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From exosomes to mitochondria and myocardial infarction: Molecular insight and therapeutic challenge

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ABSTRACT

Myocardial infarction (MI) remains a leading cause of mortality worldwide. Despite patients with MI benefit from timely reperfusion therapies, the rates of mortality and morbidity remain substantial, suggesting an enduring need for the development of new approaches. Molecular mechanisms underlying myocardial ischemic injury are associated with both cardiomyocytes and non-cardiomyocytes. Exosomes are nano-sized extracellular vesicles released by almost all eukaryotic cells. They facilitate the communication between various cells by transferring information via their cargo and altering different biological activities in recipient cells. Studies have created great prospects for therapeutic applications of exosomes in MI, as demonstrated through their beneficial effect on heart function and reducing ventricular remodeling in association with fibrosis, angiogenesis, apoptosis, and inflammation. Of note, myocardial ischemic injury is primarily due to restricted blood flow, reducing oxygen availability, and causing inefficient utilization of energy substrates. However, the impact of exosomes on cardiac energy metabolism has not been adequately investigated. Although exosomes have been engineered for targeted delivery to enhance clinical efficacy, challenges must be overcome to utilize them reliably in the clinic. In this review, we summarize the research progress of exosomes for MI with a focus on the known and unknown regarding the role of exosomes in energy metabolism in cardiomyocytes and non-cardiomyocytes; as well as potential research avenues of exosome-mitochondrial energy regulation as well as therapeutic challenges. We aim to help identify more efficient molecular targets that may promote the clinical application of exosomes.

List of abbreviations: MI, Myocardial infarction; HF, Heart failure; ATP, Adenosine triphosphate; TCA, Tricarboxylic acid; ROS, Reactive oxygen species; NO, Nitric oxide; EC, Endothelial cell; CDC, Cardio-sphere-derived cells; MSC, Mesenchymal stem cell; IPSC, Induced pluripotent stem cell; FEXO, Cardiac exosomes from healthy failing hearts; NEXO, Cardiac exosomes from healthy donor hearts; FA, Fatty acids; HIF-1α, Hypoxia-inducible factor-1α; PPP, Pentose phosphate pathway; NADPH, Nicotinamide adenine dinucleotide phosphate; VEGF, Vascular endothelial growth factor; CoA, Coenzyme A; SGLT2i, Sodium-glucose cotransporter-2 inhibitors; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; HKII, Hexokinase II; BCAA, Branched-chain amino acid; I/R, Ischemia/reperfusion; TCA cycle, Tricarboxylic acid cyclesd; GTP, Guanosine triphosphate; HAD, Hyaluronic acid-g-2-aminoethyl methacrylate hydrochloride-dopamine; TGF-b, Transforming growth factor-β; MtROS, Mitochondrial reactive oxygen species; MtCa2+, Mitochondrial calcium; BRD4, Bromodomain-containing protein 4; MR, Magnetic resonance; FOXO, Forkhead box protein O; PET, Positron emission tomography; MRS, MR spectroscopy; 31P, 31phosphorus; PCr, Phosphocreatine; LncRNA, Long non-coding RNA; NF-Kb, Nuclear factor kappa-B.

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1. Introduction

Myocardial infarction (MI) represents a leading cause of mortality worldwide due to the subsequently developed myocardial remodeling and heart failure (HF) [1,2]. Although MI patients benefit from revascularization and reperfusion therapies, the mortality rates are substantial post-percutaneous coronary intervention and coronary artery bypass grafting, putting an immense burden on society [3].This necessitates the development of new approaches to restore cardiac function.

1.1. What makes exosomes more special than other extracellular molecules in clinical applications of MI

Among the new approaches, tissue engineering, cell therapy, and protein therapy have the potential to limit cardiac damage and improve cardiac function post-MI. Although stem cell-based therapies have entered clinical investigations worldwide, they can not meet clinical requirements, due to unfavorable drawbacks and challenges [4]. Interestingly, many of the beneficial effects of stem cell therapy are mainly through the secretion of regenerative factors or extracellular vesicles (EVs) *via* interactions with the injured cells, indicative of secretory action, rather than cell replacement and differentiation mechanisms [5]. The EVs are classified into three types based on their diameters: apoptotic bodies (800–5000 nm), micro-vesicles (50–1000 nm) and exosomes (40–160 nm) [6]. Thus, cell-free therapy, a new way of using stem cells without the need for cell transplantation, has been explored in numerous studies, through which, exosomes are gradually becoming a leading star in intercellular communication [7].

The biogenesis of exosomes has been extensively discussed elsewhere [6,8]. Exosomes can secrete from most cell types [6], and deliver cargo including nucleic acids, proteins, and lipids to the recipient cells under physiological and pathological conditions, thereby regulating the fate of recipient cells through paracrine and autocrine mechanisms [6]. Exosomes are more stable than cells as they avoid opsonin's and coagulation factors. Because of enrichment in lipids, they protect cargo from degradation in the extracellular environment. Thus, they are special, at least, in two ways. First, exosomes acquire their complex cargo through intracellular processes, intimately linking them to the development of diseases, therefore being attractive sources of biomarkers for the diagnosis and prognosis of diseases [9,10]. Second, because of their natural biocompatibility, exosomes can be engineered through several modifications, such as adding specific receptors or targeting peptides to specific organs or cells [11–13], which can greatly increase the efficacy of drugs at the targeted sites to impart ultimate therapeutic effects.

1.2. Importance of mitochondrial metabolism in MI heart

Evidence has demonstrated that even partial recovery of cardiac function from MI is always difficult due to severe mitochondrial impairment [14]. Given that the heart requires a large amount of energy to support its contractility and electrical conduction, which is carried out by the intensified mitochondrial network in cardiomyocytes, decades of research have demonstrated that alterations of energy metabolism often precede ventricular function and remodeling changes [15–17]. The impaired energetics in cardiomyocytes directly contribute to cardiac injury severity post-MI [18,19], through defective substrate utilization, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation [20–22]. Apart from providing ATP, the roles of mitochondria encompass diverse regulating activities, such as apoptosis, cell proliferation, and differentiation, reactive oxygen species (ROS) signaling [23], inflammatory processes [24,25], ion homeostasis [26] as well as mitochondrial quality control [27]. Likewise, impaired energy metabolism also occurs in non-cardiomyocytes in MI heart, which contributes to cardiac remodeling through the secretion of paracrine factors, such as the nitric oxide (NO), released by endothelial NO synthase exerts beneficial effects on the remodeling process by reducing cardiac myocyte hypertrophy [28,29] and factors in association with inflammation, extracellular matrix, and coupling of gap junction [30,31]. More importantly, impaired cardiac energetics independently predict clinical mortality of HF [23]. From the therapeutic perspective, despite the effective therapies for improving energy supply in the failing heart remain lacking, due, in part, to limited knowledge regarding how effectively restore cardiac mitochondrial biogenesis and oxidative capacity, it is noteworthy that some approaches targeting the mitochondria reached the bedside [32,33], such as the treatment of thyroid hormone appears to have a reparative action on the cardiac functional recovery in patients with large infarct size through mitochondrial preservation [34]. Exosomes can modulate cell differentiation, proliferation, and angiogenesis, which are energy-consuming processes, thus, a timely question is whether and how exosomes regulate these processes through improving energy metabolism in the MI heart.

Here we briefly highlight the well-established effect of exosomes in MI heart but focus on the evidence implicating the involvement of exosome-mediated mitochondrial signaling and energy metabolism. We discuss the challenges that must be overcome before promoting using of exosomes in clinical testing and applications.

2. Exosomes ameliorate heart dysfunction in MI

2.1. Sources of exosomes

Exosomes can be classified as natural and engineered exosomes (Fig. 1). Natural exosomes are natively derived from plants and animals through mammalian cells and biofluids, including blood, urine, amniotic fluid, saliva, milk, malignant ascites, synovial fluid, and cerebrospinal fluid [35,36]. Engineered exosomes are natural exosomes with genetic or structural modifications. The modified exosomes can be loaded with specific short interfering RNAs, antisense oligonucleotides, chemotherapeutic agents, and immune modulators, or exhibit increased ability to escape immune system attack [37,38], and to target the injury sites [39–41].

2.1.1. Cardiac exosomes

Cardiac cells consist of various types of cells including cardiomyocytes and non-cardiomyocytes, such as endothelial cells (ECs), fibroblasts, and immune cells (mostly macrophages). Cardiac cells are not typical secretory cells but have proven to secrete exosomes [42], of which, levels and compositions are affected by the cell origin and the pathophysiological conditions [43,44]. Importantly, cardiomyocytes-derived exosomes can be taken up by non-cardiomyocytes [45], or vice versa during stress and pathological conditions, thereby modifying gene expression to regulate receiving cell behaviors [46,47]. It is noteworthy that most studies with cardiac fibroblast-derived exosomes failed to improve cardiac remodeling [48,49]. In contrast, Papini et al. recently demonstrated that the uptake of fibroblast-derived exosomes by cardiomyocytes could be increased by pre-treatment of fibroblasts with sulforaphane, an edible plant-derived chemical [50]. The resulting exosomes exert cardioprotection by reversing cardiac remodeling in a rat MI model [51]. This finding suggests the therapeutic importance, as natural compounds may reprogram non-cardiac cells, such as fibroblasts, which are commonly used in generating clinical-grade exosomes for treating various human diseases [52], as such, they can become a valuable source of anti-remodeling exosomes. Certainly, the regulatory mechanisms of cargo sorting and exosome secretion remain poorly understood and encourage future thorough investigations.

2.1.2. Stem cell-derived exosomes

There are two major types of stem cells, embryonic stem cells and adult stem cells. Since the use of human embryonic stem cells involves ethical and legal considerations [53], adult stem cell-derived exosomes have been preclinically explored in MI hearts with small (mouse, rat)

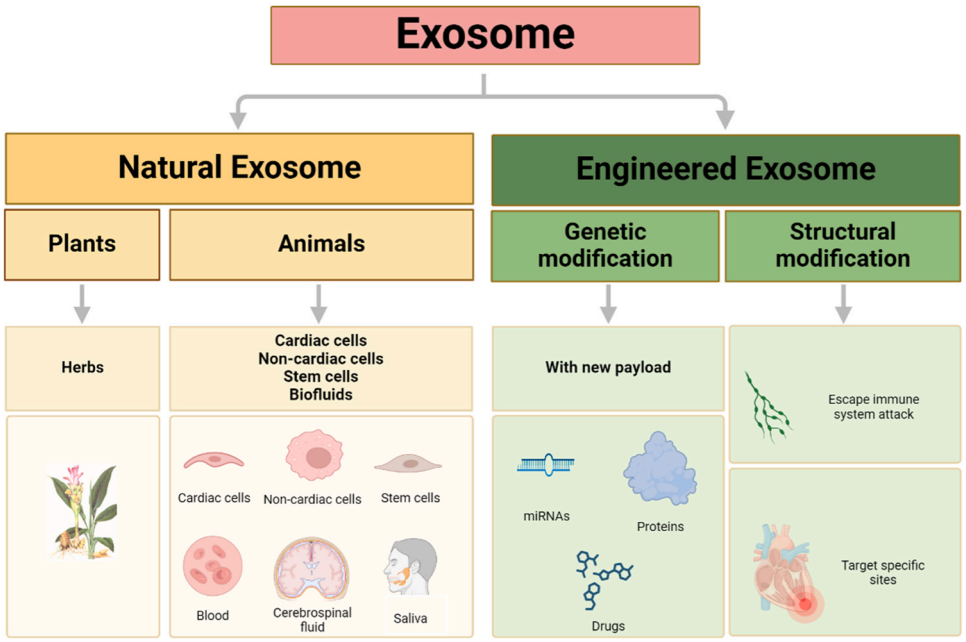

Fig. 1. Sources of exosomes for the heart. Generally, exosomes can be classified as natural and engineered exosomes. Natural exosomes are natively derived from plants (herbs et al.), and mammal animals through isolation from various cells and biofluids, including blood, urine, amniotic fluid, saliva, milk, malignant ascites, synovial fluid, and cerebrospinal fluid. Engineered exosomes are natural exosomes modified genetically or structurally, resulting in either a payload of specific short interfering RNAs, antisense oligonucleotides, chemotherapeutic agents, and immune modulators or an increased ability to escape immune system attack and enhanced capability to target the injury sites. (Created with BioRender.com).

[54], and large animals (pig and swine) models [55]. Stem cell-derived exosomes can be cardiac lineage, such as cardio-sphere-derived cells (CDC) [56,57] or non-cardiac lineages, such as mesenchymal stem cells (MSC), which can be isolated from a variety of adult tissues, and induced pluripotent stem cells (iPSC) that can be reprogrammed through inducing genes and factors to be the source of cardiomyocytes, smooth muscle cells, and endothelial cells [58,59].

2.2. Contributions of exosomes on reducing cardiac injury in MI heart

By simplified explanation, the mechanisms underlying myocardial remodeling are associated with the alterations within cardiomyocytes, such as energy metabolic changes induced loss of cardiomyocytes, and the microenvironmental changes around cardiomyocytes, such as replacement of resident macrophages by infiltrating monocytes [60]. As a result, inflammation is initiated, as is the proliferation of fibroblasts and damage to ECs.

Exosomes-mediated paracrine signaling is believed to regulate much of the cardiovascular benefit through modulating myocardial remodeling processes in MI [61]. For example, Tseliou et al. demonstrated that CDC-derived exosomes reduced scar size and improved cardiac function by converting inert dermal fibroblasts into therapeutically active cells in female Wistar Kyoto rats hearts with chronic MI [62]. This was also true in injured mouse hearts [63], and pig hearts following ischemia and reperfusion (I/R) [54]. In addition, Wang et al. compared the paracrine effect of human MSC-derived exosomes from three sources, including bone marrow, adipose, and endometrium, on apoptosis, neovascularization, infarct size, and cardiac function in a rat MI model [64]. They found that exosomal miR-21 is a specifical mediator from human endometrium MSC associated with superior cardioprotection by improving cell survival and angiogenesis [64], Similar findings were also reported by others [62,65,66]. Of note, other types of cardiac cells also secrete exosomes, such as cardiac telocytes mitigate injury after MI [67,68], while epicardial cells-derived exosomes promoted cardiomyocyte proliferation post-MI [69]. However, the potential therapeutic usefulness is less well studied.

Exosomal compositions are largely affected by environmental stimuli [70,71]. More specifically, cardiac stromal cell-derived exosomes from HF patients (FEXO) differ from those from normal donor hearts (NEXO), as reflected by an impaired ability to promote angiogenesis and cardiac function in mouse heart post-MI [71]. Likewise, the release of exosomes from human umbilical vein ECs stimulated by ischemic preconditioning exerted a great cardioprotective effect by delivering cardioprotective signals to cardiomyocytes [72]. Similarly, secretion of MSC-derived exosomal miR-210 was significantly increased under hypoxia relative to normoxia [73], thereby reducing cardiac fibrosis and protecting cells against hypoxia-induced injury [73]. Concerning angiotensin II as a key mediator of post-MI injury, Pizzino et al. demonstrated that plasma exosomal miR-21–5p prevented angiotensin-II induced hypertrophy in HL-1 cardiomyocytes [74]. Interestingly, overexpression of miR-21–5p can shift cellular energy metabolism in H9C2 cells by reducing lipid utilization and up-regulating the glycolytic pathway [75]. Thus, the left unsolved question is the direct link between exosome-mediated myocardial remodeling and energy metabolic changes in cardiac cells.

3. Mitochondrial metabolic alterations during cardiac repair in MI heart

Although the heart is a metabolically versatile organ capable of utilizing various substrates, the preference for substrate utilization is closely associated with the degree of cardiac repair. Thus, the main features of cardiac metabolic changes during MI merit a brief review.

3.1. Metabolic changes in cardiomyocytes during I/R

In a healthy adult heart, the majority of ATP is generated primarily by mitochondrial oxidation, approximately 60–90 % of the ATP from fatty acids (FA) oxidation, 10–40 % from glucose oxidation, and low amount from lactate, ketones, amino acid, or glycolysis [22,76] (Fig. 2). During mild or severe ischemia, both glucose and FA oxidation are reduced due to limited oxygen supply to the heart, thereby accelerating glycolysis to compensate for the shortage of mitochondrial ATP supply

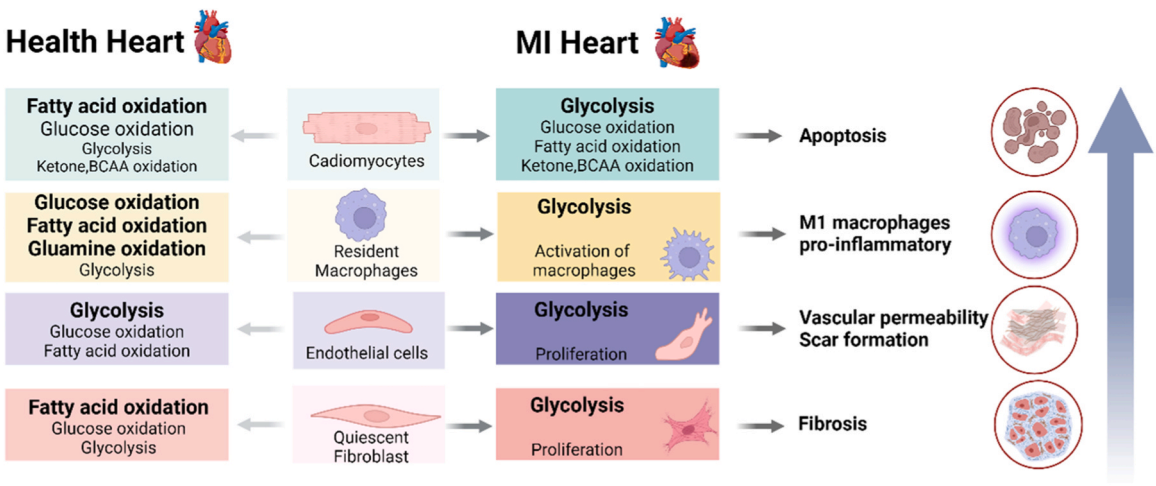

Fig. 2. Metabolic changes during cardiac injury in MI heart. In a healthy adult heart, cardiomyocytes generate ATP primarily through mitochondrial oxidative metabolism from different substrates, such as 60–90 % of the ATP from fatty acids (FA) oxidation, while 10–40 % of the ATP from glucose oxidation, and relatively low amount from lactate, ketones, amino acid, and glycolysis. During severe ischemia, mitochondrial oxidative metabolism is reduced, and glycolysis becomes the major source of ATP production. Likewise, non-activated macrophages are M2-like macrophages, that primarily rely on oxidative phosphorylation to maintain their phenotypes under physiological conditions. During MI, macrophages are polarized to the M1 phenotype, which relies on glycolytic metabolism to support proinflammatory functions. Similarly, adult cardiac fibroblasts are quiescent, and preferentially rely on FA oxidation over glucose utilization. Cardiac fibroblasts undergo metabolic reprogramming by increasing glycolysis in the MI heart, which together with increased levels of glutamine-derived α-ketoglutarate to promote the expression of profibrotic genes, resulting in fibrosis. Unlike other non-cardiomyocytes, quiescent ECs have low metabolic demands and few mitochondria and rely heavily on glycolytic metabolism for ATP production. In acute injury, further increased glycolysis in ECs promotes proliferation, whereas during chronic injury, increased oxidative phosphorylation in ECs leads to EC dysfunction. (Created with BioRender.com).

(Fig. 2), which, however, is insufficient for keeping the contractility, resulting in cardiomyocyte death.

With a reversibly ischemic heart, the contractile function can recover upon reperfusion, but the recovery degree is controlled by the type of substrate metabolized by the heart. Glycolysis is essential for cytosolic Ca^{2+} homeostasis due to the localization of glycolytic enzymes near sarcolemmal ion channels [77]. Once reperfusion occurs, FA oxidation is rapidly increased, as is glycolysis but not glucose oxidation, resulting in uncoupling between glycolysis and glucose oxidation [22]. As a result, the accumulation of lactate and protons requires ATP to re-establish ionic homeostasis rather than supporting contractility [22], which causes cell death and cardiac dysfunction. To the point of FA oxidation, several studies have demonstrated that limiting FA oxidation through inactivation of carnitine palmitoyltransferase 1b (CPT1b) in cardiomyocytes promoted cardiac repair after MI injury [78], and delayed development of HF in rat MI hearts [79,80], which suggests that inhibition of FA oxidation confers protection against MI injury. More importantly, similar cardioprotection was observed in humans [81]. It is noteworthy that CPT1b-dependent inhibition of FA occurred in conjunction with an increase in glucose oxidation in MI hearts [78,80], implicating a compensatory mechanism to support the overall ATP production [78]. Since oxidizing one molecule of FA consumes more oxygen than glucose, increasing glucose oxidation can enhance the coupling between glycolysis and glucose oxidation, thereby reducing proton production to lower the amount of ATP required to counter the ionic imbalance during reperfusion, thereby driving adequate ATP for contractility [82].

3.2. Energy metabolic alterations in non-cardiomyocytes during cardiac remodeling

Cardiac remodeling following MI is an orchestrated series of events. During the injury phase, mitochondrial alterations of cardiomyocytes are prominently involved in their apoptosis and necrosis. Dying cardiomyocytes activate innate and adaptive immune cells to migrate into the infarcted area for clearance of apoptotic cardiomyocytes [83], which also initiates the response of cardiac fibroblasts for fibrosis and damage to ECs. During the healing phase, proinflammatory macrophages become reparative phenotypes [84], which activate cardiac fibroblasts to differentiate into myofibroblasts [85], thereby generating a fibrotic scar to replace lost cardiomyocytes [86], in conjunction with EC activation for post-MI reparative angiogenesis [87].

3.2.1. Energy metabolic changes in macrophages

Although the population of anti-inflammatory neutrophils has been identified at 7 days post MI in infarcted mouse hearts [88], the information regarding their metabolic reprogramming during cardiac remodeling is inadequately addressed, as is in various T-cell subsets during MI [89,90]. Thus, we will focus on macrophages, which can be divided into pro-inflammatory M1 and anti-inflammatory M2 subtypes [91,92].

Under physiological conditions, non-activated macrophages are M2-like phenotype, primarily relying on oxidative phosphorylation [93]. During wound injury, apoptotic cells are removed through efferocytosis [94], which fills macrophages with metabolites and inflammation-resolving bioactive lipids [95]. As a result, activation of cardiac hypoxia-inducible factor-1α (HIF-1α) promotes the expression of pro-inflammatory and glycolytic genes [96], causing polarization of macrophages into the M1 subtype. Mechanistically, glycolysis represents an oxygen-efficient pathway for rapid ATP production in the infarcted myocardium, which provides glycolytic intermediates into the pentose phosphate pathway (PPP), thereby providing NADPH to fuel ROS production and promoting macrophage effector functions [97,98]. Conversely, during wound healing, proinflammatory M1 macrophages become reparative M2 phenotype [84], which is highly oxidative with down-regulation of glycolysis and PPP [96]. M2 macrophages promote the accumulation of α-ketoglutarate, thereby epigenetically down-regulating the pro-inflammatory signaling pathway [99]. Collectively, macrophages require glycolysis for survival, differentiation to the M1 phenotype (Fig. 2), and effector functions, while transforming from M1 to the M2 phenotype is controlled by mitochondrial phosphorylation and epigenetic modifications [85,92].

3.2.2. Energy metabolic changes in cardiac fibroblasts

Under physiological conditions, adult cardiac fibroblasts preferentially rely on fatty acid oxidation (Fig. 2), but utilize more glycolysis following aging [100,101]. During wound injury, cardiac fibroblasts proliferate [102] in conjunction with increased glycolysis [103]. During the repair phase, cardiac fibroblasts are activated and differentiated into myofibroblasts, which are also highly glycolytic [85], and secrete provisional extracellular matrix proteins to facilitate re-epithelialization [104]. However, myofibroblasts can also contribute to pathological fibrosis through their proliferation, resulting in excessive accumulation of extracellular matrix, causing reduced nutrient and oxygen supply and hence promoting cardiac dysfunction [105]. Evidence has shown that excessive glycolysis is associated with impaired epigenetic-mitochondria pathway, resulting in right ventricular fibrosis [106]. Thus, organ fibrotic pathology is a disorder of glycolysis [106].

3.2.3. Energy metabolic changes in ECs

In the adult hearts, ECs are quiescent (absent proliferating and migration) with few mitochondria [107]. Although FA transporters are highly expressed on the cell surface, cardiac ECs mainly rely on glycolysis rather than oxidative phosphorylation as the major source of ATP production, which reserves FA for being transported into cardiomyocytes [108].

Glycolysis in ECs plays a critical role in the regulation of angiogenesis [22,23]. ECs possess much higher glycolytic activity than cardiomyocytes and other cell types [26]. During cardiac remodeling, this property enables quiescent ECs to switch into an activated phenotype for proliferation [109], in part, through upregulating the expression of 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase, isoform 3, a key glycolytic enzyme [110,111], while also activating HIF-1α, which, in turn, activates the transcription of key angiogenic genes, such as vascular endothelial growth factor (VEGF) [112]. Conversely, mice with impaired HIF-1α signaling and glucose uptake displayed defective angiogenesis, capillary rarefaction, and diastolic dysfunction [112]. Evidence has shown that epigenetic disruption of mitochondrial dynamics in ECs promoted vascular senescence [113], which suggests that epigenetic-metabolic mechanisms control EC function [114].

4. Metabolic therapeutic considerations with exosomes in MI and remaining questions

4.1. Strategies for metabolic modulation in MI heart

Several approaches have been investigated, such as directly lowering circulating free FA levels while increasing glycolysis, thereby decreasing cardiac FA uptake to reduce FA oxidation [115], which, however, did not show a clear consensus regarding the clinical benefit for patients with acute MI [116]. Alternatively, pharmacological agents modulating enzymes involved in inhibiting FA oxidation have been investigated, such as trimetazidine, which selectively inhibits long-chain 3-ketoacyl--CoA thiolase activity and stimulating pyruvate dehydrogenase activity, resulting in reduced FA oxidation and increased myocardial glucose oxidation [117]. Clinical studies have confirmed the anti-ischemic properties of trimetazidine [118], and short-term effectiveness on cardiac functional recovery post-MI [119,120], but the long-term efficacy has not been established.

To date, the most promising drugs for improving outcomes of MI through metabolic mechanisms are the sodium-glucose cotransporter-2 inhibitors (SGLT2i), such as dapagliflozin and empagliflozin) [121–123], which largely improved ejection fraction for over 26 weeks in patients with acute MI [124]. Interestingly, SGLT2i have direct effects on both cardiomyocytes and non-cardiomyocytes [125], as reflected by improving cardiac glucose, FA, and ketone oxidation, while reducing cardiac fibrosis, improving endothelial function [125–127], and affecting macrophage polarization [127]. However, neither empagliflozin nor dapagliflozin significantly reduced mortality rates or first hospitalization rates for HF after acute MI in randomized/controlled clinical trials [128,129].

4.2. Concerning exosomes

The effect of exosomes-mediated cardiac recovery from MI injury has been studied in mouse, rat, and porcine models (Table 1). Naturally derived exosomes only provide moderate therapeutic efficiency, due to non-specific trapping, especially by the lung or liver [130,131]. Thus, the effort has been made to modify exosomes in three ways: 1) enhancing exosome capacity by packing them with additional compounds as drug delivery vehicles; For example, exosomes with over-expression of macrophage migration inhibitory factor [132], of stromal-derived factor 1 [133], of GATA [134], or with pre-treatment of hemin [135] and long non-coding RNA KLF3-AS1 [136], All of which attenuated MI progression. 2) structurally modifying exosomes by attaching external ligands to escape immune system attacks or homing peptides to enhance targeting capability; More specifically, a peptide with a sequence of CSTSMLKAC was discovered with the ability to target the ischemic region of the heart [11]. Wang et al., further elucidated that fusion of MSC-derived exosomes with CSTSMLKAC peptide significantly reduced infarct size and improved contractility in mice with acute MI [12]. Likewise, a fusion cassette that ligated a cardiomyocyte-specific peptide WLSEAGPVVTVRALRGTGSW with CDC-exosomes and Lamp2b, an exosomal transmembrane protein decreased cardiomyocyte apoptosis following MI [13]. 3) systemic administration of drugs that enhance the release of exosomes from cardiac cells, such as purinergic drug ticagrelor, a P2Y12 receptor antagonist [137], thereby limiting the death of cardiomyocytes exposed to ischemic microenvironment to exert their cardioprotective effect [138,139]. Moreover, a similar drug may reduce the release of prothrombotic platelet EVs in plasma, which otherwise may worsen clinical outcomes after acute MI [140]. This aspect opens a new avenue for developing new drugs regulating cargo and endogenous exosomes.

Regardless of the platform used in these studies, mechanistically, the authors concluded that cardiac protection is associated with inhibiting inflammatory response, ventricular remodeling, and apoptosis [12,13], in concert with promoting the angiogenic capacity of endothelial cells [69]. One significant limitation of these studies is the lack of long-term therapeutic impact on cardiac functional recovery following MI. Concerning that alterations of energy metabolism often precede ventricular function and remodeling changes; the question remains as to whether any metabolic changes occurred under these interventions.

Mitochondria have two mechanisms to ensure an active quality control system [165]. One is maintaining the mitochondrial mass through biogenesis, fission, and fusion under high energy-demanding conditions, while another is removing dysfunctional mitochondria through mitophagy [166], a protective mechanism. However, this may be oversimplified. For example, mild activation of mitophagy under acute ischemia conditions is beneficial, whereas chronic activation is detrimental, resulting in reduced ATP production and HF [167]. The mechanisms underlying exosome-mediated mitochondrial quality control systems haven't been adequately addressed in MI hearts, as most studies have focused on the expression of potential markers of fission or mitophagy. Of note, hemin pre-treated MSC-exosomes inhibited mitochondrial fission and maintained mitochondrial membrane potential through exosomal-GATA4 in mouse hearts post-MI [135], while exosomal sphingosylphosphorylcholine derived from vascular ECs attenuated myocardial I/R injury by promoting mitophagy in cardiomyocytes [168]. Furthermore, exosomes with over-expression of Sirt6 confer cardioprotection in mouse MI hearts through inhibiting pyroptosis, and promoting mitophagy in cardiomyocytes, in conjunction with decreased lactate releases, an indication of reduced glycolysis [169]. These results demonstrated that mitochondrial quality control is part of the mechanism for exosome-mediated cardiac protection during cardiac repair. As a therapeutic strategy for bioenergetic reprogramming, the first clinical

Table 1
Most of the experimental studies for exosome-based therapy of MI in small and large animals: Based on recent 8 years publications.

Source of exosomes	Exosome delivery			Observations		Species	Refs
	Dose	Timing	Route	Duration	Cardiac function		
BMMSCs	10 μg/g body weight	at the time of MI	Intramyocardial	28 d	Improved EF%	Mouse	[141]
MSCs	5 μg exosomes in 25 μl	30 mins post MI	Intramyocardial	28 d	Improved EF%	Mouse	[142]
MSCs	20 μl exosomes	at the time of MI,	Intramyocardial	4 wks	Improved EF%	Mouse	[143]
BMMSCs	600 μg exosomes	at the time of MI	Intramyocardial	28 d	Improved EF%	Female mouse	[144]
Mouse-BMMSCs	2×10^6 cells	at the time of MI	Not indicated	3 wks	Improved EF%	Mouse	[145]
Mouse-MSCs	5 μg exosome in 100ul	30 mins post I/R	Intramyocardial	12 hr	Prevented apoptosis	Mouse	[146]
ADMSCs	100 μg protein in 50 μl	25 mins post occlusion	Intramyocardial	3.5 hr	Reduced apoptosis	Mouse	[147]
HADMSCs	50 μl exosomes	25 mins post occlusion	Intramyocardial	3 hr and 3 d	Reduced apoptosis Improved EF%	Mouse	[148]
HUCMSCs	mimic patch	at the time of MI	Intramyocardial	3 and 7 d	Inhibited fibrosis	Mouse	[149]
HUCMSCs	50 μg/ml	at the time of MI	Intramyocardial	30 d	Improved EF%	Rat	[150]
HUCMSCs	400 μg/g exosomes	not indicated	Intramyocardial	not reported	Improved EF%	Rat	[151]
Rat-ADMSCs	400 μg exosomes in 200 μl	at the time of MI	intravenous injection	1 month	Inhibited apoptosis, inflammation, and fibrosis	Rat	[152]
HUCMSCs	50 μg exosomes	at the time of MI	intravenous injection	14, 18 d	Inhibited apoptosis, inflammation, and fibrosis	Rat	[153]
HUCMSCs	400 μg proteins in 200 μl	at the time of MI	Tail vein injection	4 wks	Improved EF%	Rat	[154]
Rat-BMMSCs	10 μg exosomes in 100 μl	30 mins post MI	Intramyocardial	5 wks	Improved EF%	Female rats	[155]
Rat-BMSCs	1×10^6 MSCs in 20 μl	at the time of MI	Intramyocardial	0, 28 d	Improved EF%	Rat	[73]
HBMSCs	1 μg/μl, injected 50 μl	30 mins post MI	Infarcted region injection	4 wks	Improved EF%	Rat	[156]
Rat-BMMSCs	10 μg exosomes in 100 μl	at the time of MI	Infarcted region injection	3, 7, 28 d	Improved EF%	Female rats	[157]
Rat-BMMSCs	2×10^{10} particles in 500 μl	at the time of MI	Tail vein injection	3, 14, 28 d	Improved EF%	Female rats	[158]
Rat-BMMSCs	50 μl exosomes	at the time of MI	Intramyocardial	7 d	Prevented apoptosis and improved EF%	Female rats	[159]
Rat-BMMSCs	1×10^6 BMSC in 20 μl	at the time of MI	Intramyocardial	0, 7, 28 d	Suppressed apoptosis and improved EF%	Rat	[160]
Rat-BMMSCs	20 μg exosomes/20 μl	at the time of MI	Intramyocardial	1 and 7 d	Improved EF%	Rat	[161]
HUCMSCs	50 μl of exosomes	at the time of MI	Intramyocardial	7 d	Inhibited apoptosis and promoted MI repair	Rat	[162]
HMSCs	40 μg in 300 μl PBS	not reported	Trai vein injection	7 d	Attenuates pyroptosis	Rat	[136]
ADSCs	100 μl exosomes	at the time of MI	Intramyocardial	0, 30 d	Improved EF%	Rat	[163]
MSCs	6 ml exosomes	At the time of MI	Intrapericardial	3 d	Function not recorded, proved safety and feasibility of intrapericardial injection	Male porcine	[143]
ADMSCs	20×10^6 cells	30 mins post MI	Surgical glue	6 d	Not recorded	Porcine	[164]

Abbreviation: MSC: Mesenchymal stem cells; BMMSC: Bone marrow MSC; ADSCs: Adipose-derived stem cell; ADMSCs: adipose tissue-derived MSC; HADMSCs: human adipose tissue-derived MSC; HUCMSCs: human umbilical cord mesenchymal stem.

trial on myocardial rescue through autologous mitochondrial transplantation was carried out in 2017 through intramyocardial injection to pediatric patients who required extracorporeal membrane oxygenation after ischemia−reperfusion injury [170]. A similar clinical trial aiming at testing the feasibility of mitochondrial transplantation as a treatment of MI is ongoing (NCT02851758) with direct injection of autologous mitochondria to the damaged adult myocardium due to MI. To avoid the limitations of surgical access and multiple administrations, Bhattacharya et al. recently demonstrated that EV-containing mitochondria from murine muscle can be effectively delivered to human fibroblast cells having mitochondrial DNA mutations, resulting in improved mitochondrial dynamics and metabolic functions [171]. These results indicate that mitochondrial trafficking and bioenergetic reprogramming could be a useful therapeutic strategy to integrate healthy mitochondria into functionally compromised host cells thereby refining mitochondrial structure to improve cardiac function in MI heart. Negative effects of EVs on recipient cells have been described [172], such as inflammation [173]. Given the physiological relevance, interesting observations have been reported in human age-associated conditions, such as physical frailty and Parkinson's disease, higher levels of EVs from endosomal origins were observed, while lower levels of mitochondrial electron transport chain constituents were identified as part of EV cargo in association with the expression of inflammatory mediators [174,175]. Whether the components holding the toxic function are the production of EVs or mitochondria is unknown, which warrants future studies to explore the biological roles of EV-containing mitochondria in the dynamics of mitochondrial quality control in health and disease.

Further studies should highlight the importance of balance between energy metabolism and mitochondrial quality control in MI heart. To this point, glycolytic enzymes, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and hexokinase II (HKII), are interesting to study with exosomes in MI heart. As demonstrated, the inactivation of GAPDH by site mutation at its phosphorylation site rescued mitophagy [176]. The binding of HKII to mitochondria inhibited mitochondrial permeability transition pore and prevented depletion of ATP [177]. In addition, the contribution of other metabolic pathways, such as chronic accumulation of branched-chain amino acids (BCAA) is vulnerable to I/R injury through enhancing lipid peroxidation toxicity [178]. In contrast, increased BCAA utilization was evident in MI mouse hearts with inhibition of FA oxidation by CPT1b-abrogation, which contributed

to heart repair and functional recovery from MI injury through fueling the TCA cycle [78]. Furthermore, cardiac aspartate and glutamate can be converted to succinate, an intermediate of the TCA cycle, under hypoxia/ischemic conditions, to produce ATP and GTP [179,180], which may be cardioprotective through maintaining redox potential. However, this notion remains contentious [179–181].

An additional consideration is improving the efficacy of existing drugs with modified exosomes. For example, coenzyme-Q is a lipid-soluble electron carrier that plays a central role in electron transport and ATP synthesis [182], reducing MI injury regardless of the type of animal model [182,183], and a mitochondria-targeted drug tested in humans [184,185]. Elamipretide is a small peptide targeting the mitochondrial inner membrane, resulting in mitochondrial bioenergetic improvements in various animal models of mitochondrial dysfunction [186]. A single four-hour infusion of elamipretide to HF patients was safe and well tolerated, but high-dose was required for favorable changes in left ventricular volumes [187]. Future studies can determine if a fusion cassette of exosomes with ischemic myocardium-targeting peptide can enhance their long-term efficacy in MI patients.

4.3. Metabolism modulation in non-cardiomyocytes and exosome

Inhibiting glycolysis in non-cardiomyocytes has shown promising results in preclinical models and clinical applications of MI.

4.3.1. In the context of immune cells

Dimethyl fumarate is an anti-inflammatory drug clinically approved for psoriasis and multiple sclerosis. Of interest, fumarate-replete hearts were robustly protected from I/R injury [188], through direct inhibition of glycolysis in activated myeloid and lymphoid cells [189]. This result represents a proof of concept that glycolysis is a therapeutic target in autoimmunity.

To escape immune system attacks, Ge et al. modified MSC-exosomes on membrane surface with CD47, which effectively improved inflammation and cardiac function in muse MI hearts [37]. Transcriptional activity of FOXO3 in macrophages is necessary for controlling glucose utilization, inflammatory process, and cardiac remodeling [190,191]. It remains unclear if FOXO3 contributed to exosomal-CD47 mediated effect in MI heart. Similarly the encapsulated exosomes with asymmetric HAD (hyaluronic acid-*g*-(2-aminoethyl methacrylate hydrochloride-dopamine)) hydrogels enhanced antioxidant and inflammation properties in a rat model after cardiac surgery [192]. It would be more informative if additional evidence were provided, such as the types of targeted cell populations, and the contribution to energy metabolism in the injured heart. Importantly, Liu et al. demonstrated that glutamine metabolism provides synergistic support for macrophage activation through α-ketoglutarate production via glutaminolysis to modulate metabolic and epigenetic reprogramming of M2 genes [99]. Additionally, CDC-exosomes packed with C-X-C motif chemokine receptor 4 can transfer exosomal miR-182 to macrophages, resulting in macrophage polarization and preventing MI injury [193], through a potential association with histone deacetylase 1 [191]. Thus, epigenetic reprogramming is potentially linked to macrophage metabolic alterations during cardiac repair post-MI [85].

4.3.2. In the context of cardiac fibrosis

To date, there are no efficacious therapies for directly targeting cardiac fibrosis, largely due to the consequences of cardiomyocyte hypertrophy and dysfunction [194,195]. Ongoing efforts to identify the molecular targets of cardiac fibrosis include understanding the transforming growth factor-β (TGF-β) signaling pathway, non-coding RNAs [196], and epigenetic modifiers [197]. Indirect approaches include using naturally derived biomaterials or synthetic materials to deliver bioactive factors (148), thereby decreasing cardiac fibrosis, and inflammation to improve vascularization [198]. One newly developed method is using microneedle patches to deliver exosomal miR-29b, which were efficiently internalized by cardiac fibroblasts with an increased retention time for 28 days, and prevented the progression of myocardial fibrosis by inhibiting the TGF-β-pathway [149]. Another interesting approach is taking advantage of curcumin, an antifibrotic compound derived from a natural substance of turmeric [199]. The encapsulated exosome-curcumin with decellularized extracellular matrix-based hydrogels were internalized by fibroblasts with a retention time of 28 days, resulting in reduced fibroblast transformation and fibrosis in mice with MI [200]. The safety and longer effect should be validated with larger animal models of MI for future clinical translation.

Epigenetic modifiers have added a new layer of regulation to cardiac fibrosis. Among epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, the most extensively studied is DNA methylation [201,202], and its contribution to cardiac fibrosis is evident [203,204]. Interestingly, plasma EVs derived from patients with acute coronary syndrome showed increased DNA methyltransferases (DNMTs) levels [205]. However, the roles of DNMT isoforms in regulating cardiac fibrosis are model-dependent [206–208], making it difficult to target the regulatory process involved in intricate signaling pathways. Recently, Tian et al. demonstrated an epigenetic mitochondrial-metabolic pathway by activating DNMT1/HIF1α/pyruvate dehydrogenase (PDK) axis to promote collagen production and right ventricular fibrosis [106]. PDK inhibition through sodium dichloroacetate improved glucose oxidation and reduced right ventricular fibrosis [106]. Given that PDK1 is the predominant isoform involved in the fibrogenic pathway in patients, and sodium dichloroacetate is not a specific inhibitor to PDK1, exosome-mediated benefits of metabolic vs. fibrosis-specific therapies will be required for future studies.

Owing to the established roles of fibrotic response in the injured heart, the TGF-signaling pathway has drawn increased interest as it is regulated by metabolic intermediates and epigenetic modifications [104,209]. More specifically, epigenetic activation of HIF-1α can drive the metabolic shift from glucose oxidation to glycolysis, in parallel with enhancing proliferation and collagen production during fibrosis [209]. Thus, inhibiting the upstream metabolic activators of TGF-β is suggested for treating fibrosis in MI heart [210]. In line with this, mitochondrial ROS (mtROS) generation, oxidative phosphorylation [211], and mitochondrial calcium ($mtCa^{2+}$) dynamics [104,209] have been demonstrated as the initiators of cardiac fibroblast differentiation through concerted alterations in energy metabolism and epigenetics [104,209]. These results support that the epigenetic mitochondrial-metabolic pathway can be a potential antifibrotic therapeutic target in cardiac fibroblasts. Indeed, inhibition of the epigenetic reader bromodomain-containing protein 4 (BRD4) reduced fibrosis in mice with MI, in conjunction with blocking of transactivation of TGF-β signaling and proinflammatory transcription factors [212]. Likewise, histone deacetylase inhibitors, such as Mocetinostat, reversed cardiac fibrosis by targeting cardiac fibroblast activation [213]. In addition, the increased myocardial acetylation of histone H4, due to intramyocardial administration of class I HDAC inhibitor, exerts anti-remodeling in infarcted rat heart by promoting survival of cardiac progenitor cells [214], which are a well-known source of cardioprotective exosomes [48,215]. It remains unknown regarding the inhibitory effect of BRD4 on energy metabolism in MI, and the types of targeted cells by BRD4 inhibitor *in vivo*. This raises questions about using non-coding RNAs, which have non-specific effects in regulating cardiac fibrosis [216]. Further investigation is required to understand whether exosomal non-coding RNAs and exosomal-curcumin can promote energy metabolism in cardiac fibroblasts, and their targets on the expression of epigenetic modifiers, which may facilitate translating the data into clinical practice for treating cardiac fibrosis in MI heart.

4.3.3. In the context of cardiac angiogenesis

Targeting VEGF signaling in ECs is a main therapeutic target [217]. Since HIF-1α is an upstream molecule of VEGF, it is reasonable to postulate that stimulating the HIF-1α-glycolysis axis in ECs can replicate the effect of VEGF on EC proliferation. Indeed, the defect of glycolysis in ECs limited ATP production, whereas the reverse was true with restored glycolysis in ECs, resulting in elevated NO biosynthesis [218]. Wang

et al. demonstrated that exosomal miR-205 ameliorated cardiac injury by promoting angiogenesis and microvascular EC proliferation through up-regulating HIF-1α and VEGF in mice post-MI [219]. It remains unclear to the effect of exosomal miR-205 on glycolysis, and NO metabolism in the MI heart.

4.4. Remaining questions and opportunities

Firstly, it is unclear whether interventions of exosomes at the level of substrate availability are sufficient to overcome mitochondrial dysfunction and improve the outcome of MI. In this regard, Ikeda et al. demonstrated that intramyocardial injection of mitochondria-enriched EVs was able to improve cardiac function in mice post-MI, which established a preclinical proof-of-concept that transfer of autologous mitochondria and their related energy source can restore myocardial bioenergetics in MI heart [220]. However, EVs with non-mitochondrial cargo also activated mitochondrial biogenesis in hypoxia-injured iPSC-iPSC-cardiomyocytes [220]. Thus, further studies using exosomes will undoubtedly shed light on identifying various intracellular signaling critical for activating mitochondrial biogenesis in the MI heart.

Concerning the preference for additional energy substrates in the MI heart, cardiac magnetic resonance (MR) imaging demonstrated that empagliflozin-treated pigs with MI exhibited a reduced myocardial glucose uptake, and energy substrate preference was switched toward utilization of ketone, FA, and BCAA, leading to increased myocardial ATP content and enhanced myocardial work efficiency [125]. Thus, exosomes have the advantage of directly delivering ketone and BCAA to the MI heart to clarify if they exert pleiotropic effects to restore cardiac function post-MI. In addition, based on the reparative effect of thyroid hormone on the human post-ischemic myocardium [34], the exosome-packed thyroid hormone specific for delivering to cardiomyocytes should be investigated in MI heart, which will clarify its direct role in mitochondrial function. Furthermore, exosomes can potentially activate mitochondrial quality control mechanisms by modulating oxidative stress, ROS, cytosolic, and mitochondrial Ca^{2+} overload [221]. The causal relationship between mitochondria-nuclear genome interactions is inadequately addressed, as is the data supporting mitochondrial genotype as a biomarker for stratification and treatment for HF patients. Thus, it would be interesting to use exosomes packed with mitochondrial metabolites, such as acetyl-CoA and α-ketoglutarate, for directly targeting the nucleus, to understand if they would promote epigenetic alterations in concert with any outcome of MI.

In addition, gender is an unmodifiable risk factor for causing MI, as reflected by MI onset occurs more often in men than women, irrespective of age [222]. However, information regarding sex differences in the contribution of mitochondrial energetics in MI treatment is scarce. Of interest, miR-210 deficiency exacerbated cardiac dysfunction in male mouse heart post-MI but was ineffective in female [223]. The authors concluded that miR-210 increased glycolytic activity and reduced mitochondrial ROS flux by directly inhibiting mitochondrial GAPDH in the MI heart.This study assessed glycolysis through Seahorse flux analysis, which cannot distinguish between glucose and fatty acid flux through oxidation. It remains unclear if the beneficial effect of miR-210 on cardiac function is due to an increase in glucose oxidation in concert with a decrease in FA oxidation, thereby reducing the uncoupling of glycolysis and glucose oxidation to prevent proton leak and mtROS production. Similarly, miR-199a, miR-210, and miR-499 displayed cardioprotective effects in rodent and pig models of acute MI [224–226]. Yet, their association with sex and energy metabolism remains unknown. This may be explored in future studies in great detail through engineered exosomes and miR-210 or the abovementioned exosomal-miRNAs with a peptide for directly targeting the ischemic region of the heart or even cardiomyocytes in both genders. To this point, selective cardiomyocyte targeting sequences have been reported for delivering exosomes, such as WLSEAGPVVTVRALRGTGSW [227, 228] and APHLSSQYSRT [229–231]. From a therapeutic perspective, it will be informative if clinical trials, such as testing the causal role of miR-210 for peripheral artery disease and diabetes (ClinicalTrials.gov Identifier: NCT04089943 and NCT02629406, respectively) or interventional therapies related to MI, including NCT05669144, NCT04127591, NCT06070974 and NCT02851758 (Table 2), can extend to clarify the sex-specific roles in regulating oxidative stress and hypoxic response. The rationale is that biological sex significantly affects cardiac metabolism in the human heart at rest [232], and in response to metabolic treatment [233].

Moreover, concerning the potential negative effects of exosomes on cardiac remodeling, Huang et al. demonstrated that cardiomyocyte-derived exosomes from MI mouse hearts promoted apoptosis of cardiomyocytes *in vitro* by increasing the intracellular abundance of miR-328–3p [234]. miR-21* is identified to be selectively enriched in fibroblast-derived exosomes, which can shuttle to cardiomyocytes, leading to cellular hypertrophy [49]. Likewise, exosomal miR-19a-3p in infarcted mouse hearts attenuated cardiac function by inhibiting EC proliferation and angiogenesis *via* down-regulating HIF-1α [235]. In quiescent ECs, besides HIF-1α, glycolytic gene expression is also controlled by the transcription factor FOXO1, of which, down-regulation suppresses endothelial growth and proliferation [236]. In addition, glutamine is a major carbon source of TCA cycle in ECs, deprivation of which also prevents ECs proliferation [237]. It is unclear about the association of exosomal miR-19a-3p with glutamine utilization, and FOXO1-mediated metabolic changes in response to the decline of proliferation and migration of ECs for angiogenesis, as is the contribution of miR-328–3p or miR-21* to energy metabolism in cardiomyocytes. Thus, future studies should clarify the association between exosome-mediated adverse effects and energy metabolism.

5. Metabolism assessment-related challenges for exosome applications in MI heart

The notable challenges lie in exosome isolation-purification-storage as discussed elsewhere [238,239]. To the point of exosome-mediated cardiac energy metabolism in MI heart, it is impossible to investigate mechanisms without qualitative and quantitative assessment of metabolic flux, and this principle is unlikely to change regardless of the discoveries [240]. Thus, we will focus on the methodologies to assess mitochondrial flux, *in vivo, ex vivo, or in vitro*, and the choices of cardiomyocyte-related cell lines for reproducibility of the observations.

5.1. Methodologies for assessing cardiac metabolism in vivo

Two common noninvasive approaches are available for studying cardiac metabolism with animal models and humans, which have been extensively reviewed by Yurista et al. [241]. One is positron emission tomography (PET) for quantifying the uptake of energy substrates with great resolution and quantitative capabilities but requiring radioactive tracers, and another is nuclear MR spectroscopy (MRS) for measuring the levels and turnover of cardiac high-energy phosphates with ^{31}phosphorus (^{31}P) but without radioactive tracers [242]. Of note, ^{31}P-MRS has been used for studying exosome-mediated energy metabolism in infarcted swine hearts [55]. Gao et al. demonstrated that the decrease in phosphocreatine (PCr) to ATP ratio and protein expression of mitochondrial ATPase-β was prevented by the administration of exogenous exosomes derived from hiPSC-cardiomyocytes in swine hearts post-MI [55]. Metabolic fluxes can be measured *via* ^{31}P-MRS through the estimation of creatine kinase and ATP synthase [243], and use a ratio of PCr/ATP as the marker of total energy metabolic changes [244], which, however, does not distinguish the specific flux between substrates, while technical challenges and resources are also the practical challenges. In addition, hyperpolarized [1-^{13} C] pyruvate MRS also measures cardiac metabolism in vivo, based on the principle that vanished pyruvate signal over time is followed by new peaks of lactate,

Table 2
Clinical trials of exosome-based therapy of MI: based on registration ID from ClinicalTrials.gov.

Exosomes Source	Routes to patients	Participates Enrollment	Nr	Age/Sex	Aim/Assessment	Registration ID
Human Mesenchymal Stem Cell	Intra-myocardial injection of placebo	Patients with EF<25 %, require coronary artery bypass surgery	5	35–80 year old/ Sex not recorded	To limit inflammatory/ oxidative damage/assess effect on EF%	NCT05669144
	Intracoronary and Intra-myocardial injection of mitochondria		5			
	Intracoronary and intra-myocardial injection of exosomes		5			
	Intracoronary and intra-myocardial injection of exosomes and mitochondria		5			
Peripheral blood	Non-invasive	Patients with MI	10	Not recorded	miRNA expression profile in peripheral blood exosomes	NCT04127591
Peripheral blood	Non-invasive	Patients with MI	100	Not recorded	Exosome profile and severity of myocardial	NCT06070974
Skeletal muscle from the chest wall	5–10 direct injections of autogenic mitochondria into the ischemic regions	Patients requiring extracorporeal membrane oxygenation	16	Not recorded	Ameliorate myocardial ischemia/reperfusion injury	NCT02851758

alanine, and bicarbonate as a result of pyruvate metabolism, allowing quantification of flux through pyruvate dehydrogenase, and therefore glucose oxidation. Thus, compared to PET-based methods, the advantage of this method is that it can distinguish the flux of glucose uptake from glucose oxidation, and assess the rates of bicarbonate production or anaerobic metabolism via lactate production [245]. This method has been used to study the metabolic-structural interplay in experimental MI models, such as rat [246], and pig [247,248]. The first human cardiac hyperpolarised [1-^{13}C] pyruvate images were produced in 2016 [249], but metabolism in human studies has yet to be undertaken. Given the increased interest in targeting the heart with metabolic treatments and a better understanding of glucose metabolism in different types of HF, the applications with exosomes may help unlock novel drug targets.

5.2. Methodologies for assessing cardiac metabolic flux in vitro

A key factor controlling metabolic flux is the cardiac work performed by the heart, as cardiac work decreases when less ATP is used. Thus, the two most important variables should be considered when measuring cardiac energy metabolism. One is the cardiac work representing the metabolic demand of the heart *in vivo*; Another is the physiologically relevant energy substrate supply to the heart.

5.2.1. Ex vivo assessment of metabolic flux in the isolated rodent heart

The direct measurement of metabolic flux rates is performed through *ex vivo* heart perfusion [250], by controlling both preload and afterload to the isolated heart in a sealed system, which ensures the heart maintains LV ejecting capacity so that the oxygenated perfusate delivered from the left atria to the left ventricle can be ejected through the cannulated aorta [251]. By strategic labeling of energy substrates at various sites with either ^{3}H or ^{14}C, both glycolysis and various oxidation, in the form of glucose, fatty acid, ketones, and amino acids can be characterized [251].

This method has several advantages. Firstly, the beating heart affords simultaneous assessment of cardiac work and oxygen consumption [251], thus the influence of mechanical function on metabolism is considered. Secondly, flux rates are quantitated from collecting the by-product, such as CO_2 from different substrates with ^{14}C tracer, which can identify the major factors that affect specific metabolic pathways [251]. In addition, collecting the by-product of H_2O from [^{3}H]-labeled glucose distinguishes the glycolytic pathway from the glucose oxidation pathway [251,252]. Furthermore, an oxygenated system allows the FA-bound albumin to be properly used by the heart with physiological/pathological relevant concentration. Thus, this method enables the metabolic assessment to be performed in the presence of a neurohumoral milieu to mimic the physiological and pathological status and has been used for many studies [251,252]. However, using radioactive substances and cannulating the beating heart are common technical challenges.

5.2.2. In vitro assessment of metabolic flux in cardiac cells

There are two common ways. One, using radioactive energy-providing substrates with either ^{3}H or ^{14}C to quantify $^{3}H_2O$ and $^{14}CO_2$ produced in viable cells, as a measure of energy metabolic flux through glycolysis or the mitochondrial oxidation. Another, assessing rates of mitochondrial oxygen consumption and extracellular acidification by using permeabilized cells or isolated mitochondria [253] in a transient microchamber through Seahorse technology [116].

Assessing metabolism in specific non-cardiomyocytes populations in the intact heart remains challenging, but these two methods are applicable. In contrast, significant limitations of these methods exist for cardiomyocytes, as the cardiomyocytes do not display any contractility, and the influence of mechanical work on metabolic changes cannot be considered. Due to the quiescent nature of the cardiomyocytes, the rates of oxidative metabolism even in the isolated primary viable cardiomyocytes can be 50–100 times lower than that in *ex vivo* perfused working hearts [254,255]. In addition, the Seahorse method cannot distinguish the flux of glucose from FA oxidation or *vice versa*. As a result of FA omission, rates of carbohydrate metabolism increase dramatically, which is an artificial situation, and may not be relevant in cardiomyocytes *in vivo*, especially to the hormonal or hypoxia effects on energy metabolic changes.

5.2.3. Choices of cell lines for assessing cardiac metabolic flux in vitro

The most commonly used cardiomyocyte-related cell lines are either atrial origin, such as H9C2 cells from embryonic rat heart [256] and HL-1 cells from mouse [257] or ventricular cells, such as AC16 cells from adult human ventricular biopsies [258].

Proteomic analysis has shown that undifferentiated H9C2 cells display different molecular phenotypes compared to primary neonatal and adult cardiomyocytes, as reflected by the lack of proteins essential for the formation of striated muscle myofibrils, and low oxidative capacity [259]. Upon differentiation, although H9c2 cells exhibit increased transcripts and protein levels involved in calcium handling, glycolytic and mitochondrial metabolism [260], they do not possess contractile activity, and the mitochondrial content is still low, as is the capacity for FA oxidation, compared to primary cardiomyocytes [260]. In this regard, H9C2 cells are not a good model for adult cardiomyocytes, as the majority of cardiomyocytes in adult hearts are differentiated and rely on FA oxidation as a major energy resource. In addition, the protein expression of mitochondrial quality control is higher in undifferentiated relative to differentiated H9C2 [260], indicating different impacts of mitophagy-related protein expression on ischemic injury in these cells. Collectively, caution and verification

should be taken for interpreting research findings obtained from exosome studies with H9C2 cells.

In contrast, mouse HL-1 and human AC16 demonstrate characteristics of differentiated adult cardiomyocytes towards contractility and their signaling for transcriptional and metabolic regulation [258,261], which makes them useful for metabolic studies under various pathological conditions [262]. The study numbers with these cell lines for exosome-associated cardioprotection are increasing [48,263,264]. As noted, exosomes derived by cardiac progenitor cells from patients who underwent heart valve were taken up by HL-1 cardiomyocytes and resulted in a time and dose-dependent increase in miRNAs, such as miRNA-210 and miR-132 with anti-apoptotic and proangiogenic activities [48]. More importantly, cardiac progenitor cell- exosomes, rather than fibroblast-exosomes, inhibited cardiomyocyte apoptosis, promoted angiogenesis, and ameliorated cardiac function in rat heart post-MI [48]. Likewise, up-regulation of exosomal LncRNA HCG15 accounts for acute MI injury through the NF-κB/p65 and p38 pathways in AC16 cardiomyocytes [265]. Of interest, serum exosomes derived from patients with sepsis displayed a significant inhibitory effect on glycolysis, concomitant with enhanced apoptosis in human AC16 cells, in which, however, over-expression of solute carrier family 2 member 1, an essential mediator in energy metabolism, reversed all the exosomal effect [266].

To date, no studies have shown the exact mechanism, by which the engineered exosomes can interact with cardiomyocytes to restore energy production and support the pumping function. Apart from cell-specific peptides, the combinational method is another option with targets for cell-specific receptors/ligands, antibodies/nanobodies, or pH-sensitive surface markers, to enhance the efficiency of endocytosis of exosomes in the heart, especially in large animal models of MI with a long-term goal of clinical translation [13]. Thus, if these special exosome-mediated metabolic pathways are measured in MI models, the *ex vivo* beating heart system is a better choice than cell lines, whereas HL-1 and AC16 cells are not ideal as adult cardiomyocytes but are preferred options over H9C2 cells and isolated mitochondria. The rationale for avoiding isolated mitochondria is that, even with advanced techniques, it is difficult to obtain functional mitochondria.

More sensitive assessments of energy metabolism in non-cardiomyocytes are required as they present in much lower quantities than cardiomyocytes in the heart. In this regard, Lewis et al. successfully performed MRS with hyperpolarized [1-^{13}C] pyruvate in macrophage-like cell lines for detecting pyruvate-derived [1-^{13}C]lactate signals, as an indicator of glycolysis [267]. They demonstrated that macrophage activation and polarization occurred in conjunction with an enhanced lactate flux *in vitro*, while the reverse was observed with inhibition of glycolysis. A near-identical hyperpolarized lactate flux was also evident in pig and rodent hearts post-MI [267]. It remains to be investigated if hyperpolarized [1-^{13}C] pyruvate MRS can detect the metabolic changes in cardiac fibroblasts and ECs post-MI. Of note, a retrospective cohort study at Tehran Heart Center (ClinicalTrials.gov ID NCT05669144) is ongoing, aiming at transplanting mitochondria with MSC-derived exosomes to minimize oxidative stress and inflammatory damage in the MI hearts. We hope that hyperpolarized [1-^{13}C] pyruvate MRS can be applied for metabolic imaging in non-cardiomyocytes, and to identify patients with the highest degree of myocardial inflammation, thereby providing the most benefit from exosome-mediated immunomodulatory therapies for them.

6. Conclusion

The application of exosomes in MI is still in the exploration stage. Engineered exosomes intervene more efficiently in the post-MI hearts, and deserve further investigations, especially with questions as to whether the engineered exosomes exhibit a role in regulating energy metabolism in cardiomyocytes and non-cardiomyocytes. Besides energy metabolism, there are more targets to be addressed in several aspects. To achieve the classification of accuracy and reproducibility of the results, there is an enduring need for developing more sensitive and feasible methodologies to quantify metabolic flux in the MI heart. To improve the therapeutic efficacy of exosomes, it is important to develop novel engineering strategies and refine longitudinal clinical studies by optimizing the timing, route of administration and dosing regimens of exosomes. To understand the impact of biological sex on cardiac metabolic changes in response to metabolic stress and medications, it is necessary to consider sexual dimorphism in any exosome-related studies for the MI heart. To understand the reporter metabolites, it is important to investigate new MI diagnostic markers by exploring exosomes. We believe that a well-developed translational platform for clinical exosome applications in MI heart is on the way as research progresses.

CRediT authorship contribution statement

Chang Liu: Writing – original draft, Resources, Investigation. **Dengwen Zhang:** Writing – original draft, Resources, Investigation, Funding acquisition. **Jia Li:** Writing – review & editing. **Kenneth King-Yip Cheng:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Yin Cai:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Wensheng Qi:** Writing – original draft. **Lei Pang:** Writing – review & editing, Funding acquisition. **Kekao Long:** Writing – original draft.

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.

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References

[1] G.A. Roth, G.A. Mensah, C.O. Johnson, et al., Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: update From the GBD 2019 Study, J. Am. Coll. Cardiol. 76 (25) (2020) 2982–3021.
[2] Y. Cai, F. Ying, H. Liu, et al., Deletion of Rap1 protects against myocardial ischemia/reperfusion injury through suppressing cell apoptosis via activation of STAT3 signaling, FASEB J. 34 (3) (2020) 4482–4496.
[3] M. Writing Group, D. Mozaffarian, E.J. Benjamin, et al., Heart disease and stroke statistics-2016 update: a report from the american heart association, Circulation 133 (4) (2016) e38–e360.
[4] C.D. Correia, A. Ferreira, M.T. Fernandes, et al., Human stem cells for cardiac disease modeling and preclinical and clinical applications-are we on the road to success? Cells 12 (13) (2023).
[5] J. Tang, D. Shen, T.G. Caranasos, et al., Therapeutic microparticles functionalized with biomimetic cardiac stem cell membranes and secretome, Nat. Commun. 8 (2017) 13724.
[6] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (6478) (2020).
[7] J. Phan, P. Kumar, D. Hao, et al., Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy, J. Extra Vesicles 7 (1) (2018) 1522236.
[8] C. Han, J. Yang, J. Sun, et al., Extracellular vesicles in cardiovascular disease: biological functions and therapeutic implications, Pharm. Ther. 233 (2022) 108025.
[9] J. Yang, X.F. Yu, Y.Y. Li, et al., Decreased HSP70 expression on serum exosomes contributes to cardiac fibrosis during senescence, Eur. Rev. Med Pharm. Sci. 23 (9) (2019) 3993–4001.

[10] C.W. Chen, M. Fu, Z.H. Du, et al., Long Noncoding RNA MRPL23-AS1 Promotes Adenoid Cystic Carcinoma Lung Metastasis, Cancer Res 80 (11) (2020) 2273–2285.
[11] S. Kanki, D.E. Jaalouk, S. Lee, et al., Identification of targeting peptides for ischemic myocardium by in vivo phage display, J. Mol. Cell Cardiol. 50 (5) (2011) 841–848.
[12] X. Wang, Y. Chen, Z. Zhao, et al., Engineered exosomes with ischemic myocardium-targeting peptide for targeted therapy in myocardial Infarction, J. Am. Heart Assoc. 7 (15) (2018) e008737.
[13] K.I. Mentkowski, J.K. Lang, Exosomes Engineered to Express a Cardiomyocyte Binding Peptide Demonstrate Improved Cardiac Retention in Vivo, Sci. Rep. 9 (1) (2019) 10041.
[14] D.J. Hausenloy, D.M. Yellon, Ischaemic conditioning and reperfusion injury, Nat. Rev. Cardiol. 13 (4) (2016) 193–209.
[15] Y. Cai, H. Liu, E. Song, et al., Deficiency of telomere-associated repressor activator protein 1 precipitates cardiac aging in mice via p53/PPARα signaling, Theranostics 11 (10) (2021) 4710.
[16] L. Pang, X. Jiang, X. Lian, et al., Caloric restriction-mimetics for the reduction of heart failure risk in aging heart: with consideration of gender-related differences, Mil. Med. Res. 9 (1) (2022) 33.
[17] W. Xia, M. Zhang, C. Liu, et al., Exploring the therapeutic potential of tetrahydrobiopterin for heart failure with preserved ejection fraction: a path forward, Life Sci. (2024) 122594.
[18] C. Duan, L. Wang, J. Zhang, et al., Mdivi-1 attenuates oxidative stress and exerts vascular protection in ischemic/hypoxic injury by a mechanism independent of Drp1 GTPase activity, Redox Biol. 37 (2020) 101706.
[19] M. Wang, K. Smith, Q. Yu, et al., Mitochondrial connexin 43 in sex-dependent myocardial responses and estrogen-mediated cardiac protection following acute ischemia/reperfusion injury, Basic Res Cardiol. 115 (1) (2019) 1.
[20] S.C. Kolwicz Jr., D.P. Olson, L.C. Marney, et al., Cardiac-specific deletion of acetyl CoA carboxylase 2 prevents metabolic remodeling during pressure-overload hypertrophy, Circ. Res 111 (6) (2012) 728–738.
[21] R. Ventura-Clapier, A. Garnier, V. Veksler, et al., Bioenergetics of the failing heart, Biochim Biophys. Acta 1813 (7) (2011) 1360–1372.
[22] G.D. Lopaschuk, Q.G. Karwi, R. Tian, et al., Cardiac Energy Metabolism in Heart Failure, Circ. Res 128 (10) (2021) 1487–1513.
[23] R. Tian, W.S. Colucci, Z. Arany, et al., Unlocking the Secrets of Mitochondria in the Cardiovascular System: path to a Cure in Heart Failure-A Report from the 2018 National Heart, Lung, and Blood Institute Workshop, Circulation 140 (14) (2019) 1205–1216.
[24] Q. Zhang, M. Raoof, Y. Chen, et al., Circulating mitochondrial DAMPs cause inflammatory responses to injury, Nature 464 (7285) (2010) 104–107.
[25] S. Wang, L. Ge, D. Zhang, et al., MiR-181c-5p promotes inflammatory response during hypoxia/reoxygenation injury by downregulating protein tyrosine phosphatase nonreceptor type 4 in H9C2 cardiomyocytes, Oxid. Med. Cell. Longev. 2020 (1) (2020) 7913418.
[26] T.S. Luongo, J.P. Lambert, P. Gross, et al., The mitochondrial Na(+)/Ca(2+) exchanger is essential for Ca(2+) homeostasis and viability, Nature 545 (7652) (2017) 93–97.
[27] B. Zhou, R. Tian, Mitochondrial dysfunction in pathophysiology of heart failure, J. Clin. Invest 128 (9) (2018) 3716–3726.
[28] H. Otani, The role of nitric oxide in myocardial repair and remodeling, Antioxid. Redox Signal 11 (8) (2009) 1913–1928.
[29] K.C. Wollert, H. Drexler, Regulation of cardiac remodeling by nitric oxide: focus on cardiac myocyte hypertrophy and apoptosis, Heart Fail Rev. 7 (4) (2002) 317–325.
[30] C. Humeres, N.G. Frangogiannis, Fibroblasts in the Infarcted, Remodeling, and Failing Heart, JACC Basic Transl. Sci. 4 (3) (2019) 449–467.
[31] A.J. Mouton, E.C. El Hajj, V.K. Ninh, et al., Inflammatory cardiac fibroblast phenotype underlies chronic alcohol-induced cardiac atrophy and dysfunction, Life Sci. 245 (2020) 117330.
[32] F. Forini, C. Kusmic, G. Nicolini, et al., Triiodothyronine prevents cardiac ischemia/reperfusion mitochondrial impairment and cell loss by regulating miR30a/p53 axis, Endocrinology 155 (11) (2014) 4581–4590.
[33] F. Forini, V. Lionetti, H. Ardehali, et al., Early long-term L-T3 replacement rescues mitochondria and prevents ischemic cardiac remodelling in rats, J. Cell. Mol. Med. 15 (3) (2011) 514–524.
[34] C.I. Pantos, K.P. Grigoriou, A.G. Trikas, et al., Translating thyroid hormone into clinical practice: lessons learned from the post-hoc analysis on data available from the ThyRepair study, Front Endocrinol. (Lausanne) 15 (2024) 1405251.
[35] Y. Liang, S. Sahoo, Exosomes explosion for cardiac resuscitation, J. Am. Coll. Cardiol. 66 (6) (2015) 612–615.
[36] S. Sahoo, D.W. Losordo, Exosomes and cardiac repair after myocardial infarction, Circ. Res 114 (2) (2014) 333–344.
[37] Z. Wei, Z. Chen, Y. Zhao, et al., Mononuclear phagocyte system blockade using extracellular vesicles modified with CD47 on membrane surface for myocardial infarction reperfusion injury treatment, Biomaterials 275 (2021) 121000.
[38] J. Yao, K. Huang, D. Zhu, et al., A minimally invasive exosome spray repairs heart after myocardial infarction, ACS Nano 15 (7) (2021) 11099–11111.
[39] N. Zhang, Y. Song, Z. Huang, et al., Monocyte mimics improve mesenchymal stem cell-derived extracellular vesicle homing in a mouse MI/RI model, Biomaterials 255 (2020) 120168.
[40] S. Hu, X. Wang, Z. Li, et al., Platelet membrane and stem cell exosome hybrid enhances cellular uptake and targeting to heart injury, Nano Today 39 (2021).
[41] A. Vandergriff, K. Huang, D. Shen, et al., Targeting regenerative exosomes to myocardial infarction using cardiac homing peptide, Theranostics 8 (7) (2018) 1869–1878.
[42] G. Bellin, C. Gardin, L. Ferroni, et al., Exosome in cardiovascular diseases: a complex world full of hope, Cells 8 (2) (2019).
[43] O.G. de Jong, M.C. Verhaar, Y. Chen, et al., Cellular stress conditions are reflected in the protein and RNA content of endothelial cell-derived exosomes, J. Extra Vesicles 1 (2012).
[44] J. Cosme, H. Guo, S. Hadipour-Lakmehsari, et al., Hypoxia-induced changes in the fibroblast secretome, exosome, and whole-cell proteome using cultured, cardiac-derived cells isolated from neonatal mice, J. Proteome Res 16 (8) (2017) 2836–2847.
[45] J. Yang, X. Yu, F. Xue, et al., Exosomes derived from cardiomyocytes promote cardiac fibrosis via myocyte-fibroblast cross-talk, Am. J. Transl. Res 10 (12) (2018) 4350–4366.
[46] J. Halkein, S.P. Tabruyn, M. Ricke-Hoch, et al., MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy, J. Clin. Invest 123 (5) (2013) 2143–2154.
[47] L. Lyu, H. Wang, B. Li, et al., A critical role of cardiac fibroblast-derived exosomes in activating renin angiotensin system in cardiomyocytes, J. Mol. Cell Cardiol. 89 (Pt B) () (2015) 268–279.
[48] L. Barile, V. Lionetti, E. Cervio, et al., Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction, Cardiovasc Res 103 (4) (2014) 530–541.
[49] C. Bang, S. Batkai, S. Dangwal, et al., Cardiac fibroblast-derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy, J. Clin. Invest 124 (5) (2014) 2136–2146.
[50] V. Lionetti, B.S. Tuana, V. Casieri, et al., Importance of functional food compounds in cardioprotection through action on the epigenome, Eur. Heart J. 40 (7) (2019) 575–582.
[51] G. Papini, G. Furini, M. Matteucci, et al., Cardiomyocyte-targeting exosomes from sulforaphane-treated fibroblasts affords cardioprotection in infarcted rats, J. Transl. Med 21 (1) (2023) 313.
[52] P. Orozco, Y. Montoya, J. Bustamante, Development of endomyocardial fibrosis model using a cell patterning technique: in vitro interaction of cell coculture of 3T3 fibroblasts and RL-14 cardiomyocytes, PLoS One 15 (2) (2020) e0229158.
[53] R.M. Green, Can we develop ethically universal embryonic stem-cell lines? Nat. Rev. Genet 8 (6) (2007) 480–485.
[54] R. Gallet, J. Dawkins, J. Valle, et al., Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction, Eur. Heart J. 38 (3) (2017) 201–211.
[55] L. Gao, L. Wang, Y. Wei, et al., Exosomes secreted by hiPSC-derived cardiac cells improve recovery from myocardial infarction in swine, Sci. Transl. Med 12 (561) (2020).
[56] T. Le, J. Chong, Cardiac progenitor cells for heart repair, Cell Death Discov. 2 (2016) 16052.
[57] E. Messina, L. De Angelis, G. Frati, et al., Isolation and expansion of adult cardiac stem cells from human and murine heart, Circ. Res 95 (9) (2004) 911–921.
[58] K. Bieback, S. Kern, H. Kluter, et al., Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood, Stem Cells 22 (4) (2004) 625–634.
[59] M.F. Pittenger, B.J. Martin, Mesenchymal stem cells and their potential as cardiac therapeutics, Circ. Res 95 (1) (2004) 9–20.
[60] M. Park, Y.T. Shen, V. Gaussin, et al., Apoptosis predominates in nonmyocytes in heart failure, Am. J. Physiol. Heart Circ. Physiol. 297 (2) (2009) H785–H791.
[61] G. de Couto, R. Gallet, L. Cambier, et al., Exosomal MicroRNA transfer into macrophages mediates cellular postconditioning, Circulation 136 (2) (2017) 200–214.
[62] E. Tseliou, J. Fouad, H. Reich, et al., Fibroblasts rendered antifibrotic, antiapoptotic, and angiogenic by priming with cardiosphere-derived extracellular membrane vesicles, J. Am. Coll. Cardiol. 66 (6) (2015) 599–611.
[63] A.G. Ibrahim, K. Cheng, E. Marban, Exosomes as critical agents of cardiac regeneration triggered by cell therapy, Stem Cell Rep. 2 (5) (2014) 606–619.
[64] K. Wang, Z. Jiang, K.A. Webster, et al., Enhanced cardioprotection by human endometrium mesenchymal stem cells driven by exosomal MicroRNA-21, Stem Cells Transl. Med 6 (1) (2017) 209–222.
[65] Y. Wang, X. Song, Z. Li, et al., MicroRNA-103 protects coronary artery endothelial cells against H(2)O(2)-induced oxidative stress via bnip3-mediated end-stage autophagy and antipyroptosis pathways, Oxid. Med Cell Longev. 2020 (2020) 8351342.
[66] T.M. Ribeiro-Rodrigues, T.L. Laundos, R. Pereira-Carvalho, et al., Exosomes secreted by cardiomyocytes subjected to ischaemia promote cardiac angiogenesis, Cardiovasc Res 113 (11) (2017) 1338–1350.
[67] Z. Liao, Y. Chen, C. Duan, et al., Cardiac telocytes inhibit cardiac microvascular endothelial cell apoptosis through exosomal miRNA-21-5p-targeted cdip1 silencing to improve angiogenesis following myocardial infarction, Theranostics 11 (1) (2021) 268–291.
[68] J. Yang, Y. Li, F. Xue, et al., Exosomes derived from cardiac telocytes exert positive effects on endothelial cells, Am. J. Transl. Res 9 (12) (2017) 5375–5387.
[69] C.V. Del Campo, N.Y. Liaw, M. Gunadasa-Rohling, et al., Regenerative potential of epicardium-derived extracellular vesicles mediated by conserved miRNA transfer, Cardiovasc Res 118 (2) (2022) 597–611.
[70] Y. Hu, R. Tao, L. Chen, et al., Exosomes derived from pioglitazone-pretreated MSCs accelerate diabetic wound healing through enhancing angiogenesis, J. Nanobiotechnol. 19 (1) (2021) 150.

[71] L. Qiao, S. Hu, S. Liu, et al., microRNA-21-5p dysregulation in exosomes derived from heart failure patients impairs regenerative potential, J. Clin. Invest 129 (6) (2019) 2237–2250.
[72] S.M. Davidson, J.A. Riquelme, Y. Zheng, et al., Endothelial cells release cardioprotective exosomes that may contribute to ischaemic preconditioning, Sci. Rep. 8 (1) (2018) 15885.
[73] H. Cheng, S. Chang, R. Xu, et al., Hypoxia-challenged MSC-derived exosomes deliver miR-210 to attenuate post-infarction cardiac apoptosis, Stem Cell Res Ther. 11 (1) (2020) 224.
[74] F. Pizzino, G. Furini, V. Casieri, et al., Late plasma exosome microRNA-21-5p depicts magnitude of reverse ventricular remodeling after early surgical repair of primary mitral valve regurgitation, Front Cardiovasc Med 9 (2022) 943068.
[75] V.L. Nasci, S. Chuppa, L. Griswold, et al., miR-21-5p regulates mitochondrial respiration and lipid content in H9C2 cells, Am. J. Physiol. Heart Circ. Physiol. 316 (3) (2019) H710–H721.
[76] L. Wang, Y. Cai, L. Jian, et al., Impact of peroxisome proliferator-activated receptor-α on diabetic cardiomyopathy, Cardiovasc. Diabetol. 20 (2021) 1–15.
[77] S. Despa, D.M. Bers, Na(+) transport in the normal and failing heart - remember the balance, J. Mol. Cell Cardiol. 61 (2013) 2–10.
[78] X. Li, F. Wu, S. Gunther, et al., Inhibition of fatty acid oxidation enables heart regeneration in adult mice, Nature 622 (7983) (2023) 619–626.
[79] V. Lionetti, A. Linke, M.P. Chandler, et al., Carnitine palmitoyl transferase-I inhibition prevents ventricular remodeling and delays decompensation in pacing-induced heart failure, Cardiovasc Res 66 (3) (2005) 454–461.
[80] E. Liepinsh, M. Makrecka-Kuka, J. Kuka, et al., Inhibition of L-carnitine biosynthesis and transport by methyl-gamma-butyrobetaine decreases fatty acid oxidation and protects against myocardial infarction, Br. J. Pharm. 172 (5) (2015) 1319–1332.
[81] G. Fragasso, A. Salerno, G. Lattuada, et al., Effect of partial inhibition of fatty acid oxidation by trimetazidine on whole body energy metabolism in patients with chronic heart failure, Heart 97 (18) (2011) 1495–1500.
[82] J.R. Ussher, W. Wang, M. Gandhi, et al., Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury, Cardiovasc Res 94 (2) (2012) 359–369.
[83] E. Wan, X.Y. Yeap, S. Dehn, et al., Enhanced efferocytosis of apoptotic cardiomyocytes through myeloid-epithelial-reproductive tyrosine kinase links acute inflammation resolution to cardiac repair after infarction, Circ. Res 113 (8) (2013) 1004–1012.
[84] L. Honold, M. Nahrendorf, Resident and monocyte-derived macrophages in cardiovascular disease, Circ. Res 122 (1) (2018) 113–127.
[85] D. Weissman, C. Maack, Mitochondrial function in macrophages controls cardiac repair after myocardial infarction, J. Clin. Invest 133 (4) (2023).
[86] S.W. van den Borne, J. Diez, W.M. Blankesteijn, et al., Myocardial remodeling after infarction: the role of myofibroblasts, Nat. Rev. Cardiol. 7 (1) (2010) 30–37.
[87] K.E. Glinton, W. Ma, C. Lantz, et al., Macrophage-produced VEGFC is induced by efferocytosis to ameliorate cardiac injury and inflammation, J. Clin. Invest 132 (9) (2022).
[88] Y. Ma, A. Yabluchanskiy, R.P. Iyer, et al., Temporal neutrophil polarization following myocardial infarction, Cardiovasc Res 110 (1) (2016) 51–61.
[89] U. Hofmann, S. Frantz, Role of T-cells in myocardial infarction, Eur. Heart J. 37 (11) (2016) 873–879.
[90] S.E. Corcoran, L.A. O'Neill, HIF1alpha and metabolic reprogramming in inflammation, J. Clin. Invest 126 (10) (2016) 3699–3707.
[91] P.J. Murray, Macrophage Polarization, Annu Rev. Physiol. 79 (2017) 541–566.
[92] C. Porta, E. Riboldi, A. Ippolito, et al., Molecular and epigenetic basis of macrophage polarized activation, Semin Immunol. 27 (4) (2015) 237–248.
[93] J. Van den Bossche, L.A. O'Neill, D. Menon, Macrophage Immunometabolism: where Are We (Going)? Trends Immunol. 38 (6) (2017) 395–406.
[94] I.K. Poon, C.D. Lucas, A.G. Rossi, et al., Apoptotic cell clearance: basic biology and therapeutic potential, Nat. Rev. Immunol. 14 (3) (2014) 166–180.
[95] C.N. Serhan, J. Savill, Resolution of inflammation: the beginning programs the end, Nat. Immunol. 6 (12) (2005) 1191–1197.
[96] S. Zhang, G. Bories, C. Lantz, et al., Immunometabolism of Phagocytes and Relationships to Cardiac Repair, Front Cardiovasc Med 6 (2019) 42.
[97] M.N. Sack, Mitochondrial fidelity and metabolic agility control immune cell fate and function, J. Clin. Invest 128 (9) (2018) 3651–3661.
[98] A.P. West, I.E. Brodsky, C. Rahner, et al., TLR signalling augments macrophage bactericidal activity through mitochondrial ROS, Nature 472 (7344) (2011) 476–480.
[99] P.S. Liu, H. Wang, X. Li, et al., alpha-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming, Nat. Immunol. 18 (9) (2017) 985–994.
[100] D.J. Gorski, A. Petz, C. Reichert, et al., Cardiac fibroblast activation and hyaluronan synthesis in response to hyperglycemia and diet-induced insulin resistance, Sci. Rep. 9 (1) (2019) 1827.
[101] T. Nacarelli, A. Azar, O. Altinok, et al., Rapamycin increases oxidative metabolism and enhances metabolic flexibility in human cardiac fibroblasts, Geroscience 40 (3) (2018) 243–256.
[102] P. Camelliti, T.K. Borg, P. Kohl, Structural and functional characterisation of cardiac fibroblasts, Cardiovasc Res 65 (1) (2005) 40–51.
[103] K. Bernard, N.J. Logsdon, S. Ravi, et al., Metabolic reprogramming is required for myofibroblast contractility and differentiation, J. Biol. Chem. 290 (42) (2015) 25427–25438.
[104] A.A. Lombardi, A.A. Gibb, E. Arif, et al., Mitochondrial calcium exchange links metabolism with the epigenome to control cellular differentiation, Nat. Commun. 10 (1) (2019) 4509.
[105] K.T. Weber, Y. Sun, S.K. Bhattacharya, et al., Myofibroblast-mediated mechanisms of pathological remodelling of the heart, Nat. Rev. Cardiol. 10 (1) (2013) 15–26.
[106] L. Tian, D. Wu, A. Dasgupta, et al., Epigenetic Metabolic Reprogramming of Right Ventricular Fibroblasts in Pulmonary Arterial Hypertension: a pyruvate dehydrogenase kinase-dependent shift in mitochondrial metabolism promotes right ventricular fibrosis, Circ. Res 126 (12) (2020) 1723–1745.
[107] K.D. Falkenberg, K. Rohlenova, Y. Luo, et al., The metabolic engine of endothelial cells, Nat. Metab. 1 (10) (2019) 937–946.
[108] M. Potente, P. Carmeliet, The link between angiogenesis and endothelial metabolism, Annu Rev. Physiol. 79 (2017) 43–66.
[109] V. Guarani, M. Potente, SIRT1 - a metabolic sensor that controls blood vessel growth, Curr. Opin. Pharm. 10 (2) (2010) 139–145.
[110] K. De Bock, M. Georgiadou, S. Schoors, et al., Role of PFKFB3-driven glycolysis in vessel sprouting, Cell 154 (3) (2013) 651–663.
[111] S. Schoors, K. De Bock, A.R. Cantelmo, et al., Partial and transient reduction of glycolysis by PFKFB3 blockade reduces pathological angiogenesis, Cell Metab. 19 (1) (2014) 37–48.
[112] X. He, H. Zeng, S.T. Chen, et al., Endothelial specific SIRT3 deletion impairs glycolysis and angiogenesis and causes diastolic dysfunction, J. Mol. Cell Cardiol. 112 (2017) 104–113.
[113] Y. You, X. Chen, Y. Chen, et al., Epigenetic modulation of Drp1-mediated mitochondrial fission by inhibition of S-adenosylhomocysteine hydrolase promotes vascular senescence and atherosclerosis, Redox Biol. 65 (2023) 102828.
[114] S.F. Glaser, A.W. Heumuller, L. Tombor, et al., The histone demethylase JMJD2B regulates endothelial-to-mesenchymal transition, Proc. Natl. Acad. Sci. USA 117 (8) (2020) 4180–4187.
[115] R. Diaz, E.A. Paolasso, L.S. Piegas, et al., Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group, Circulation 98 (21) (1998) 2227–2234.
[116] H. Taegtmeyer, M.E. Young, G.D. Lopaschuk, et al., Assessing cardiac metabolism: a scientific statement from the american heart association, Circ. Res 118 (10) (2016) 1659–1701.
[117] P.F. Kantor, A. Lucien, R. Kozak, et al., The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, Circ. Res 86 (5) (2000) 580–588.
[118] Y. Zhang, X.J. Ma, D.Z. Shi, Effect of trimetazidine in patients undergoing percutaneous coronary intervention: a meta-analysis, PLoS One 10 (9) (2015) e0137775.
[119] J. Hao, H. Du, W.W. Li, et al., Effects of atorvastatin combined with trimetazidine on myocardial injury and inflammatory mediator in unstable angina patients during perioperative of percutaneous coronary intervention, Eur. Rev. Med Pharm. Sci. 19 (23) (2015) 4642–4646.
[120] K.I. Amber, N.R. Hadi, B.M. Muhammad-Baqir, et al., Trimetazidine attenuates the acute inflammatory response induced by Novolimus eluting bioresorbable coronary scaffold implantation, Int J. Cardiol. 220 (2016) 514–519.
[121] T.A. Zelniker, S.D. Wiviott, I. Raz, et al., SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials, Lancet 393 (10166) (2019) 31–39.
[122] S. Verma, S. Rawat, K.L. Ho, et al., Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors, JACC Basic Transl. Sci. 3 (5) (2018) 575–587.
[123] C.S.P. Lam, C. Chandramouli, V. Ahooja, et al., SGLT-2 Inhibitors in Heart Failure: current management, unmet needs, and therapeutic prospects, J. Am. Heart Assoc. 8 (20) (2019) e013389.
[124] D. von Lewinski, E. Kolesnik, N.J. Tripolt, et al., Empagliflozin in acute myocardial infarction: the EMMY trial, Eur. Heart J. 43 (41) (2022) 4421–4432.
[125] C.G. Santos-Gallego, J.A. Requena-Ibanez, R. San Antonio, et al., Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics, J. Am. Coll. Cardiol. 73 (15) (2019) 1931–1944.
[126] W. Chen, Y. Zhang, Z. Wang, et al., Dapagliflozin alleviates myocardial ischemia/reperfusion injury by reducing ferroptosis via MAPK signaling inhibition, Front Pharm. 14 (2023) 1078205.
[127] R. Chen, Y. Zhang, H. Zhang, et al., SGLT2 inhibitor dapagliflozin alleviates intramyocardial hemorrhage and adverse ventricular remodeling via suppressing hepcidin in myocardial ischemia-reperfusion injury, Eur. J. Pharm. 950 (2023) 175729.
[128] S. James, D. Erlinge, R.F. Storey, et al., Dapagliflozin in myocardial infarction without diabetes or heart failure, NEJM Evid. 3 (2) (2024) EVIDoa2300286.
[129] J. Butler, W.S. Jones, J.A. Udell, et al., Empagliflozin after acute myocardial infarction, N. Engl. J. Med 390 (16) (2024) 1455–1466.
[130] Y.T. Ko, W.C. Hartner, A. Kale, et al., Gene delivery into ischemic myocardium by double-targeted lipoplexes with anti-myosin antibody and TAT peptide, Gene Ther. 16 (1) (2009) 52–59.
[131] K.I. Mentkowski, J.D. Snitzer, S. Rusnak, et al., Therapeutic potential of engineered extracellular vesicles, AAPS J. 20 (3) (2018) 50.
[132] X. Liu, X. Li, W. Zhu, et al., Exosomes from mesenchymal stem cells overexpressing MIF enhance myocardial repair, J. Cell Physiol. 235 (11) (2020) 8010–8022.
[133] X.H. Gong, H. Liu, S.J. Wang, et al., 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 (8) (2019) 13878–13893.

[134] B. Yu, H.W. Kim, M. Gong, et al., 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.
[135] H. Zheng, X. Liang, Q. Han, et al., Hemin enhances the cardioprotective effects of mesenchymal stem cell-derived exosomes against infarction via amelioration of cardiomyocyte senescence, J. Nanobiotechnol. 19 (1) (2021) 332.
[136] Q. Mao, X.L. Liang, C.L. Zhang, et al., 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 (1) (2019) 393.
[137] B. Wernly, D. Erlinge, J. Pernow, et al., Ticagrelor: a cardiometabolic drug targeting erythrocyte-mediated purinergic signaling? Am. J. Physiol. Heart Circ. Physiol. 320 (1) (2021) H90–H94.
[138] V. Casieri, M. Matteucci, E.M. Pasanisi, et al., Ticagrelor enhances release of anti-hypoxic cardiac progenitor cell-derived exosomes through increasing cell proliferation in vitro, Sci. Rep. 10 (1) (2020) 2494.
[139] C.V. Bitirim, Z.B. Ozer, D. Aydos, et al., Cardioprotective effect of extracellular vesicles derived from ticagrelor-pretreated cardiomyocyte on hyperglycemic cardiomyocytes through alleviation of oxidative and endoplasmic reticulum stress, Sci. Rep. 12 (1) (2022) 5651.
[140] A. Gasecka, R. Nieuwland, M. Budnik, et al., Ticagrelor attenuates the increase of extracellular vesicle concentrations in plasma after acute myocardial infarction compared to clopidogrel, J. Thromb. Haemost. 18 (3) (2020) 609–623.
[141] L.P. Zhu, T. Tian, J.Y. Wang, et al., Hypoxia-elicited mesenchymal stem cell-derived exosomes facilitates cardiac repair through miR-125b-mediated prevention of cell death in myocardial infarction, Theranostics 8 (22) (2018) 6163–6177.
[142] C. Xiao, K. Wang, Y. Xu, et al., Transplanted mesenchymal stem cells reduce autophagic flux in infarcted hearts via the exosomal transfer of miR-125b, Circ. Res 123 (5) (2018) 564–578.
[143] D. Zhu, Z. Li, K. Huang, et al., Minimally invasive delivery of therapeutic agents by hydrogel injection into the pericardial cavity for cardiac repair, Nat. Commun. 12 (1) (2021) 1412.
[144] T. Ma, Y. Chen, Y. Chen, et al., MicroRNA-132, Delivered by Mesenchymal Stem Cell-Derived Exosomes, Promote Angiogenesis in Myocardial Infarction, Stem Cells Int 2018 (2018) 3290372.
[145] S. Wang, L. Li, T. Liu, et al., miR-19a/19b-loaded exosomes in combination with mesenchymal stem cell transplantation in a preclinical model of myocardial infarction, Regen. Med 15 (6) (2020) 1749–1759.
[146] Y. Peng, J.L. Zhao, Z.Y. Peng, et al., Exosomal miR-25-3p from mesenchymal stem cells alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2, Cell Death Dis. 11 (5) (2020) 317.
[147] T.C. Lai, T.L. Lee, Y.C. Chang, et al., MicroRNA-221/222 Mediates ADSC-Exosome-Induced Cardioprotection Against Ischemia/Reperfusion by Targeting PUMA and ETS-1, Front Cell Dev. Biol. 8 (2020) 569150.
[148] T.L. Lee, T.C. Lai, S.R. Lin, et al., Conditioned medium from adipose-derived stem cells attenuates ischemia/reperfusion-induced cardiac injury through the microRNA-221/222/PUMA/ETS-1 pathway, Theranostics 11 (7) (2021) 3131–3149.
[149] J. Yuan, H. Yang, C. Liu, et al., Microneedle patch loaded with exosomes containing MicroRNA-29b prevents cardiac fibrosis after myocardial infarction, Adv. Health Mater. 12 (13) (2023) e2202959.
[150] J. Ni, X. Liu, Y. Yin, et al., 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.
[151] L. Huang, L. Yang, Y. Ding, et al., Human umbilical cord mesenchymal stem cells-derived exosomes transfers microRNA-19a to protect cardiomyocytes from acute myocardial infarction by targeting SOX6, Cell Cycle 19 (3) (2020) 339–353.
[152] J. Pan, M. Alimujiang, Q. Chen, et al., Exosomes derived from miR-146a-modified adipose-derived stem cells attenuate acute myocardial infarction-induced myocardial damage via downregulation of early growth response factor 1, J. Cell Biochem 120 (3) (2019) 4433–4443.
[153] L.S.Wenwu Zhu, Pengcheng Zhao, Yaowu Liu, Jian Zhang, Yuelin Zhang, Yimei Hong, Yeqian Zhu, Yao Lu, Wei Zhao, Xinguang Chen, Fengxiang Zhang, Macrophage migration inhibitory factor facilitates the therapeutic efficacy of mesenchymal stem cells derived exosomes in acute myocardial infarction through upregulating miR-133a-3p, J. Nanobiotechnol. 19 (1) (2021) 61.
[154] X.L. Wang, Y.Y. Zhao, L. Sun, et al., Exosomes derived from human umbilical cord mesenchymal stem cells improve myocardial repair via upregulation of Smad7, Int J. Mol. Med 41 (5) (2018) 3063–3072.
[155] P. Huang, L. Wang, Q. Li, et al., Combinatorial treatment of acute myocardial infarction using stem cells and their derived exosomes resulted in improved heart performance, Stem Cell Res Ther. 10 (1) (2019) 300.
[156] L. Sun, W. Zhu, P. Zhao, et al., Down-Regulated Exosomal MicroRNA-221 - 3p Derived From Senescent Mesenchymal Stem Cells Impairs Heart Repair, Front Cell Dev. Biol. 8 (2020) 263.
[157] P. Huang, L. Wang, Q. Li, et al., 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 (2) (2020) 353–367.
[158] J. Sun, H. Shen, L. Shao, et al., HIF-1alpha overexpression in mesenchymal stem cell-derived exosomes mediates cardioprotection in myocardial infarction by enhanced angiogenesis, Stem Cell Res Ther. 11 (1) (2020) 373.
[159] D.L. Fu, H. Jiang, C.Y. Li, et al., MicroRNA-338 in MSCs-derived exosomes inhibits cardiomyocyte apoptosis in myocardial infarction, Eur. Rev. Med Pharm. Sci. 24 (19) (2020) 10107–10117.
[160] Y. Chen, Y. Zhao, W. Chen, et al., MicroRNA-133 overexpression promotes the therapeutic efficacy of mesenchymal stem cells on acute myocardial infarction, Stem Cell Res Ther. 8 (1) (2017) 268.
[161] L. Shao, Y. Zhang, B. Lan, et al., MiRNA-Sequence indicates that mesenchymal stem cells and exosomes have similar mechanism to enhance cardiac repair, Biomed. Res Int 2017 (2017) 4150705.
[162] C.X. Li, J. Song, X. Li, et al., Circular RNA 0001273 in exosomes derived from human umbilical cord mesenchymal stem cells (UMSCs) in myocardial infarction, Eur. Rev. Med Pharm. Sci. 24 (19) (2020) 10086–10095.
[163] S. Shafei, M. Khanmohammadi, H. Ghanbari, et al., Effectiveness of exosome mediated miR-126 and miR-146a delivery on cardiac tissue regeneration, Cell Tissue Res 390 (1) (2022) 71–92.
[164] M. Monguio-Tortajada, C. Prat-Vidal, M. Moron-Font, et al., Local administration of porcine immunomodulatory, chemotactic and angiogenic extracellular vesicles using engineered cardiac scaffolds for myocardial infarction, Bioact. Mater. 6 (10) (2021) 3314–3327.
[165] G.W. Dorn 2nd, R.N. Kitsis, The mitochondrial dynamism-mitophagy-cell death interactome: multiple roles performed by members of a mitochondrial molecular ensemble, Circ. Res 116 (1) (2015) 167–182.
[166] S. Patergnani, P. Pinton, Mitophagy and mitochondrial balance, Methods Mol. Biol. 1241 (2015) 181–194.
[167] G. Morciano, S. Patergnani, M. Bonora, et al., Mitophagy in Cardiovascular Diseases, J. Clin. Med 9 (3) (2020).
[168] Y. Yu, Z. Li, Y. Cai, et al., Vascular endothelial cell-derived exosomal sphingosylphosphorylcholine attenuates myocardial ischemia-reperfusion injury through NR4A2-mediated mitophagy, Int J. Mol. Sci. 25 (6) (2024).
[169] K. Liu, H. Wang, Y. Wang, et al., Exploring the therapeutic potential of Sirt6-enriched adipose stem cell-derived exosomes in myocardial ischemia-reperfusion injury: unfolding new epigenetic frontiers, Clin. Epigenetics 16 (1) (2024) 7.
[170] S.M. Emani, B.L. Piekarski, D. Harrild, et al., Autologous mitochondrial transplantation for dysfunction after ischemia-reperfusion injury, J. Thorac. Cardiovasc Surg. 154 (1) (2017) 286–289.
[171] D. Bhattacharya, M.B. Slavin, D.A. Hood, Muscle mitochondrial transplantation can rescue and maintain cellular homeostasis, Am. J. Physiol. Cell Physiol. 325 (4) (2023) C862–C884.
[172] A. Picca, F. Guerra, R. Calvani, et al., Mitochondrial-derived vesicles: the good, the bad, and the ugly, Int J. Mol. Sci. 24 (18) (2023).
[173] F. Puhm, T. Afonyushkin, U. Resch, et al., Mitochondria are a subset of extracellular vesicles released by activated monocytes and induce Type I IFN and TNF responses in endothelial cells, Circ. Res 125 (1) (2019) 43–52.
[174] A. Picca, R. Beli, R. Calvani, et al., Older adults with physical frailty and sarcopenia show increased levels of circulating small extracellular vesicles with a specific mitochondrial signature, Cells 9 (4) (2020).
[175] A. Picca, F. Guerra, R. Calvani, et al., Mitochondrial signatures in circulating extracellular vesicles of older adults with Parkinson's disease: results from the exosomes in PArkiNson's Disease (EXPAND) study, J. Clin. Med 9 (2) (2020).
[176] G. Yogalingam, S. Hwang, J.C. Ferreira, et al., Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) phosphorylation by protein kinase Cdelta (PKCdelta) inhibits mitochondria elimination by lysosomal-like structures following ischemia and reoxygenation-induced injury, J. Biol. Chem. 288 (26) (2013) 18947–18960.
[177] I. Khaliulin, R. Ascione, L.N. Maslov, et al., Preconditioning or Postconditioning with 8-Br-cAMP-AM Protects the Heart against Regional Ischemia and Reperfusion: a role for mitochondrial permeability transition, Cells 10 (5) (2021).
[178] Y. Li, Z. Xiong, W. Yan, et al., Branched chain amino acids exacerbate myocardial ischemia/reperfusion vulnerability via enhancing GCN2/ATF6/PPAR-alpha pathway-dependent fatty acid oxidation, Theranostics 10 (12) (2020) 5623–5640.
[179] T. Sanborn, W. Gavin, S. Berkowitz, et al., Augmented conversion of aspartate and glutamate to succinate during anoxia in rabbit heart, Am. J. Physiol. 237 (5) (1979) H535–H541.
[180] H. Taegtmeyer, Metabolic responses to cardiac hypoxia. Increased production of succinate by rabbit papillary muscles, Circ. Res 43 (5) (1978) 808–815.
[181] R.J. Wiesner, P. Rosen, M.K. Grieshaber, Pathways of succinate formation and their contribution to improvement of cardiac function in the hypoxic rat heart, Biochem Med Metab. Biol. 40 (1) (1988) 19–34.
[182] K. Awad, A. Sayed, M. Banach, Coenzyme Q(10) reduces infarct size in animal models of myocardial ischemia-reperfusion injury: a meta-analysis and summary of underlying mechanisms, Front Cardiovasc Med 9 (2022) 857364.
[183] S. Liang, Z. Ping, J. Ge, Coenzyme Q10 regulates antioxidative stress and autophagy in acute myocardial ischemia-reperfusion injury, Oxid. Med Cell Longev. 2017 (2017) 9863181.
[184] M.J. Rossman, J.R. Santos-Parker, C.A.C. Steward, et al., Chronic supplementation with a mitochondrial antioxidant (MitoQ) improves vascular function in healthy older adults, Hypertension 71 (6) (2018) 1056–1063.
[185] S.A. Mortensen, F. Rosenfeldt, A. Kumar, et al., The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial, JACC, Heart Fail 2 (6) (2014) 641–649.
[186] H.N. Sabbah, R.C. Gupta, S. Kohli, et al., Chronic therapy with elamipretide (MTP-131), a novel mitochondria-targeting peptide, improves left ventricular and mitochondrial function in dogs with advanced heart failure, Circ. Heart Fail 9 (2) (2016) e002206.
[187] M.A. Daubert, E. Yow, G. Dunn, et al., Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide, Circ. Heart Fail 10 (12) (2017).
[188] H. Ashrafian, G. Czibik, M. Bellahcene, et al., Fumarate is cardioprotective via activation of the Nrf2 antioxidant pathway, Cell Metab. 15 (3) (2012) 361–371.

[189] M.D. Kornberg, P. Bhargava, P.M. Kim, et al., Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity, Science 360 (6387) (2018) 449–453.
[190] J. Zhao, X. Li, J. Hu, et al., Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization, Cardiovasc Res 115 (7) (2019) 1205–1216.
[191] S. Zhou, P. Liu, G. Zhang, et al., Histone Deacetylase 1 depletion alleviates coronary heart disease via the MicroRNA-182-mediated transforming growth factor beta/smad signaling pathway, J. Cardiovasc Pharm. 79 (6) (2022) 815–826.
[192] L. Wang, P. Chen, Y. Pan, et al., Injectable photocurable Janus hydrogel delivering hiPSC cardiomyocyte-derived exosome for post-heart surgery adhesion reduction, Sci. Adv. 9 (31) (2023) eadh1753.
[193] Y. Ma, M. Su, W. Qian, et al., CXCR4-overexpressed exosomes from cardiosphere-derived cells attenuate myocardial ischemia/reperfusion injury by transferring miRNA to macrophages and regulating macrophage polarization, Cell Mol. Biol. 69 (12) (2023) 98–103.
[194] M. Gyongyosi, J. Winkler, I. Ramos, et al., Myocardial fibrosis: biomedical research from bench to bedside, Eur. J. Heart Fail 19 (2) (2017) 177–191.
[195] M.D. Tallquist, Cardiac fibroblast diversity, Annu Rev. Physiol. 82 (2020) 63–78.
[196] X. Qu, X. Song, W. Yuan, et al., Expression signature of lncRNAs and their potential roles in cardiac fibrosis of post-infarct mice, Biosci. Rep. 36 (3) (2016).
[197] M.B. Felisbino, T.A. McKinsey, Epigenetics in cardiac fibrosis: emphasis on inflammation and fibroblast activation, JACC Basic Transl. Sci. 3 (5) (2018) 704–715.
[198] B. Deng, L. Shen, Y. Wu, et al., Delivery of alginate-chitosan hydrogel promotes endogenous repair and preserves cardiac function in rats with myocardial infarction, J. Biomed. Mater. Res A 103 (3) (2015) 907–918.
[199] J. Zhao, Y. Chen, Q. Chen, et al., Curcumin ameliorates cardiac fibrosis by regulating macrophage-fibroblast crosstalk via IL18-P-SMAD2/3 signaling pathway inhibition, Front Pharm. 12 (2021) 784041.
[200] K. Wu, Y. Wang, H. Yang, et al., Injectable Decellularized Extracellular Matrix Hydrogel Containing Stromal Cell-Derived Factor 1 Promotes Transplanted Cardiomyocyte Engraftment and Functional Regeneration after Myocardial Infarction, ACS Appl. Mater. Interfaces 15 (2) (2023) 2578–2589.
[201] G. Egger, G. Liang, A. Aparicio, et al., Epigenetics in human disease and prospects for epigenetic therapy, Nature 429 (6990) (2004) 457–463.
[202] A. Parry, S. Rulands, W. Reik, Active turnover of DNA methylation during cell fate decisions, Nat. Rev. Genet 22 (1) (2021) 59–66.
[203] H. Tao, Z.Y. Song, X.S. Ding, et al., Epigenetic signatures in cardiac fibrosis, special emphasis on DNA methylation and histone modification, Heart Fail Rev. 23 (5) (2018) 789–799.
[204] J. Shao, J. Liu, S. Zuo, Roles of epigenetics in cardiac fibroblast activation and fibrosis, Cells 11 (15) (2022).
[205] C. Schiano, C. Balbi, J. Burrello, et al., De novo DNA methylation induced by circulating extracellular vesicles from acute coronary syndrome patients, Atherosclerosis 354 (2022) 41–52.
[206] C.J. Watson, P. Collier, I. Tea, et al., Hypoxia-induced epigenetic modifications are associated with cardiac tissue fibrosis and the development of a myofibroblast-like phenotype, Hum. Mol. Genet 23 (8) (2014) 2176–2188.
[207] K. Zhao, L. Weng, T. Xu, et al., Low-intensity pulsed ultrasound prevents prolonged hypoxia-induced cardiac fibrosis through HIF-1alpha/DNMT3a pathway via a TRAAK-dependent manner, Clin. Exp. Pharm. Physiol. 48 (11) (2021) 1500–1514.
[208] H. Tao, P. Shi, X.D. Zhao, et al., DNMT1 deregulation of SOCS3 axis drives cardiac fibroblast activation in diabetic cardiac fibrosis, J. Cell Physiol. 236 (5) (2021) 3481–3494.
[209] J. Ritterhoff, S. Young, O. Villet, et al., Metabolic remodeling promotes cardiac hypertrophy by directing glucose to aspartate biosynthesis, Circ. Res 126 (2) (2020) 182–196.
[210] S. Park, N.B. Nguyen, A. Pezhouman, et al., Cardiac fibrosis: potential therapeutic targets, Transl. Res 209 (2019) 121–137.
[211] S. Shrishrimal, E.A. Kosmacek, R.E. Oberley-Deegan, Reactive oxygen species drive epigenetic changes in radiation-induced fibrosis, Oxid. Med Cell Longev. 2019 (2019) 4278658.
[212] Q. Duan, S. McMahon, P. Anand, et al., BET bromodomain inhibition suppresses innate inflammatory and profibrotic transcriptional networks in heart failure, Sci. Transl. Med 9 (390) (2017).
[213] S. Yoon, G.H. Eom, HDAC and HDAC Inhibitor: from cancer to cardiovascular diseases, Chonnam Med J. 52 (1) (2016) 1–11.
[214] V. Lionetti, S. Cantoni, C. Cavallini, et al., Hyaluronan mixed esters of butyric and retinoic acid affording myocardial survival and repair without stem cell transplantation, J. Biol. Chem. 285 (13) (2010) 9949–9961.
[215] L. Barile, E. Cervio, V. Lionetti, et al., Cardioprotection by cardiac progenitor cell-secreted exosomes: role of pregnancy-associated plasma protein-A, Cardiovasc Res 114 (7) (2018) 992–1005.
[216] R. Micheletti, I. Plaisance, B.J. Abraham, et al., The long noncoding RNA Wisper controls cardiac fibrosis and remodeling, Sci. Transl. Med 9 (395) (2017).
[217] Y. Oduk, W. Zhu, R. Kannappan, et al., VEGF nanoparticles repair the heart after myocardial infarction, Am. J. Physiol. Heart Circ. Physiol. 314 (2) (2018) H278–H284.
[218] L.P. Bharath, J.M. Cho, S.K. Park, et al., Endothelial cell autophagy maintains shear stress-induced nitric oxide generation via glycolysis-dependent purinergic signaling to endothelial nitric oxide synthase, Arterioscler. Thromb. Vasc. Biol. 37 (9) (2017) 1646–1656.
[219] T. Wang, T. Li, X. Niu, et al., ADSC-derived exosomes attenuate myocardial infarction injury by promoting miR-205-mediated cardiac angiogenesis, Biol. Direct 18 (1) (2023) 6.
[220] G. Ikeda, M.R. Santoso, Y. Tada, et al., Mitochondria-Rich extracellular vesicles from autologous stem cell-derived cardiomyocytes restore energetics of ischemic myocardium, J. Am. Coll. Cardiol. 77 (8) (2021) 1073–1088.
[221] R.M. Denton, J.G. McCormack, The calcium sensitive dehydrogenases of vertebrate mitochondria, Cell Calcium 7 (5-6) (1986) 377–386.
[222] M.A. Khan, M.J. Hashim, H. Mustafa, et al., Global epidemiology of ischemic heart disease: results from the global burden of disease study, Cureus 12(7 (2020) e9349.
[223] R. Song, C. Dasgupta, C. Mulder, et al., MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction, Circulation 145 (15) (2022) 1140–1153.
[224] S. Hu, M. Huang, Z. Li, et al., MicroRNA-210 as a novel therapy for treatment of ischemic heart disease (11 Suppl), Circulation 122 (2010) S124–S131.
[225] R. Hinkel, D. Penzkofer, S. Zuhlke, et al., Inhibition of microRNA-92a protects against ischemia/reperfusion injury in a large-animal model, Circulation 128 (10) (2013) 1066–1075.
[226] K. Gabisonia, G. Prosdocimo, G.D. Aquaro, et al., MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs, Nature 569 (7756) (2019) 418–422.
[227] M.J. McGuire, K.N. Samli, S.A. Johnston, et al., In vitro selection of a peptide with high selectivity for cardiomyocytes in vivo, J. Mol. Biol. 342 (1) (2004) 171–182.
[228] J. Gu, J. You, H. Liang, et al., Engineered bone marrow mesenchymal stem cell-derived exosomes loaded with miR302 through the cardiomyocyte specific peptide can reduce myocardial ischemia and reperfusion (I/R) injury, J. Transl. Med 22 (1) (2024) 168.
[229] M. Zahid, B.E. Phillips, S.M. Albers, et al., Identification of a cardiac specific protein transduction domain by in vivo biopanning using a M13 phage peptide display library in mice, PLoS One 5 (8) (2010) e12252.
[230] M. Zahid, K.S. Feldman, G. Garcia-Borrero, et al., Cardiac Targeting Peptide, a Novel Cardiac Vector: studies in bio-distribution, imaging application, and mechanism of transduction, Biomolecules 8 (4) (2018).
[231] D.A. Sahagun, J.B. Lopuszynski, K.S. Feldman, et al., Toxicity Studies of Cardiac-Targeting Peptide Reveal a Robust Safety Profile, Pharmaceutics 16 (1) (2024).
[232] L.R. Peterson, P.F. Soto, P. Herrero, et al., Sex differences in myocardial oxygen and glucose metabolism, J. Nucl. Cardiol. 14 (4) (2007) 573–581.
[233] M.R. Lyons, L.R. Peterson, J.B. McGill, et al., Impact of sex on the heart's metabolic and functional responses to diabetic therapies, Am. J. Physiol. Heart Circ. Physiol. 305 (11) (2013) H1584–H1591.
[234] J. Huang, F. Wang, X. Sun, et al., Myocardial infarction cardiomyocytes-derived exosomal miR-328-3p promote apoptosis via Caspase signaling, Am. J. Transl. Res 13 (4) (2021) 2365–2378.
[235] L. Gou, C. Xue, X. Tang, et al., Inhibition of Exo-miR-19a-3p derived from cardiomyocytes promotes angiogenesis and improves heart function in mice with myocardial infarction via targeting HIF-1alpha, Aging (Albany NY) 12 (23) (2020) 23609–23618.
[236] K. Wilhelm, K. Happel, G. Eelen, et al., FOXO1 couples metabolic activity and growth state in the vascular endothelium, Nature 529 (7585) (2016) 216–220.
[237] B. Kim, J. Li, C. Jang, et al., Glutamine fuels proliferation but not migration of endothelial cells, EMBO J. 36 (16) (2017) 2321–2333.
[238] M. Gimona, K. Pachler, S. Laner-Plamberger, et al., Manufacturing of human extracellular vesicle-based therapeutics for clinical use, Int J. Mol. Sci. 18 (6) (2017).
[239] S. Araujo-Abad, M. Saceda, C. de Juan Romero, Biomedical application of small extracellular vesicles in cancer treatment, Adv. Drug Deliv. Rev. 182 (2022) 114117.
[240] S.C. Landis, S.G. Amara, K. Asadullah, et al., A call for transparent reporting to optimize the predictive value of preclinical research, Nature 490 (7419) (2012) 187–191.
[241] S.R. Yurista, R.A. Eder, D.H. Kwon, et al., Magnetic resonance imaging of cardiac metabolism in heart failure: how far have we come? Eur. Heart J. Cardiovasc Imaging 23 (10) (2022) 1277–1289.
[242] L.E. Hudsmith, S. Neubauer, Magnetic resonance spectroscopy in myocardial disease, JACC Cardiovasc Imaging 2 (1) (2009) 87–96.
[243] M. Schar, A.M. El-Sharkawy, R.G. Weiss, et al., Triple repetition time saturation transfer (TRiST) 31P spectroscopy for measuring human creatine kinase reaction kinetics, Magn. Reson Med 63 (6) (2010) 1493–1501.
[244] A.J. Bakermans, D. Abdurrachim, B.J. van Nierop, et al., In vivo mouse myocardial (31)P MRS using three-dimensional image-selected in vivo spectroscopy (3D ISIS): technical considerations and biochemical validations, NMR Biomed. 28 (10) (2015) 1218–1227.
[245] A. Apps, J. Lau, M. Peterzan, et al., Hyperpolarised magnetic resonance for in vivo real-time metabolic imaging, Heart 104 (18) (2018) 1484–1491.
[246] R.S. Tougaard, C. Laustsen, T.R. Lassen, et al., Remodeling after myocardial infarction and effects of heart failure treatment investigated by hyperpolarized [1-(13) C]pyruvate magnetic resonance spectroscopy, Magn. Reson Med 87 (1) (2022) 57–69.
[247] G.D. Aquaro, F. Frijia, V. Positano, et al., 3D CMR mapping of metabolism by hyperpolarized 13C-pyruvate in ischemia-reperfusion, JACC Cardiovasc Imaging 6 (6) (2013) 743–744.
[248] M. Fuetterer, J. Traechtler, J. Busch, et al., Hyperpolarized metabolic and parametric cmr imaging of longitudinal metabolic-structural changes in experimental chronic infarction, JACC Cardiovasc Imaging 15 (12) (2022) 2051–2064.

[249] C.H. Cunningham, J.Y. Lau, A.P. Chen, et al., Hyperpolarized 13C Metabolic MRI of the Human Heart: initial experience, Circ. Res 119 (11) (2016) 1177–1182.
[250] J.R. Neely, H.E. Morgan, Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle, Annu Rev. Physiol. 36 (1974) 413–459.
[251] R.L. Barr, G.D. Lopaschuk, Methodology for measuring in vitro/ex vivo cardiac energy metabolism, J. Pharm. Toxicol. Methods 43 (2) (2000) 141–152.
[252] B. Liu, Z. el Alaoui-Talibi, A.S. Clanachan, et al., Uncoupling of contractile function from mitochondrial TCA cycle activity and MVO2 during reperfusion of ischemic hearts, Am. J. Physiol. 270 (1 Pt 2) (1996) H72–H80.
[253] E.N. Dedkova, L.A. Blatter, Measuring mitochondrial function in intact cardiac myocytes, J. Mol. Cell Cardiol. 52 (1) (2012) 48–61.
[254] M.M. Awan, E.D. Saggerson, Malonyl-CoA metabolism in cardiac myocytes and its relevance to the control of fatty acid oxidation (Pt 1), Biochem J. 295 (Pt 1) (1993) 61–66.
[255] M. Saddik, J. Gamble, L.A. Witters, et al., Acetyl-CoA carboxylase regulation of fatty acid oxidation in the heart, J. Biol. Chem. 268 (34) (1993) 25836–25845.
[256] J. Hescheler, R. Meyer, S. Plant, et al., Morphological, biochemical, and electrophysiological characterization of a clonal cell (H9c2) line from rat heart, Circ. Res 69 (6) (1991) 1476–1486.
[257] S.M. White, P.E. Constantin, W.C. Claycomb, Cardiac physiology at the cellular level: use of cultured HL-1 cardiomyocytes for studies of cardiac muscle cell structure and function, Am. J. Physiol. Heart Circ. Physiol. 286 (3) (2004) H823–H829.
[258] W.C. Claycomb, N.A. Lanson Jr., B.S. Stallworth, et al., HL-1 cells: a cardiac muscle cell line that contracts and retains phenotypic characteristics of the adult cardiomyocyte, Proc. Natl. Acad. Sci. USA 95 (6) (1998) 2979–2984.
[259] J. Lenco, O. Lencova-Popelova, M. Link, et al., Proteomic investigation of embryonic rat heart-derived H9c2 cell line sheds new light on the molecular phenotype of the popular cell model, Exp. Cell Res 339 (2) (2015) 174–186.
[260] A.F. Branco, S.P. Pereira, S. Gonzalez, et al., Gene expression profiling of H9c2 myoblast differentiation towards a cardiac-like phenotype, PLoS One 10 (6) (2015) e0129303.
[261] M.M. Davidson, C. Nesti, L. Palenzuela, et al., Novel cell lines derived from adult human ventricular cardiomyocytes, J. Mol. Cell Cardiol. 39 (1) (2005) 133–147.
[262] C. Kovacshazi, S. Hambalko, N.V. Sayour, et al., Effect of hypercholesterolemia on circulating and cardiomyocyte-derived extracellular vesicles, Sci. Rep. 14 (1) (2024) 12016.
[263] J. Guo, L.W. Chen, Z.Q. Huang, et al., Suppression of the Inhibitory Effect of circ_0036176-Translated Myo9a-208 on Cardiac Fibroblast Proliferation by miR-218-5p, J. Cardiovasc Transl. Res 15 (3) (2022) 548–559.
[264] C. Liang, Y. Liu, H. Xu, et al., Exosomes of Human Umbilical Cord MSCs Protect Against Hypoxia/Reoxygenation-Induced Pyroptosis of Cardiomyocytes via the miRNA-100-5p/FOXO3/NLRP3 Pathway, Front Bioeng. Biotechnol. 8 (2020) 615850.
[265] B. Lin, X. Chen, C. Lu, et al., Loss of exosomal LncRNA HCG15 prevents acute myocardial ischemic injury through the NF-kappaB/p65 and p38 pathways, Cell Death Dis. 12 (11) (2021) 1007.
[266] F. Sun, H. Geng, Y. Sun, et al., Exosomes derived from the blood of patients with sepsis regulate apoptosis and aerobic glycolysis in human myocardial cells via the hsa-miR-1262/SLC2A1 signaling pathway, Mol. Med Rep. 25 (4) (2022).
[267] A.J.M. Lewis, J.J. Miller, A.Z. Lau, et al., Noninvasive immunometabolic cardiac inflammation imaging using hyperpolarized magnetic resonance, Circ. Res 122 (8) (2018) 1084–1093.