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Review Article

Extracellular RNAs as communicators in cardiovascular disease: a narrative review

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Background and Objective: Cardiovascular disease (CVD) is a leading cause of death in industrialized countries. It consists of different etiologies and has linked to other types of diseases (e.g., diabetes, renal failure). Thus, understanding the disease mechanisms of CVD is of a great interest in the cardiovascular field. Because mammalian cardiomyocytes do not regenerate at a significant rate, if any, upon damage, cell therapy is an attractive therapeutic method to fight against CVD. To understand the disease mechanism as well as therapeutic approaches of CVD, recent advances in the field of extracellular RNAs (exRNAs) are increasing being appreciated for their involvement as cell-cell communication materials. Here, we summarize the current status of cardiac exRNAs to raise the awareness of this important field of study.

Methods: For this mini-review, relevant articles related to exRNA by focusing on the CVD were searched in the PubMed database for publications written in English and published up to April 26, 2022.

Key Content and Findings: These searches identified a number of non-coding RNAs [e.g., microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)] as cardiac extracellular vehicles (EVs) affecting the cellular physiologies of cardiac cells as well as differentially expressed in CVD patients or animals compared to healthy donors, non-failing hearts, or control animals.

Conclusions: By specifically focusing on publications with mechanistic findings, we highlight the importance of further research using genetic models and understanding the amount of exRNAs being transferred from one cell type to another to affect the phenotypes observed.

Keywords: Cardiovascular; circular RNA (circRNA); extracellular RNA (exRNA); long non-coding RNA (lncRNA); microRNA (miRNA); RNA

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Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality with ~18 million deaths each year (1). Due to the socio-economic burden resulting from CVD, many approaches have been taken to uncover the molecular mechanisms underlying different etiologies of CVD. The common features within various etiologies [e.g., heart failure (HF) after myocardial infarction (MI)] is cell death, which is regulated by complex networks of signaling pathways (2). Furthermore, increasing evidence suggest the complex cell-cell communication among different cell types during the remodeling of the heart after injury (3). For example, MI leads to loss of heart muscle (cardiomyocytes) that is replaced by non-contracting scar tissue (4). Although healing after MI is necessary for scar formation, it is often accompanied by adverse remodeling of the remaining viable

myocardium and progression of pump failure. The immune system, in which macrophages play a key role, is a double-edged sword in the remodeling process (5). Macrophages are necessary for repair in the acute phase as their systemic depletion results in impaired scar formation and left ventricle (LV) rupture (6). However, their accumulation in non-infarcted regions of LV in the chronic phase contributes to progressive myocyte attrition, collagen deposition by myofibroblasts (activated fibroblasts), and loss of the pump function. Thus, understanding the cell-cell communication during the remodeling of the heart is important in uncovering the disease mechanisms of CVD.

Extracellular RNAs (exRNAs) are produced by a donor cell and are released into the extracellular environment (e.g., body fluid, circulation) (7). ExRNAs could be received by recipient cells, where exRNAs may function as cell-cell communication materials. They can be found to be contained in the lipid particles, such as extracellular vehicles (EVs), including exosomes. ExRNAs include protein-coding mRNAs and non-protein-coding RNAs, including transfer RNAs (tRNAs), small interfering RNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Due to the availability of commercial products to isolate EVs and RNA sequencing (RNA-seq) to characterize exRNAs, this field of study has exploded in recent years, including exRNAs in CVD (8). In this narrative review, we will summarize the recent developments in this field by particularly focusing on their functional and mechanistic roles (*Figure 1*). We present the following article in accordance with the Narrative Review reporting checklist (available at https://exrna.amegroups.com/article/view/10.21037/exrna-22-3/rc).

Methods

A literature review was performed using PubMed to search all scientific articles published through to April 26, 2022. The search terms used included: “extracellular”, “heart”, “cardiovascular disease”, “RNA”, “miRNA”, “circRNA”, “lncRNA”. We use a table (*Table 1*) to present detailed search strategy. Focus was placed on original articles in English about exRNAs in cardiovascular system and disease; it excluded articles that have no information about cardiac exRNAs.

Extracellular miRNAs in CVD

MiRNAs are short RNAs with ~22 nucleotides (nt) in their mature form that regulate mRNA decay and translation by binding to the 3'-untranslated region (UTR) of mRNAs (9). Typically, one miRNA has several hundreds of mRNAs as its targets and is conserved across species. Furthermore, miRNAs are rather stable in the circulation, which are investigated as diagnostic biomarkers for various diseases, including CVD (10-13). Because of their stabilities, they are often found as exRNAs (14,15) (*Table 2*). For example, exosomes derived from angiotensin II-induced hypertrophied neonatal rat cardiomyocytes induced the secretion of inflammatory cytokines, IL-6 and IL-8, when co-cultured with the murine macrophage cell line RAW264.7 (16). RNA-seq analysis revealed that *miR-155* was enriched in exosomes derived from hypertrophied cardiomyocytes compared to non-induced cardiomyocytes. *In vitro*, it was shown that exosomal *miR-155* regulates the MAPK signaling pathway via the phosphorylation of p38, ERK1/2, and JNK, to activate macrophages. Not only cardiomyocytes secrete miRNAs as exRNAs, but also other cell types in the heart, especially those in diseased hearts, regulate changes in cellular phenotypes triggered by miRNAs as exRNAs. For example, the same miRNA, *miR-155*, was shown to be released in exosomes from macrophages in a uremic mouse model by removing parts of kidneys to study uremic cardiomyopathy (17). Using *miR-155* knockout mice compared to wildtype C57BL/6 mice, it was demonstrated that exosomal *miR-155* was released into the cytosol of cardiomyocytes, which targets the forkhead transcription factor, *FoxO3a*, to promote cardiomyocyte pyroptosis (pro-inflammatory programmed cell death) and uremic cardiomyopathy changes, such as cardiac hypertrophy and fibrosis. It is rather paradoxical that the same miRNA is shown to be released as exRNAs from both cell types that these two studies reported to influence the phenotypic changes in each other, which highlights the confusing findings in this field of study.

The mammalian adult cardiomyocytes cannot regenerate themselves at a significant rate, if any, to replace the damaged hearts (26). Thus, external ways to regenerate damaged hearts are attractive therapies for CVD. Of such methods, the injection of cells (collectively called as cell therapy) is of particular interest in recent years (27). These cells include mesenchymal cells (multipotent stromal cells) from various cell sources, such as adipocytes, bone marrow, cardiac and skeletal muscle. Originally thought that these injected cells transdifferentiate into cardiomyocytes, it is now widely accepted that the injected cells secrete macromolecules (DNA, RNA, and proteins) that function

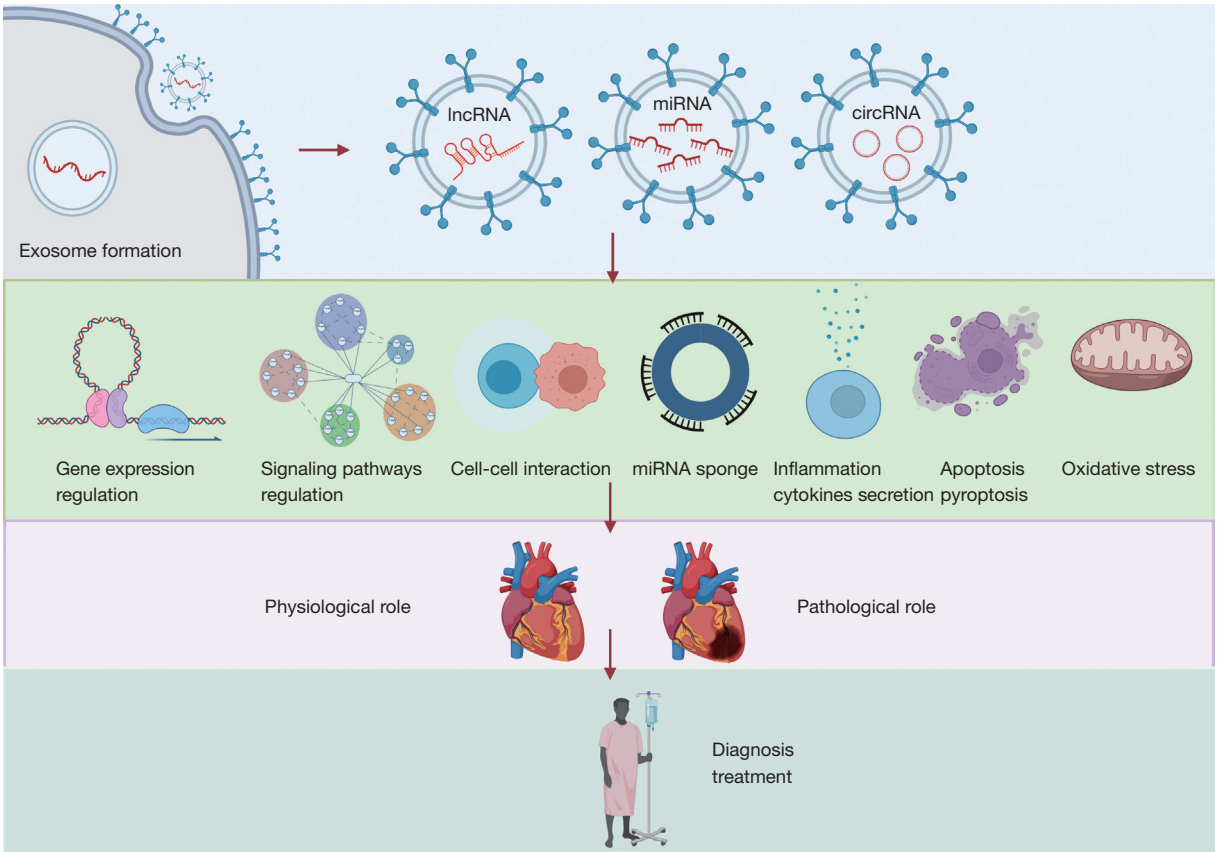

Figure 1 Biology of cardiac exRNAs. Cardiac exRNAs—lncRNAs, miRNAs, circRNAs—can be released by cardiac cells—including cardiomyocytes, endothelial cells, fibroblasts, macrophages—via extracellular vehicles, including exosomes. ExRNAs play roles in cell-cell interaction, gene expression regulation by targeting transcription factors, regulation of signaling pathways, apoptosis, oxidative stress, inflammation, and cytokine secretion, and as miRNA sponges. ExRNAs maintain normal cardiac structure and function under physiological conditions as well as under pathological processes and contribute to the development of CVD. Thus, exRNAs hold great potential for the development of diagnostic markers and possible treatments for CVD. Created with BioRender.com accessed on 01 March 2022. exRNAs, extracellular RNAs; circRNA, circular RNA; lncRNA, long non-coding RNA; miRNA, microRNA; CVD, cardiovascular disease.

Table 1 The search strategy summary

Items	Specification
Date of search	April 26, 2022
Databases and other sources searched	PubMed
Search terms used	Extracellular, heart, cardiovascular disease, RNA, miRNA, circRNA, lncRNA
Timeframe	January 3, 2014–April 26, 2022
Inclusion and exclusion criteria	Focus was placed on original articles in English about exRNAs in cardiovascular system and disease; it excluded articles that have no information about cardiac exRNAs

circRNA, circular RNA; lncRNA, long non-coding RNA; exRNAs, extracellular RNAs.

Table 2 List of functionally and mechanistically characterized exRNAs

RNA	Sources	Phenotypes/mechanisms	Reference
miR-155	Angiotensin II-induced hypertrophied neonatal rat cardiomyocytes	Regulates the MAPK signaling pathway via the phosphorylation of p38, ERK1/2, and JNK, to activate macrophages	(16)
miR-155	Macrophages in a uremic mouse model by removing parts of kidneys to study uremic cardiomyopathy	Targets the forkhead transcription factor, FoxO3a, to promote cardiomyocyte pyroptosis and uremic cardiomyopathy changes	(17)
miR-25-3p	Mesenchymal cells isolated from murine bone marrow	Targets the pro-apoptotic *Fasl* and *Pten* mRNAs to regulate their protein levels as well as Ezh2, in turn derepress the cardioprotective gene *eNOS* and anti-inflammatory gene *Socs3*	(18)
PVT1	Angiotensin II-induced cultured human cardiac cardiomyocytes	Functions as miRNA sponge to sequester *miR-145-5p* in macrophages to promote its polarization to pro-inflammatory M1 macrophages	(19)
MALAT1	Endothelial cells	Interacts with the transcription factor NRF2, thereby inhibits the accumulation of reactive oxygen species and maturation of dendritic cells	(20)
MALAT1	Endothelial cells	Affects the formation of neutrophil extracellular traps in a mouse model of atherosclerosis	(21)
HCP5	Human bone marrow mesenchymal stem cells	Functions as miRNA sponge to sequester *miR-497*, which targets *IGF1* to activate IGF1/PI3K/AKT pathway	(22)
UCA1	Human mesenchymal stem cells	Functions as miRNA sponge to sequester *miR-873*, which targets the anti-apoptotic *XIAP*	(23)
UCA1	Human umbilical cord mesenchymal stem cells	Functions as miRNA sponge to sequester *miR-143*, which targets the apoptosis-related gene *BCL2* to regulate myocyte survival	(24)
circHIPK3	Hypoxia-induced cardiomyocytes	Functions as miRNA sponge to sequester *miR-29a*, which targets *VEGFA* to promote cell cycle progression and proliferation of cardiac endothelial cells	(25)

exRNAs, extracellular RNAs.

in a paracrine manner, instead of differentiating into cardiomyocytes (28). Of these paracrine factors, miRNAs, especially those considered as exRNAs, are becoming a hot topic to be investigated (29). For example, exosomes derived from mesenchymal cells isolated from murine bone marrow protected cardiomyocytes in an *in vitro* oxygen-glucose deprivation model and alleviated the adverse effects in a mouse model of ischemia-reperfusion (I/R) injury (18). Mechanistically, exosomal *miR-25-3p* targets the pro-apoptotic *Fasl* and *Pten* mRNAs to regulate their protein levels as well as the enzymatic component of the polycomb repressive complex 2 (PRC2), *Ezh2*, in turn derepress the cardioprotective gene *eNOS* and anti-inflammatory gene *Socs3*. However, it should be noted that most of these studies use extensively cultured cells (primary cells or cell lines) to produce exRNAs to be injected into the host animals (usually rodents). Furthermore, mesenchymal cells isolated from a tissue source are heterogenous populations of cells. Thus, it is often difficult to pinpoint the observed effects based on one miRNA as there are other factors being involved, including other exRNAs being injected at the same time. Of course, there is no perfect experimental system nor it could also be that the additive effects of several exRNAs, which makes it harder to know the exact mechanism of action of miRNA as exRNA, especially one miRNA has several hundred target mRNAs.

Could lncRNAs be a key to understand exRNAs?

Any non-coding RNAs (ncRNAs) longer than 200 nt are currently categorized as lncRNAs (30-32). Due to this broad definition, the number of lncRNAs is much more than that of protein-coding genes (33). LncRNAs are subcategorized based on their genomic locations to nearby protein-coding genes, such as sense, antisense, intergenic, enhancer, and promoter lncRNAs (34). Their functions

are diverse and depend on their macromolecular binding partners (DNA, RNA, and proteins), including recruiting of epigenetic and transcriptional complexes, decoy, splicing, and translational regulations. Furthermore, lncRNAs also found as exRNAs, where it is speculated to contribute to cell-cell communications (35) (*Table 2*). For example, the lncRNA *PVT1* (Pvt1 oncogene) is highly expressed in the exosomes isolated from angiotensin II-induced cultured human cardiac cardiomyocytes (19). Mechanistically, the exosomal *PVT1* increased the expression of IL-16 via sequestering *miR-145-5p* (thus, functioning as miRNA sponge) in macrophages to promote its polarization to pro-inflammatory M1 macrophages.

The nuclear lncRNA, *MALAT1* (metastasis associated lung adenocarcinoma transcript 1; also known as *NEAT2*), is another lncRNA implicated as cardiac exRNA. This abundantly expressed nuclear lncRNA is highly studied in the context of cancer and is conserved among mammals (36). In cardiovascular system, *MALAT1* is known to regulate endothelial function and vessel growth (37). Furthermore, *Malat1* knockout mice displayed pro-atherosclerotic phenotype due to enhanced accumulation of hematopoietic cells involved in inflammatory responses (38). Not only *MALAT1* is functional in nuclei, *MALAT1* is secreted as exRNA. *MALAT1* in exosomes isolated from endothelial cells is transferred to immature dendritic cells, where *MALAT1* interacts with the transcription factor NRF2, thereby inhibits the accumulation of reactive oxygen species and maturation of dendritic cells (20). In a mouse model of atherosclerosis (ApoE knockout mice fed with a high-fat diet for 12 weeks), it was observed that the decreased level of exosomal *Malat1* is associated with the progression of atherosclerosis. Another study shows that exosomal *MALAT1* isolated from endothelial cells also affects the formation of neutrophil extracellular traps, which is associated with hyperlipidemia and inflammatory response in a mouse model of atherosclerosis (21), further indicating the functional roles of *MALAT1* outside of the cellular nuclei.

As it was the case for exosomal miRNAs, lncRNAs are also implicated in cardiac cell therapy as exRNAs. For example, the exosomal lncRNA *HCP5* (HLA complex P5) isolated from human bone marrow mesenchymal stem cells increased the viability of cardiomyocytes while decreasing apoptosis in the hearts of rat model of myocardial I/R (22). Mechanistically, *HCP5* sequesters *miR-497*, which targets *IGF1* to activate IGF1/PI3K/AKT pathway. Another example is the lncRNA *UCA1* (urothelial cancer associated 1). The exosomal *UCA1* isolated from human mesenchymal stem cells injected intramyocardially in a rat model of MI showed improved heart functions and reduced fibrosis compared to the PBS-injected rats (23). Mechanistically, *UCA1* sponges *miR-873*, which targets the anti-apoptotic *XIAP*. The same lncRNA, *UCA1*, is also reported to bind yet another miRNA when isolated as exosomal lncRNA from human umbilical cord mesenchymal stem cells and injected into a rat model of I/R (24). Similar to the previous study (23), the injection of exosomes showed cardioprotective effects. Mechanistically, *UCA1* sponges *miR-143*, which targets the apoptosis-related gene *BCL2* to regulate myocyte survival (24). Among several studies of exosomal lncRNAs in cardiac cell therapy, the lncRNAs functioning as miRNA sponges seem to be a common mechanism. However, as mentioned above, each miRNA targets several hundreds of mRNAs. Furthermore, one lncRNA bind several miRNAs as in the case of *UCA1*. Thus, it will be necessary to map the signaling pathways being affected by the lncRNA-miRNA-mRNAs axes to understand the effects of mixture of exRNAs being injected to the donor animals.

circRNAs as diagnostic biomarkers

CircRNAs are a subclass of lncRNAs that are generated by backsplicing events of exons and/or introns of both protein-coding and ncRNA genes (39). They lack free ends necessary for exonuclease-mediated degradation. This makes them relatively stable in circulation (40); thus, they are attractive candidates for diagnostic biomarkers, including in CVD (41-46) (*Table 2*). For example, the circRNA, *circHIPK3*, is shown to be a key factor in exosomes isolated from hypoxia-induced cardiomyocytes, which regulate oxidative stress damage in cardiac endothelial cells (25). Mechanistically, *circHIPK3* sponges *miR-29a*, which targets *VEGFA* to promote cell cycle progression and proliferation of cardiac endothelial cells. There are several other studies indicating that exosomal circRNAs function as miRNA sponges in cardiac cells (47-50). However, the current problem in the circRNA research is that the detailed characterization of circRNAs (e.g., genomic locations, biogenesis from the host gene, copy number and the amount in the circulation) is missing in most studies. This is especially problematic when circRNAs are reported as miRNA sponges because circRNAs are expressed at very low level, whereas miRNAs are abundantly present. Thus, it is not clear how one circRNA can sponge the excessive

amounts of miRNAs, especially circRNAs are detected as exRNAs in the circulation.

Conclusions

Because of the importance of CVD and the establishment of detection and characterization methods of exRNAs, the number of publications about cardiac exRNAs is rapidly increasing. Although we mainly covered miRNAs, lncRNAs, and circRNAs as cardiac exRNAs here, other exRNAs are increasing being studies, such as tRNA-derived small RNAs (tDRs) with distinct fragmentation signatures in plasma from patients on cardiopulmonary bypass (51) and in children with fulminant myocarditis (52). As mentioned above, even the same miRNA (i.e., *miR-155*) is indicated to be secreted as exRNAs from the same cell types (i.e., cardiomyocytes and macrophages) to have effects in one another. It is a chicken and egg problem that further research is needed, yet one study used a clear genetic model [i.e., *miR-155* knockout mice (17)]. Also, it is not clear how much (in amount or copy number) transfer of exRNAs is needed to have phenotypic effects as suggested because such information is utmost importance to move this field forward beyond using them as potential diagnostic biomarkers of CVD. To solve these problems, more systematic analysis as well as functional and mechanistic studies of cardiac exRNAs are urgently needed to firmly establish the importance of exRNAs as therapeutic tools for CVD.

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