Review Article

Potential clinical applications of exosomes in the diagnosis, treatment, and prognosis of cardiovascular diseases: a narrative review

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Background and Objective: Cardiovascular diseases (CVDs) have been one of the most common threats to human health in recent decades. At present, despite many diagnostic, prognostic and therapeutic methods being applied in the clinic, the prevalence of CVDs continues to rise. Therefore, new discovery is needed and exosomes have received extensive attention. Exosomes are extracellular vesicles that enable communication between cells. They are widely distributed in biofluids, suggesting that they may be useful in CVD diagnosis and prognosis. Furthermore, exosomes are ideal drug transporters with relatively high transport efficiency and the capability to target different kinds of tissues. However, the present research concentrates, for the most part, on mechanistic studies with less attention to clinical applications.

Methods: More than 150 relevant scientific articles from databases like PubMed, Web of Science were screened and analysed for this narrative review. Data of clinical trials are collected from clinicaltrials.gov.

Key Content and Findings: In this review, we concentrate on different exosomes and CVDs, and we summarize the physiological and pathological roles of CVD-related exosomes. We focused on the role exosomes may have as biomarkers of CVDs, therapeutic opportunities, and possible hurdles to the clinical application of exosomes, aiming to provide a useful reference for its translational use in the CVD field.

Conclusions: Specific changes in exosome cargos (mainly miRNAs and proteins) are in accordance with the occurrence and development of CVDs including acute myocardial infarction (AMI), arrhythmia, coronary artery disease (CAD), heart failure (HF) and cardiomyopathy, therefore meaningful for diagnosis and prognosis of CVDs. For exosome related therapeutic methods, potential ways consist of direct administration of exosomes, targeting on exosome synthesis, processing and release, and working as adjuvants. All in all, exosomes are expected to serve as meaningful tools in the diagnosis, treatment and prognosis of CVDs.

Keywords: Exosomes; cardiovascular diseases (CVDs); miRNA; clinical applications

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Introduction

Cardiovascular diseases (CVDs) remain among of the greatest sources of mortality and morbidity in developed countries (1). Despite significant investment in research and therapy, the overall outcomes remain suboptimal. At present, although biomarkers like cardiac troponins, creatine kinase, and brain natriuretic peptides have been widely employed in CVD diagnosis and prognosis, their value may be limited

by factors such as age, genetic background, lifestyle, heart associated diseases, etc. (2). Besides, regardless of numerous options for CVD treatment, including angiotensin-converting enzyme inhibitors, sartans, beta-blockers, calcium channel blockers, statins, etc., the prevalence of CVDs keeps an increasing trend still (1). Thereby, new discovery is essential and attention is given to exosomes.

Exosomes are vesicles originating from endosomes, and they are approximately 40 to 160 nm (average 100 nm) in diameter (3). The membrane of an exosome is roughly the same as a plasma membrane, consisting of a phospholipid bilayer. Under certain physiological or pathological stimulation, the plasma membrane invaginates to form endocytic vesicles, which mainly contain proteins, lipids, small molecules, and ions. After invaginating into the cytoplasm, many endocytic vesicles may fuse together and constitute early-sorting endosomes (ESEs). Then, ESEs endocytose mitochondria, the endoplasmic reticulum, the Golgi apparatus, and nucleic acids to develop into late-sorting endosomes (LSEs), which invaginate again to form multiple intraluminal vesicles (ILVs) under the control of protein complexes called endosomal sorting complexes required for transport (ESCRT). Because LSEs containing ILVs resemble multivesicular vesicles, they are called multivesicular bodies (MVBs). MVBs have two main fates as follows: they are degraded by fusion with autophagosomes and lysosomes, and they are then recycled by cells; or they dock on a cell membrane and release ILVs by exocytosis. The ILVs released by exocytosis are called exosomes (4,5). The contents of exosomes can be different from the contents of their parental cells, indicating that the sorting and packing mechanisms are specific (6,7). Sorting processes are fulfilled by particular sequence motifs, posttranscriptional modifications, or subcellular localization (8).

Exosomes function to transmit information between cells (9). Exosomes can transfer substances, including proteins, lipids, metabolites, RNA, mitochondrial DNA, and even activated receptors, to recipient cells, which affects the signaling pathways of the recipient cells, consequently modulating protein expression and phenotype (3,7,10,11). Because exosomes have a small diameter, they can be transported through body fluids, and their phospholipid bilayer protects internal molecules from degradation. Compared to the direct transfer of signaling molecules, exosomes are relatively more reliable for sending molecules to target cells (12-14). Additionally, exosomes can home to target tissues or cells and penetrate biological barriers, such as the blood–brain barrier. In certain situations, exosomes are taken up by receptor-mediated endocytosis, which has a high degree of accuracy and can facilitate the consecutive and stable transport of exosome cargo, suggesting that exosomes may function in drug delivery (15,16). In animal models of CVDs and in cell culture models, exosomes mitigate injury. Not surprisingly, exosome-based therapy has been proposed as a novel therapeutic option in CVDs (10,17,18).

Additionally, exosomes and exosome cargos are detectable in the blood, supporting a possible role as biomarkers of CVDs (19). Specific molecular patterns are associated with CVDs, and exosomes may provide real-time information for these changes. As a diagnostic and prognostic method, an exosome test is minimally invasive and highly efficient, and it can be used alone or combined with traditional methods to increase the sensitivity and specificity of traditional methods. Indeed, exosome profiles and cargo are being investigated as biomarkers for the diagnosis and prognosis of diseases, such as acute myocardial infarction (AMI), arrhythmia, coronary artery disease (CAD), and heart failure (HF). Of translational importance, exosomes are already employed in the diagnosis of some tumors, such as the ExoDx™ Lung (ALK) test, thereby validating the potential clinical application of exosomes in CVDs. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-619/rc).

Methods

We reviewed many updated review articles on exosomes. Then, the blank field with few exosome applications, CVDs, was screened out and literature about exosomes in CVDs was searched up to October 2021. More than 100 relevant scientific articles were reviewed, screened and analysed. Also, clinical trials were searched and analysed (literature and data collected from databases including PubMed, Web of Science and clinicaltrials.gov). The search strategy summary is shown in *Table 1* and the detailed search strategy of PubMed is shown in Table S1 as an example.

Discussion

Roles of CVD-related exosomes

The development of CVDs is a complex process. Numerous molecules are secreted by disordered cells, which subsequently induce responses throughout the

Table 1 The search strategy summary

Items	Specification
Date of search	October 15th, 2021
Databases and other sources searched	PubMed, Web of Science and clinicaltrials.gov
Search terms used	Keywords: exosome, cardiovascular disease, biomarker, clinical trial, therapy
Timeframe	1987–2021
Inclusion and exclusion criteria	All kinds of studies are included; language restricted to English
Selection process	Xuyang Chen and Qi Luo conducted the selection together; selecting literature from aspects including correlation with subjects, time of publication and experimental design

body. Exosomes are secreted by distinct kinds of cells, either as an initial response to disorders or subsequent responses to preceding signals (20). The exosomes discussed in this section are critical to various processes of CVD development as representative mechanisms for regulation induced by exosomes, but some are not directly connected with CVDs. Additionally, important elements are discussed to clarify the roles of exosomes in CVD diagnosis, treatment, prognosis, and other potential clinical tasks.

Exosomes derived from platelets

Platelet-derived exosomes contain coagulation proteins, anticoagulation proteins, bioactive lipids, and cytokines (21). These exosomes are known to promote and inhibit inflammation, thrombosis, tissue repair, angiogenesis, endothelial apoptosis, myocardial dysfunction, and atherosclerosis (AS) (22-26). Platelet-rich plasma exosomes can encapsulate growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) (26). In this way, these exosomes promote the proliferation and migration of endothelial cells by regulating the PI3K/Akt and MAPK-Erk signaling pathways to promote angiogenesis. Additionally, platelet-derived exosomes activate Yes-associated protein (YAP) and stimulate fibroblast proliferation, fibroblast migration, and collagen synthesis, collectively enhancing angiogenesis (26).

Platelet exosomes also contain miRNAs, including miR-21, miR-191, miR-233, miR-320, and miR-339 (27). These miRNAs affect platelet aggregation and blood coagulation, which in turn affect AS formation. miR-191, miR-233, and miR-320 in platelet-derived exosomes are anti-inflammatory and cardioprotective; these miRNAs decrease the release of inflammatory factors by inhibiting the expression of intercellular adhesion molecule-1 (ICAM-1), which suppresses AS (25,28,29). Furthermore, platelet-derived exosomes impede AS formation by inhibiting CD36 expression in macrophages, which prevents macrophages from phagocytosing oxidized low-density lipoprotein and cholesterol to decrease foam cell formation (30).

Exosomes derived from stem cells

Many types of stem cells produce exosomes that function to lessen CVDs in benchtop and animal studies. Hypoxic preconditioning increases the exosome secretion of umbilical cord (UC)-mesenchymal stem cells (MSCs). Treatment of H9C2 cells with UC-MSC-derived exosomes limits hypoxia- and serum depletion-mediated apoptosis. In addition, treatment with these exosomes downregulates LC3B-II/I and beclin-1 but upregulates P62, p-Akt/Akt, and p-mTOR/mTOR (31). Adipose-derived stem cell (ADSC) exosomes overexpressing miR-126 downregulate inflammatory factors and alleviate myocardial injury (32). Bone marrow stromal cell-derived exosomes protect cardiomyocytes from ischemia reperfusion injury. Exosome miR-486-5p inhibits cardiomyocyte apoptosis by suppressing PTEN expression and activating the PI3K/AKT signaling pathway (33).

Exosomes derived from cardiac cells

Most heart cells, including cardiomyocytes, cardiac fibroblasts, cardiac endothelial cells, and cardiac progenitor cells, secrete exosomes and modulate cardiac function (10). Cardiomyocyte-derived exosomes vary depending upon the clinical scenario.

Goto-Kakizaki type 2 diabetic rat cardiomyocyte exosomes inhibit the proliferation, migration, and tube-like formation of murine cardiac endothelial cells (MCECs) through miR-320. In contrast, exosomes derived from Wistar

rat cardiomyocytes are proangiogenic (34). Additionally, cardiomyocyte-derived exosomes are crucial to miR-92a-mediated postinfarct cardiac fibroblast activation (35).

Cardiac progenitor cells (CPCs) have been studied in relation to heart repair and regeneration. miR-210 found in CPC-derived exosomes inhibits cardiomyocyte apoptosis-induced angiogenesis and improves function (36-38). CPC-derived exosomes also improve right ventricular heart failure and reduce postinfarction scar formation (39,40). Treatment with CPC-derived exosomes attenuates doxorubicin- and trastuzumab-induced cardiac oxidative stress, in part, via miR-146a-5p (41). Finally, CPC-derived exosomes containing the matricellular protein, periostin, promote cardiomyocyte cell cycle reentry (42). Cardiac fibroblasts secrete miRNA-enriched exosomes containing miR-21-3p/miR-21, which stimulate the production of angiotensin II (Ang II) and promote cardiomyocyte hypertrophy (6). In a feedback manner, Ang II, via endogenous receptor signaling, increases cardiac fibroblast-derived exosome release. These exosomes increase renin, angiotensinogen, AT1R, and AT2R but decrease angiotensin-converting enzyme 2, and they also stimulate cell hypertrophy via mitogen-activated protein kinases (MAPKs) and the Akt pathway (43).

Exosomes derived from macrophages

In mice, cardiac miR-155 expression is increased after myocardial infarction. Pri-miR-155 and miR-155 are present in macrophage-derived exosomes and cardiac fibroblasts. Exosomes containing Pri-mir-155 and miR-155 suppress Son of Sevenless 1, and they inhibit cardiac fibroblast proliferation. Additionally, these exosomes increase inflammation by decreasing the expression of suppressor of cytokine signaling 1 (SOCS1). *In vivo*, mir-155-deficient mice have a lower rate of cardiac rupture and better function than control mice; fibroblast proliferation and collagen production are elevated, and cardiac inflammation is reduced postinfarction (44). Macrophage foam cell-derived exosomes transport proteins, such as integrins, into vascular smooth muscle cells (VSMCs), activating the extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) pathways, and facilitating cell migration and adhesion to promote atherosclerosis (45).

Exosomes as biomarkers in CVD diagnosis and prognosis

The secretion of exosomes is an essential phenomenon that exists in both physiological and pathological processes. Different processes determine the surface molecules and contents of exosomes. Therefore, blood exosomes may mimic the health and disease of specific cell types and organs. Additionally, blood-borne exosomes are a convenient method to assess otherwise inaccessible tissues because they provide useful information for identifying and classifying individual risk conditions in patients, diagnosing and monitoring disease conditions, effectively adjusting treatments, and estimating prognosis. Thus, exosomes and their contents are viewed as biomarkers (46). Indeed, studies have suggested that exosomes are noninvasive biomarkers for CVDs (47,48).

Exosomes carry miRNAs, indicating that they participate in the circulation and presentation of miRNAs (49). The stable existence of miRNAs in body fluids is promoted by miRNAs binding with carriers, such as exosomes, which offer protection from degradation (50). Studies that have focused on miRNA biomarkers in CVD diagnosis and prognosis are summarized in *Table 2*.

Compared to miRNAs, exosome proteins are less studied as biomarkers.

In individuals with cerebrovascular disease, endothelial-derived exosomes show increased levels of vascular proteins, such as VCAM-1, von Willebrand factor, platelet-derived growth factor (PDGF)-BB, angiopoietin-1, and lysyl oxidase-2, in addition to cerebrovascular-selective proteins, including glucose transporter 1, permeability-glycoprotein, and large neutral amino acid transporter 1. In platelet-derived exosomes, PDGF-AA, platelet glycoprotein VI, integrin-linked kinase-1, high mobility group box-1 protein, CXCL4 (chemokine), and antiangiogenic thrombospondin-1 are increased. Elevation of these atherosclerosis-promoting proteins underscores the possible role of exosomes in tracking atherosclerotic cerebrovascular disease (89).

Exosomes as a CVD treatment method

The therapeutic effects of exosomes in treating CVDs are well documented in preclinical studies. The exosomes discussed in this section have the potential to be used in exosome therapies for CVDs. However, safety issues remain a concern in human trials due to the potential for off-target effects.

Potential therapeutic methods with direct administration of exosomes

The studies below consider exosomes of identified origin

Table 2 Important miRNAs for CVD diagnosis and prognosis

Disease	miRNA	Regulation	Purpose	Ref.
Acute myocardial infarction (AMI)	miR-1	↑	Diagnostic	(51-55)
		↑	Prognostic: death	(53)
		↑	Prognostic: LVEF	(55)
	miR-133a/b	↑	Diagnostic	(52-54,56-60)
		↑	Prognostic: death	(53)
		↑	Prognostic: left ventricle remodeling	(59)
	miR-208a/b	↑	Diagnostic	(53,57,60-64)
		↑	Prognostic: death	(53)
		↑	Prognostic: left ventricle remodeling	(63)
	miR-423-5p	↑	Diagnostic	(54,59)
		↑	Prognostic: left ventricle remodeling	(59)
	miR-499	↑	Diagnostic	(52,54,60,61,65)
	miR-126	↑	Prognostic: AMI	(66)
	miR-21	↑	Diagnostic	(54,55)
	miR-29b	↑	Diagnostic	(55)
	miR-106a-5p	↓	Prognostic: AMI	(67)
	miR-223	↓	Prognostic: AMI	(66)
Arrhythmia: tachycardia	miR-1	↓	Diagnostic	(59)
Arrhythmia: atrial fibrillation (AF)	miR-29b	↓	Diagnostic	(68)
	miR-150	↓	Diagnostic	(69)
	miR-328	↓	Diagnostic	(70)
		↓	Prognostic: AF	(70)
Arrhythmia: postoperative atrial fibrillation (POAF)	miR-23a	↓	Prognostic: POAF	(71)
	miR-26a	↓	Prognostic: POAF	(71)
Coronary artery disease (CAD)	miR-1	↑	Diagnostic	(72)
	miR-133a/b	↑	Diagnostic	(72,73)
	miR-208a/b	↑	Diagnostic	(73)
	miR-122	↑	Diagnostic	(72)
	miR-126	↑	Diagnostic	(72,74)
		↑	Prognostic: major adverse cardiovascular event	(74)
	miR-134	↑	Diagnostic	(75)
	miR-199a	↑	Diagnostic	(72,74)
		↑	Prognostic: major adverse cardiovascular event	(74)
	miR-126	↓	Diagnostic	(73)
	miR-145	↓	Diagnostic	(73)
	miR-146a	↓	Diagnostic	(76)
	miR-30c/d	↓	Diagnostic	(76)

Table 2 (*continued*)

Table 2 (*continued*)

Disease	miRNA	Regulation	Purpose	Ref.
Heart failure (HF)	miR-1	↑	Diagnostic	(77)
	miR-133a/b	↑	Diagnostic	(77)
	miR-208a/b	↑	Diagnostic	(77)
	miR-423-5p	↑	Diagnostic	(78,79)
	miR-499	↑	Diagnostic	(77)
	miR-145	↑	Diagnostic/prognostic: CRT	(80)
	miR-26a	↑	Diagnostic: response to CRT	(80)
	miR-1254	↑	Diagnostic	(81,82)
		↑	Diagnostic/prognostic: death and HF hospitalization	(81)
	miR-1306-5p	↑	Diagnostic	(81,82)
		↑	Diagnostic/prognostic: death and HF hospitalization	(81)
	miR-106a-5p	↓	Diagnostic/prognostic: mortality	(83)
	miR-146a	↓	Diagnostic	(84)
	miR-199a	↓	Diagnostic/prognostic: mortality	(83)
	miR-26a	↓	Diagnostic/prognostic: mortality	(83)
	miR-27a	↓	Diagnostic/prognostic: mortality	(83)
	miR-30c/d	↓	Diagnostic	(83,84)
		↓	Prognostic: mortality	(83)
	miR-328	↓	Diagnostic	(84)
	miR-30d	↓	Diagnostic	(85)
		↓	Prognostic: response to CRT	(85)
Hypertrophic cardiomyopathy	miR-199a	↑	Diagnostic	(86)
	miR-21	↑	Diagnostic	(87)
	miR-27a	↑	Diagnostic	(86)
	miR-30c/d	↑	Diagnostic	(87)
Takotsubo cardiomyopathy	miR-1	↑	Diagnostic	(88)
	miR-133a/b	↑	Diagnostic	(88)
	miR-26a	↑	Diagnostic	(88)

↑, upregulated; ↓, downregulated. CVD, cardiovascular disease; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; POAF, postoperative atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; HF, heart failure.

but indefinite cargo or identified and edited single cargos (*Table 3*). Intravenous or local injection of exosomes is the primary mode of administration.

Therapy for post-MI regeneration

The injured myocardium presents a variety of responses to injury, including necrosis, inflammation, apoptosis, remodeling, and fibrosis. In AMI, myocardial secretion of exosomes increases with increasing ischemia (102). In peri-infarcted areas, the paracrine effects of non-injured myocardium-derived exosomes may reprogram cardiomyocytes and rescue the peri-infarcted region by

Table 3 Potential therapeutic methods with direct administration of exosomes

Exosome origin	Substance	CVD	Effect	Model type	Ref
MSC	miR125b-5p	MI	Promoted repair of ischemic myocardium by limiting apoptosis	Mouse exosome, mouse model	(90)
MSC	–		Reduced infarct size, facilitated functional recovery and increased neoangiogenesis	Human exosome, mouse model	(91,92)
MSC	miR-25-3p		Reduced cardiomyocyte apoptosis and inflammatory responses	Mouse exosome, mouse model (*in vivo*), human primary cardiomyocytes (*in vitro*)	(93)
GATA-4 overexpression MSC	miR-19a		Restored cardiac contractile function and decreased infarct size	Mouse exosome, mouse model	(94)
Human $CD34^+$ cell	–		Stimulated angiogenesis	Human exosome, mouse model	(95)
$CD34^{Shh}$ cell	Shh protein		Decreased infarct size and elevated border zone capillary density	Human exosome, mouse model	(96)
endothelial stem cell	miR-294		Promoted CPC survival and proliferation	Mouse exosome, mouse model	(97)
MSC	miR-133b	Stroke	Promoted neurogenesis, angiogenesis, and neurite remodeling	Mouse exosome, mouse model	(98)
M2 macrophage	(Loaded with hexyl 5-aminolevulinate hydrochloride)	AS	Alleviated AS	Mouse exosome, mouse model	(99)
MSC	miR-223	Sepsis	Decreased inflammation and cell death	Mouse exosome, mouse model	(100)
Cardiomyocyte overexpressing heat shock protein 20	–	Cardiomyocyte Hypertrophy	Improved the myocardial function of diabetic mice, preventing diabetes-caused cardiac injury	Mouse exosome, mouse model	(101)

CVD, cardiovascular disease; MSC, mesenchymal stem cell; MI, myocardial infarction; CPC, cardiac progenitor cell; AS, atherosclerosis.

transferring molecules, such as RNAs and peptides, to alleviate necrosis, inflammation, apoptosis, remodeling, and fibrosis (103). In these situations, myocardial exosomes can activate the release of stem cells and exosomes derived from bone marrow, which, in a feedback fashion, can repair and restore damaged tissue (20).

In most animal studies, stem cell-derived exosomes are administered via intramyocardial delivery. Hypoxic MSC-derived exosomes promote repair of ischemic myocardium by limiting apoptosis. Moreover, miR-125b-5p mediates this effect (mouse exosomes in a mouse model) (90). Human $CD34^+$ cell exosomes (which are a type of MSC) show a paracrine effect, stimulating angiogenesis (95). Similarly, $CD34^{Shh}$ cell-derived exosomes preserve murine cardiac function after acute myocardial infarction (human exosomes in a mouse model) (96). Following ischemia and reperfusion, MSC-derived exosomes increase ATP levels, reduce oxidative stress, and activate the PI3K/Akt pathway to enhance cardiomyocyte viability. Infarct size is reduced by 45% in animals treated with exosomes (human exosomes in a mouse model) (91). Moreover, combinatorial treatment with microvesicles and exosomes reduces infarct size, facilitates functional recovery, and increases neoangiogenesis (human exosomes in a mouse model) (92).

GATA-4 overexpression of MSC-derived exosomes restores cardiac contractile function and decreases infarct

size effects mediated, in part, by anti-apoptotic miR-19a (mouse exosomes in a mouse model) (94).

Murine endothelial stem cell-derived exosomes modulate the cardiomyocyte and CPC-based repair program in the heart, and these exosomes promote CPC survival and proliferation. A significant increase in the miR290-295 cluster has been observed in exosomes, and miR-294 mediates this salutary effect (mouse exosomes in a mouse model) (97). MSC-derived exosomes mediate the transfer of miR-25-3p and ameliorate MI by targeting pro-apoptotic proteins and EZH2 (mouse exosomes in a mouse model; and human primary cardiomyocytes *in vitro*) (93).

Human CPC-derived exosomes inhibit cardiomyocyte apoptosis and promote cardiac function post-MI (human exosomes in a mouse model) (104).

Following direct injection, cardiosphere-derived exosomes improve cardiac function, promote angiogenesis, and inhibit apoptosis (human exosomes in a mouse model); miR-146a is enriched in these exosomes and may contribute to the beneficial effects (105). CPC-derived exosomes with high levels of GATA4-responsive miR-451 inhibit cardiomyocyte apoptosis (mouse exosomes in a mouse model) (106).

Therapy for stroke, AS, septic cardiomyopathy, and cardiomyocyte hypertrophy

In rats with experimentally induced stroke, intravenous administration of MSC-derived exosomes improves function and promotes neurogenesis, angiogenesis, and neurite remodeling via miR-133b (mouse exosomes in a mouse model) (98,107).

M2 macrophage-derived exosomes loaded with hexyl 5-aminolevulinate hydrochloride homes to areas of neural inflammation. Exosomes function in an anti-inflammatory manner to alleviate AS. In addition, exosomes are capable of imaging and tracking AS by fluorescence (mouse exosomes in a mouse model) (99).

In sepsis, MSC-derived exosome transfer of miR-223 to cardiomyocytes and macrophages decreases inflammation and cell death (mouse exosomes in a mouse model) (100).

Exosomes derived from heat shock protein 20 (Hsp20)-overexpressing cardiomyocytes significantly decrease cell hypertrophy and improve the myocardial function of diabetic mice (mouse exosomes in a mouse model) (101).

Potential therapeutic methods target exosome synthesis, processing, and release

Regulation of exosome synthesis, process, and release are important areas of fundamental research. However, such studies are hampered by the fine line between beneficial physiological roles and harmful pathological roles of exosomes. It can be difficult to clarify those relationships. Compared to the direct administration of exosomes with defined components, exosome regulation methods need additional verification before clinical applications.

Because certain exosomes exacerbate CVDs (108), one therapeutic approach is to limit the secretion of so-called detrimental exosomes. Ang II increases the levels of miR-21-3p in cardiac fibroblast-derived exosomes and promotes cardiomyocyte hypertrophy (6). Conversely, the exosome inhibitors, GW4869 and DMA, block the release of these exosomes to limit Ang II-mediated myocardial hypertrophy and cardiac fibrosis (rat exosomes in a rat model) (43).

Apart from inhibition, some drugs are applicable in cell or animal models as regulators of the release or composition of exosomes. Simvastatin regulates the release of cardiomyocyte-derived exosomes and alleviates Ang II-induced cardiac fibrosis. Additionally, in cardiomyocyte-derived exosomes after treatment with simvastatin, decorin is increased, and periostin is decreased (human exosomes, *in vitro*) (109). Additionally, carvedilol increases ABCA1 levels in serum exosomes interfering with NF-κB and Akt signaling to limit atherosclerosis (mouse exosomes in a mouse model) (110).

Exosomes as an adjuvant to improve the therapeutic effects of other drugs

Combination with other therapies to improve the therapeutic effect is another option for the therapeutic role of exosomes. Intramyocardial delivery of bone marrow MSC-derived exosomes followed by MSC transplantation into the heart improves cardiac function, decreases infarct size, and increases neovascularization compared to animals treated with MSCs alone (rat exosomes in a rat AMI model) (111).

Clinical trials of exosome therapy

Preclinical studies have shown the beneficial therapeutic effects of exosomes in CVDs (90-101). Nevertheless, clinical investigations of exosome-based therapy are rare.

The NCT03384433 clinical trial (recruiting) entitled, "Allogenic Mesenchymal Stem Cell Derived Exosome in Patients with Acute Ischemic Stroke", aims to evaluate the effects of allogenic MSC-derived exosomes in the treatment of acute ischemic stroke. Therapeutic exosomes

are enriched with miR-124 by miR-124 transfection via stereotaxic administration. The NCT03478410 clinical trial entitled, "Role of Exosomes Derived from Epicardial Fat in Atrial Fibrillation", aims to assess the biomarker and therapeutic potential of epicardial fat-derived exosomes in patients with atrial fibrillation. The NCT04356300 clinical trial entitled, "Exosome of Mesenchymal Stem Cells for Multiple Organ Dysfunction Syndrome (MODS) After Surgical Repair of Acute Type A Aortic Dissection", aims to evaluate the safety and therapeutic efficiency of MSC-derived exosomes after surgical repair for acute type A aortic dissection. The NCT04356300 clinical trial has two parts. First, 150 mg of MSC-derived exosomes will be administered i.v. immediately after ascending aortic replacement followed by continuous administration of 150 mg of exosomes daily.

Conclusions

Exosomes are generated from different cells under specific pathophysiological conditions, and they function as carriers of signaling molecules, such as miRNAs and proteins. Exosomes are involved in CVDs by transporting specific exosomal cargo, either promoting or limiting disease.

Exosome cargo is specific to the situation and cell or origin, providing opportunities for developing novel diagnostic and prognostic methods. Studies have indicated that changes in exosomal cargo, such as miRNAs, are of significance in several pathologies, including AMI, arrhythmia, AF, CAD, HF, and cardiomyopathy, thus suggesting a role in the diagnosis of these conditions. Although many clinical studies concentrate on diagnostic and prognostic roles of exosome contents, shortcomings including relatively small cohorts of patients, different methods of contents extraction, and lack of consistency and standardization are major obstacles in front of its clinical applications (112). Taking all those factors into consideration and making a consensus on the standard experimental design at the start of a study might be one of the possible solutions.

For exosomes therapy, despite a large amount of published data from cell and rodent studies, exosome-based therapies are only now being tested in clinical trials. As safety is the major concern of clinical applications, preventing off-target effects and determining appropriate doses are of vital importance. Validation is needed before translation and wide use.

Finally, no matter for diagnosis, treatment or prognosis, lack of sufficient knowledge about the function and mechanisms of CVD-related exosomes will be hurdles for its development and application. Therefore further basic science researches on exosomes are indispensable for boosting the progress of exosome applications.

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Footnote

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