Role and relevance of exosome-mediated epigenetic regulation in the pathogenesis, diagnosis and treatment of cardiovascular diseases (Review)

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Abstract. Cardiovascular diseases (CVDs) are among the main factors impacting negatively human health on a global scale. Every year, there is an increase in the prevalence of CVDs despite advancements in therapy for managing traditional risk factors. Research on exosomes is has garnered great interest due to their role in regulating intercellular communication. Exosome-mediated epigenetic regulation is involved in the interaction between circulating cells and blood arteries, as well as in intercellular communication processes, and exosomes serve as biomarkers of cell activation. The present study aimed to summarize the recent research on exosome-mediated epigenetic regulation mechanisms, as well as the roles of exosomes in the pathology and diagnosis of CVDs, which may increase the current understanding of the precise functions that exosomes play in the development of CVDs.

Contents

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Abbreviations: CVDs, cardiovascular diseases; HF, heart failure; CHD, coronary heart disease; circRNAs, circular RNAs; lncRNAs, long noncoding RNAs; MI/R, myocardial ischemia/reperfusion; miRNAs, microRNAs; ncRNAs, noncoding RNAs; MVBs, multivesicular bodies; ESCRT, endosomal sorting complexes required for transport; DNMT, DNA methyltransferase; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; AMI, acute myocardial infarction; SHRs, spontaneously hypertensive rats; NETs, neutrophilic extranuclear traps; HUVECs, human umbilical vein endothelial cells

Key words: cardiovascular diseases, exosomes, epigenetic regulation, mechanism, diagnosis and treatment

1. Introduction

Cardiovascular diseases (CVDs), including heart failure (HF), hypertension, coronary heart disease (CHD), vascular calcification and others, are among the primary causes of health deterioration in humans worldwide. The Global Health Assessment 2019 report by the World Health Organization (1) indicated that heart disease has remained the leading cause of mortality globally for the past two decades. Improving the prognosis and course of treatment for CVDs requires early detection and diagnosis. Every year, there is an increase in the prevalence of CVDs despite advancements in therapy for controlling traditional risk factors. Furthermore, the number of CVD-associated mortalities is predicted to increase to ~23.6 million by 2030 as a result of aging and changing lifestyles (2,3). Thus, in-depth studies to broaden the current understanding of CVDs mechanisms, diagnosis and treatment are imperative.

Research on exosomes is part of a newly emerged field, which has attracted great attention due to their role in regulating intercellular communication. Exosomes are a subtype of extracellular vesicles with a typical size of ~100 nm, which can carry a range of lipids, carbohydrates, nucleic acids and proteins (4). Numerous CVDs are directly impacted by different circular RNAs (circRNAs), long noncoding RNAs

(lncRNAs), messenger RNAs, short nucleolar RNAs and microRNAs (miRNA) transported by exosomes. Due to these properties, exosomes have also been proposed as potential diagnostic and/or prognostic biomarkers for CVD, as well as novel potential therapeutic modalities (5). Epigenetics regulates the function and expression levels of CVD-associated genes primarily through ncRNA regulation and DNA methylation, thereby influencing the progression of CVD (6). Exosome-mediated epigenetic regulation participates in the interaction between blood vessels and circulating cells, as well as in intercellular communication processes, and exosomes serve as biomarkers of cell activation (7).

The aim of the present study was to examine the molecular mechanism behind exosome-mediated epigenetic regulation in the development of CVDs, and to explore the potential roles of exosome-mediated epigenetic regulation in the diagnosis and treatment of CVDs.

2. Exosome-mediated epigenetic mechanisms

Epigenetics and exosome biogenesis. Epigenetics is considered chromosomal changes that lead to stable genetic phenotypes in the absence of changes in the DNA sequence (8). Epigenetic markers are typically present in the first stages of CVD, and are valuable molecular markers for the diagnosis, evaluation and prediction of CVD response to treatment (9). Controlling these changed genes and proteins could also provide a novel focus for the management of heart disease, which is of considerable relevance for certain diseases that are becoming more common as the population ages and are yet challenging to treat clinically. This is because epigenetic modifications are reversible. In CVDs, through DNA methylation and ncRNA regulation, epigenetics primarily controls the function and expression level of associated genes, thus influencing the development of CVD (6,10).

Exosomes participate in intercellular communication among cells via direct communication with neighboring cells or via secretion of soluble factors under physiological and pathological conditions, which can extend the interaction over long distances (11,12). Exosome formation involves a number of processes, including synthesis of intraluminal vesicles, secretion and fusion with target cells, and cargo loading. The process of exosomal biogenesis commences with endosomal membrane invagination, resulting in the formation of multivesicular bodies (MVBs) *in vivo* (13). During this step, MVBs integrate proteins and cytoplasmic nucleic acids (14). On the one hand, when MVBs fuse with lysosomes, the encapsulated contents are degraded. When endosomes fuse with parental cell membranes, they are secreted in exosomes (15), as illustrated in Fig. 1. Since endosomes are the result of plasma membrane budding, the membrane protein orientation of the exosomes generated by this second invagination process is identical to that of the parental cells (16). Cargo sorting to exosomes is generally handled by endosomal sorting complexes required for transport (ESCRT) or sphingolipids (ESCRT-dependent or ESCRT-independent pathways). Cargo, such as proteins and RNA, can remain in the extracellular space unbroken if it is not part of the exosome lipid bilayer. Depending on the source, target and environment, target cells absorb exosomes through a variety of methods, such as membrane fusion, ligand receptor binding and endocytosis. Exosomes can enter adjacent target cells and bodily fluids, and even reach distant cells once they are secreted (8,9). This diagram illustrates the process of exosome biogenesis, including endosomal invagination, multivesicular body formation, cargo sorting, and exosome release. Exosomes facilitate intercellular communication by transferring genetic material (such as ncRNAs) to target cells through fusion, receptor binding or endocytosis. This process plays a key role in regulating gene expression and epigenetic changes in CVDs.

Epigenetic cargo of exosomes

Exosomal ncRNAs. LncRNAs, circRNAs and miRNAs are examples of ncRNAs, which are generally not translated into proteins but function through the regulation of gene expression. Instead, they carry out their specific biological roles at the RNA level (6). MiRNAs are ~22 nucleotides in length, and are mainly transcribed by large primary miRNAs that are involved in the post-transcriptional regulation of gene expression, and are produced by RNA polymerase II. Pri-miRNAs comprise one or more hairpin (stem-loop) structures, each of which is consists of ~70 nucleotides (17). In addition to being the targets of epigenetic changes such as DNA methylation, miRNAs also function as histone deacetylase and DNA methyltransferase (DNMT) regulators (18). LncRNAs are noncoding RNAs that control gene expression patterns by modifying the accessibility of DNA and the structure of chromatin via molecular mechanisms such as scaffolding, decoy, guiding and signal transduction (19). CircRNAs are long, noncoding endogenous RNA molecules that have no 5'cap or 3'cluster (A) end, and have single-stranded covalently closed RNA rings that can be used as templates for protein synthesis. CircRNAs interact with miRNAs to regulate target gene expression and mRNA translation, and bind to functional proteins or RNA-binding proteins in order to control their transport and function (20,21), as illustrated in Table I.

The role of ncRNAs in CVDs has attracted great attention, particularly due to their potential in early disease detection and prevention. MiRNAs, lncRNAs and circRNAs offer new perspectives for understanding the progression of CVDs. Notably, lncRNAs can exert both protective and detrimental effects in CVD, and this dual regulatory role makes them a key focus on cardiovascular research, as illustrated in Fig. 2. First, miRNAs act as essential regulatory factors in diseases such as coronary heart disease, myocardial infarction and vascular calcification (22,23). Furthermore, miRNAs also play a critical role in atherosclerosis. In endothelial cells (ECs), miR-342-5p exerts an anti-atherosclerotic effect by suppressing inflammatory responses (24), whereas miR-92a promotes the progression of atherosclerosis (25). Similarly, in pulmonary arterial hypertension, miR-181a-5p and miR-324-5p confer protective effects by inhibiting pulmonary vascular remodeling, thereby slowing disease progression (26). Similar to miRNAs, lncRNAs in CVDs can exert both protective effects and promote disease progression. For instance, lncRNA LEENE has been shown to inhibit atherosclerosis *in vitro* through its interaction with miR-1 (23,27). In addition, specific lncRNAs, including APF, CAIF and Mirf, have been demonstrated to regulate cardiac autophagy, which may

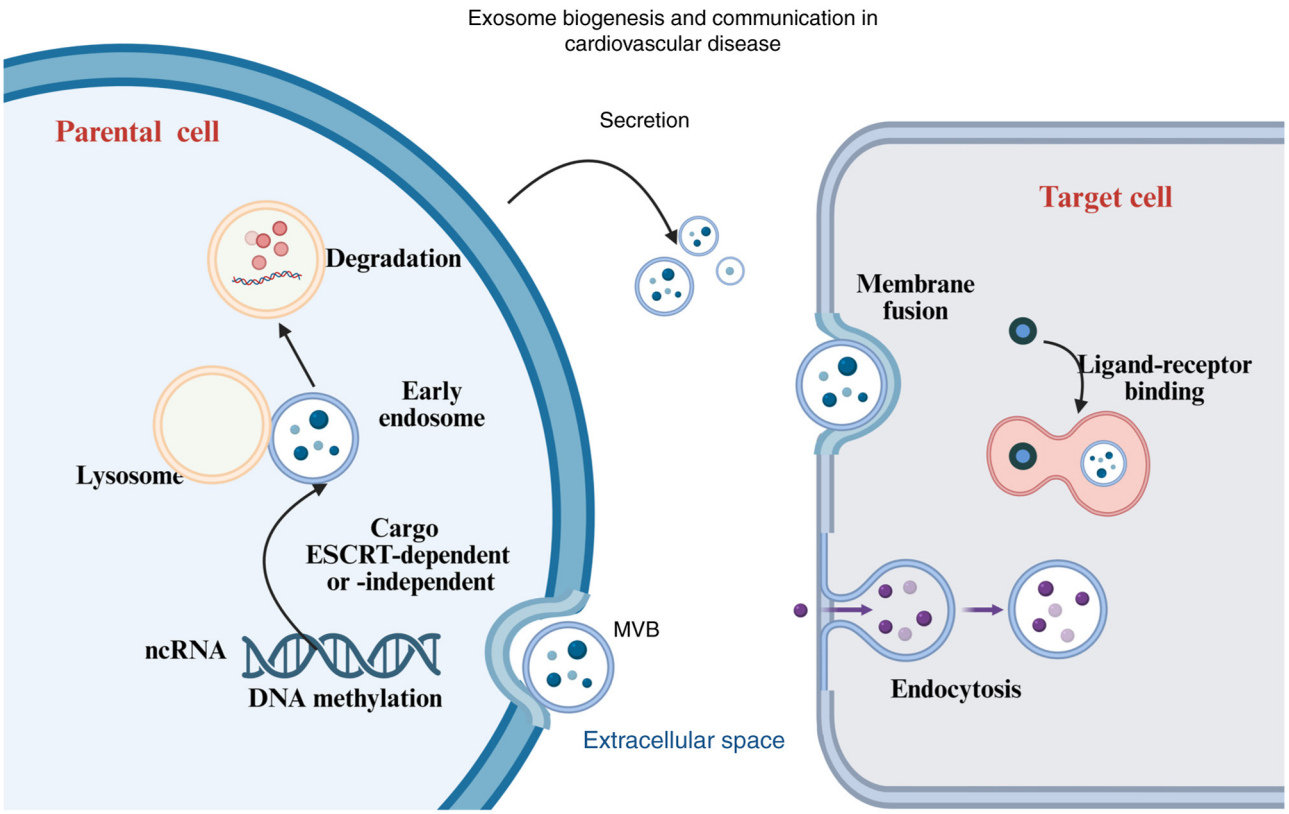

Figure 1. Exosome biogenesis and communication in cardiovascular disease. The diagram illustrates the process of exosome biogenesis, including endosomal invagination, MVB formation, cargo sorting and exosome release. ESCRT, endosomal sorting complexes required for transport; ncRNA, noncoding RNA; MVB, multivesicular body.

play a critical role during myocardial infarction-induced injury (28,29). Additionally, lncRNAs RNA-H19, LIPCAR and COL1A1 have been proposed as biomarkers for risk assessment and prediction of HF (30-32). Furthermore, circRNAs, as novel regulatory molecules, also play an important role in CVDs. For example, circRNAs can modulate the migration and proliferation of vascular smooth muscle cells (VSMCs) by interacting with miRNAs such as miRNA-939 and miRNA-221, thereby contributing to the development of atherosclerosis (33,34). In cardiomyocytes, circRNAs also play a crucial role, and are considered novel regulatory elements involved in hypertrophy, fibrosis, autophagy and apoptosis (35). Among them, mmu_circ_0005019 and circRNA CDYL have been identified as key regulators in the progression of HF (36,37). Notably, the overexpression of certain miRNAs may also lead to adverse effects. For example, excessive levels of miRNA-765, miRNA-483-3p and miRNA-143/145 can disrupt the renin-angiotensin system and increase the blood pressure (38). Similarly, circACTA2 interacts with miRNA-548F-5p, which targets the 3'-untranslated region of α-SMA mRNA to promote VSMC contraction and regulate vascular tone, thereby contributing to the development of hypertension (39). In summary, miRNAs, lncRNAs and circRNAs play multifaceted roles in CVDs. In-depth research on these RNA molecules may offer novel insights and potential biomarkers for the early diagnosis, treatment and prevention of CVDs.

miRNAs are the most abundant ncRNAs packaged within exosomes. Exosomal miRNAs derived from the heart and vascular system exhibit distinct expression patterns under various pathophysiological conditions. Their abundance and composition depend not only on the state of CVD but also on specific stimuli (40). The incorporation of miRNAs into exosomes relies on distinct selective packaging mechanisms, a process that is critical for their functional roles within the cardiovascular system (41). Previous studies in mouse models have further advanced the understanding of the role of miRNAs in cardiac development. Notably, cardiac-specific downregulation of the Dicer gene markedly disrupts miRNA synthesis in neonatal mice, resulting in atrial hypertrophy, cardiac dysfunction, ventricular remodeling and dilation, and ultimately early mortality (42,43). These findings underscore the critical importance of miRNAs in cardiac development and functional regulation. Among the numerous cardiac-specific miRNAs (44), miR-1 is particularly abundant, representing ~24% of the total miRNA population in the human heart and exhibiting pronounced enrichment in cardiac tissue (45). The miR-1 sequence is composed of two almost identical transcripts known as miR-1-1 and miR-1-2. While the loss of both transcripts results in mortality, the deletion of any of these transcripts causes defective cardiomyocyte differentiation and impaired cardiac electrical conduction (42,46). These findings indicate that miR-1 plays an indispensable role in normal cardiac development and functional maintenance. However, dysregulated expression of miRNAs, particularly abnormal levels within exosomes, may contribute to the onset of CVDs. For instance, excessive expression of certain

Table I. Common extracellular vesicle-derived ncRNAs and their roles in CVDs.

ncRNA type	Representative ncRNAs	Molecular regulatory mechanisms	Targets and roles in CVD	Regulatory roles in other diseases	(Refs.)
miRNA	miR-145, miR-143, miRNA-92a, miRNA-765, miRNA-571	Act as epigenetic targets by modulating the activity of histone deacetylases and DNA methyltransferases.	Regulate cardiomyocyte apoptosis, cardiac remodeling and myocardial injury; certain miRNAs may serve as biomarkers for CVD	Influence VSMC migration, regulate pulmonary vascular remodeling and blood pressure; overexpression may lead to imbalance of the RAS	(18,22-26)
lncRNA	LEENE, APF, CAIF, Mirf, H19, LIPCAR, COL1A1	Regulate gene expression by modifying DNA accessibility and chromatin structure through scaffold, decoy or signaling molecular mechanisms	Modulate cardiac autophagy and inflammatory responses, alleviate the progression of myocardial infarction and heart failure, and contribute to CVD risk prediction	Attenuate endothelial inflammatory pathways and help reduce the risk of atherosclerosis	(19,28-34)
circRNA	circSATB2, circCDYL, circACTA2	Serve as templates for protein synthesis, regulate miRNA activity, target gene expression and translation, and modulate the transport and function of functional or RNA-binding proteins	Involved in myocardial hypertrophy, fibrosis and autophagy, and regulate VSMC contraction	Influence vascular tone and smooth muscle function, and contribute to hypertension and vascular remodeling	(20,21,36-39)

ncRNA, noncoding RNA; CVD, cardiovascular disease; miRNA or miR, microRNA; VSMCs, vascular smooth muscle cells; RAS, renin-angiotensin system; lncRNA, long noncoding RNA; LEENE, lncRNA enhancing endothelial nitric oxide synthase expression; APF, autophagy-promoting factor; CAIF, cardiac autophagy inhibitory factor; Mirf, miRNA regulatory factor; H19, lncRNA H19; LIPCAR, long intergenic noncoding RNA predicting cardiac remodeling; COL1A1, collagen type I alpha 1 chain; circRNA, circular RNA; SATB2, special AT-rich sequence-binding protein 2; CDYL, chromodomain Y-like; ACTA2, actin alpha 2, smooth muscle, aorta.

miRNAs, such as miR-195 and miR-208, *in vitro* can lead to concentric ventricular hypertrophy and the development of heart failure (47,48). Therefore, measuring circulating miRNA levels and identifying specific exosomal miRNA signatures may provide critical information for the early diagnosis, monitoring and treatment of CVDs. Dysregulation of specific miRNAs, such as upregulation of miR-21 and miR-155 (49,50), or downregulation of miR-126 (51), is closely associated with the progression of cardiac atherosclerosis, and these miRNAs hold promise as potential biomarkers for cardiac defects, as summarized in Table I.

Exosome-mediated transfer of DNMTs. DNA methylation is a common modification in eukaryotic cells, which, by

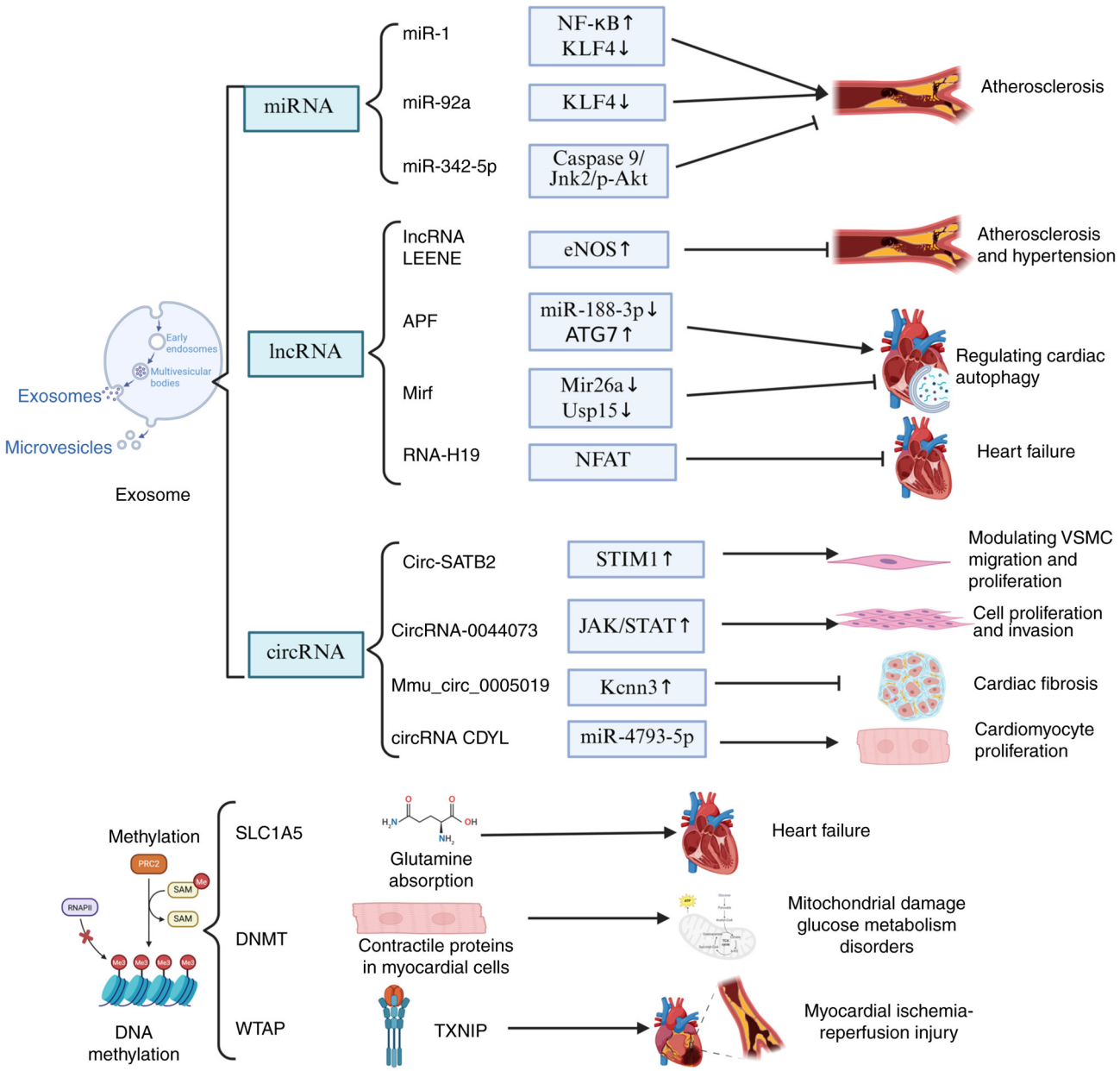

Figure 2. Mechanisms by which exosomal ncRNAs and DNA methylation regulate CVDs. Exosomal miRNAs, lncRNAs and circRNAs modulate gene expression in target cells through post-transcriptional and epigenetic mechanisms, thereby influencing vascular function and myocardial remodeling. In addition, exosome-delivered DNA methyltransferases and associated factors can reshape the epigenetic landscape of recipient cells, contributing to the onset and progression of CVDs. miRNA or miR, microRNA; lncRNA, long noncoding RNA; circRNA, circular RNA; p-, phosphorylated; CVDs, cardiovascular diseases.

controlling DNA methyltransferases (DNMT), can transfer genetic information to the DNA of the offspring (52). Accumulating evidence has suggested that aberrant methylation status of candidate genes, such as AHRR (53), F2RL3 (54) and CDKN2B-AS1 (55), can be used as indicators to assess the progression of cardiovascular disorders, as illustrated in Fig. 2. The expression of potential genes linked to CHD, HF hypertension and other CVDs has been reported to be strongly correlated with DNA methylation (56), as illustrated in Table II.

Specifically, alterations at multiple gene methylation sites have been demonstrated to be strongly associated with CVDs. Previous studies have identified that three DNA methylation areas, including the SLC9A1 (57), SLC1A5 (58) and TNRC6C genes (59), are associated with CVDs. Among them, the methylation of one CpG (CG22304262) in SLC1A5 is strongly associated with incident CHD, and shows significant associations with diabetes, blood pressure and all-cause mortality (60-62). The primary role of SLC1A5 in the heart is to regulate glutamine uptake. However, in patients with HF, reduced SLC1A5 expression leads to impaired glutamine absorption, resulting in disrupted cardiac glutamine storage and an imbalance in glutamine homeostasis, which ultimately compromises myocardial function and health (63). In addition to SLC1A5 methylation, previous epigenomic studies revealed broader associations between differential DNA methylation patterns and atherosclerosis as well as CHD (64). For instance, specific loci such as AHRR (cg05575921) and F2RL3

(cg03636183) in blood-derived DNA have been linked to both smoking exposure and increased risk of incident CHD (65,66). Similarly, epigenome-wide studies have identified methylation signatures related to chronic inflammation and lipid metabolism that correlate with atherosclerosis progression (67,68). Importantly, these epigenetic markers (e.g., methylation of AHRR and LINE-1 elements) have been shown to provide greater predictive value for CHD than traditional risk factors alone (69). Additionally, alterations in the methylation levels of genes associated with acute myocardial infarction (AMI), such as Csf1r, Ptpn6, Map3k14 and Col6a1, further support the mechanistic role of DNA methylation in cardiovascular pathophysiology (70). Previous studies have shown that upregulation of thioredoxin-interacting protein is associated with myocardial ischemia/reperfusion (MI/R) injury (71), potentially through aberrant activation of the m6A methyltransferase complex component WTAP (72). *In vivo* experiments further demonstrated that exosome-mediated delivery of WTAP small interfering RNA effectively alleviated MI/R injury (73).

Furthermore, DNA methylation mediated by DNMT3a plays a critical role in maintaining the structural and metabolic homeostasis of human cardiomyocytes (74), thus underscoring its relevance in CVDs. Previous research has shown that DNMT3a deficiency alters the expression of contractile protein genes in cardiomyocytes, leading to mitochondrial damage and glucose metabolism disorders (75), which may represent a critical therapeutic target for cardiac diseases. Furthermore, extracellular vesicles in the circulation of patients with acute coronary syndrome are enriched in DNMTs, particularly showing markedly increased expression of the *de novo* methyltransferases DNMT3A and DNMT3B. These enzymes can modulate the methylome and signaling pathways of recipient cells, thereby contributing to CVDs (76). Further *in vitro* studies revealed that downregulation of DNMTs not only participates in the physiological regulation of cardiomyocytes but also plays a crucial role in pathological conditions such as cardiac hypertrophy (77). Notably, the DNMT inhibitor RG108 has been shown to attenuate pressure overload-induced cardiac hypertrophy in animal models, possibly by modulating epigenetic mechanisms in non-myocyte cells (78). A previous study showed that selenium supplementation exerts beneficial effects in alleviating HF symptoms (79). By reducing cardiomyocyte death and reactive oxygen species production, selenium not only helps mitigate HF, but also indirectly improves the epigenetic state of cardiomyocytes by inhibiting the DNMT2-mediated methylation of the glutathione peroxidase 1 gene promoter (80).

Beyond genes that directly affect cardiac health, DNA methylation also plays a critical role in other physiological systems. In mouse models, the loss of the Wnt receptor LRP6 in aortic VSMCs leads to increased methylation of GTPase-activating protein-binding proteins, which may be linked to the transcriptional responses that trigger arterial calcification (81). Furthermore, DNA methylation patterns in the placenta have also been found to be associated with maternal blood pressure and CVDs. A previous study revealed that mothers with a family history of hypertension exhibited lower global placental DNA methylation levels in placental samples, which as accompanied by higher mean arterial pressure, thus highlighting the potential role of placental epigenetics in the development of CVDs (82). Additionally, in the field of cancer research, DNMTs have been shown to play a crucial role in mediating tumor drug resistance and progression through exosome-based delivery mechanisms (83-85).

In summary, DNA methylation, as a key epigenetic regulatory mechanism, is likely to play an important role in the onset and progression of CVDs. However, the mechanisms underlying exosome-mediated DNA methylation in the cardiovascular system remain to be fully elucidated. Although these pathways have been extensively studied in cancer, such as hepatocellular carcinoma (86), colorectal cancer (87) and acute myeloid leukemia (88), as well as in other diseases including Alzheimer's disease (89), type 2 diabetes (90) and systemic lupus erythematosus (91), direct evidence in CVDs is relatively limited, highlighting the urgent need for systematic investigations to clarify their specific roles and clinical implications. Future research focusing on the role of exosomes in epigenetic regulation may provide novel insights into the pathogenesis of CVDs.

3. Exosome-mediated epigenetic mechanisms in CVDs

The homeostasis of the cardiovascular system is maintained through the interplay of various cell types, including cardiac fibroblasts, ECs, VSMCs, cardiomyocytes, immune cells and resident stem cells (92). These cells release exosomes that mediate intercellular signaling, thereby contributing to tissue repair, remodeling and the regulation of pathological responses in the cardiovascular system. Notably, exosomes are not merely structural vesicles, but functional carriers that transport epigenetic information and influence gene expression in recipient cells. Consequently, exosome-mediated epigenetic regulatory mechanisms are increasingly recognized as critical contributors to the onset and progression of CVDs. Previous studies have demonstrated that exosomes of different cellular origins, such as ECs, erythrocytes, platelets and leukocytes, exhibit donor cell-specific profiles of RNAs, proteins and modifying enzymes, thereby reflecting the physiological or pathological state of their source cells (93,94). For example, exosomes derived from ECs are essential for the phenotypic transition of VSMCs (95), while exosomal miRNA profiles in the plasma of atherosclerotic patients have been investigated as potential early biomarkers (59,60). These findings suggest that pathological alterations in the cellular microenvironment not only influence exosome abundance and secretion dynamics, but also profoundly reshape their epigenetic regulatory cargo.

CVDs, including HF, hypertension, atherosclerosis, atrial fibrillation and AMI, continue to be the primary causes worldwide rates of morbidity and mortality, despite continuous advancements in the clinical diagnosis and treatment of heart disease. Exosomes are involved in the movement and interchange of molecules that signal, which makes them a crucial component in controlling the course of CVDs, as shown in Table III. Furthermore, ncRNAs found in exosomes function as novel regulators in dyslipidemia, which raises the risk of CVD caused by atherosclerosis. For example, miR-26a is markedly downregulated in exosomes from obese mice and overweight individuals, and its restoration reverses multiple markers associated with dysregulated lipid metabolism, suggesting a pivotal role for exosomal miRNAs in the cardiometabolic axis.

Table II. Gene regulation associated with cardiovascular diseases via DNA methylation.

Key genes	Methylation mechanism	Associated diseases	Functional impact	(Refs.)
SLC1A5	Methylation at CpG site 22304262	Coronary artery disease and HF	Involved in the regulation of glutamine metabolic homeostasis	(58,63)
DNMT3a	Promoter region methylation-mediated regulation	Acute myocardial infarction and HF	Regulates mitochondrial function and glucose metabolism, and is associated with the expression and metabolism of myocardial contractile proteins	(74-76)
LRP6	Loss-induced upregulation of GTPase methylation	Atherosclerosis	Regulates vascular smooth muscle cell calcification and vascular remodeling	(81,82)

HF, heart failure; SLC1A5, solute carrier family 1 member 5; DNMT3a, DNA (cytosine-5)-methyltransferase 3 alpha; LRP6, low-density lipoprotein receptor-related protein 6.

Importantly, exosome-mediated epigenetic mechanisms exhibit substantial heterogeneity across different CVD subtypes. For instance, in HF, exosomal ncRNAs may contribute to the regulation of myocardial autophagy and fibrosis, whereas, in atherosclerosis, they are more likely to influence inflammatory cell infiltration and endothelial repair processes. Exosomes associated with hypertension are often enriched in miRNAs involved in vascular tone regulation, whereas those related to AMI tend to carry factors that modulate cardiomyocyte apoptosis and stress responses. These differences underscore the importance of analyzing exosomal epigenetic functions in a disease-specific context, which represents a promising direction for precision cardiovascular therapy. Accordingly, the following section aimed to systematically explore the roles of exosomal ncRNAs and DNA methylation-related factors in the pathophysiological mechanisms of four major CVD subtypes, namely HF, hypertension, atherosclerosis and myocardial infarction, with the aim of providing a theoretical basis for understanding their regulatory networks and clinical potential.

HF. In HF, exosomal miRNAs play a pivotal role in regulating myocardial remodeling, and exhibit potential as both biomarkers and therapeutic targets, as shown in Table III. In a rat model of chronic HF, exosomal miR-124 derived from human umbilical cord mesenchymal stem cells was found to target PRSS23 and suppress associated fibrotic signaling pathways, thereby reducing the expression of the endothelial marker CD31, alleviating myocardial ischemic injury, and promoting angiogenesis and cellular repair (96). A clinical study also highlighted the critical role of exosomal miRNAs in HF (97). Previous studies have shown that patients with HF and reduced ejection fraction exhibit elevated levels of exosomal miR-92b-5p (97,98). This miRNA correlates positively with left atrial diameter, systolic blood pressure and left ventricular end-diastolic diameter, while it correlates negatively with fractional shortening and left ventricular ejection fraction (97), suggesting its potential involvement in the structural and functional remodeling of the left-side of the heart. In addition, miR-425 and miR-744 have also exhibited beneficial effects in mitigating myocardial fibrosis. In angiotensin-induced models, overexpression of these two miRNAs effectively suppresses collagen production and fibrotic processes in fibroblasts, whereas their downregulation is accompanied by significant upregulation of α-SMA and COL1, further confirming their critical regulatory role in cardiac fibrosis (99). Therefore, miR-425 and miR-744, as exosome-delivered epigenetic regulators, represent promising therapeutic targets and potential novel tools for reversing cardiac remodeling in HF. Notably, the regulatory effects of exosomal miRNAs may be bidirectional. Previous research has reported that serum exosomal miR-27a levels are significantly reduced in patients with HF, and this decrease is closely associated with poor prognosis (100). Additionally, aberrant expression of miR-126 in peripheral blood mononuclear cells of patients with chronic HF has been shown to exacerbate cardiac injury (101). Collectively, exosomal miRNAs modulate myocardial fibrosis through multiple targets and mechanisms, thus playing a critical role in the structural and functional remodeling of the heart.

Hypertension. Hypertension is a major risk factor for cardiovascular events such as coronary artery disease, HF, stroke and myocardial infarction (102,103). In addition, its onset and progression are also governed by a variety of molecular and cellular processes. In recent years, exosome-mediated ncRNA signaling has been recognized as a key epigenetic regulatory mechanism linking these pathological processes (104,105). According to previous studies, numerous cellular and molecular

Table III. Roles of key extracellular vesicle-derived ncRNAs in cardiovascular diseases.

Disease type	Key extracellular vesicle-derived ncRNAs	Primary targets	Main functions	Clinical relevance	(Refs.)
HF	miR-92b-5p	Left ventricular function marker	Regulates ventricular dilation and ejection performance	Diagnostic biomarker for HF	(97)
	miR-425, miR-744	Cardiac fibroblasts	Inhibit myocardial fibrosis, reverse cardiac remodeling	Therapeutic targets for myocardial remodeling	(99)
HTN	miR-155-5p	Renin-angiotensin system	Inhibits VSMC proliferation and vascular remodeling, reducing blood pressure	Regulates blood pressure	(108)
	miR-27a	eNOS phosphorylation and Mas receptor	Inhibits vasodilation and increases blood pressure	Early risk biomarker for hypertension	(109)
	miR-17	ICAM-1 expression and endothelial inflammatory responses	Attenuates endothelial inflammation and ameliorates vascular injury	A potential therapeutic target for inflammation-related hypertension	(110)
AS	miR-19b	STAT3	EC proliferation and migration	Delays the progression of unstable atherosclerotic plaques	(43)
	miR-221/222	PTEN/AKT axis	Inhibits VSMC autophagy	Participates in vascular remodeling	(121)
	miR-223	MAPK/NF-κB axis	Suppresses ICAM-1 expression and attenuates inflammatory responses	Anti-vascular inflammation	(122)
	miR-146a	IRAK1 and NETs formation	Regulates EC inflammation and NETs activation	Therapeutic target for immune-inflammatory intervention	(123, 136)

Table III. Continued.

Disease type	Key extracellular vesicle-derived ncRNAs	Primary targets	Main functions	Clinical relevance	(Refs.)
	miR-4532	SP1	Promotes EC injury	Aggravates endothelial dysfunction	(124)
	miR-33a-5p	ABCA1/ApoA1	Regulates cholesterol efflux and inhibits foam cell formation	Therapeutic intervention target for foam cell development	(129)
	miR-16-5p	SMAD7	Activates inflammation and oxidative stress	Exacerbates atherosclerosis	(130)
	miR-203-3p	p38/MAPK axis	Inhibits atherosclerosis progression	Reverses atherosclerotic progression	(132)
	lncRNA GAS5	THP-1/ECs	Induces EC apoptosis and regulates inflammation	Potential molecular biomarker for AS risk	(141)
	lncRNA MALAT1	Macrophages, NETs	Modulates macrophage polarization and NETs formation	Exhibits dual regulatory functions	(142,143)
	circRNA 0006896	TG, LDL	Enhances EC proliferation and migration	Associated with unstable plaque formation	(144,146)
AMI	miR-146a, miR-25-3p, miR-301	Cardiac inflammation	Suppresses inflammatory cytokine release in cardiomyocytes	Myocardial protection and inflammation-targeted intervention	(155,158)
	miR-22/21	Myocardial fibrosis	Reduces myocardial fibrosis, inhibits EC apoptosis and promotes angiogenesis	Cardiac protection and tissue repair	(162)
	lncRNA MALAT1	Myocardial ischemia	Inhibits miR-92a and promotes neovascularization	Hyperoxia-induced pathway for myocardial repair	(164)
	lncRNA AK139128	Cardiac remodeling	Inhibits the proliferation, invasion and migration of cardiac fibroblasts	Anti-fibrotic effects and remodeling modulation	(166)

ncRNA, noncoding RNA; HF, heart failure; miR, microRNA; HTN, hypertension; VSMC, vascular smooth muscle cell; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; AS, atherosclerosis; STAT3, signal transducer and activator of transcription 3; PTEN, phosphatase and tensin homolog; EC, endothelial cell; MAPK, mitogen-activated protein kinase; SP1, specificity protein 1; ABCA1, ATP-binding cassette transporter A1; ApoA1, apolipoprotein A1; SMAD7, mothers against decapentaplegic homolog 7; MAPK, mitogen-activated protein kinase; lncRNA, long noncoding RNA; GAS5, growth arrest-specific 5; THP-1, human acute monocytic leukemia cell line; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; IRAK1, interleukin-1 receptor-associated kinase 1; NETs, neutrophil extracellular traps; circRNA, circular RNA; TG, triglycerides; LDL, low-density lipoprotein; AMI, acute myocardial infarction.

processes, such as the renin-angiotensin-aldosterone system, endothelial dysfunction, vascular remodeling, oxidative stress, angiogenesis, VSMC proliferation and inflammation, are regulated by a number of exosomal ncRNAs, which ultimately lead to the development of hypertension (77,106).

Exosomal miRNAs can influence the development and occurrence of hypertension in a positive or negative manner. In spontaneously hypertensive rats (SHRs), compared with Wistar-Kyoto rats, 23 exosomal miRNAs were upregulated and 4 were downregulated, indicating a systemic alteration in circulating exosomal miRNA profiles under hypertensive conditions (107). For example, miR-155-5p was significantly downregulated in exosomes derived from adventitial fibroblasts of SHR aortas (1). This miRNA could suppress ACE/Ang II signaling, reduce oxidative stress and inflammation, and thereby inhibit VSMCs migration in SHRs (108). On the other hand, certain exosomal miRNAs have been shown to exert pro-hypertensive effects. Exosomal miR-27a derived from THP-1 monocytes could inhibit the phosphorylation of endothelial nitric oxide synthase in mesenteric arteries, and reduce Mas receptor expression in ECs, thereby impairing vasodilation and elevating blood pressure (109). Following Ang II treatment, the levels of intercellular adhesion molecule-1 in THP-1 cells increased, whereas exosomal miR-17 could downregulate its expression, thus modulating endothelial inflammatory responses and indirectly affecting the vascular tone (110). In addition, exosomal miR-106b-5p, released from macrophages, could be transferred to glomerular mesangial cells, where it suppressed the transcription factors Pde3b and E2f1, thus mediating tissue responses associated with inflammatory hypertension (111). A previous epidemiological study reported that extracellular vesicle-derived miRNAs, particularly miR-199a/b and miR-223-3p, exhibited significant interactions with elevated systolic blood pressure, thus potentially contributing to hypertension through mechanisms involving vascular function, inflammatory responses and oxidative stress (112). In summary, miRNAs play a critical regulatory role in the onset and progression of hypertension. They modulate vascular tone and remodeling through multiple pathways, such as exosomal miR-155 (113), which impairs endothelial nitric oxide signaling and promotes vascular inflammation, and exosomal miR-505 (114), which enhances vascular smooth muscle cell proliferation and migration, reflecting their unique and complex functional characteristics in hypertensive pathology. However, current research on miRNAs in hypertension remains largely preclinical (115), with a lack of systematic validation in large populations and limited progress in translational applications.

Atherosclerosis. Atherosclerosis is a long-term immunoinflammatory disease characterized by the accumulation of lipid-rich particles in arterial plaques, which is one of the main causes of CVDs, with serious clinical consequences such as myocardial infarction and stroke. In recent years (116,117), exosome-mediated regulation of ncRNAs has been recognized as one of the key epigenetic mechanisms driving the development and progression of atherosclerosis (AS), as shown in Table III. Exosomal ncRNAs primarily regulate lipid metabolism, vascular inflammation and cell survival, which have crucial regulatory functions in the onset and advancement of atherosclerosis.

Numerous studies have demonstrated that, in both patients and animal models of atherosclerosis, miRNAs, serving as key epigenetic molecules within exosomes, can significantly influence the pathological progression of AS through changes in their expression levels (116,118). In patients with unstable angina, 28 miRNAs were upregulated, among which miR-19b showed the most pronounced increase. This miRNA may inhibit the transcriptional activity of the STAT3 signaling pathway, thereby suppressing the proliferation, migration and angiogenesis of ECs, ultimately delaying the formation and progression of unstable plaques (41). Dysfunction of ECs can lead to atherosclerosis by causing EC senescence, inflammation, hyperpermeability, oxidative stress and vasodilation abnormalities (119). Previous studies have shown that exosomal ncRNAs play a major role in this process. Human smooth muscle cells in the aorta produce miR-221/222, which inhibits autophagy in these cells by regulating the PTEN/Akt axis (120,121). Thrombin-stimulated platelet exosomes showed enhanced miR-21, miR-339 and miR-223 levels, and miR-223 could inhibit the expression of intercellular adhesion molecule-1 (ICAM-1) in inflammatory processes by regulating the MAPK/NF-κB axis (122). In addition, exosomal miR-146a modulates inflammatory responses in ECs by inhibiting interleukin-1 receptor-associated kinase 1 (123), whereas miR-4532 exacerbates EC injury through its interaction with SP1 (124). A previous study showed that upregulation of miR-155 can regulate the interaction between ECs and VSMCs, inhibiting EC migration, proliferation and reendothelialization (113). This, in turn, weakens the endothelial barrier, increases vascular wall permeability and promotes the progression of atherosclerotic plaque (125).

In addition, the pathophysiology of atherosclerosis is regulated by exosomal miRNAs derived from non-cardiomyocyte cell types, such as endothelial cell-derived exosomal miR-92a that promotes vascular inflammation (126), macrophage-derived exosomal miR-146a that modulates inflammatory signaling (127), and vascular smooth muscle cell-derived exosomal miR-221/222 that enhances cell proliferation and migration (128). Macrophages in particular possess the unique ability to engulf aggregated and oxidized low-density lipoprotein via micropinocytosis and scavenger receptor-mediated uptake, subsequently transforming into lipid-laden foam cells that constitute the core of atherosclerotic plaques. Exosomal miR-33a-5p, secreted by these cells, can regulate ABCA1 expression and promote apoA1-mediated cholesterol efflux, thereby affecting foam cell formation (129). miR-16-5p accelerates inflammation and oxidative stress in atherosclerosis by downregulating SMAD7, and promotes apoptosis (130), thereby facilitating the progression of atherosclerotic lesions. Endothelial dysfunction is one of the key initiating factors in the early stages of atherosclerosis. Previous *in vitro* studies have shown that circ_0124644 promotes endothelial injury by modulating the miR-149-5p/PAPP-A axis, highlighting its pathogenic role in the progression of AS and its potential as a target for clinical intervention (131). In addition, the miR-203-3p/cathepsin S pathway, which functions along the p38/MAPK axis, has been shown to reverse atherosclerosis (132). Neutrophil extracellular traps (NETs)

have also been identified as contributors to the amplification of immune-inflammatory responses in AS (133,134). NETs are a network of densified chromatin, nuclear histones and granular antimicrobial proteins that are released by neutrophils in response to microbial antigens (135). Exosomal miR-146a released from macrophages upon oxidized low-density lipoprotein (oxLDL) stimulation can induce the formation of NETs and promote the progression of atherosclerosis (136). Following oxLDL treatment, human umbilical vein ECs (HUVECs) exhibit enhanced NF-κB pathway activation, which upregulates miR-505 expression. MiR-505 then targets SIRT3, leading to increased reactive oxygen species production and elevated NET formation (88). VSMCs participate in plaque formation during the early stages of AS and contribute to plaque stability in the later stages.

In addition to the aforementioned miRNAs, lncRNAs are also important epigenetic regulators, and have been shown to be significantly upregulated in both animal models and patients with atherosclerosis. Previous studies have shown that exosomal lncRNA LIPCAR regulates CDK2 and participates in the phenotypic transformation of VSMCs (137,138). MiR-106a-3p modulates apoptosis by targeting CASP9 (139), and the LINC01005/miR-128-3p/KLF4 axis influences VSMC migration and proliferation (140). These lncRNAs mediate intercellular communication via exosomes, and serve as key regulatory nodes in the evolution and stability of atherosclerotic plaques. In THP-1 cells, lncRNA GAS5 can induce and regulate apoptosis in both THP-1 monocytes and ECs (141). By contrast, EC-derived lncRNA MALAT1 exhibits bidirectional effects: On one hand, it promotes M2 macrophage polarization and protects against atherosclerosis (142), while, on the other hand, it may also facilitate the formation of NETs, thereby accelerating the progression of atherosclerosis (143). In addition, several studies have found that exosomal circRNA-0006896 is closely associated with the pathogenesis of atherosclerosis (144,145). It is significantly upregulated in patients with unstable atherosclerotic plaques, and its levels are positively correlated with triglycerides, low-density lipoprotein and C-reactive protein. Mechanistically, circRNA-0006896 may promote EC proliferation and migration by activating the NF-κB signaling pathway (144,146). Previous *in vitro* studies have shown that exosome levels are significantly elevated in the serum of patients with coronary artery disease, which can exacerbate inflammatory responses and apoptosis in HUVECs, thereby promoting endothelial injury and atherosclerosis progression (147,148). Conversely, exosomal circ_0001785 can alleviate endothelial damage through the miR-513a-5p/TGFBR3 axis, thus exhibiting a protective effect (149).

In summary, exosome-derived miRNAs, lncRNAs and circRNAs in atherosclerosis profoundly participate in immune inflammation, apoptosis, lipid metabolism and plaque stability by targeting multiple key signaling pathways, including MAPK, NF-κB, STAT3 and p38. These epigenetic factors not only hold promise as diagnostic biomarkers for AS, but also offer new strategies for intervening in plaque progression and enhancing therapeutic precision.

Myocardial infarction. AMI is typically caused by sudden coronary artery occlusion and is characterized by myocardial cell necrosis and loss of function, which can have severe clinical consequences (150). Previous studies have shown that exosomal miRNAs play a pivotal regulatory role in the onset and progression of myocardial infraction (MI) by modulating a variety of pathological processes, including autophagy, inflammation, angiogenesis and apoptosis (151,152), as shown in Table III.

Multiple studies have found that the exosomal miRNA expression profile derived from cardiomyocytes is significantly altered in patients with MI. Notably, exosomal miR-125b, miR-499, miR-133, miR-22, miR-21 and miR-301, which originate from cardiomyocytes, are markedly upregulated following MI (153,154). These miRNAs are encapsulated within cardiomyocyte-derived exosomes and are broadly expressed in damaged myocardial regions. By inhibiting cardiomyocyte death, modulating local inflammatory responses and promoting ischemic tissue repair, they help alleviate pathological injury following MI and may partially contribute to the prevention of complications such as atherosclerosis (155,156). Furthermore, inflammation-associated miRNAs, such as miR-146a and miR-25-3p, are upregulated in the immune environment induced by MI. Notably, exosomal miR-301 is also elevated and has been shown to suppress autophagy in cardiomyocytes (109,157). At the translational level, exosomal miR-499 and miR-133a are significantly elevated in patients with MI compared to those with stable coronary artery disease or acute coronary syndrome, demonstrating their potential utility for clinical diagnosis and disease stratification (94). In addition, miR-26b-5p promotes ferroptosis by targeting SLC7A11, and its downregulation in exosomes from patients with AMI helps attenuate myocardial injury (158), thus offering new perspectives for anti-ferroptosis therapies.

In addition to those derived from cardiomyocytes, exosomal ncRNAs from other cell types also play important roles in the pathology of MI. For example, during ischemic episodes, the expression of miR-22 in mesenchymal stem cell-derived exosomes is reduced (159); however, *in vivo* supplementation of this miRNA can significantly attenuate cardiac fibrosis (160), highlighting its therapeutic potential after AMI. High expression of miR-21 in mesenchymal stem cell-derived exosomes can significantly inhibit EC apoptosis and promote angiogenesis, thereby exerting a protective effect on cardiomyocytes (161). In addition, lncRNAs are involved in the epigenetic regulation of MI. LncRNA BC002059 has been shown to reduce infarct size in mice with coronary artery ligation (162). Mechanistically, BC002059 exerts its cytoprotective effects by influencing the downstream target gene ABHD10 and subsequently regulating the expression of miR-19b-3p (163). The roles of other lncRNAs in the process of MI should not be overlooked, such as MALAT and H19 (164,165). After AMI, the levels of MALAT1 in exosomes released from cardiomyocytes are significantly increased under hyperoxic conditions. MALAT1 enhances neovascularization by suppressing miR-92a expression (117), thereby contributing to ischemic tissue repair. Atorvastatin treatment has been shown to induce an increase in lncRNA H19 release from mesenchymal stem cells (118). By contrast, under hypoxic conditions, cardiomyocyte-derived exosomal lncRNA AK139128 regulates cardiac fibrosis by affecting the proliferation, migration and apoptosis of cardiac fibroblasts (165).

These findings suggest that exosomal lncRNAs not only play functional roles in response to ischemic injury, but may also serve as important molecular targets for the treatment of MI.

Overall, exosomal ncRNAs play critical roles in myocardial infarction as well as other CVDs, including hypertension, atherosclerosis and HF. Previous research in both animal models and clinical samples has identified numerous potential therapeutic targets, such as exosomal miR-92b-5p regulating cardiomyocyte apoptosis (166), lncRNA H19 enhancing the efficacy of mesenchymal stem cell-derived exosomes in myocardial infarction (167). However, there is considerable heterogeneity in the mechanisms, target pathways and functional roles of ncRNAs among different types of CVDs. In HF, exosomal miRNAs primarily regulate fibroblast activity and influence myocardial remodeling, demonstrating potential for anti-fibrotic effects and cardiac structural modulation. By contrast, exosomal ncRNAs associated with atherosclerosis are more focused on regulating endothelial function and lipid metabolism, reflecting microenvironment-specific regulatory characteristics within atherosclerotic lesions. By comparison, those involved in hypertension predominantly participate in the regulation of vascular tone and remodeling.

Although these findings reveal distinct mechanisms by which exosomal ncRNAs act in different CVDs, as shown in Table III, their clinical translation still faces important challenges. The majority of previous studies rely on animal models and *in vitro* experiments, with a lack of validation in large-scale human samples. Future research urgently requires multicenter clinical data to further clarify the specific mechanisms of exosomal ncRNAs in cardiovascular pathology.

4. Exosome-epigenetic cargo as a prognostic biomarker and treatment for CVDs

Prognostic biomarkers may be employed for identification of diseases and/or prognostic indicators. The most crucial and essential qualities of effective biomarkers are their sensitivity, specificity, stability and relative noninvasive detection. Notably, recent studies (166,168) are focusing on exosomes as possible biomarkers due to their easy and affordable detection in multiple bodily fluids, and their ability to function as a protective transport system against enzymatic degradation. Exosomes possess the capacity to serve as helpful biomarkers for the early detection of CVDs, since their cargo for epigenetic pathways varies depending on the type of CVD (169,170). Therefore, exosomes may be used as biomarkers to assist diagnosis according to their abnormal manifestations in different CVDs.

Therapeutic potential of exosomes in CVDs. Previous studies have shown that exosomal ncRNAs exhibit diverse biological functions within the cardiovascular system. Dicer's heart-specific downregulation in young mice degrades miRNAs, particularly miR-1, miR-133a, miR-208 and miR-499 (171,172), resulting in atrial expansion, ventricular remodeling and enlargement, reduced cardiac function, and early mortality (173,174). By contrast, overexpression of certain specific miRNAs *in vitro* can induce cardiac hypertrophy and HF (44,45), indicating that the balance of miRNA expression is essential for maintaining cardiac homeostasis (173). Therefore, exosomal miRNAs and other epigenetic cargos not only reflect disease states but may also serve as potential targets for therapeutic intervention.

As therapeutic agents, exosomes hold promise as viable delivery vehicles due to a range of advantages, including minimal immunogenicity and toxicity, high biocompatibility, efficient bio-barrier permeability and natural availability (174). It has been attempted to alter exosomes through genetic engineering for medicinal uses (175,176). The potential to use exosomes as carriers to deliver certain cargo to particular tissues or organs is made possible by the capacity to change isolated and purified exosomes with target molecules and surface-loaded mimics or inhibitors of epigenetic payload (172,177). This gene regulation points to exosome epigenetic cargo as a potentially effective treatment strategy for a range of human diseases.

Previous animal studies have demonstrated the therapeutic potential of exosomes in various CVD models (168,178,179). Engineered exosomes enriched with low-density lipoprotein receptor mRNA have been shown to effectively alleviate hypercholesterolemia in mice (180). Additionally, mesenchymal stem/stromal cell (MSC)-derived exosomes can reduce cardiomyocyte apoptosis after myocardial infarction by suppressing SOCS2 signaling via miRNA-185 (181-183). A previous study further confirmed that pharmacological agents can modulate exosomes to intervene in the development and progression of CVDs (165). Furthermore, a previous study found that phenol can attenuate inflammatory responses in HUVECs, which deaccelerates the progression of atherosclerosis, and decreases the expression levels of STAT3 and phosphorylated STAT3 in HUVECs by increasing the quantity of exosome miR-223 in HUVECs treated with THP-1 and exosomes (184). In an I/R injury model in mice, the injection of cortical diaphysial-derived exosomes decreased the size of the infarct (185). On the contrary, chrysin reduced miR-92a expression in HCAEC cells and accelerated the progression of atherosclerosis (186). Furthermore, exosomal miR-21-3p derived from nicotine-treated macrophages could bind to PTEN, thereby promoting VSMC migration and proliferation, and exacerbating the progression of atherosclerosis (187). In addition, exosomes have shown a promising potential in promoting cardiac regeneration. Multiple studies using models of ischemic heart disease have demonstrated that injection of mesenchymal stem cell-derived exosomes can effectively improve myocardial remodeling, enhance cardiomyocyte survival (188,189), and promote EC proliferation, thereby partially restoring cardiac function (190,191). This 'cell-free therapy' offers a safer and more controllable alternative to traditional cell transplantation.

Current status and challenges of exosome-based therapies. In recent years, exosome-based therapeutic strategies have attracted increasing attention for the treatment of CVDs (192). Exosomes are nanoscale, membrane-bound vesicles secreted by cells, and their unique structural and functional properties make them highly promising as therapeutic carriers (176,193). The bilayer lipid membrane of exosomes effectively protects encapsulated bioactive molecules, such as miRNAs and proteins, enhancing their stability and biological activity *in vivo* (194). For example, compared with free curcumin,

curcumin encapsulated in exosomes exhibits higher plasma concentrations and greater anti-inflammatory effects (195). Furthermore, as non-living particulate structures, exosomes offer greater controllability compared to viral vectors or live cell systems, and lack tumorigenic potential (196). In multiple studies, exosomes have demonstrated a favorable safety profile (197,198).

However, despite the numerous advantages of exosomes as therapeutic tools, their clinical application still faces notable challenges. First, safety concerns cannot be ignored. While exosomes derived from autologous cells are generally considered to have low immunogenicity, artificially engineered exosome delivery systems may still pose immunogenic risks, follow unintended pathways away from target recipient cell types, and result in unexpected off-target effects (199). More importantly, exosomes lack specific biodistribution *in vivo*. Once cleared from the bloodstream, exosomes tend to accumulate in organs such as the lungs, spleen and liver (200,201), which can result in off-target effects, reduced therapeutic efficacy and even potential toxicity. Due to the tendency of RNA to aggregate or degrade, loading specific RNA cargos into exosomes using conventional electroporation or sonication techniques presents remarkable technical challenges, and the efficacy of these approaches remains uncertain (202). In addition, there may be a risk of infection when these particles enter the human bloodstream. More challenging is the substantial variability in exosomal drug loading capacity and the lack of uniformity, making it difficult to optimize exosome dosing (140). Furthermore, the optimal therapeutic time window for exosome administration *in vivo* has not yet been determined, which further increases the uncertainty of clinical translation (203). Therefore, before advancing exosomes as RNA delivery vehicles for clinical use, it is essential to ensure their safety *in vivo* and to minimize immune responses or off-target effects. In addition, optimization of loading techniques is needed to improve RNA stability and achieve a uniform cargo distribution.

Furthermore, the industrialization and clinical translation of exosomes face important technical bottlenecks. Currently, ultracentrifugation is the most commonly used isolation method for exosomes; however, it is labor-intensive, inefficient, and has limited yield, thus making it difficult to meet the demands of large-scale clinical applications. On one hand, there is still a lack of unified and standardized Good Manufacturing Practice-grade manufacturing processes (204). On the other hand, exosomes derived from different cell sources show significant variations in composition, function and efficacy, leading to poor batch-to-batch reproducibility and substantial challenges in quality control. Furthermore, delivery efficiency remains one of the most critical issues. Exosomes are commonly administered for the treatment of CVDs via intravenous, intracoronary or intramyocardial injection; however, these approaches are often associated with procedural complexity or low cardiac retention rates in clinical practice. Although surface engineering modifications can enhance targeted delivery (205), exosomes still face challenges such as off-target effects, rapid clearance and the need for rigorous safety validation in the complex human physiological environment.

In summary, exosomes hold great therapeutic promise for CVDs, particularly due to their advantages in targeting specificity, delivery efficiency and epigenetic regulation. However, several key issues must be addressed before exosome-based therapies can be translated into clinical practice, including ensuring safety, improving manufacturing processes and enhancing consistency in therapeutic efficacy.

5. Conclusions and future perspectives

The present study aimed to review in detail the exosome-mediated epigenetic mechanisms, such as exosomal ncRNAs and exosome-mediated DNA methylation, and their role in CVDs. Concurrently, the present study examined the function of exosomal phylogenetic pathways in CVD detection and treatment. The miRNA cargo of exosomes is of particular importance, as these molecules have the capacity to control the expression of proteins. At present, research on the mechanisms by which exosomes influence cardiovascular epigenetics is still ongoing, with current studies mainly focusing on exosomal ncRNAs. Targeted approaches for the treatment of CVDs are feasible, as exosomes are capable of delivering therapeutic agents directly to damaged cells and tissues. The application of exosomes as delivery vehicles for CVD therapy is highly promising. Both animal studies and preliminary clinical trials have shown encouraging results, suggesting that exosome-based therapies could represent a breakthrough in CVD treatment. Given that CVD remains a leading cause of mortality worldwide, this strategy is particularly meaningful for high-risk populations, including those with comorbidities such as diabetes and hypertension, or individuals with a history of angina or myocardial infarction.

However, the clinical application of exosomes still faces multiple challenges. First, there is a lack of standardized protocols for exosome isolation, characterization and cargo detection, resulting in poor reproducibility of experimental results and efficacy validation across studies, which limits translational progress. Second, the low loading efficiency and instability of functional RNAs compromise the stability and controllability of exosome-based delivery systems. In addition, the non-specific biodistribution of exosomes *in vivo* leads to risks of rapid clearance and off-target effects, which highlights the need for improved delivery strategies such as surface modification and magnetic guidance to enhance targeting. Particularly in the cardiovascular field, achieving safe, stable and effective therapeutic delivery in complex microenvironments requires further systematic research and validation.

However, as research on exosomes continues to advance, their prospects in precision medicine remain highly promising. In particular, exosomes offer novel insights into epigenetic regulation and intercellular communication underlying the pathogenesis and progression of CVDs. Future studies should focus on both mechanistic exploration and the establishment of technical standards to facilitate the critical transition from laboratory research to clinical application.

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Authors' contributions

Conceptualization and study design: LZ and JL. Writing of the first manuscript draft: YZ. Literature search, figure reparation (created with BioRender) and manuscript editing: WJ and YL. Data curation, writing, reviewing and editing: YZ and SZ. Supervision and project administration: LZ and JL. All authors contributed to the critical revision of the manuscript, read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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