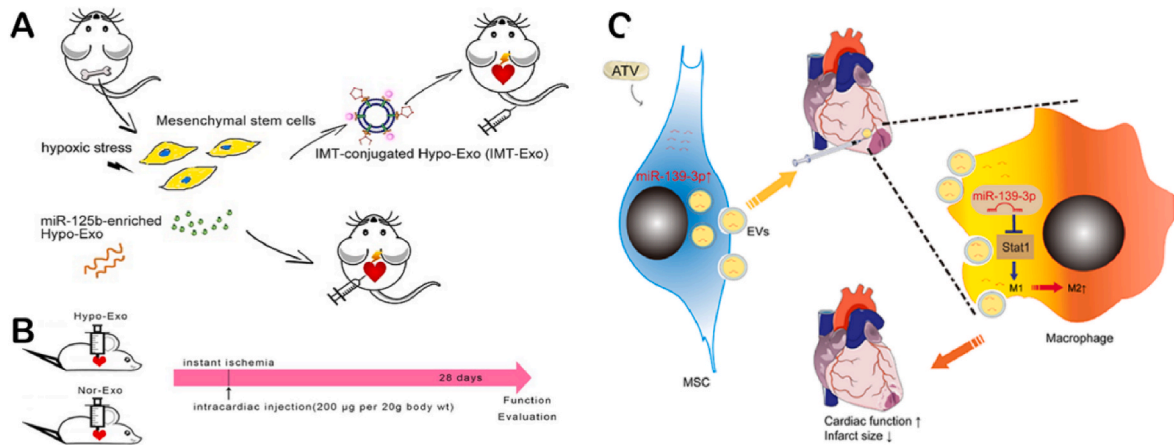
Fig. 3. MSC-derived EVs for the treatment of MI. (A) Schematic diagram of Hypoxia-elicited MSC-derived EVs (Hypo-Exo) mediated miR-125b for cardiac repair. (B) Enhanced cardiac function post-MI mice model transplanted with Hypo-Exo. Reproduced with permission [92]. Copyright 2018, Ivyspring Inernational Publisher. (C) EVs derived from MSCs pretreated with atorvastatin (MSC^ATV-EV) regulated macrophage polarization and promoted cardiac repair via targeting microRNA-139-3p/Stat1 pathway. Reproduced with permission [15]. Copyright 2023, Ning, Y et al.

phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, and inhibition of c-Jun N-terminal kinase (c-JNK). In-vivo experiments by Arslan et al. validated the above mechanism, with exosome reducing the infarct size of I/R-injured mice by 45 % and significantly reducing the local and systemic inflammatory response compared to saline treatment [8]. Exosomes derived from MSCs exert a protective effect on cell damage through the delivery of specific miR-NAs. For instance, miR-144 delivered by exosomes regulates the PI3K/AKT pathway, reducing apoptosis in CMs. It was shown that miR-144 mimics prevented apoptosis in cardiomyocytes under hypoxic conditions, while its inhibitors had the opposite effect [85]. Similarly, miR-25-3p present in MSC-derived exosomes directly targets pro-apoptotic proteins and EZH2, thereby exerting a cardioprotective effect [86]. Liu et al. conducted experiments in rats wherein exosomes generated from MSCs were injected into areas of myocardial infarction (MI). It was found that these exosomes enhanced autophagy through the AMPK/mTOR and Akt/mTOR pathways, ultimately reducing the extent of infarction and improve cardiac function [9].

Exosomes could enhance angiogenesis by activating the vascular endothelial growth factor receptor (VEGFR2) to promote the proliferation of human umbilical vein endothelial cells (HUVECs) [87]. Teng et al. found that MSC-derived exosomes exert an anti-inflammatory role by improving MI microenvironment, stimulating vascular neogenesis and inhibiting T cell function, thus improving the blood flow of MI rats [10]. This pro-angiogenic effect is mainly mediated through the release of the extracellular matrix metalloproteinase inducer (EMMPRIN) contained within the exosomes [88]. Platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) signaling are also key mediators in the induction of angiogenesis. In comparison, Xu et al. observed that exosomes derived from adipose tissue mesenchymal stem cells (ADMSCs), bone marrow mesenchymal stem cells (BMMSCs) and umbilical cord blood mesenchymal stem cells (UCBMSCs) were all able to promote angiogenesis at the infarct site by increasing levels of rat VEGF, basic fibroblast growth factor and other factors associated with promoting angiogenesis at the heart attack site [11].

EVs can also modulate the inflammatory response by influencing immune cell polarization and reducing monocyte recruitment, thereby leading to a decrease in the secretion of pro-inflammatory cytokines [89]. Zhao et al. found that MSC-derived EVs regulated the polarization state of macrophages by delivering miR-182, which targeted Toll-like receptor 4 (TLR4). This modulation resulted in a reduction of myocardial I/R injury in mice [12]. In addition, EVs derived from MSCs have been shown to inhibit fibroblast (FBs) proliferation by inhibiting transforming growth factor (TGF-β), thereby reducing fibrosis and

inhibiting adverse ventricular remodeling [90]. For example, miR-4732-3p, enriched in MSC-EVs, has been found to protect the heart under hypoxic conditions by reducing scar tissue and fibrosis in areas of MI [13].

By treating MSC with stimulants such as hypoxia, we can obtain EVs containing nucleic acids that promote myocardial repair. The anti-apoptotic effect of miR-22 is achieved through its direct targeting of methyl CpG-binding protein 2 (Mecp2). The delivery of miR-22-enriched exosomes obtained after ischemic preconditioning (Exo(IPC)) has been shown to reduce cardiac fibrosis [91]. There is also miR-125b-5p which attenuates the expression of pro-apoptotic genes in CMs (Fig. 3A and B) and miR-210 that increases the expression of neutral sphingomyelinase 2 (nSMase2) to mediate cardioprotective effects [92, 93]. Li et al. observed that pretreatment of MSC with hypoxia-preconditioned (HP) mesenchymal stem cells (HP-sEVs) resulted in upregulation of miR-486-5p expression, while overexpression of miR-486-5p inhibited MMP19 cleavage signaling to VEGFA [14]. Thus, in a non-human primate (NHP) model of MI, HP-sEVs safely and effectively enhanced angiogenesis and promoted cardiac repair. Similarly, treatment with atorvastatin (ATV) resulted in bone marrow mesenchymal stem cell-derived extracellular vesicles (MSC^ATV-EV) that improved cardiac function and reduced infarct size by producing miR-139-3p (Fig. 3C) [15]. MiR-139-3p is a heart repair factor that mediates macrophage polarization. Thus, MSC^ATV-EV significantly decreased the expression of M1 markers and upregulated the expression of M2 markers in macrophages. In addition, MSC^ATV-EV has also been shown to promote endothelial cell function and enhance the survival of CMs through the upregulation of long chain non-coding RNA (lncRNA H19) in MSCs [94].

The combination of magnetic nanoparticles and custom magnets have been shown to significantly enhance cardiomyocyte implantation. Li et al. utilized iron oxide nanoparticles (IONPs) in conjunction with MSCs (IONP-MSCs) to obtain IONPs-containing exosome-mimicking extracellular nanovesicles (IONP-NVs) [16]. Through magnetic guidance, the injection of IONP-NVs into the infarcted heart to reduce apoptosis and fibrosis and improved the therapeutic efficacy of MSC-derived exosomes.

Cardiac progenitor cells(CPCs), being the stem cells specific to the heart, offer potential advantages for cardiac cell therapy through their derived EVs. The increased expression of pregnancy-associated plasma protein A (PAPP-A) in CPC-derived exosomes contributes to their enhanced cardioprotective effects, as PAPP-A promotes the release of IGF-1 with immunomodulatory properties [95]. Cheng et al. were the first to show that CPC-derived exosomes isolated from mouse hearts

protected CMs from oxidative stress and inhibiting apoptosis in an acute mouse I/R model [17]. Subsequent studies have further investigated the underlying mechanism, mainly primarily focusing on microRNAs enriched in CPC-secreted EVs. Notably, miR-210, miR-132 and miR-146a-3p have been found to down-regulated their specific targets to inhibit apoptosis of CMs while promoting angiogenesis [18]. Furthermore, injection of these EVs into the peri-infarct zone of the rat AMI model 60 min after ligation validated the above mechanism and increased left ventricular ejection fraction. Hypoxia-treated CPC exosomes and EVs released from human embryonic stem cell-derived cardiovascular progenitor cells (hESC-Pg) have both shown improvement in heart function [96,97]. Similarly, MSC-derived exosomes pretreated with CPCs can also promote its survival and proliferation [98]. These examples all provide new insights into the potential use of cardiac-derived stem or progenitor cell-derived EVs to treat MI.

Cardiosphere-derived cells (CDCs) are a type of precursor cell found in the heart that can be obtained through cardiac biopsy specimens. The CADUCEUS Phase 1 and ALLSTAR Phase 2 clinical trials of CDCs demonstrated the safety of intracoronary administration of allogeneic CDCs and their efficacy in reducing infarct size in patients who have experienced a MI [99,100]. In experiments conducted on mice with induced heart injuries, it was observed that injecting CDC-derived exosomes into the infarcted region inhibited apoptosis and stimulated the growth of human umbilic vein endothelial cells (HUVEC), thereby promoting angiogenesis and protecting cardiac function [101]. These benefits effects of CDC exosomes appear to be primarily attributed to the presence of miR-146a, which is associated with the down-regulation of interleukin 1 receptor-associated kinase 1 (IRAK1) and tumour necrosis factor receptor-associated factor 6 (TRAF6), and also inhibits oxidative stress through the downregulation of NADPH oxidase 4 (NOX-4) [19]. Exosomes produced by CDC can also improve cardiac function by regulating macrophage polarization [20]. Couto et al. found that CDCs transferred miR-181b from extracellular to macrophages, influencing their polarization and ultimately exerting a cardioprotective effect when exosomes were injected intramyocardially into the infarcted region in a rat and pig AMI model [20]. It has also been suggested that the cardioprotective effect of CDCs-derived EVs may be related to the Y RNA fragment, which regulates the expression and secretion of IL-10 [102].

Embryonic stem cells (ESCs) are a type of pluripotent cell that originates from the inner cell mass of the blastocyst. These cells have the remarkable ability to continuously self-renew and differentiate into various cell types. When considering their application, it has been observed that EVs derived from ESCs carry a lower risk of embryonic tumors compared to the application of intact ESCs [103]. Limited research findings suggested that mouse ESC-derived exosomes (mES Ex) reduced cardiac fibrosis by improving CMs survival and angiogenesis. Additionally, these mES Ex have been shown to enhance the survival and proliferation of CPCs in vivo [21]. These beneficial effects are mainly achieved through the delivery of the microRNA-290 family. However, ethical considerations surrounding the use of embryonic stem cells have limited further exploration in this area.

Induced pluripotent stem cells (iPSCs) are reprogrammed cells with the potential to differentiate into CMs and endothelial cells as well as avoid ethical issues [67]. In the study conducted by Adamiak et al., iPSC-derived EVs were identified as a safer alternative for potential therapeutic applications in patients with myocardial injury [22]. In mice MI model, these EVs demonstrated improvements in overall left ventricular function and prevented left ventricular from remodeling, hypertrophy and interstitial fibrosis compared to controls. It has also been shown that iPSC-derived exosomes can inhibit the apoptosis of H9C2 CMs by inhibiting caspase 3/7 activation under H2O2-induced oxidative stress [104]. These therapeutic effects may be associated with the enrichment of miR-21 and miR-210. Gao et al. also investigated the administration of EVs from CMs, endothelial cells and smooth muscle cells derived from human-induced iPSC (hiPSC) in swines model following MI [23]. The results showed that HiPSC-derived cells-secreted

exosomes effectively reduced CM apoptosis and promoted ATP generation, while improving myocardial recovery. Ikeda et al. also found that HiPSCs-differentiated CM-secreted EVs could facilitate the transfer of functional mitochondria and their associated energy sources, thereby enhancing cardiomyocyte bioenergetics and improving cardiac function [105]. This is a novel therapy holds promise for the treatment of mitochondria-related diseases.

Sahoo et al. verified that EVs from human CD34$^+$ haematopoietic stem cells (HSCs) promoted angiogenesis both in vitro and in vivo, and that it may be a key paracrine factor in the induction of neovascularization [106]. To enhance the angiogenic potential of CD34$^+$ stem cells, Mackie and colleagues genetically modified them to express the sonichedgehog (Shh) protein [24]. This modification resulted in the production of exosomes from Shh-modified CD34$^+$ cells (CD34(Shh)) that demonstrated promising outcomes in prevented ventricular dilation associated with AMI and improving cardiac function when tested in mouse models.

2.1.2. Exosomes secreted from cardiac cells

In addition to the EVs from MSCs, ESCs and iPSCs mentioned above, it has been observed that cardiac cells are also capable of producing EVs that can be utilized for myocardial infarction (MI) treatment.

Despite not being considered secretory cells, cardiomyocytes are capable of releasing exosomes. Furthermore, CMs release exosomes that are enriched with proteins, DNA and RNA, which can modulate various biological processes in target cells. For instance, they can alter signal transduction and gene expression through their cargo [107]. For the first time, Gupta et al. made a significant discovery by identifying exosomes released from CMs of adult rats that were loaded with cardiac heat shock protein (HSP) 60 [108]. The presence of extracellular HSP60 was found to induce apoptosis in CMs through activation of the TLR4 pathway. Additionally, the secretion capacity of exosomes was observed to be influenced by stimulation from reactive oxygen species (ROS) and ethanol [109]. Studies have shown that hypoxic ischemia is also an effective substance in promoting the secretion of CMs-derived exosomes. Under hypoxic conditions, Yu et al. observed that hypoxia-inducible factor (HIF)-1α induced CMs-derived exosome mediated TNF-α expression, whereas excessive TNF-α expression is known to be detrimental to MI [110]. Another study found that HIF-1α induced upregulation of miR-30a expression in CM-derived exosomes, which inhibited exosomes secretion through paracrine effects and contributed to the maintenance of autophagy after hypoxia [111]. Similarly, CMs exhibited higher levels of secreted exosomal MMP under ischemic conditions and improved cardiac neovascularization through the in vitro transfer of miR-222 and miR-143 [112]. Furthermore, when cultured HL-1 cells were stimulated with different growth factors, variations in the mRNA content of the exosomes they released [113]. Another study conducted on type 2 diabetic rats showing that their CMs-derived EVs have an inhibitory effect on angiogenesis, which may be achieved by transporting miR-320 to endothelial cells [114]. However, the current researches on CM-derived EVs is predominantly limited to cellular-level investigations and lacks extensive validation in animal models, suggesting the need more promising avenues of future research.

It has also been found that endothelial progenitor cell-derived exosomes (EPCs) have a positive impact on cardiac function and scar reduction in mice model of heart attack [25]. These therapeutic effects are associated with the ability of IL-10 to mitigate excessive enrichment of integrin-linked kinase (ILK) in CMs. ILK has deleterious effects such as pro-cardiomyocyte fibrosis and pro-inflammation. Another study showed that ECs-derived EVs stimulated receptor cells migration and angiogenesis via miR-214, which controls endothelial cell function and angiogenesis as a core element in exosome-mediated signaling between ECs [115].

In addition to CMs and ECs, several other types of cardiac cells such as cardiac fibroblasts (CFs) and cardiac distal cells, have been identified as potential sources of exosomes that could provide valuable insights
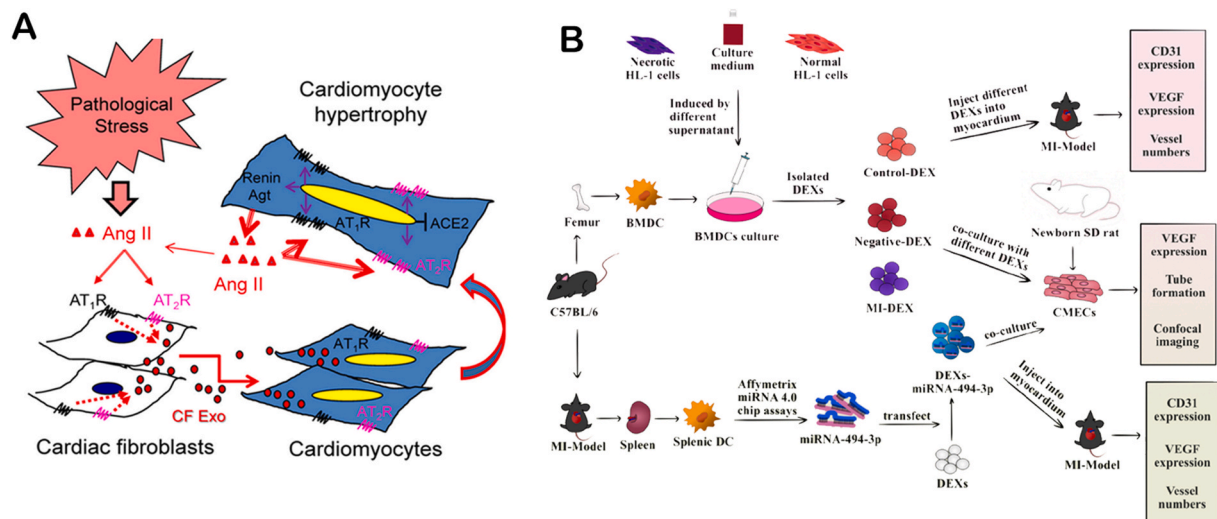
Fig. 4. Other cells derived EVs for the treatment of MI. (A) Angiotensin II (Ang II) enhances pro-hypertrophic signalling in CMs by increasing CFs-secreted exosomes. Reproduced with permission [117]. Copyright 2015, Elsevier. (B) Flowchart of dendritic cell-derived exosomes (DEXs) to promote angiogenesis post-MI. Reproduced with permission [27]. Copyright 2021, Liu et al.
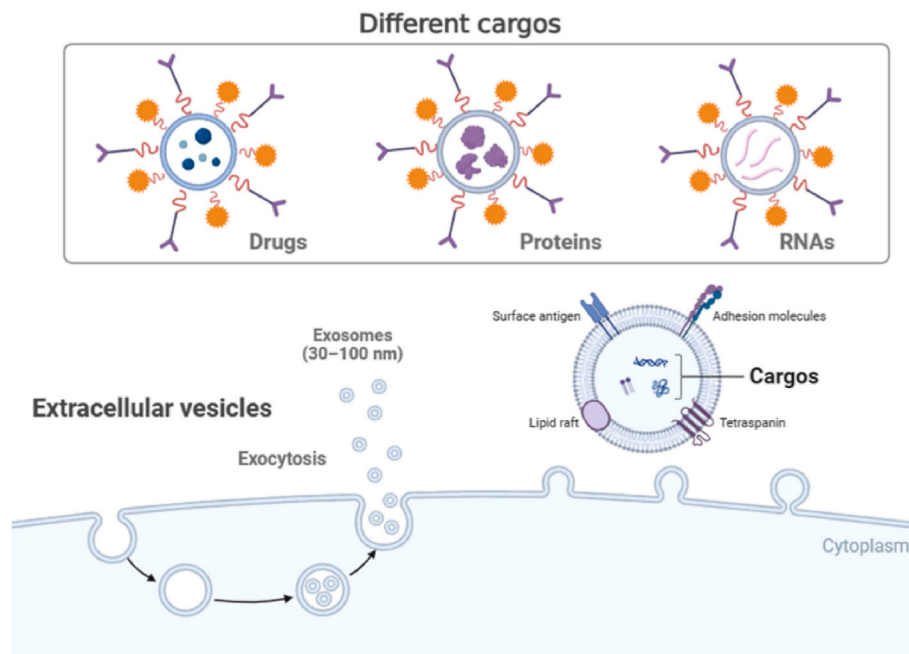

Fig. 5. Overview diagram of EVs as therapeutic delivery system. Created with BioRender.com.

into MI therapy. CFs-secreted exosomes enrich in astrocytic miRNAs. MiR-21-3p derived from exosomes induces CM hypertrophy through paracrine action, make it a potential therapeutic target [116]. Angiotensin (Ang) II stimulates the release of exosomes from CFs, thereby exacerbating the hypertrophy of CMs. Therefore, specifically targeting the release of CFs-derived exosomes induced by Ang II may be a new approach to treat adverse ventricular remodeling after MI (Fig. 4A) [117]. A new type of mesenchymal cell called Cardiac telocytes (CTs) has also been implicated in post-MI angiogenesis within the myocardium [26]. Subsequent studies have found that exosomes derived from CTs contain miRNA-21-5p, which can target and silence the cell death-inducing P53 target 1 (Cdip1) gene. This silencing effect inhibits apoptosis in cardiac microvascular endothelial cells and serve as a mean to promote angiogenesis after MI and achieve more efficient myocardial regeneration [118].

2.1.3. EVs originated from other cells

The dendritic cell-derived exosome (DEX) has been shown to improve wound healing post-MI by mediating CD4$^+$ T cells [119]. And subsequent studies have also found that DEX improves cardiac function by upregulating miR-494-3p to promote tubular formation and angiogenesis in post-MI mouse macrophages (Fig. 4B) [27]. Furthermore, M2 macrophage-derived EVs have shown a protective effect on CMs against hypoxia-induced apoptosis by carrying miR-1271-5p to downregulate SOX6 expression [28].

2.1.4. Circulating EVs

EVs are not only released by different types of cells, but be presented in most body fluids, suggesting their potential involvement in cardioprotective mechanisms [120]. For example, myocardial damage following acute myocardial infarction (AMI) leads to the release of

Table 2
Summary of EVs loading therapeutics for the treatment of MI.

| Category	Therapeutics	Model	Administration route	Results	Ref.
Loading drugs	Curcumin and miRNA-144-3p	MI mice	Intravenous injection	Increases both active targeting and cardioprotection of the heart	[36]
Loading proteins	Akt overexpressing	MI rats	Tail vein injection	Promoted the proliferation and migration of vascular ECs	[37]
	SDF-1 overexpressing	MI mice	Myocardial injection	Inhibited apoptosis and autophagy in CMs and promoted tubular formation in ECs by activating the PI3K signaling pathway	[38]
	TIMP2 overexpressing	MI rats	3 site injections in the infarct margins	Reduced collagen deposition by attenuating MI-induced oxidative stress and inhibited ECM remodeling	[39]
	N1ICD overexpressing	MI mice	Injections in the infarct margins	Showed a strong pro-angiogenic effect and reduced fibrosis to improve cardiac function	[40]
	GATA4 overexpressing	MI rats	Intramyocardial injection	Restored cardiac contractile function and reduced infarct size	[41]
	MIF overexpressing	MI rats	Intramuscular injection in the infarct margins	Enhanced heart function, less CMs mitochondrial fragmentation and reduced cell apoptosis	[42]
	HIF1 overexpressing	MI mice	Injections in the infarct margins	Improved survival of transplanted CPCs and increased tolerance of CPCs to hypoxic environments due to enrichment of miR-126 and miR-210	[43]
Loading nucleic acids	miR-21	MI mice	Intramyocardial injection	Promoted miR-21 expression and inhibited CMs apoptosis by reducing PDCD4	[44]
	miR-126	MI rats	Tail vein injection	Reduced areas of myocardial injury by reducing the expression of inflammatory factors, inhibiting fibrosis and promoting angiogenesis	[45]
	miR-93-5p	MI rats	Intravenous injection	Targeted the autophagy-related proteins ATG7 and TLR4 inhibited hypoxia-induced autophagy and indirectly attenuated the inflammatory response	[46]
	miR-101a	MI mice	Tail vein injection	Reduced infarct size by targeting the expression of transforming growth factor β and type I collagen α1 to inhibit fibrosis	[47]
	miR-138-5p	MI rats	Injection	Reduced apoptosis and delayed the progression of MI by regulating the expression of the deacetylase Sirtuin 1	[48]
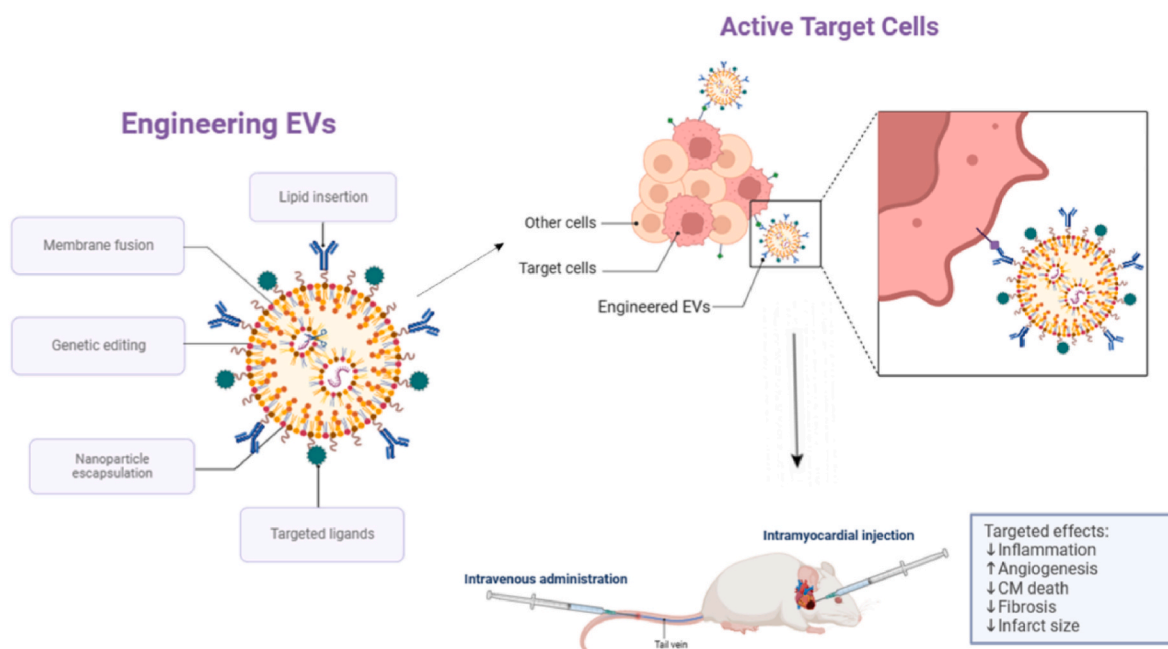
Fig. 6. Overview diagram of Engineered EVs targeting the infarcted heart. Created with BioRender.com.

Table 3
Summary of Engineered EVs targeting the infarcted heart.

| Category	Modified method	Model	Administration route	Targeted effects	Ref.
Exosomes	Conjugated with CHP	I/R rats	Intravenous administration	Targeting exosomes to the infarcted heart reduced fibrosis and promoted cell proliferation	[49]
MSCs-derived exosomes	Lamp2b fused with CSTSMLKAC (IMTP)	MI mice	Tail vein injection	Specially targeted ischemic myocardium and enhanced therapeutic effects	[50]
CDCs-derived exosomes	Lamp2b fused to CMP	Normal mice	Intramyocardial injection	Increased uptake by CMs, decreased CMs apoptosis, and higher cardiac retention	[51]
CPCs-derived exosomes	Overexpressing exosomal CXCR4	I/R rats	Intravenous injection	targeted infarct size and increased the cardiac uptake and protection of CPC-derived exosomes	[52]
MSCs-derived exosomes	Overexpressing CD47	I/R mice	Intravenous injection	Escaped the clearance of immune cells and preferentially accumulated in the heart	[53]
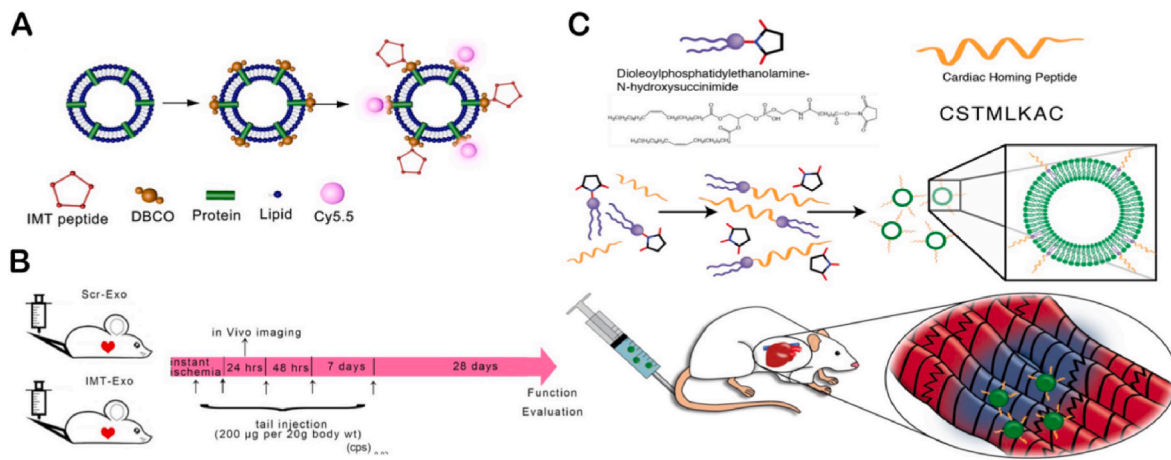
Fig. 7. Lipid insertion for EVs targeting the infarcted heart. (A) Schematic of combining ischemic myocardium-targeting peptide (IMT) with Hypo-EXO. (B) Schematic representation of targeting Hypo-Exo injection in a MI mouse model. Reproduced with permission [92]. Copyright 2018, Ivyspring International Publisher. (C) Schematic diagram of fabricating myocardium-targeting exosomes by using cardiac homing peptide. Reproduced with permission [133]. Copyright 2018, Ivyspring International Publisher.

miR-1 and miR-133a, which serve as biomarkers for the diagnosis of CVD [121]. There is also evidence that long non-coding RNAs (lncRNAs) have an effect on myocardial fibrosis and may become novel biomarkers of MI [122]. It has also been shown that plasma exosomes from human volunteers protect against I/R-induced apoptosis by activating the TLR-4 and HSP27 pathways in CMs [123]. Giricz et al. showed that effects such as reduction of infarcted heart size by distal ischaemic pre-conditioning (IPC) may be mediated through circulating exosomes [124].

2.2. EVs as therapeutic delivery system

EVs themselves can serve as nanomaterials for loading therapeutic drugs, proteins or nucleic acids, and other bioactive substances [125]. As delivery vehicles for therapeutic agents, EVs are biocompatible, have a high ability to traverse cellular barriers and exhibit relatively stable in circulation, as well as provide protection to carrier agents against degradation [126] (see Fig. 5 and Table 2).

2.2.1. EVs loading drugs

The utilization of extracellular vesicles (EVs) to carry therapeutic agents, such as curcumin for anti-inflammatory purposes and chemo-therapeutic agents like paclitaxel to enhance efficacy and reduce tox-icities, has been extensively studied. However, there is limited research on the use of EVs carrying therapeutic agents specifically for myocardial infarction (MI) treatment [127,128]. Currently, NPs loaded with pio-glitazone are being investigated to target circulating monocytes or macrophages in the IR heart, aiming to attenuate IR injury [129]. Kang developed cardiac-targeting EVs (CTP-EVs) and loaded curcumin onto these CTP-EVs (CTP-EVs-CUR) to enhance its bioavailability. They demonstrated that the protective effect of curcumin was mediated by miR-144-3p carried by the EVs [36]. Next, simultaneous loading of curcumin and miR-144-3p into CTP-EVs resulted in enhanced cardiac targeting and cardioprotection, offering a potentially effective strategy for delivering therapeutic molecules for MI treatment.

2.2.2. EVs loading proteins

Previous studies on exosomes as delivery vehicles for protein mac-romolecules have primarily focused on their ability to cross the blood-brain barrier. However, this study specifically investigates the use of exosomes overexpressing certain cytokines to improve cardiac function [130]. As is known to all that activation of the PI3K/Akt signaling pathway has been implicated in the regulation of autophagy and cardioprotection induced by stem cells such as MSC. MA et al. synthe-sized Akt-Exo, an exosome released from MSCs overexpressing Akt, and platelet-derived growth factor D (PDGF-D) expression was significantly upregulated in Akt-Exo [37]. Akt-Exo significantly promoted the pro-liferation and migration of vascular ECs, while its treatment signifi-cantly improved cardiac function in rats with MI as assessed by echocardiography. Exo-SDF1, derived from MSCs overexpressing stromal-derived factor 1 (SDF1), inhibited apoptosis and autophagy in CMs and promoted tubular formation in ECs by activating the PI3K signaling pathway [38]. Study had shown that Exo-SDF1 protected cardiac function and inhibited myocardial tissue injury in MI mice. Exosomes overexpressing tissue matrix metalloproteinase inhibitor 2 (TIMP2) obtained from human umbilical cord mesenchymal stem cells (huc-exoTIMP2) not only reduced the secretion of MMP2 and MMP9, but also increased the expression of the anti-apoptotic gene Bcl2 and decreased the expression of the pro-apoptotic genes Bax and caspase-9 [39]. It reduced collagen deposition by attenuating MI-induced oxida-tive stress and inhibiting extracellular matrix (ECM) remodeling.

Inhibition of myocardial repair expression worsens myocardial injury in ischamic states, and notch signaling plays a role in cardiac repair after myocardial injury. Xuan et al. synthesized EVs from cardiac mesenchymal stem cells (C-MSCs) overexpressing the notch1 intracel-lular domain (N1ICD) and injected C-MSCsN1ICD-EVs into the infarct marginal zone of MI mice for treatment [40]. For example, MSCs over-expressing GATA4 secreted exosomes inhibited apoptosis and reduced the area of MI by delivering anti-apoptotic microRNAs and activating multiple signaling pathways involved in cell survival [41]. Moreover, bone marrow mesenchymal stem cells (BM-MSCs) derived exosomes overexpressing macrophage inhibitory factor (MIF), when injected into a rat model of myocardial infarction, protected cardiac function by reducing mitochondrial division in cardiomyocytes (CMs) [42]. The results showed a strong pro-angiogenic effect and superior efficacy compared to treatment with C-MSC-derived EVs solely in reducing fibrosis and improving cardiac function. Hypoxia-inducible factor-1 (HIF-1), a transcription factor involved in the adaptive response to hypoxic environments, was co-delivered with CPCs using a non-viral small circle plasmid carrying HIF1 (MC-HIF1) into the myocardium after MI [43]. It was found that exosomes from CPCs overexpressing HIF1 were enriched in miR-126 and miR-210, resulting in improving the survival of transplanted CPCs and increasing the tolerance of CPCs to hypoxic environment.
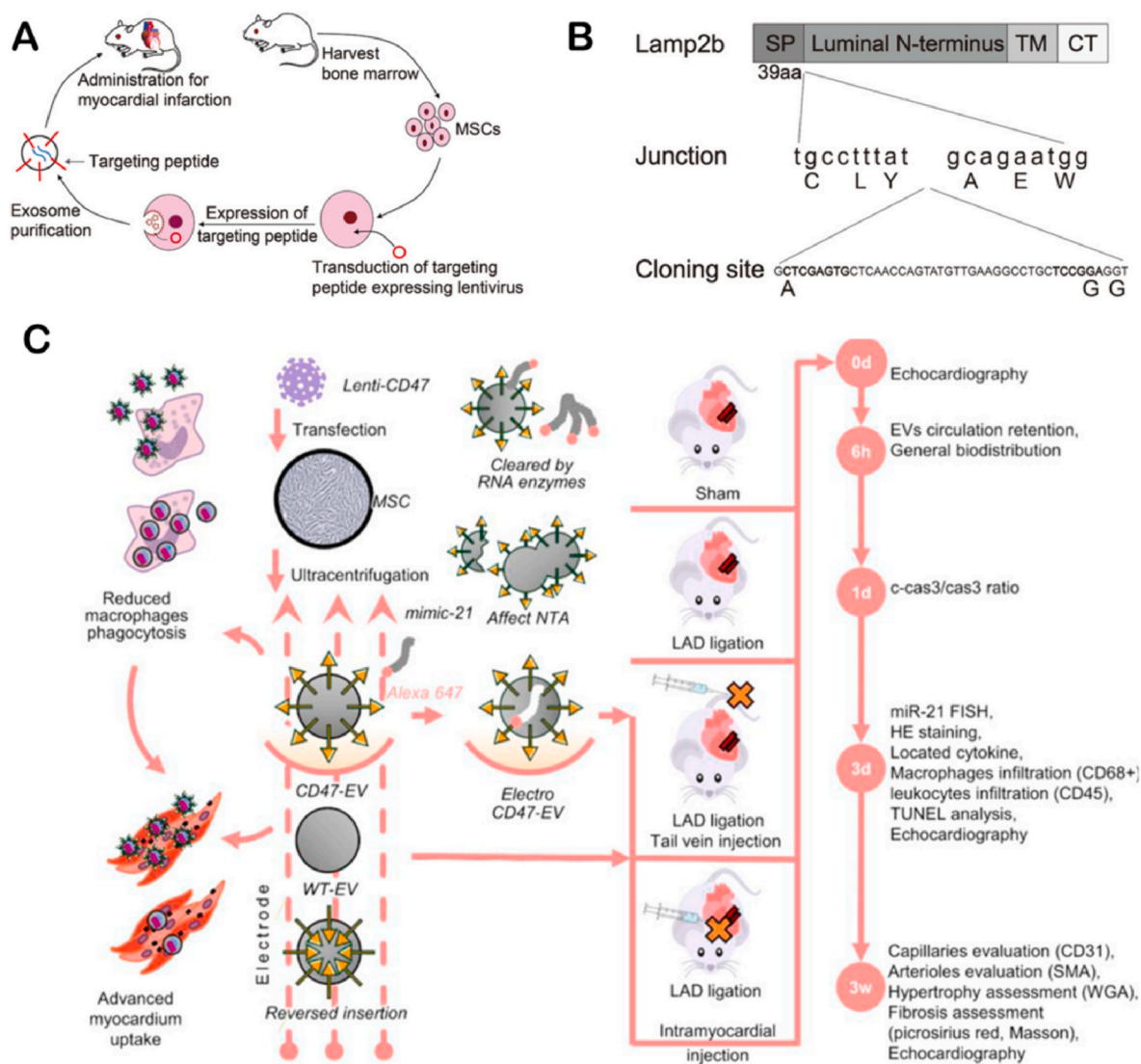
Fig. 8. Genetic editing for EVs targeting the infarcted heart. (A) Schematic diagram of exosomes exhibited with myocardium-targeting peptide CSTSMLKAC fused with Lamp2b. (B) Schematic diagram of administration of Lamp2b protein. Reproduced with permission [50]. Copyright 2018, American Heart Association. (C) Schematic illustration of MI treatment by EVs blocking mononuclear phagocyte system with CD47 modified on membrane surface. Reproduced with permission [53]. Copyright 2021, Elsevier.

2.2.3. EVs loading nucleic acids

EVs have been recognized for their ability to naturally transport various types of RNAs, indicating their potential as therapeutic carriers for delivering nucleic acids [125]. Song et al. obtained EVs enriched with miR-21 and targeted CMs by incorporating programmed cell death 4 (PDCD4) using a human embryonic kidney cell line [44]. In vitro and in vivo experiments showed that miR-21-EVS greatly promoted miR-21 expression and inhibited cardiomyocyte apoptosis by reducing PDCD4 levels.

Studies have shown that miR-126 overexpression in adipose-derived stromal cells (ADSCs) reduced areas of myocardial injury by downregulating the expression of inflammatory factors, inhibiting fibrosis and promoting angiogenesis [45]. Moreover, miR-93-5p overexpressing in ADSCs-derived exosomes significantly inhibited autophagy and inflammatory factor expression in CMs by targeting Atg7 and TLR4, respectively, thereby further enhancing the protective effect against MI [46]. Also, MSC-EVS loaded with miR-101a significantly reduced infarct size by targeting the expression of transforming growth factor β and type I collagen α1 to inhibit fibrosis [47]. Mao et al. injected exosomes of lncRNA KLF3-AS1 overexpressed hMSCs into MI rat models or incubated

them with hypoxic cardiomyocytes [48]. Both cellular and animal experiments demonstrated that overexpression of KLF3-AS1 in exosomes resulted in reducing apoptosis and delaying the progression of MI. This therapeutic effect was attributed to the competitive binding of miR-138-5p by KLF3-AS1, which regulates the expression of the deacetylase Sirtuin 1 (Sirt1).

2.3. Engineered EVs targeting the infarcted heart

Although stem cell-derived EVs have good therapeutic effects in cardioprotection, their translation into clinical therapies is hindered by limitations such as poor bioavailability, off-target effects and retention in the liver, spleen and lungs followed by rapid clearance after administration [131]. Therefore, there is a need to construct engineered exosomes or hybridize with other materials to develop novel exosome carriers. Engineered exosomes can be created using methods such as lipid insertion, membrane fusion, genetic editing and nanoparticle encapsulation [69]. Among them, membrane fusion and nanoparticle encapsulation both involve the utilization of cell membranes, which will be further discussed in the section on cell membranes (see Fig. 6 and
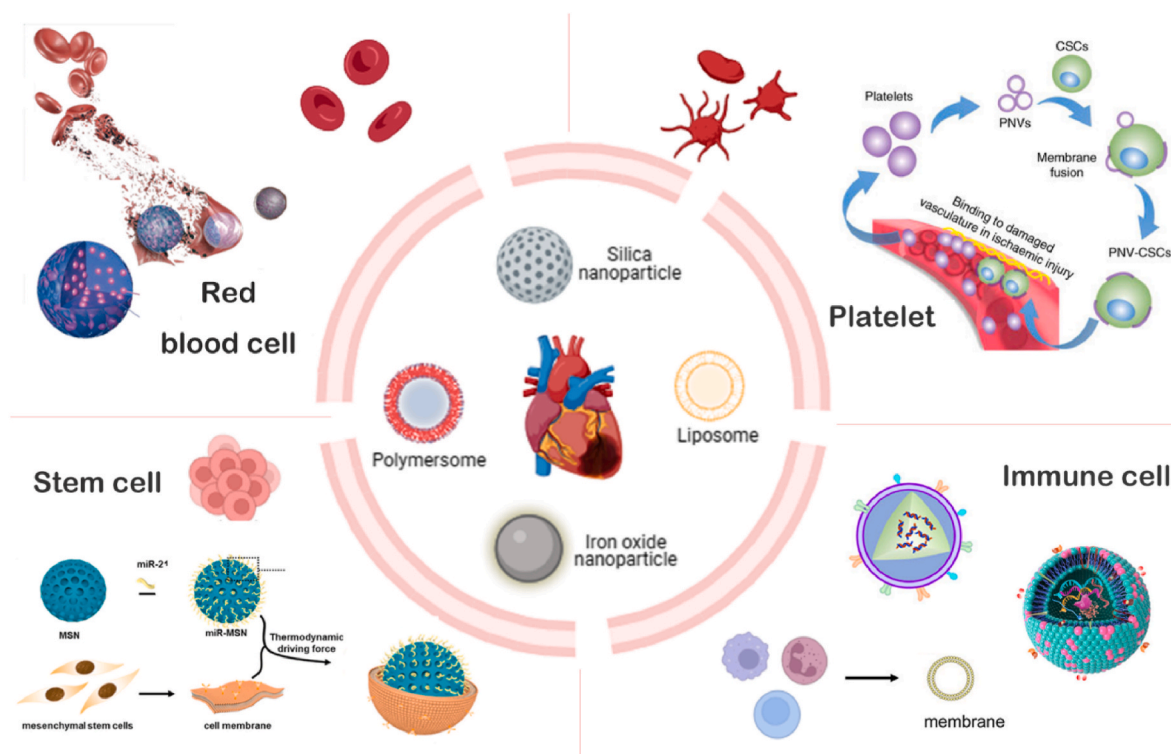
Fig. 9. Overview diagram of biomimetic nanomaterials based on cell membranes. Reproduced with permission [29,34,35,134].

Table 3).

Lipid insertion involves the attachment of functional ligands to membranes through the use of lipid anchors [132]. One example is the specific binding of EVs to cardiac homing peptides to target ischemic myocardial tissue, such as the CSTSMLKAC peptide sequence [49]. Vangergriff et al. incorporated CSTSMLKAC (referred to as CHP peptide exosomes) into exosomal membranes and demonstrated in vitro experiments that it increased exosome uptake and reduced apoptosis (Fig. 7C) [133]. In rats model of I/R, intravenous administration of CHP peptide exosomes targeting ischemic myocardium could reduce fibrosis and promote cell proliferation. Similarly, the studies described above have indicated that combining an ischemic myocardium-targeting peptide (IMTP) with Hypo-EXO also improves the specificity for targeting the ischemic myocardium (Fig. 7A and B) [92].

Wang et al. used molecular cloning and lentiviral packaging techniques to insert the CSTSMLKAC peptide into the Lamp2b gene sequence, a transmembrane protein commonly enriched on the surface of exosomes (referred to as IMTP-exosomes) (Fig. 8A and B) [50]. In mice model of MI, IMTP-exosomes exhibited increased accumulation in the ischemic region compared to blank exosomes. At the same time, MSC-derived IMTP-exosomes reduced inflammation and apoptosis, decreased fibrosis and improved cardiac function. Similarly, Mentkowski also expressed Lamp2b in cardiosphere derived cell (CDC)-secreted exosomes and fused them with cardiomyocyte-specific peptides (CMP), resulting in modified CDCs that displayed enhanced centripetal properties and exerted better cardioprotective effects [51].

In addition, overexpression of CXCR4 in CPC-derived exosomes targeted the infarcted myocardium and increased their cardiac uptake capacity following systemic administration by regulating the Akt signaling pathway post-infarction [52]. Wei and colleagues modified the transmembrane protein CD47 on the surface of MSCs, which allowed EVs to evade clearance by immune cells through the binding of CD47 and signal-regulated protein α (Fig. 8C) [53]. Compared with unmodified EVs, overexpressing CD47 of EVs still exhibited enrichment at the infarcted myocardium at 8 hours post-injection. Using similar approaches, additional engineered exosomes with cardiac targeting

peptides have been designed and modified. However, further investigations are required to determine whether intravenously administered targeted exosomes can safely and effectively improve cardiac function, thereby reducing the need for invasive intracardiac injections.

3. Biomimetic nanomaterials based on cell membranes

In recent years, there has been a growing interest in the study of cell membrane-based bionic nanodrug carriers, which are composed of bionic substances and NPs [62,135]. Cell membrane biomimetic nanomaterials are new nanomaterials that involves physically coating cell membranes onto the surface of NPs or fusing them with EVs extracted from specific cells by extrusion or ultrasound methods [136]. The main cell membranes currently used are red blood cell membranes, immune cell membranes, platelet membranes and so on. Compared to traditional DDS, cell membrane-encapsulated bionanotechnology not only retains the biological characteristics of natural cells, but also offers improved safety and biocompatibility and active targeting of lesions, as well as the structure and function of multifunctional core nanocarriers [71]. Currently, research on cell membrane-based bionanomaterials primarily focuses on their potential application in treating atherosclerosis [137, 138], with therapeutic applications in MI still being investigated (see Fig. 9).

3.1. Red blood cell membrane

Red blood cells (RBCs) have a half-life of approximately 120 days and are the most abundant type of cell in the blood, to their abundance and longevity RBC membranes have been utilized as the first choice for encapsulate NPs [139]. In addition, the surface of the RBC membrane is enriched with protein receptors such as CD47, which allows for immune system evasion [140]. Therefore, the use of RBC membranes to prepare bionanomaterials can enhance NPs circulation within the blood system and enable 'invisible' functions [141]. The absence of a nucleus and various organelles in mature red blood cells simplifies their extraction and purification process. With an average of 500 million red blood cells
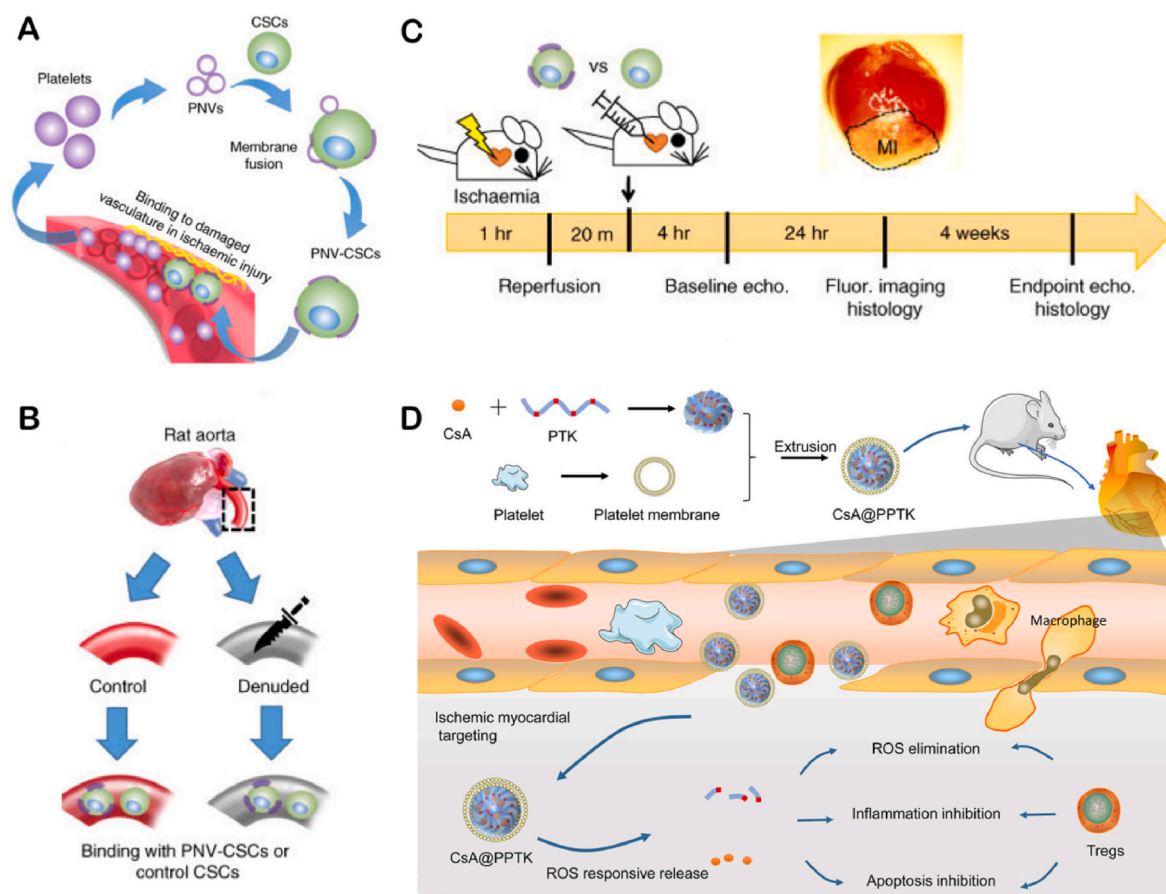
Fig. 10. Platelets membrane coated NPs for the treatment of MI. (A) The overview of characterization and treatment of PNV-CSCs. (B) Schematic showing of PNV decoration to promote vascular binding of CSC to the rat aorta. (C) The administration of PNV-CSCs in rats with MI. Reproduced with permission [29]. Copyright 2018, Nature portfolio. (D) Schematic view of CsA@PPTK and treatment of MI/RI mouse by mimicking the ROS elimination, inflammation and apoptosis inhibition of Tregs. Reproduced with permission [30]. Copyright 2022, Li, F et al.

per millilitre of human blood, a substantial number of drug carriers can be encapsulated and functionalized [136]. Classical examples of erythrocyte membrane bionanotechnology in atherosclerosis applications are already available, such as erythrocyte membrane-encapsulated PLGA nano drugs loaded with rapamycin, nanomicelles with reactive oxygen responsive prednisolone prodrugs, among others [134,142]. However, in the field of cardiac repair, it is currently only used to provide a potential sustained release system of H2S. Hydrogen sulphide (H2S) is considered to be a gaseous transmitter that plays a key role in the homeostasis of the cardiovascular system and is particularly protective against myocardial I/R, but the lack of ideal donors has hindered the clinical use of H2S. Huang et al. addressed this challenge by utilizing RBC membranes loaded with diallyl trisulfides (DATS) carrying mesoporous iron oxide nanoparticles (MIONs) (RBC-DATS-MIONs). The results showed that RBC-DATS-MIONs exhibited better protection against I/R damage and controlled release of H2S [143].

3.2. Platelet membrane

Platelets act as circulating sentinels for detecting vascular injury and aggressive microorganisms. Due to the inherent properties of platelets, such as having a natural targeting of the site of vascular injury [144]. Therefore, platelet membranes can be applied to functionalize nanoparticles, with specific membrane proteins on the platelet membrane recognizing the site of injury and enabling targeted drug delivery [144]. Their application in anticoagulation and thrombolysis may be more widespread [145], but they have also been studied in the treatment of MI.

Tang and colleagues demonstrated that platelets can enhance the targeted delivery of cardiac stem cells (CSCs) to the site of MI injury through their natural myocardial infarction homing capacity (Fig. 10A–C) [29]. They developed PNV-CSCs decorated with platelet nanovesicles (PNV) on the surface of CSCs, and in rat and swine models of AMI, the modified CSCs increased retention and reduced infarct size. CsA@PPTK, a bionanophore, was created by utilizing platelet membranes as a shell to camouflage regulatory T cells (Tregs), could imitate a series of functions of Tregs. It significantly scavenges ROS and regulates macrophage polarization in the ischemic myocardium of MI mice. In addition, it attenuated left ventricular remodeling in MI mice by regulating the protein expression of MMP-9 as well as Cx43 in the ischemic myocardium (Fig. 10 D) [30]. Su et al. developed platelet-initiated nano cells (PINC) with CSC core and outer layers made from platelet membranes modified with prostaglandin E2 (PGE2) and cardiac stromal cell secretory factors [31]. By leveraging the natural homing ability of platelet membranes and using PGE2 as a signaling molecule to promote endogenous repair processes, PINC demonstrated targeted delivery to I/R-injured myocardium and participated in myocardial tissue repair and pro-angiogenesis processes.

3.3. Immune cell membrane

White blood cells (WBCs) exert evitable immune function in diseases like cancer, infection and inflammatory diseases [146]. Membrane-encapsulated WBC-NPs with multifunction were designed by combining the plasma membranes of WBCs such as macrophages, neutrophils, T cells and natural killer cells with synthetic NPs. Compared to
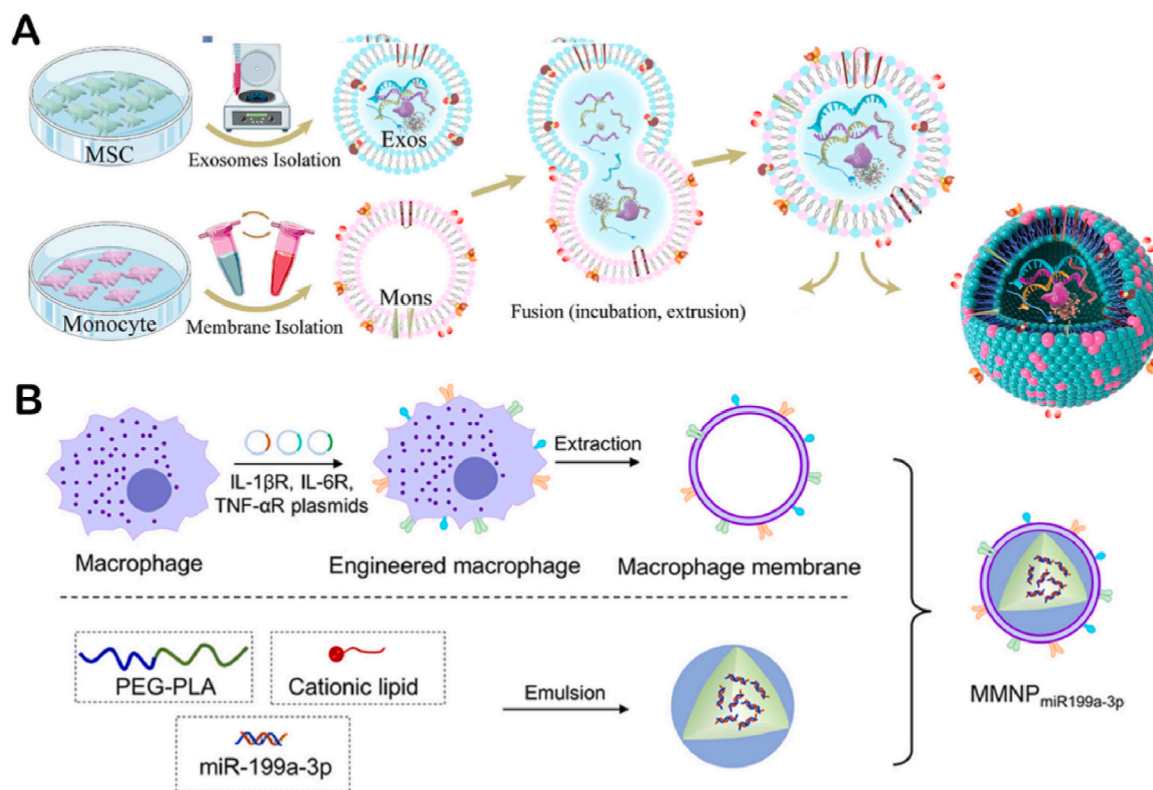
Fig. 11. Immunocytes membrane coated NPs for the treatment of MI. (A) Preparation of Monocyte membrane-encapsulated MSCs exosomes (Mon-EXOs). Reproduced with permission [34]. Copyright 2020, Elsevier. (B) Schematic diagram of engineered macrophages membrane-encapsulated NPs loading miR199a-3p. Reproduced with permission [147]. Copyright 2020, Xue et al.

red blood cells and platelets, immune cells have more complex structures and function as well as offer greater advantages in terms of long circulation and biocompatibility [136]. Therefore, WBC-NPs inherit antigens from all cell membrane surfaces of origin and mimic their wide range of biological capabilities as "decoys", presenting attractive therapeutic potential.

Macrophages are important cells of natural immunity, characterized by their phagocytic activity, antigen-presenting ability and flexible phenotype. Due to their inherent affinity for sites of inflammation, macrophage membrane-encapsulated nanoparticles are likely to accumulate at sites of chronic inflammation. This not only contributes to the accumulation of inflammatory sites (Fig. 11B) [147], but also effectively neutralize inflammatory cytokines. Xue et al. prepared macrophage membrane-encapsulated nanoparticles (MMNPs) loaded with miR-199a-3p and found that MMNPs could bind to IL-1β, IL-6 and TNF-α inflammatory factors and their receptors. Thus, MMNPs could prevent left ventricular remodeling and protect the heart by inhibiting inflammatory responses and myocardial fibrosis in MI mice [32]. Other researchers synthesized neutrophil membrane camouflaged nanoparticles (NM-NPIL-5) by camouflaging IL-5 nanoparticles in neutrophil membranes [33]. Targeted delivery of NM-NPIL-5 promoted post-infarction eosinophil (EOS) accumulation and angiogenesis while safeguarding CMs from excessive inflammation-induced apoptosis, thereby inhibiting adverse cardiac remodeling after AMI. In addition, Zhang et al. mimicked the recruitment of inflammatory factors by monocytes after MI using monocyte membrane-encapsulated MSCs-derived EVs to enhance the targeting of EVs to injured myocardium (Fig. 11A) [34].

3.4. Stem cell membrane

The NPs exhibit excellent homing ability and tend to localize at sites of injury or stimulation when bound to the stem cell membrane [148]. Similar to the above, stem cells encapsulated by membranes with

nanoparticles not only provide selective targeting, but also enhance cellular uptake. Yao et al. constructed a nanocomposite for stem cell membrane camouflage by self-assembling mesenchymal stem cell membranes onto the surface of mesoporous silica nanoparticles loaded with miRNA (Fig. 12) [35]. This approach facilitated targeted delivery of miRNA and inhibit the translation of apoptosis-related proteins to promote cardiomyocyte proliferation. The exosome-mimetic nanocomplex effectively enhanced cardiac function in mice model of myocardial infarction. Bionic adipose stem cell ADSC-derived nanovesicles (ADSC NVs) were also prepared as a cell-free treatment for MI. These ADSC NVs were loaded with melatonin (Mel), which possesses antioxidant effects, resulting in the formation of Mel@NVs [149]. The results showed that under ischemic conditions, MEL@NVS mitigated excessive production of ROS, which further alleviated mitochondrial dysfunction and eventually led to myocardial repair.

4. Challenge and prospectives

The process of cardiac injury is complex and irreversible, necessitating the development of new treatments for MI to enhance CMs survival and prevent progression to heart failure. In recent years, NP-based therapeutic applications for the treatment of MI have been promising. Ideal nanodrug carriers should possess attributes such as prolonged in vivo circulation, immune escape, targeted delivery and controlled release in a targeted manner [150]. Therefore, bionanomaterials offer greater advantages in these aspects than conventional nanomaterials. This review systematically examines the use of EVs, artificially modified EVs, and biofilm-coated biomimetic nanomaterials in the treatment of myocardial infarction, and many biomimetic delivery vehicles have been developed to transport therapeutic agents and deliver them to the injury site. In short, biomimetic delivery systems are expected to be a potentially beneficial technology for MI treatment, amplifying the value of nanomedicine in CVD treatment. However, each of these three
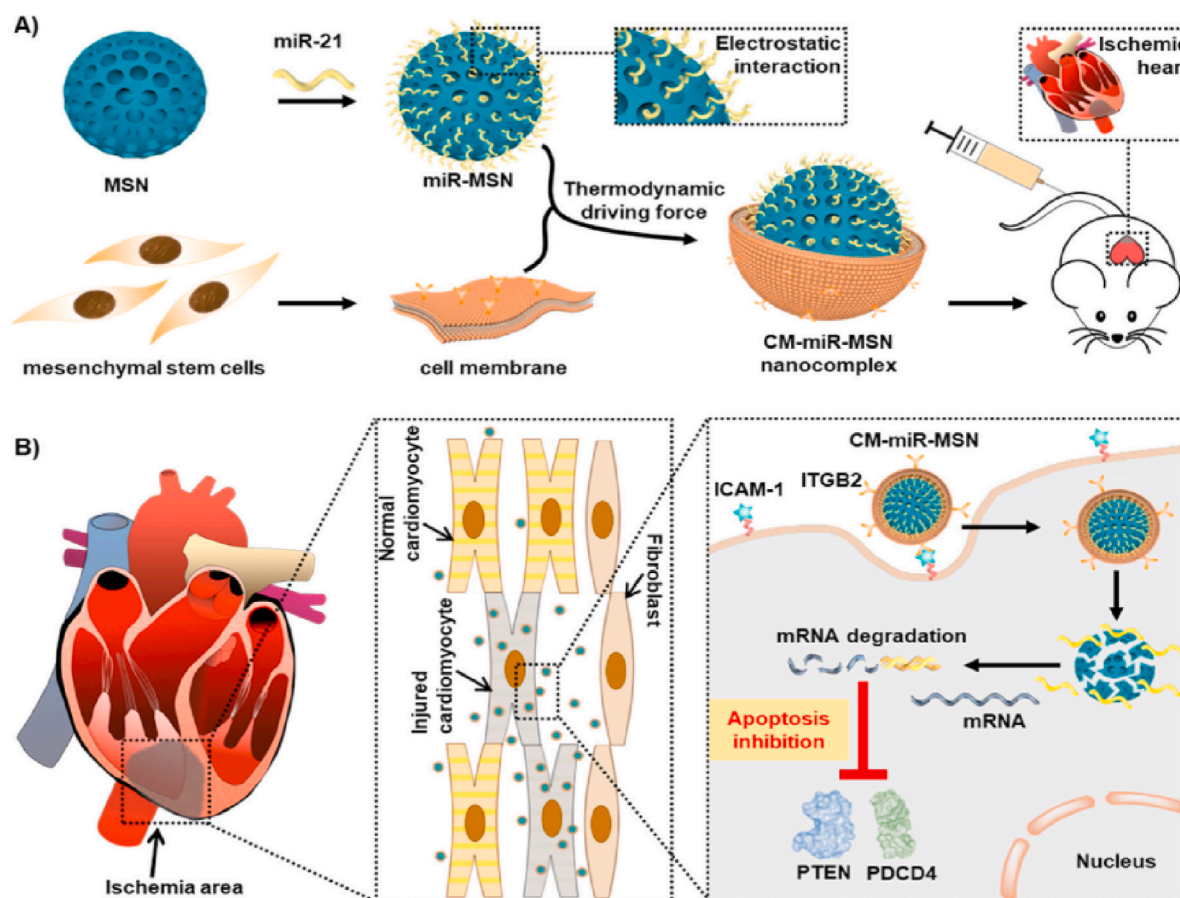
Fig. 12. Stem Cells membrane coated NPs for the treatment of MI. (A) Synthetics of stem cell membrane-camouflaged mimicking nanocomplex. (B) CM-miR-MSN targeted to injured CMs and mediated repair of MI damage via miRNA. Reproduced with permission [35]. Copyright 2020, Elsevier.

Table 4
Comparison of the advantages and limitations of the three approaches.

Approach	Advantage	Shortcoming
EVs	Have their own potential for myocardial repair, high circulatory stability, simpler and easier technique	Suffer from off-target effects, low bioavailability, difficulties in scalable production
Artificially modified EVs	More actively targeted, improve the bioavailability of therapeutic agents	More difficult to genetically engineer for modification, have potential safety issues
Biofilm-coated nanocarriers	Better immune escape, longer circulation times, retention of the intrinsic properties of the cell membrane	More technically demanding, difficult to ensure the structural integrity of the cell membrane and the functional activity of surface biokines

approaches has its own set of advantages and disadvantages, which are summarized in a comparative table below (see Table 4).

Unfortunately, NPs still present significant challenges in translating into clinical practice [151]. Firstly, scalable isolation and purification processes for exosomes, a type of NP, are lacking. Intensive research is ongoing to address this issue and explore methods for mass production while maintaining the integrity and potency of active ingredients [152]. There is currently no consensus on guidelines or standards for NP production and management, with the exception of Good Manufacturing Practice (GMP) guidelines for mesenchymal stem cell-sourced extracellular vesicles [153]. Secondly, the loading efficiency of therapeutic agents into NPs, including both extracellular vesicles (EVs) and bionic cell membranes, remains limited and poses a challenge [125]. Moreover, bionic biomaterials are recommended to be stored at −70 °C, which

leads to high costs associated with storage and transportation [154]. In addition, concerns regarding the biosafety of biomimetic nanomaterials persist. Although animal studies and some clinical trials have confirmed their safety [155], it should be noted that animal models often differ significantly from humans. Therefore, caution must be exercised when extrapolating results from animal studies to human applications. The clinical translation of NPs still has a long way to go.

In recent years, condition-responsive NPs have also attracted attention for DDS. These smart nanoparticles have been developed to respond to various endogenous and exogenous stimuli, including changes in pH, reactive oxygen species (ROS), magnetic fields, and ultrasound [156, 157]. For instance, Lin et al. prepared a biointelligent nanoparticle (MTSNP) with microenvironment targeting and adaptability for the treatment of myocardial ischemia [158]. Also, inorganic iron oxide NPs are commonly used in imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) due to their magnetic properties [159]. In conclusion, future researches will also focus on integration of traditional NPs with novel bionanotechnology strategies, engineering exosomes, developing smart nanomaterials that respond to optical, electrical or magnetic signals, and enhancing the specific targeting capabilities of nanomaterials. These efforts aim to accelerate the translation of NPs-based MI therapeutic strategies into practical clinical applications.

CRediT authorship contribution statement

Tingting Yu: Writing – review & editing, Writing – original draft. **Qiaxin Xu:** Writing – review & editing, Writing – original draft. **Xu Chen:** Writing – review & editing, Writing – original draft. **Xiujiao Deng:** Visualization, Data curation. **Nenghua Chen:** Visualization, Data

curation. **Man Teng Kou:** Visualization, Data curation. **Yanyu Huang:** Visualization, Data curation. **Jun Guo:** Supervision, Funding acquisition, Conceptualization. **Zeyu Xiao:** Supervision, Funding acquisition, Conceptualization. **Jinghao Wang:** Supervision, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Chat GPT in order to check the terminology of this manuscript to ensure that it is as scientific and objective as possible. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

Abbreviations

MI	myocardial infarction
CVD	cardiovascular disease
WHO	World Health Organization
CM	cardiomyocyte
PCI	percutaneous coronary intervention
GABA	coronary artery bypass grafting
I/R	ischemia-reperfusion
DDS	drug delivery systems
NPs	nanoparticles
PEG	polyethylene glycol
EVs	extracellular vesicles
ESCs	embryonic stem cells
CPCs	cardiac progenitor cells
MSCs	mesenchymal stromal cells
PI3K	phosphoinositide 3-kinase
Akt	protein kinase B
c-JNK	c-Jun N-terminal kinase
E2H2	enhancer of zest homologue 2
AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
mTOR	mammalian target of rapamycin
VEGFR2	vascular endothelial growth factor receptor 2
EMMPRIN	extracellular matrix metalloproteinase inducer
PDGF	platelet-derived growth factor
EGF	epidermal growth factor
ADMSCs	adipose tissue mesenchymal stem cells
BMMSCs	bone marrow mesenchymal stem cells
UCBMSCs	umbilical cord blood mesenchymal stem cells
VEGF	vascular endothelial growth factor
TLR4	toll-like receptor 4

FBs	fibroblast
TGF-β	transforming growth factor β
Mecp2	methyl CpG-binding protein 2
nSMase2	neutral sphingomyelinase 2
HP-sEVs	hypoxia-preconditioned mesenchymal stem cells
MMP19	matrix metalloproteinase 19
NHP	non-human primate
GATA4	Globulinum Antihaemophiliae Humanum 4
MIF	macrophage inhibitory factor
IONPs	iron oxide nanoparticles
PAPP-A	pregnancy-associated plasma protein A
IGF-1	Insulin-like growth factor 1
hESC-Pg	human embryonic stem cell-derived cardiovascular progenitor cells
CDCs	cardiosphere-derived cells
HUVEC	human umbilic vein endothelial cells
IRPAK1	interleukin 1 receptor-associated kinase 1
TRAF6	tumour necrosis factor receptor-associated factor 6
NOX-4	nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4
AMI	acute myocardial infarction
IL-10	Interleukin 10
mES-Ex	ESC-derived exosomes
iPSCs	induced pluripotent stem cells
ADSCs	adipose-derived stromal cells
ATG7	autophagy related 7 gene
HSCs	haematopoietic stem cells
Shh	sonichedgehog
HSP	heat shock protein
ROS	reactive oxygen species
HIF	hypoxia-inducible factor
TNF-α	tumor necrosis factor α
HL-1, ECPs/ECs	endothelial progenitor cell-derived exosomes
ILK	integrin-linkes kinase
CFs	cardiac fibroblasts
Ang II	Angiotensin II
CTs	cadiac telocytes
Cdip1	cell death inducing P53 target 1
DEX	dendritic cell-derived exosome
IPC	ischaemic preconditioning
SDF1	stromal-derived factor 1
TIMP2	tissue matrix metalloproteinase inhibitor 2
ECM	extracellular matrix
C-MSCs	cardiac mesenchymal stem cells
N1ICD	notch1 intracellular domain
PDCD4	programmed cell death 4 gene
ATV	atorvastatin
Sirt1	sirtuin 1
IMTP	ischemic myocardium-targeting peptide
CXCR4	C-X-C motif chemokine receptor 4
RBCs	Red blood cells
H2S	Hydrogen sulphide
PLGA	poly (lactic-*co*-glycolic acid)
DATS	diallyl trisulfides
MIONs	mesoporous iron oxide nanoparticles
PNV	platelet nanovesicles
CSCs	cardiac stem cells
Tregs	regulatory T cells
Cx43	connexin 43
PINC	platelet-initiated nano cells
PGE2	prostaglandin E2
WBCs	white blood cells
MMNPs	macrophage membrane-encapsulated nanoparticles
EOS	eosinophil
Mel	melatonin

References

[1] C.W. Tsao, A.W. Aday, Z.I. Almarzooq, A. Alonso, A.Z. Beaton, M.S. Bittencourt, A.K. Boehme, A.E. Buxton, A.P. Carson, Y. Commodore-Mensah, M.S.V. Elkind, K. R. Evenson, C. Eze-Nliam, J.F. Ferguson, G. Generoso, J.E. Ho, R. Kalani, S. S. Khan, B.M. Kissela, K.L. Knutson, D.A. Levine, T.T. Lewis, J. Liu, M.S. Loop, J. Ma, M.E. Mussolino, S.D. Navaneethan, A.M. Perak, R. Poudel, M. Rezk-Hanna, G.A. Roth, E.B. Schroeder, S.H. Shah, E.L. Thacker, L.B. VanWagner, S.S. Virani, J.H. Voecks, N.Y. Wang, K. Yaffe, S.S. Martin, Heart disease and stroke statistics-2022 update: a report from the American heart association, Circulation 145 (2022) e153–e639.

[2] G.A. Roth, G.A. Mensah, C.O. Johnson, G. Addolorato, E. Ammirati, L. M. Baddour, N.C. Barengo, A.Z. Beaton, E.J. Benjamin, C.P. Benziger, A. Bonny, M. Brauer, M. Brodmann, T.J. Cahill, J. Carapetis, A.L. Catapano, S.S. Chugh, L. T. Cooper, J. Coresh, M. Criqui, N. DeCleene, K.A. Eagle, S. Emmons-Bell, V. L. Feigin, J. Fernández-Solà, G. Fowkes, E. Gakidou, S.M. Grundy, F.J. He, G. Howard, F. Hu, L. Inker, G. Karthikeyan, N. Kassebaum, W. Koroshetz, C. Lavie, D. Lloyd-Jones, H.S. Lu, A. Mirijello, A.M. Temesgen, A. Mokdad, A. E. Moran, P. Muntner, J. Narula, B. Neal, M. Ntsekhe, G. Moraes de Oliveira, C. Otto, M. Owolabi, M. Pratt, S. Rajagopalan, M. Reitsma, A.L.P. Ribeiro, N. Rigotti, A. Rodgers, C. Sable, S. Shakil, K. Sliwa-Hahnle, B. Stark, J. Sundström, P. Timpel, I.M. Tleyjeh, M. Valgimigli, T. Vos, P.K. Whelton, M. Yacoub, L. Zuhlke, C. Murray, V. Fuster, Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (2020) 2982–3021.

[3] S.S. Dani, A.N. Lone, Z. Javed, M.S. Khan, M. Zia Khan, E. Kaluski, S.S. Virani, M. D. Shapiro, M. Cainzos-Achirica, K. Nasir, S.U. Khan, Trends in premature mortality from acute myocardial infarction in the United States, 1999 to 2019, J. Am. Heart Assoc. 11 (2022) e021682.

[4] I. Cicha, R. Singh, C.D. Garlichs, C. Alexiou, Nano-biomaterials for cardiovascular applications: clinical perspective, J. Contr. Release 229 (2016) 23–36.

[5] J. Majumder, O. Taratula, T. Minko, Nanocarrier-based systems for targeted and site specific therapeutic delivery, Adv. Drug Deliv. Rev. 144 (2019) 57–77.

[6] T. Matoba, K. Egashira, Nanoparticle-mediated drug delivery system for cardiovascular disease, Int. Heart J. 55 (2014) 281–286.

[7] R.C. Lai, F. Arslan, M.M. Lee, N.S. Sze, A. Choo, T.S. Chen, M. Salto-Tellez, L. Timmers, C.N. Lee, R.M. El Oakley, G. Pasterkamp, D.P. de Kleijn, S.K. Lim, Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury, Stem Cell Res. 4 (2010) 214–222.

[8] F. Arslan, R.C. Lai, M.B. Smeets, L. Akeroyd, A. Choo, E.N. Aguor, L. Timmers, H. V. van Rijen, P.A. Doevendans, G. Pasterkamp, S.K. Lim, D.P. de Kleijn, Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury, Stem Cell Res. 10 (2013) 301–312.

[9] L. Liu, X. Jin, C.F. Hu, R. Li, Z. Zhou, C.X. Shen, Exosomes derived from mesenchymal stem cells rescue myocardial ischaemia/reperfusion injury by inducing cardiomyocyte autophagy via AMPK and Akt pathways, Cell. Physiol. Biochem. 43 (2017) 52–68.

[10] X. Teng, L. Chen, W. Chen, J. Yang, Z. Yang, Z. Shen, Mesenchymal stem cell-derived exosomes improve the microenvironment of infarcted myocardium contributing to angiogenesis and anti-inflammation, Cell. Physiol. Biochem. 37 (2015) 2415–2424.

[11] H. Xu, S. Wang, L. Liu, B. Zhang, B. Li, Exosomes derived from adipose tissue, bone marrow, and umbilical cord blood for cardioprotection after myocardial infarction, J. Cell. Biochem. 121 (2020) 2089–2102.

[12] J. Zhao, X. Li, J. Hu, F. Chen, S. Qiao, X. Sun, L. Gao, J. Xie, B. Xu, Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization, Cardiovasc. Res. 115 (2019) 1205–1216.

[13] R. Sánchez-Sánchez, M. Gómez-Ferrer, I. Reinal, V. Buigues, E. Villanueva-Bádenas, I. Ontoria-Oviedo, A. Hernándiz, H. González-King, E. Peiró-Molina, A. Dorronsoro, P. Sepúlveda, miR-4732-3p in extracellular vesicles from mesenchymal stromal cells is cardioprotective during myocardial ischemia, Front. Cell Dev. Biol. 9 (2021) 734143.

[14] Q. Li, Y. Xu, K. Lv, Y. Wang, Z. Zhong, C. Xiao, K. Zhu, C. Ni, K. Wang, M. Kong, X. Li, Y. Fan, F. Zhang, Q. Chen, Y. Li, Q. Li, C. Liu, J. Zhu, S. Zhong, J. Wang, Y. Chen, J. Zhao, D. Zhu, R. Wu, J. Chen, W. Zhu, H. Yu, R. Ardehali, J.J. Zhang, J. Wang, X. Hu, Small extracellular vesicles containing miR-486-5p promote angiogenesis after myocardial infarction in mice and nonhuman primates, Sci. Transl. Med. 13 (2021).

[15] Y. Ning, P. Huang, G. Chen, Y. Xiong, Z. Gong, C. Wu, J. Xu, W. Jiang, X. Li, R. Tang, L. Zhang, M. Hu, J. Xu, J. Xu, H. Qian, C. Jin, Y. Yang, Atorvastatin-pretreated mesenchymal stem cell-derived extracellular vesicles promote cardiac repair after myocardial infarction via shifting macrophage polarization by targeting microRNA-139-3p/Stat1 pathway, BMC Med. 21 (2023) 96.

[16] J.R. Lee, B.W. Park, J. Kim, Y.W. Choo, H.Y. Kim, J.K. Yoon, H. Kim, J.W. Hwang, M. Kang, S.P. Kwon, S.Y. Song, I.O. Ko, J.A. Park, K. Ban, T. Hyeon, H.J. Park, B. S. Kim, Nanovesicles derived from iron oxide nanoparticles-incorporated mesenchymal stem cells for cardiac repair, Sci. Adv. 6 (2020) eaaz0952.

[17] L. Chen, Y. Wang, Y. Pan, L. Zhang, C. Shen, G. Qin, M. Ashraf, N. Weintraub, G. Ma, Y. Tang, Cardiac progenitor-derived exosomes protect ischemic myocardium from acute ischemia/reperfusion injury, Biochem. Biophys. Res. Commun. 431 (2013) 566–571.

[18] L. Barile, V. Lionetti, E. Cervio, M. Matteucci, M. Gherghiceanu, L.M. Popescu, T. Torre, F. Siclari, T. Moccetti, G. Vassalli, Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction, Cardiovasc. Res. 103 (2014) 530–541.

[19] A.G. Ibrahim, K. Cheng, E. Marbán, Exosomes as critical agents of cardiac regeneration triggered by cell therapy, Stem Cell Rep. 2 (2014) 606–619.

[20] G. de Couto, R. Gallet, L. Cambier, E. Jaghatspanyan, N. Makkar, J.F. Dawkins, B. P. Berman, E. Marbán, Exosomal MicroRNA transfer into macrophages mediates cellular postconditioning, Circulation 136 (2017) 200–214.

[21] M. Khan, E. Nickoloff, T. Abramova, J. Johnson, S.K. Verma, P. Krishnamurthy, A. R. Mackie, E. Vaughan, V.N. Garikipati, C. Benedict, V. Ramirez, E. Lambers, A. Ito, E. Gao, S. Misener, T. Luongo, J. Elrod, G. Qin, S.R. Houser, W.J. Koch, R. Kishore, Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction, Circ. Res. 117 (2015) 52–64.

[22] M. Adamiak, G. Cheng, S. Bobis-Wozowicz, L. Zhao, S. Kedracka-Krok, A. Samanta, E. Karnas, Y.T. Xuan, B. Skupien-Rabian, X. Chen, U. Jankowska, M. Girgis, M. Sekula, A. Davani, S. Lasota, R.J. Vincent, M. Sarna, K.L. Newell, O. L. Wang, N. Dudley, Z. Madeja, B. Dawn, E.K. Zuba-Surma, Induced pluripotent stem cell (iPSC)-Derived extracellular vesicles are safer and more effective for cardiac repair than iPSCs, Circ. Res. 122 (2018) 296–309.

[23] L. Gao, L. Wang, Y. Wei, P. Krishnamurthy, G.P. Walcott, P. Menasché, J. Zhang, Exosomes secreted by hiPSC-derived cardiac cells improve recovery from myocardial infarction in swine, Sci. Transl. Med. 12 (2020).

[24] A.R. Mackie, E. Klyachko, T. Thorne, K.M. Schultz, M. Millay, A. Ito, C.E. Kamide, T. Liu, R. Gupta, S. Sahoo, S. Misener, R. Kishore, D.W. Losordo, Sonic hedgehog-modified human CD34+ cells preserve cardiac function after acute myocardial infarction, Circ. Res. 111 (2012) 312–321.

[25] Y. Yue, C. Wang, C. Benedict, G. Huang, M. Truongcao, R. Roy, M. Cimini, V.N. S. Garikipati, Z. Cheng, W.J. Koch, R. Kishore, Interleukin-10 deficiency alters endothelial progenitor cell-derived exosome reparative effect on myocardial repair via integrin-linked kinase enrichment, Circ. Res. 126 (2020) 315–329.

[26] C.G. Manole, V. Cismaşiu, M. Gherghiceanu, L.M. Popescu, Experimental acute myocardial infarction: telocytes involvement in neo-angiogenesis, J. Cell Mol. Med. 15 (2011) 2284–2296.

[27] H. Liu, Y. Zhang, J. Yuan, W. Gao, X. Zhong, K. Yao, L. Lin, J. Ge, Dendritic cell-derived exosomal miR-494-3p promotes angiogenesis following myocardial infarction, Int. J. Mol. Med. 47 (2021) 315–325.

[28] R. Long, L. Gao, Y. Li, G. Li, P. Qin, Z. Wei, D. Li, C. Qian, J. Li, G. Yang, M2 macrophage-derived exosomes carry miR-1271-5p to alleviate cardiac injury in acute myocardial infarction through down-regulating SOX6, Mol. Immunol. 136 (2021) 26–35.

[29] J. Tang, T. Su, K. Huang, P.U. Dinh, Z. Wang, A. Vandergriff, M.T. Hensley, J. Cores, T. Allen, T. Li, E. Sproul, E. Mihalko, L.J. Lobo, L. Ruterbories, A. Lynch, A. Brown, T.G. Caranasos, D. Shen, G.A. Stouffer, Z. Gu, J. Zhang, K. Cheng, Targeted repair of heart injury by stem cells fused with platelet nanovesicles, Nat. Biomed. Eng. 2 (2018) 17–26.

[30] F. Li, D. Liu, M. Liu, Q. Ji, B. Zhang, Q. Mei, Y. Cheng, S. Zhou, Tregs biomimetic nanoparticle to reprogram inflammatory and redox microenvironment in infarct tissue to treat myocardial ischemia reperfusion injury in mice, J. Nanobiotechnol. 20 (2022) 251.

[31] T. Su, K. Huang, H. Ma, H. Liang, P.U. Dinh, J. Chen, D. Shen, T.A. Allen, L. Qiao, Z. Li, S. Hu, J. Cores, B.N. Frame, A.T. Young, Q. Yin, J. Liu, L. Qian, T. G. Caranasos, Y. Brudno, F.S. Ligler, K. Cheng, Platelet-inspired nanocells for targeted heart repair after ischemia/reperfusion injury, Adv. Funct. Mater. 29 (2019).

[32] Y. Xue, G. Zeng, J. Cheng, J. Hu, M. Zhang, Y. Li, Engineered macrophage membrane-enveloped nanomedicine for ameliorating myocardial infarction in a mouse model, Bioeng Transl Med 6 (2021) e10197.

[33] D. Han, F. Wang, Z. Qiao, B. Wang, Y. Zhang, Q. Jiang, M. Liu, Y. Zhuang, Q. An, Y. Bai, J. Shangguan, J. Zhang, G. Liang, D. Shen, Neutrophil membrane-camouflaged nanoparticles alleviate inflammation and promote angiogenesis in ischemic myocardial injury, Bioact. Mater. 23 (2023) 369–382.

[34] N. Zhang, Y. Song, Z. Huang, J. Chen, H. Tan, H. Yang, M. Fan, Q. Li, Q. Wang, J. Gao, Z. Pang, J. Qian, J. Ge, Monocyte mimics improve mesenchymal stem cell-derived extracellular vesicle homing in a mouse MI/RI model, Biomaterials 255 (2020) 120168.

[35] C. Yao, W. Wu, H. Tang, X. Jia, J. Tang, X. Ruan, F. Li, D.T. Leong, D. Luo, D. Yang, Self-assembly of stem cell membrane-camouflaged nanocomplex for microRNA-mediated repair of myocardial infarction injury, Biomaterials 257 (2020) 120256.

[36] J.Y. Kang, H. Kim, D. Mun, N. Yun, B. Joung, Co-delivery of curcumin and miRNA-144-3p using heart-targeted extracellular vesicles enhances the therapeutic efficacy for myocardial infarction, J. Contr. Release 331 (2021) 62–73.

[37] J. Ma, Y. Zhao, L. Sun, X. Sun, X. Zhao, X. Sun, H. Qian, W. Xu, W. Zhu, Exosomes derived from akt-modified human umbilical cord mesenchymal stem cells improve cardiac regeneration and promote angiogenesis via activating platelet-derived growth factor D, Stem Cells Transl Med 6 (2017) 51–59.

[38] X.H. Gong, H. Liu, S.J. Wang, S.W. Liang, G.G. Wang, Exosomes derived from SDF1-overexpressing mesenchymal stem cells inhibit ischemic myocardial cell apoptosis and promote cardiac endothelial microvascular regeneration in mice with myocardial infarction, J. Cell. Physiol. 234 (2019) 13878–13893.

[39] J. Ni, X. Liu, Y. Yin, P. Zhang, Y.W. Xu, Z. Liu, Exosomes derived from TIMP2-modified human umbilical cord mesenchymal stem cells enhance the repair effect in rat model with myocardial infarction possibly by the akt/sfrp2 pathway, Oxid. Med. Cell. Longev. 2019 (2019) 1958941.

[40] W. Xuan, M. Khan, M. Ashraf, Extracellular vesicles from notch activated cardiac mesenchymal stem cells promote myocyte proliferation and neovasculogenesis, Front. Cell Dev. Biol. 8 (2020) 11.

[41] B. Yu, H.W. Kim, M. Gong, J. Wang, R.W. Millard, Y. Wang, M. Ashraf, M. Xu, Exosomes secreted from GATA-4 overexpressing mesenchymal stem cells serve as a reservoir of anti-apoptotic microRNAs for cardioprotection, Int. J. Cardiol. 182 (2015) 349–360.

[42] X. Liu, X. Li, W. Zhu, Y. Zhang, Y. Hong, X. Liang, B. Fan, H. Zhao, H. He, F. Zhang, Exosomes from mesenchymal stem cells overexpressing MIF enhance myocardial repair, J. Cell. Physiol. 235 (2020) 8010–8022.

[43] S.G. Ong, W.H. Lee, M. Huang, D. Dey, K. Kodo, V. Sanchez-Freire, J.D. Gold, J. C. Wu, Cross talk of combined gene and cell therapy in ischemic heart disease: role of exosomal microRNA transfer, Circulation 130 (2014) S60–S69.

[44] Y. Song, C. Zhang, J. Zhang, Z. Jiao, N. Dong, G. Wang, Z. Wang, L. Wang, Localized injection of miRNA-21-enriched extracellular vesicles effectively restores cardiac function after myocardial infarction, Theranostics 9 (2019) 2346–2360.

[45] Q. Luo, D. Guo, G. Liu, G. Chen, M. Hang, M. Jin, Exosomes from MiR-126-overexpressing adscs are therapeutic in relieving acute myocardial ischaemic injury, Cell. Physiol. Biochem. 44 (2017) 2105–2116.

[46] J. Liu, M. Jiang, S. Deng, J. Lu, H. Huang, Y. Zhang, P. Gong, X. Shen, H. Ruan, M. Jin, H. Wang, miR-93-5p-Containing exosomes treatment attenuates acute myocardial infarction-induced myocardial damage, Mol. Ther. Nucleic Acids 11 (2018) 103–115.

[47] J. Wang, C.J. Lee, M.B. Deci, N. Jasiewicz, A. Verma, J.M. Canty, J. Nguyen, MiR-101a loaded extracellular nanovesicles as bioactive carriers for cardiac repair, Nanomedicine 27 (2020) 102201.

[48] Q. Mao, X.L. Liang, C.L. Zhang, Y.H. Pang, Y.X. Lu, LncRNA KLF3-AS1 in human mesenchymal stem cell-derived exosomes ameliorates pyroptosis of cardiomyocytes and myocardial infarction through miR-138-5p/Sirt1 axis, Stem Cell Res. Ther. 10 (2019) 393.

[49] S. Kanki, D.E. Jaalouk, S. Lee, A.Y. Yu, J. Gannon, R.T. Lee, Identification of targeting peptides for ischemic myocardium by in vivo phage display, J. Mol. Cell. Cardiol. 50 (2011) 841–848.

[50] X. Wang, Y. Chen, Z. Zhao, Q. Meng, Y. Yu, J. Sun, Z. Yang, Y. Chen, J. Li, T. Ma, H. Liu, Z. Li, J. Yang, Z. Shen, Engineered exosomes with ischemic myocardium-targeting peptide for targeted therapy in myocardial infarction, J. Am. Heart Assoc. 7 (2018) e008737.

[51] K.I. Mentkowski, J.K. Lang, Exosomes engineered to express a cardiomyocyte binding peptide demonstrate improved cardiac retention in vivo, Sci. Rep. 9 (2019) 10041.

[52] A. Ciullo, V. Biemmi, G. Milano, S. Bolis, E. Cervio, E.T. Fertig, M. Gherghiceanu, T. Moccetti, G.G. Camici, G. Vassalli, L. Barile, Exosomal expression of CXCR4 targets cardioprotective vesicles to myocardial infarction and improves outcome after systemic administration, Int. J. Mol. Sci. 20 (2019).

[53] Z. Wei, Z. Chen, Y. Zhao, F. Fan, W. Xiong, S. Song, Y. Yin, J. Hu, K. Yang, L. Yang, B. Xu, J. Ge, Mononuclear phagocyte system blockade using extracellular vesicles modified with CD47 on membrane surface for myocardial infarction reperfusion injury treatment, Biomaterials 275 (2021) 121000.

[54] M. Karam, D. Fahs, B. Maatouk, B. Safi, A.A. Jaffa, R. Mhanna, Polymeric nanoparticles in the diagnosis and treatment of myocardial infarction: challenges and future prospects, Mater Today Bio 14 (2022) 100249.

[55] Q. Pan, J. Xu, C.J. Wen, Y.Y. Xiong, Z.T. Gong, Y.J. Yang, Nanoparticles: promising tools for the treatment and prevention of myocardial infarction, Int. J. Nanomed. 16 (2021) 6719–6747.

[56] K.L. Aillon, Y. Xie, N. El-Gendy, C.J. Berkland, M.L. Forrest, Effects of nanomaterial physicochemical properties on in vivo toxicity, Adv. Drug Deliv. Rev. 61 (2009) 457–466.

[57] T.A. George, C.C. Hsu, A. Meeson, D.J. Lundy, Nanocarrier-based targeted therapies for myocardial infarction, Pharmaceutics 14 (2022).

[58] K. Shiraishi, K. Kawano, Y. Maitani, T. Aoshi, K.J. Ishii, Y. Sanada, S. Mochizuki, K. Sakurai, M. Yokoyama, Exploring the relationship between anti-PEG IgM behaviors and PEGylated nanoparticles and its significance for accelerated blood clearance, J. Contr. Release 234 (2016) 59–67.

[59] D. Bamberger, D. Hobernik, M. Konhäuser, M. Bros, P.R. Wich, Surface modification of polysaccharide-based nanoparticles with PEG and dextran and the effects on immune cell binding and stimulatory characteristics, Mol. Pharm. 14 (2017) 4403–4416.

[60] Y. Xue, Y. Wu, Q. Wang, L. Xue, Z. Su, C. Zhang, Cellular vehicles based on neutrophils enable targeting of atherosclerosis, Mol. Pharm. 16 (2019) 3109–3120.

[61] K.X. Tan, S. Pan, J. Jeevanandam, M.K. Danquah, Cardiovascular therapies utilizing targeted delivery of nanomedicines and aptamers, Int. J. Pharm. 558 (2019) 413–425.

[62] J.H. Park, D. Dehaini, J. Zhou, M. Holay, R.H. Fang, L. Zhang, Biomimetic nanoparticle technology for cardiovascular disease detection and treatment, Nanoscale Horiz 2 (2020) 25–42.

[63] J. Zhuang, Y. Duan, Q. Zhang, W. Gao, S. Li, R.H. Fang, L. Zhang, Multimodal enzyme delivery and therapy enabled by cell membrane-coated metal-organic framework nanoparticles, Nano Lett. 20 (2020) 4051–4058.

[64] H. Wang, Y. Liu, R. He, D. Xu, J. Zang, N. Weeranoppanant, H. Dong, Y. Li, Cell membrane biomimetic nanoparticles for inflammation and cancer targeting in drug delivery, Biomater. Sci. 8 (2020) 552–568.

[65] S. Yaman, U. Chintapula, E. Rodriguez, H. Ramachandramoorthy, K.T. Nguyen, Cell-mediated and cell membrane-coated nanoparticles for drug delivery and cancer therapy, Cancer Drug Resist 3 (2020) 879–911.

[66] J. Gao, S. Wang, Z. Wang, High yield, scalable and remotely drug-loaded neutrophil-derived extracellular vesicles (EVs) for anti-inflammation therapy, Biomaterials 135 (2017) 62–73.

[67] J. Rezaie, R. Rahbarghazi, M. Pezeshki, M. Mazhar, F. Yekani, M. Khaksar, E. Shokrollahi, H. Amini, S. Hashemzadeh, S.E. Sokullu, M. Tokac, Cardioprotective role of extracellular vesicles: a highlight on exosome beneficial effects in cardiovascular diseases, J. Cell. Physiol. 234 (2019) 21732–21745.

[68] A. Prakash, G.E. Crespo-Avilan, S. Hernandez-Resendiz, S.G. Ong, D.J. Hausenloy, Extracellular vesicles - mediating and delivering cardioprotection in acute myocardial infarction and heart failure, Cond Med 3 (2020) 227–238.

[69] J. Lai, C. Huang, Y. Guo, L. Rao, Engineered extracellular vesicles and their mimics in cardiovascular diseases, J. Contr. Release 347 (2022) 27–43.

[70] J. Laura Francés, C. Pagiatakis, V. Di Mauro, M. Climent, Therapeutic potential of EVs: targeting cardiovascular diseases, Biomedicines 11 (2023).

[71] N.H. Lee, S. You, A. Taghizadeh, M. Taghizadeh, H.S. Kim, Cell membrane-cloaked nanotherapeutics for targeted drug delivery, Int. J. Mol. Sci. 23 (2022).

[72] M. Guo, C. Xia, Y. Wu, N. Zhou, Z. Chen, W. Li, Research progress on cell membrane-coated biomimetic delivery systems, Front. Bioeng. Biotechnol. 9 (2021) 772522.

[73] L.M. Doyle, M.Z. Wang, Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis, Cells 8 (2019).

[74] C. Pezzana, F. Agnely, A. Bochot, J. Siepmann, P. Menasché, Extracellular vesicles and biomaterial design: new therapies for cardiac repair, Trends Mol. Med. 27 (2021) 231–247.

[75] A. Beach, H.G. Zhang, M.Z. Ratajczak, S.S. Kakar, Exosomes: an overview of biogenesis, composition and role in ovarian cancer, J. Ovarian Res. 7 (2014) 14.

[76] S. Sarker, K. Scholz-Romero, A. Perez, S.E. Illanes, M.D. Mitchell, G.E. Rice, C. Salomon, Placenta-derived exosomes continuously increase in maternal circulation over the first trimester of pregnancy, J. Transl. Med. 12 (2014) 204.

[77] H.F. Heijnen, A.E. Schiel, R. Fijnheer, H.J. Geuze, J.J. Sixma, Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules, Blood 94 (1999) 3791–3799.

[78] G. van Niel, G. D'Angelo, G. Raposo, Shedding light on the cell biology of extracellular vesicles, Nat. Rev. Mol. Cell Biol. 19 (2018) 213–228.

[79] C. Emanueli, A.I. Shearn, G.D. Angelini, S. Sahoo, Exosomes and exosomal miRNAs in cardiovascular protection and repair, Vasc. Pharmacol. 71 (2015) 24–30.

[80] N. Li, L. Rochette, Y. Wu, N. Rosenblatt-Velin, New insights into the role of exosomes in the heart after myocardial infarction, J Cardiovasc Transl Res 12 (2019) 18–27.

[81] A. Tan, J. Rajadas, A.M. Seifalian, Exosomes as nano-theranostic delivery platforms for gene therapy, Adv. Drug Deliv. Rev. 65 (2013) 357–367.

[82] Y.Y. Xiong, Z.T. Gong, R.J. Tang, Y.J. Yang, The pivotal roles of exosomes derived from endogenous immune cells and exogenous stem cells in myocardial repair after acute myocardial infarction, Theranostics 11 (2021) 1046–1058.

[83] M. Gnecchi, H. He, O.D. Liang, L.G. Melo, F. Morello, H. Mu, N. Noiseux, L. Zhang, R.E. Pratt, J.S. Ingwall, V.J. Dzau, Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells, Nat. Med. 11 (2005) 367–368.

[84] H. Zhang, M. Xiang, D. Meng, N. Sun, S. Chen, Inhibition of myocardial ischemia/reperfusion injury by exosomes secreted from mesenchymal stem cells, Stem Cell. Int. 2016 (2016) 4328362.

[85] Z. Wen, Z. Mai, X. Zhu, T. Wu, Y. Chen, D. Geng, J. Wang, Mesenchymal stem cell-derived exosomes ameliorate cardiomyocyte apoptosis in hypoxic conditions through microRNA144 by targeting the PTEN/AKT pathway, Stem Cell Res. Ther. 11 (2020) 36.

[86] Y. Peng, J.L. Zhao, Z.Y. Peng, W.F. Xu, G.L. Yu, Exosomal miR-25-3p from mesenchymal stem cells alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2, Cell Death Dis. 11 (2020) 317.

[87] X. Zhang, X. Wang, H. Zhu, E.G. Kranias, Y. Tang, T. Peng, J. Chang, G.C. Fan, Hsp20 functions as a novel cardiokine in promoting angiogenesis via activation of VEGFR2, PLoS One 7 (2012) e32765.

[88] K.R. Vrijsen, J.A. Maring, S.A. Chamuleau, V. Verhage, E.A. Mol, J.C. Deddens, C. H. Metz, K. Lodder, E.C. van Eeuwijk, S.M. van Dommelen, P.A. Doevendans, A. M. Smits, M.J. Goumans, J.P. Sluijter, Exosomes from cardiomyocyte progenitor cells and mesenchymal stem cells stimulate angiogenesis via EMMPRIN, Adv. Healthcare Mater. 5 (2016) 2555–2565.

[89] N. He, Y. Zhang, S. Zhang, D. Wang, H. Ye, Exosomes: cell-free therapy for cardiovascular diseases, J Cardiovasc Transl Res 13 (2020) 713–721.

[90] Y. Cheng, Y. Wang, R. Yin, Y. Xu, L. Zhang, Y. Zhang, L. Yang, D. Zhao, Central role of cardiac fibroblasts in myocardial fibrosis of diabetic cardiomyopathy, Front. Endocrinol. 14 (2023) 1162754.

[91] Y. Feng, W. Huang, M. Wani, X. Yu, M. Ashraf, Ischemic preconditioning potentiates the protective effect of stem cells through secretion of exosomes by targeting Mecp2 via miR-22, PLoS One 9 (2014) e88685.

[92] L.P. Zhu, T. Tian, J.Y. Wang, J.N. He, T. Chen, M. Pan, L. Xu, H.X. Zhang, X. T. Qiu, C.C. Li, K.K. Wang, H. Shen, G.G. Zhang, Y.P. Bai, Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction, Theranostics 8 (2018) 6163–6177.

[93] J. Zhu, K. Lu, N. Zhang, Y. Zhao, Q. Ma, J. Shen, Y. Lin, P. Xiang, Y. Tang, X. Hu, J. Chen, W. Zhu, K.A. Webster, J. Wang, H. Yu, Myocardial reparative functions of exosomes from mesenchymal stem cells are enhanced by hypoxia treatment of the

cells via transferring microRNA-210 in an nSMase2-dependent way, Artif. Cells, Nanomed. Biotechnol. 46 (2018) 1659–1670.

[94] P. Huang, L. Wang, Q. Li, X. Tian, J. Xu, J. Xu, Y. Xiong, G. Chen, H. Qian, C. Jin, Y. Yu, K. Cheng, L. Qian, L. Yang, Atorvastatin enhances the therapeutic efficacy of mesenchymal stem cells-derived exosomes in acute myocardial infarction via up-regulating long non-coding RNA H19, Cardiovasc. Res. 116 (2020) 353–367.

[95] L. Barile, E. Cervio, V. Lionetti, G. Milano, A. Ciullo, V. Biemmi, S. Bolis, C. Altomare, M. Matteucci, D. Di Silvestre, F. Brambilla, T.E. Fertig, T. Torre, S. Demertzis, P. Mauri, T. Moccetti, G. Vassalli, Cardioprotection by cardiac progenitor cell-secreted exosomes: role of pregnancy-associated plasma protein-A, Cardiovasc. Res. 114 (2018) 992–1005.

[96] W.D. Gray, K.M. French, S. Ghosh-Choudhary, J.T. Maxwell, M.E. Brown, M. O. Platt, C.D. Searles, M.E. Davis, Identification of therapeutic covariant microRNA clusters in hypoxia-treated cardiac progenitor cell exosomes using systems biology, Circ. Res. 116 (2015) 255–263.

[97] A. Kervadec, V. Bellamy, N. El Harane, L. Arakélian, V. Vanneaux, I. Cacciapuoti, H. Nemetalla, M.C. Périer, H.D. Toeg, A. Richart, M. Lemitre, M. Yin, X. Loyer, J. Larghero, A. Hagège, M. Ruel, C.M. Boulanger, J.S. Silvestre, P. Menasché, N. K. Renault, Cardiovascular progenitor-derived extracellular vesicles recapitulate the beneficial effects of their parent cells in the treatment of chronic heart failure, J. Heart Lung Transplant. 35 (2016) 795–807.

[98] Z. Zhang, J. Yang, W. Yan, Y. Li, Z. Shen, T. Asahara, Pretreatment of cardiac stem cells with exosomes derived from mesenchymal stem cells enhances myocardial repair, J. Am. Heart Assoc. 5 (2016).

[99] R.R. Makkar, R.R. Smith, K. Cheng, K. Malliaras, L.E. Thomson, D. Berman, L. S. Czer, L. Marbán, A. Mendizabal, P.V. Johnston, S.D. Russell, K.H. Schuleri, A. C. Lardo, G. Gerstenblith, E. Marbán, Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial, Lancet 379 (2012) 895–904.

[100] T. Chakravarty, R.R. Makkar, D.D. Ascheim, J.H. Traverse, R. Schatz, A. DeMaria, G.S. Francis, T.J. Povsic, R.R. Smith, J.A. Lima, J.M. Pogoda, L. Marbán, T. D. Henry, ALLogeneic heart STem cells to achieve myocardial regeneration (ALLSTAR) trial: rationale and design, Cell Transplant. 26 (2017) 205–214.

[101] E.A. Mol, M.J. Goumans, J.P.G. Sluijter, Cardiac progenitor-cell derived exosomes as cell-free therapeutic for cardiac repair, Adv. Exp. Med. Biol. 998 (2017) 207–219.

[102] L. Cambier, G. de Couto, A. Ibrahim, A.K. Echavez, J. Valle, W. Liu, M. Kreke, R. R. Smith, L. Marbán, E. Marbán, Y RNA fragment in extracellular vesicles confers cardioprotection via modulation of IL-10 expression and secretion, EMBO Mol. Med. 9 (2017) 337–352.

[103] E.A. Mayhall, N. Paffett-Lugassy, L.I. Zon, The clinical potential of stem cells, Curr. Opin. Cell Biol. 16 (2004) 713–720.

[104] Y. Wang, L. Zhang, Y. Li, L. Chen, X. Wang, W. Guo, X. Zhang, G. Qin, S.H. He, A. Zimmerman, Y. Liu, I.M. Kim, N.L. Weintraub, Y. Tang, Exosomes/ microvesicles from induced pluripotent stem cells deliver cardioprotective miRNAs and prevent cardiomyocyte apoptosis in the ischemic myocardium, Int. J. Cardiol. 192 (2015) 61–69.

[105] G. Ikeda, M.R. Santoso, Y. Tada, A.M. Li, E. Vaskova, J.H. Jung, C. O'Brien, E. Egan, J. Ye, P.C. Yang, Mitochondria-rich extracellular vesicles from autologous stem cell-derived cardiomyocytes restore energetics of ischemic myocardium, J. Am. Coll. Cardiol. 77 (2021) 1073–1088.

[106] S. Sahoo, E. Klychko, T. Thorne, S. Misener, K.M. Schultz, M. Millay, A. Ito, T. Liu, C. Kamide, H. Agrawal, H. Perlman, G. Qin, R. Kishore, D.W. Losordo, Exosomes from human CD34(+) stem cells mediate their proangiogenic paracrine activity, Circ. Res. 109 (2011) 724–728.

[107] E.A. Woodcock, S.J. Matkovich, Cardiomyocytes structure, function and associated pathologies, Int. J. Biochem. Cell Biol. 37 (2005) 1746–1751.

[108] S. Gupta, A.A. Knowlton, HSP60 trafficking in adult cardiac myocytes: role of the exosomal pathway, Am. J. Physiol. Heart Circ. Physiol. 292 (2007) H3052–H3056.

[109] Z.A. Malik, K.S. Kott, A.J. Poe, T. Kuo, L. Chen, K.W. Ferrara, A.A. Knowlton, Cardiac myocyte exosomes: stability, HSP60, and proteomics, Am. J. Physiol. Heart Circ. Physiol. 304 (2013) H954–H965.

[110] X. Yu, L. Deng, D. Wang, N. Li, X. Chen, X. Cheng, J. Yuan, X. Gao, M. Liao, M. Wang, Y. Liao, Mechanism of TNF-α autocrine effects in hypoxic cardiomyocytes: initiated by hypoxia inducible factor 1α, presented by exosomes, J. Mol. Cell. Cardiol. 53 (2012) 848–857.

[111] Y. Yang, Y. Li, X. Chen, X. Cheng, Y. Liao, X. Yu, Exosomal transfer of miR-30a between cardiomyocytes regulates autophagy after hypoxia, J. Mol. Med. (Berl.) 94 (2016) 711–724.

[112] T.M. Ribeiro-Rodrigues, T.L. Laundos, R. Pereira-Carvalho, D. Batista-Almeida, R. Pereira, V. Coelho-Santos, A.P. Silva, R. Fernandes, M. Zuzarte, F.J. Enguita, M. C. Costa, P. Pinto-do-Ó, M.T. Pinto, P. Gouveia, L. Ferreira, J.C. Mason, P. Pereira, B.R. Kwak, D.S. Nascimento, H. Girão, Exosomes secreted by cardiomyocytes subjected to ischaemia promote cardiac angiogenesis, Cardiovasc. Res. 113 (2017) 1338–1350.

[113] N. Gennebäck, U. Hellman, L. Malm, G. Larsson, G. Ronquist, A. Waldenström, S. Mörner, Growth factor stimulation of cardiomyocytes induces changes in the transcriptional contents of secreted exosomes, J. Extracell. Vesicles 2 (2013).

[114] X. Wang, W. Huang, G. Liu, W. Cai, R.W. Millard, Y. Wang, J. Chang, T. Peng, G. C. Fan, Cardiomyocytes mediate anti-angiogenesis in type 2 diabetic rats through the exosomal transfer of miR-320 into endothelial cells, J. Mol. Cell. Cardiol. 74 (2014) 139–150.

[115] B.W. van Balkom, O.G. de Jong, M. Smits, J. Brummelman, K. den Ouden, P.M. de Bree, M.A. van Eijndhoven, D.M. Pegtel, W. Stoorvogel, T. Würdinger, M. C. Verhaar, Endothelial cells require miR-214 to secrete exosomes that suppress

[116] C. Bang, S. Batkai, S. Dangwal, S.K. Gupta, A. Foinquinos, A. Holzmann, A. Just, J. Remke, K. Zimmer, A. Zeug, E. Ponimaskin, A. Schmiedl, X. Yin, M. Mayr, R. Halder, A. Fischer, S. Engelhardt, Y. Wei, A. Schober, J. Fiedler, T. Thum, Cardiac fibroblast-derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy, J. Clin. Invest. 124 (2014) 2136–2146.

[117] L. Lyu, H. Wang, B. Li, Q. Qin, L. Qi, M. Nagarkatti, P. Nagarkatti, J.S. Janicki, X. L. Wang, T. Cui, A critical role of cardiac fibroblast-derived exosomes in activating renin angiotensin system in cardiomyocytes, J. Mol. Cell. Cardiol. 89 (2015) 268–279.

[118] Z. Liao, Y. Chen, C. Duan, K. Zhu, R. Huang, H. Zhao, M. Hintze, Q. Pu, Z. Yuan, L. Lv, H. Chen, B. Lai, S. Feng, X. Qi, D. Cai, Cardiac telocytes inhibit cardiac microvascular endothelial cell apoptosis through exosomal miRNA-21-5p-targeted cdip1 silencing to improve angiogenesis following myocardial infarction, Theranostics 11 (2021) 268–291.

[119] H. Liu, W. Gao, J. Yuan, C. Wu, K. Yao, L. Zhang, L. Ma, J. Zhu, Y. Zou, J. Ge, Exosomes derived from dendritic cells improve cardiac function via activation of CD4(+) T lymphocytes after myocardial infarction, J. Mol. Cell. Cardiol. 91 (2016) 123–133.

[120] S.M. Davidson, K. Takov, D.M. Yellon, Exosomes and cardiovascular protection, Cardiovasc. Drugs Ther. 31 (2017) 77–86.

[121] Y. D'Alessandra, P. Devanna, F. Limana, S. Straino, A. Di Carlo, P.G. Brambilla, M. Rubino, M.C. Carena, L. Spazzafumo, M. De Simone, B. Micheli, P. Biglioli, F. Achilli, F. Martelli, S. Maggiolini, G. Marenzi, G. Pompilio, M.C. Capogrossi, Circulating microRNAs are new and sensitive biomarkers of myocardial infarction, Eur. Heart J. 31 (2010) 2765–2773.

[122] E.E. Creemers, E. van Rooij, Function and therapeutic potential of noncoding RNAs in cardiac fibrosis, Circ. Res. 118 (2016) 108–118.

[123] J.M. Vicencio, D.M. Yellon, V. Sivaraman, D. Das, C. Boi-Doku, S. Arjun, Y. Zheng, J.A. Riquelme, J. Kearney, V. Sharma, G. Multhoff, A.R. Hall, S.M. Davidson, Plasma exosomes protect the myocardium from ischemia-reperfusion injury, J. Am. Coll. Cardiol. 65 (2015) 1525–1536.

[124] Z. Giricz, Z.V. Varga, T. Baranyai, P. Sipos, K. Pálóczi, Á. Kittel, E.I. Buzás, P. Ferdinandy, Cardioprotection by remote ischemic preconditioning of the rat heart is mediated by extracellular vesicles, J. Mol. Cell. Cardiol. 68 (2014) 75–78.

[125] D. Ha, N. Yang, V. Nadithe, Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges, Acta Pharm. Sin. B 6 (2016) 287–296.

[126] E.L.A. S, I. Mäger, X.O. Breakefield, M.J. Wood, Extracellular vesicles: biology and emerging therapeutic opportunities, Nat. Rev. Drug Discov. 12 (2013) 347–357.

[127] X. Zhuang, X. Xiang, W. Grizzle, D. Sun, S. Zhang, R.C. Axtell, S. Ju, J. Mu, L. Zhang, L. Steinman, D. Miller, H.G. Zhang, Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain, Mol. Ther. 19 (2011) 1769–1779.

[128] A. Pessina, A. Bonomi, V. Coccè, G. Invernici, S. Navone, L. Cavicchini, F. Sisto, M. Ferrari, L. Viganò, A. Locatelli, E. Ciusani, G. Cappelletti, D. Cartelli, C. Arnaldo, E. Parati, G. Marfia, R. Pallini, M.L. Falchetti, G. Alessandri, Mesenchymal stromal cells primed with paclitaxel provide a new approach for cancer therapy, PLoS One 6 (2011) e28321.

[129] M. Tokutome, T. Matoba, Y. Nakano, A. Okahara, M. Fujiwara, J.I. Koga, K. Nakano, H. Tsutsui, K. Egashira, Peroxisome proliferator-activated receptor-gamma targeting nanomedicine promotes cardiac healing after acute myocardial infarction by skewing monocyte/macrophage polarization in preclinical animal models, Cardiovasc. Res. 115 (2019) 419–431.

[130] M.J. Haney, N.L. Klyachko, Y. Zhao, R. Gupta, E.G. Plotnikova, Z. He, T. Patel, A. Piroyan, M. Sokolsky, A.V. Kabanov, E.V. Batrakova, Exosomes as drug delivery vehicles for Parkinson's disease therapy, J. Contr. Release 207 (2015) 18–30.

[131] H. Yu, K. Lu, J. Zhu, J. Wang, Stem cell therapy for ischemic heart diseases, Br. Med. Bull. 121 (2017) 135–154.

[132] X. Ai, S. Wang, Y. Duan, Q. Zhang, M.S. Chen, W. Gao, L. Zhang, Emerging approaches to functionalizing cell membrane-coated nanoparticles, Biochemistry 60 (2021) 941–955.

[133] A. Vandergriff, K. Huang, D. Shen, S. Hu, M.T. Hensley, T.G. Caranasos, L. Qian, K. Cheng, Targeting regenerative exosomes to myocardial infarction using cardiac homing peptide, Theranostics 8 (2018) 1869–1878.

[134] Y. Wang, K. Zhang, X. Qin, T. Li, J. Qiu, T. Yin, J. Huang, S. McGinty, G. Pontrelli, J. Ren, Q. Wang, W. Wu, G. Wang, Biomimetic nanotherapies: red blood cell based core-shell structured nanocomplexes for atherosclerosis management, Adv. Sci. 6 (2019) 1900172.

[135] R. Rampado, P. Caliceti, M. Agostini, Latest advances in biomimetic cell membrane-coated and membrane-derived nanovectors for biomedical applications, Nanomaterials 12 (2022).

[136] M. Imran, L.A. Jha, N. Hasan, J. Shrestha, R. Pangeni, N. Parvez, Y. Mohammed, S.K. Jha, K.R. Paudel, "Nanodecoys" - future of drug delivery by encapsulating nanoparticles in natural cell membranes, Int. J. Pharm. 621 (2022) 121790.

[137] G. Wu, W. Wei, J. Zhang, W. Nie, L. Yuan, Y. Huang, L. Zuo, L. Huang, X. Xi, H. Y. Xie, A self-driven bioinspired nanovehicle by leukocyte membrane-hitchhiking for early detection and treatment of atherosclerosis, Biomaterials 250 (2020) 119963.

[138] C. Gao, Q. Huang, C. Liu, C.H.T. Kwong, L. Yue, J.B. Wan, S.M.Y. Lee, R. Wang, Treatment of atherosclerosis by macrophage-biomimetic nanoparticles via targeted pharmacotherapy and sequestration of proinflammatory cytokines, Nat. Commun. 11 (2020) 2622.

[139] C.M. Hu, L. Zhang, S. Aryal, C. Cheung, R.H. Fang, L. Zhang, Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 10980–10985.

[140] P.A. Oldenborg, A. Zheleznyak, Y.F. Fang, C.F. Lagenaur, H.D. Gresham, F. P. Lindberg, Role of CD47 as a marker of self on red blood cells, Science 288 (2000) 2051–2054.

[141] N. Legrand, N.D. Huntington, M. Nagasawa, A.Q. Bakker, R. Schotte, H. Strick-Marchand, S.J. de Geus, S.M. Pouw, M. Böhne, A. Voordouw, K. Weijer, J.P. Di Santo, H. Spits, Functional CD47/signal regulatory protein alpha (SIRP(alpha)) interaction is required for optimal human T- and natural killer- (NK) cell homeostasis in vivo, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 13224–13229.

[142] B. Ma, H. Xu, Y. Wang, L. Yang, W. Zhuang, G. Li, Y. Wang, Biomimetic-coated nanoplatform with lipid-specific imaging and ROS responsiveness for atherosclerosis-targeted theranostics, ACS Appl. Mater. Interfaces 13 (2021) 35410–35421.

[143] K. Huang, S. Wen, W. Wang, J.E. Zhou, J. Huang, F. Wang, L. Pang, Y. Wang, X. Sun, Erythrocyte membrane coated nanoparticle-based control releasing hydrogen sulfide system protects ischemic myocardium, Nanomedicine (Lond) 16 (2021) 465–480.

[144] C.M. Hu, R.H. Fang, K.C. Wang, B.T. Luk, S. Thamphiwatana, D. Dehaini, P. Nguyen, P. Angsantikul, C.H. Wen, A.V. Kroll, C. Carpenter, M. Ramesh, V. Qu, S.H. Patel, J. Zhu, W. Shi, F.M. Hofman, T.C. Chen, W. Gao, K. Zhang, S. Chien, L. Zhang, Nanoparticle biointerfacing by platelet membrane cloaking, Nature 526 (2015) 118–121.

[145] B. Choi, W. Park, S.B. Park, W.K. Rhim, D.K. Han, Recent trends in cell membrane-cloaked nanoparticles for therapeutic applications, Methods 177 (2020) 2–14.

[146] C. Gao, Z. Wu, Z. Lin, X. Lin, Q. He, Polymeric capsule-cushioned leukocyte cell membrane vesicles as a biomimetic delivery platform, Nanoscale 8 (2016) 3548–3554.

[147] Y. Zhang, K. Cai, C. Li, Q. Guo, Q. Chen, X. He, L. Liu, Y. Zhang, Y. Lu, X. Chen, T. Sun, Y. Huang, J. Cheng, C. Jiang, Macrophage-membrane-coated nanoparticles for tumor-targeted chemotherapy, Nano Lett. 18 (2018) 1908–1915.

[148] N.E. Toledano Furman, Y. Lupu-Haber, T. Bronshtein, L. Kaneti, N. Letko, E. Weinstein, L. Baruch, M. Machluf, Reconstructed stem cell nanoghosts: a natural tumor targeting platform, Nano Lett. 13 (2013) 3248–3255.

[149] Y. Zhang, N. Yang, X. Huang, Y. Zhu, S. Gao, Z. Liu, F. Cao, Y. Wang, Melatonin engineered adipose-derived biomimetic nanovesicles regulate mitochondrial functions and promote myocardial repair in myocardial infarction, Front Cardiovasc Med 9 (2022) 789203.

[150] M. Moloudizargari, M.H. Asghari, A. Goel, The therapeutic triad of extracellular vesicles: as drug targets, as drugs, and as drug carriers, Biochem. Pharmacol. 192 (2021) 114714.

[151] P. Yang, J. Ren, L. Yang, Nanoparticles in the new era of cardiovascular therapeutics: challenges and opportunities, Int. J. Mol. Sci. 24 (2023).

[152] W. Meng, C. He, Y. Hao, L. Wang, L. Li, G. Zhu, Prospects and challenges of extracellular vesicle-based drug delivery system: considering cell source, Drug Deliv. 27 (2020) 585–598.

[153] P. Vader, E.A. Mol, G. Pasterkamp, R.M. Schiffelers, Extracellular vesicles for drug delivery, Adv. Drug Deliv. Rev. 106 (2016) 148–156.

[154] K. Pachler, T. Lener, D. Streif, Z.A. Dunai, A. Desgeorges, M. Feichtner, M. Öller, K. Schallmoser, E. Rohde, M. Gimona, A Good Manufacturing Practice-grade standard protocol for exclusively human mesenchymal stromal cell-derived extracellular vesicles, Cytotherapy 19 (2017) 458–472.

[155] S. Dai, D. Wei, Z. Wu, X. Zhou, X. Wei, H. Huang, G. Li, Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer, Mol. Ther. 16 (2008) 782–790.

[156] X. Xu, P.E. Saw, W. Tao, Y. Li, X. Ji, S. Bhasin, Y. Liu, D. Ayyash, J. Rasmussen, M. Huo, J. Shi, O.C. Farokhzad, ROS-responsive polyprodrug nanoparticles for triggered drug delivery and effective cancer therapy, Adv. Mater. 29 (2017).

[157] R. Zhang, R. Liu, C. Liu, L. Pan, Y. Qi, J. Cheng, J. Guo, Y. Jia, J. Ding, J. Zhang, H. Hu, A pH/ROS dual-responsive and targeting nanotherapy for vascular inflammatory diseases, Biomaterials 230 (2020) 119605.

[158] Y. Lin, J. Liu, R. Bai, J. Shi, X. Zhu, J. Liu, J. Guo, W. Zhang, H. Liu, Z. Liu, Mitochondria-inspired nanoparticles with microenvironment-adapting capacities for on-demand drug delivery after ischemic injury, ACS Nano 14 (2020) 11846–11859.

[159] B.F. Zhang, H. Jiang, J. Chen, Q. Hu, S. Yang, X.P. Liu, Silica-coated magnetic nanoparticles labeled endothelial progenitor cells alleviate ischemic myocardial injury and improve long-term cardiac function with magnetic field guidance in rats with myocardial infarction, J. Cell. Physiol. 234 (2019) 18544–18559.