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REVIEW

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Exosomal non-coding RNAs: key regulators of inflammation-related cardiovascular disorders

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Abstract

Inflammation is a complex, tightly regulated process involving biochemical and cellular reactions to harmful stimuli. Often termed "the internal fire", it is crucial for protecting the body and facilitating tissue healing. While inflammation is essential for survival, chronic inflammation can be detrimental, leading to tissue damage and reduced survival. The innate immune system triggers inflammation, closely linked to the development of heart diseases, with significant consequences for individuals. Inflammation in arterial walls or the body substantially contributes to atherosclerotic disease progression, affecting the cardiovascular system. Altered lipoproteins increase the risk of excessive blood clotting, a hallmark of atherosclerotic cardiovascular disease and its complications. Integrating inflammatory biomarkers with established risk assessment techniques can enhance our ability to identify at-risk individuals, assess their risk severity, and recommend appropriate CVD prevention strategies. Exosomes, a type of extracellular vesicle, are released by various cells and mediate cell communication locally and systemically. In the past decade, exosomes have been increasingly studied for their vital roles in health maintenance and disease processes. They can transport substances like non-coding RNAs, lipids, and proteins between cells, influencing immune responses and inflammation to elicit harmful or healing effects. This study focuses on the critical role of inflammation in heart disease progression and how non-coding RNAs in exosomes modulate the inflammatory process, either exacerbating or alleviating inflammation-related damage in the cardiovascular system.

Keywords Cardiovascular disease, Inflammation, Exosome, MicroRNA, LncRNA

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Introduction

Numerous studies consistently indicate that inflammation and conventional risk factors for heart disease can collaborate to promote vascular illness, ultimately resulting in the development of cardiovascular events [1]. Many different systemic conditions that cause inflammation, including but not limited to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), medium to large vessel vasculitis, and psoriatic arthritis, are linked to a higher chance of developing atherosclerosis and experiencing cardiovascular diseases at an earlier age [2]. It is noteworthy that acute inflammation, such as sepsis, greatly amplifies the chances of developing cardiovascular health issues in the future [3]. Although they have different properties related to autoimmune reactions and inflammation, atherosclerosis can be seen as an outcome of the same problem: localized inflammation in the subintimal and perivascular layers of blood vessels. Across time, a gradual and complex inflammatory progression takes place in regions of the artery prone to lesions due to various disease-specific factors [1, 4]. Despite ongoing research, there is still limited knowledge about how systemic inflammatory diseases and vascular inflammation are connected on a physiological level. However, advancements in understanding the human genome, which reveals that up to 90% of it is actively transcribed during the developmental process, offer potential for further investigation into this relationship [5–7].

Less than 1% of the human genome produces proteins. However, the remaining 99% still play important roles in regulating and structurally supporting various cellular processes through the production of non-coding RNAs [8]. Interestingly, as organisms evolved from simpler forms to humans, the proportion of non-coding RNAs has significantly increased compared to the relatively small increase in protein-coding genes, points to the domination of ncRNAs in humans [9]. Novel types of genetic material called ncRNAs, including miRs, siRNAs, and lncRNAs, regulate cardiovascular risk factors and cellular functions [10]. As a result, they are being considered as potential tools for improving the accuracy of diagnostics and prognostic assessments. Moreover, the identification of these ncRNAs has greatly enhanced our ability to effectively address and manage various ailments [10]. While it was previously thought that only coding sequences in the human genome were clinically relevant, the results from the *ENCODE* project and other scientific investigations have proven otherwise [11]. Numerous non-coding genetic variations have been associated with significant human diseases, underscoring the need to also consider these regions [12]. Furthermore, ncRNAs have proven to be essential in controlling the expression of genes and vital cellular functions, opening up potential opportunities for specific and targeted treatment methods [13–21]. It is crucial to include non-coding elements in the study of disease development, and a comprehensive analysis of the transcriptome must cover both large and small ncRNAs as well as protein-coding genes [22].

Newly conducted research has placed emphasis on the crucial function of exosome-derived ncRNAs in controlling intercellular communication among interconnected signaling pathways [23]. The ncRNAs have recently drawn substantial interest due to their significant impact on regulating inflammation during ischemic stroke and myocardial infarction [24–28]. An important point to mention is that non-coding RNAs (ncRNAs) are specifically found in high levels in exosomes, and these transferred molecules are essential for controlling numerous factors involved in the onset and advancement of damages in both the brain and heart [29]. The interconnectedness of cardiovascular and cerebrovascular events is underscored by the common inflammatory pathways and responses they share. New evidence suggests that exosomal non-coding RNAs are involved in regulating inflammation in these conditions [23]. There is an abundance of proof to back up the established idea that exosome-derived non-coding RNAs have a considerable impact on the progression of MI and ischemic stroke [30–33]. There is a substantial amount of investigation indicating the important involvement of exosome-derived non-coding RNAs in controlling inflammation in both situations [34–36]. This study focuses on the critical role of inflammation in heart disease progression and how non-coding RNAs in exosomes modulate the inflammatory process, either exacerbating or alleviating inflammation-related damage in the cardiovascular system.

Inflammation and cardiovascular disorders

Inflammation is an important contributing factor to all stages of atherothrombosis (Fig. 1) [37]. At the beginning of the development of atherosclerotic plaques, there is damage to the endothelial and the buildup of cholesterol underneath triggers an inflammatory reaction [38]. As a result of this, the level of substances involved in attracting and directing inflammatory cells, like monocytes and T helper cells, to the areas where plaque is forming is increasing. When monocytes reach the subendothelial region, they have the potential to transform into macrophages [39]. The creation of the NLRP3 inflammasome within macrophages plays a crucial role in promoting inflammation at a cellular level [40]. The mechanism known as the inflammasome, consisting of numerous proteins within the cell's cytosol, is triggered when macrophages are induced by the NF-kB to activate genes associated with inflammation [41]. If the macrophages are then exposed to additional stimuli, such as absorption

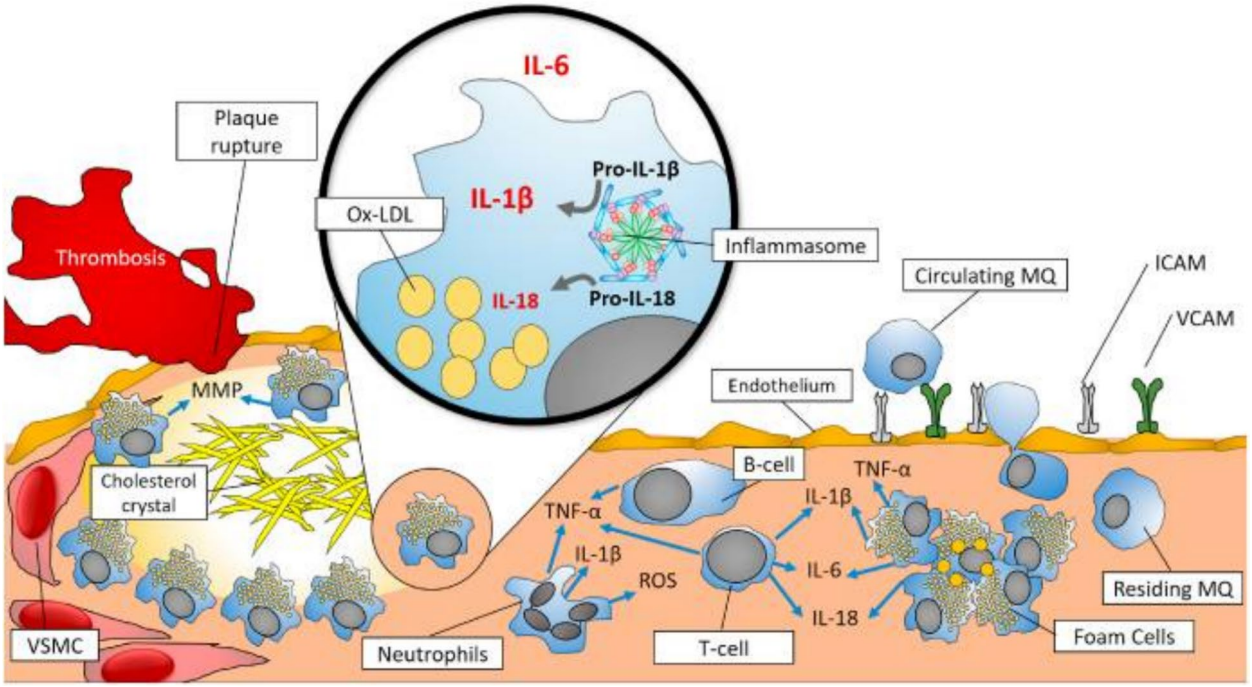

Fig. 1 In every stage of atherosclerosis, inflammation holds crucial significance

of cholesterol crystals or cellular hypoxia, the inflammasome is assembled. This leads to the generation of IL-1β from preexisting pro-IL-1β molecules [40]. In the same way, pro-IL-18 undergoes a process of cleavage to become IL-18, its active form. These particular cytokines are then discharged to rouse a diverse range of inflammatory cells and generate the release of IL-6. This, in turn, prompts the liver to produce CRP and enhances the inflammatory series of events within the endothelial [42].

The advancement of atherosclerotic plaque is a complex process characterized by multiple layers and interconnected mechanisms, with inflammation playing a major role [43]. This involves the activation of various cytokines and interleukins, along with the generation of reactive oxygen species such as peroxide, superoxide anion, and peroxynitrite [37, 39, 40, 42, 44]. In addition, mast cells, T-cells, and dendritic cells play a role in the inflammatory process by increasing the production and signaling of cytokines, including interferon-γ and TNF-α, which affect the development and progression of plaques [45, 46]. Over time, foam cells build up and result in the creation of a dead core made of lipids. This is caused by the macrophages'inability to effectively remove these materials [47].

Inflammation is important in maintaining the structural strength of intricate atherosclerotic plaque through its impact on the creation and breakdown of collagen in the protective fibrous layer [38]. Signals from T-cells, foam cells, and other cells prompt VSMC to enter the inner layers of the artery and generate interstitial collagens that make up the surrounding extracellular matrix, enclosing the necrotic fatty core [48]. At a fundamental level, IL-1β is involved in the creation of three specific enzymes, matrix metalloproteases 1, 8, and 13. These enzymes are responsible for breaking down collagen within the fibrous cap [48]. The gradual decline of the fibrous cap, coupled with the expansion of the lipid core, ultimately causes the plaque to become unstable. This instability increases the risk of a rupture occurring and a thrombus forming on top of the plaque. In turn, this can lead to the development of acute coronary syndromes and a blockage of blood flow to the heart [48]. Endothelin-1 (ET-1), a potent vasoconstrictor peptide, plays a significant role in vascular homeostasis and is increasingly recognized for its contribution to inflammation-driven cardiovascular complications, particularly in the context of metabolic disorders. Zhang et al. (2023) explored the multifaceted role of ET-1 in diabetic kidney disease, revealing its involvement in promoting oxidative stress, inflammatory cytokine release, and endothelial dysfunction [49]. These findings have broader implications in cardiovascular research, where ET-1 may serve as a critical link between metabolic imbalance and vascular injury. Furthermore, its interaction with ncRNAs, including microRNAs and lnRNAs, offers a promising avenue for therapeutic intervention. As such, the inclusion of

ET-1-related mechanisms strengthens the discussion on molecular drivers of vascular inflammation and underscores the therapeutic potential of targeting ET-1 signaling pathways in cardiovascular disease [49].

In the process of calcifying atheromatous plaques, inflammation is extremely important [50]. When macrophages in these plaques become active, they produce pro-inflammatory cytokines that cause vascular smooth muscle cells to undergo apoptosis [50]. Furthermore, the release of matrix vesicles, which have high levels of calcium and phosphate, creates a favorable setting for the deposition of calcium within the plaque [51, 52]. Additionally, inflammatory molecules known as pro-inflammatory cytokines, specifically TNF-α, stimulate the transformation of VSMC into cells resembling osteoblasts, which contributes to the development of intimal calcification within the plaque [53]. At first, the clusters of calcium are recognized as regions of large calcium buildup. This leads to an ongoing inflammatory reaction that triggers more cell death, the weakening of the fibrous cap, and a rise in mechanical pressure within the buildup, all of which contribute to the eventual breaking open of the plaque [54]. Small deposits of calcium, known as microcalcifications, are frequently overlooked when using contrast-enhanced CT scans. However, they can be more accurately identified by employing non-contrast cardiac-gated CT imaging with thin slices (0.5 mm or less in thickness) or by utilizing advanced molecular imaging methods such as positron emission tomography (PET)/CT with the use of [^{18}F] fluoride as a tracer to pinpoint newly developing microcalcifications [55, 56].

When the inflammatory cytokine expression decreases, the survival of VSMC improves and mineralization within the plaque is controlled, resulting in the buildup of calcium layers within the plaque [57]. Ultimately, this can lead to macrocalcification, which is a clear indication of inflammation and is typically found in less inflamed plaques that are more stable and less prone to rupturing [58, 59]. There is a possibility that this observation can illuminate the reason why treatment plans involving anti-inflammatory components such as statins are linked to a decrease in cardiovascular disease risk, but also a growth in plaque macrocalcification due to a calming of inflamed plaques [59, 60]. One can find interesting evidence through observation that the advancement of macrocalcification while using statin medication may be lessened if also taking PCSK9 inhibitors [61]. PCSK9 inhibitors effectively diminish nearby vascular inflammation and hasten the clearing of plaque in the presence of statins [62]. In contrast to statins, PCSK9 inhibitors offer the added advantage of reducing the presence of lipoprotein A, which is linked to enhancing the process of vascular calcification [63]. Cardiac-gated CT imaging without contrast is the most effective way to view macrocalcifications. The amount of macrocalcification in the coronary arteries is closely linked to overall atherosclerotic disease burden, which also takes into account the amount of noncalcified plaque present [64].

Interestingly, there is a similarity in the contribution of inflammation to the formation of coronary artery calcification (CAC) and aortic valve calcification [65]. Earlier beliefs that calcific aortic stenosis was solely a result of natural degeneration have been discredited due to mounting evidence indicating that inflammation significantly contributes to the advancement of the disease [66]. Initial findings from research on disease within the body show that the same substances that make up atherosclerotic plaque can also be found in the aortic valve leaflets. This includes a large number of foam cells and an inflammatory buildup, which can occur before calcification takes place [67]. When ox-LDL is present below the endothelial layer, it triggers a rise in pro-inflammatory cytokines, which in turn causes the accumulation of immune cells like macrophages, B-cells, and T-cells. This sequence ultimately results in an amplified production of IL-6 and TNF-α [68]. Osteoprogenitor cells, akin to coronary plaque, transform into osteoblast-like cells as a result of inflammatory mediators, prompting the deposition of calcium [69]. Inadequate removal of calcium deposits promotes the accumulation of calcium layers, leading to decreased movement of the leaflets and eventual narrowing of the aortic valve over time [68].

Research on animals suggests that inflammation may significantly contribute to the swift growth of atherosclerotic plaque after a MI [70]. This impact is present for several weeks after the heart attack [70]. Using an ApoE knock-out mouse as a model, researchers found that inducing myocardial infarction through selective coronary artery ligation led to an upregulation of inflammatory genes and greater infiltration of inflammatory cells into atherosclerotic plaques [70]. Furthermore, after experiencing a heart attack, these mice show faster development of plaques in their arteries, along with larger areas of dead tissue, heightened levels of enzymes that break down tissue, and thinner protective layers in distant arterial plaques that remained present even 3 weeks after the heart attack. Individuals who have had a heart attack show significantly increased inflammation in their aortic plaques compared to those with stable chest pain. This was observed through 18-F PET imaging conducted within a median of 11 days after the heart attack, despite the common prescription of aspirin and statin drugs [71]. Furthermore, there is a notable rise in [^{18}F] FDG PET activity in the spleen and bone marrow, as these vital organs are responsible for mobilizing inflammatory cells

to aid in the recovery of the heart (known as the cardiosplenic axis) [72].

While much attention has been given to the initiation and progression of inflammation in cardiovascular disease, the resolution phase is equally vital for the restoration of tissue integrity and prevention of chronic inflammatory damage [73]. This active, regulated process is mediated by specialized pro-resolving mediators (SPMs)—such as lipoxins, resolvins, protectins, and maresins—which work to inhibit further neutrophil recruitment, promote macrophage-mediated clearance of apoptotic cells, and facilitate tissue repair. Emerging evidence also suggests that exosomal ncRNAs, including specific miRNAs and lncRNAs, may contribute to inflammation resolution by modulating immune cell phenotypes and cytokine profiles [73, 74]. For example, exosomal miR-223 and miR-146a have been implicated in shifting macrophages toward an anti-inflammatory M2 phenotype, thereby supporting the resolution of vascular inflammation. Understanding how exosomal ncRNAs influence both the onset and resolution of inflammation offers a more complete picture of their therapeutic potential in cardiovascular disease [73].

Non-coding RNAs and inflammation in cardiovascular disorders

In recent years, numerous research efforts have demonstrated a definitive link between miRNAs and the functionality of the cardiac system [75]. To support this connection, Chen et al. provided evidence that when Dicer is not present in the heart, it can lead to dilated cardiomyopathy, heart failure, and death after birth [76]. Furthermore, once *Dicer* was selectively removed in the postnatal heart, it caused unprovoked alterations in the heart's configuration such as reconstruction, expansion, and scarring [76, 77]. Additional research has demonstrated the involvement of miRNAs utilizing a comparable approach. Hartmann and colleagues developed a model in which endothelial cells were lacking in Dicer, a key enzyme involved in miRNA production, and found that the resulting atherosclerosis was intensified due to the influence of miR-103 on the regulation of KLF4 [78]. Studies have recently shown that microRNAs participate in VSMCs in cardiovascular diseases. A study specifically demonstrated this through the use of a specialized mouse model with *Dicer* deficiency specifically in VSMCs [79]. The researchers demonstrated that removing *Dicer* from VSMCs is essential for repairing blood vessels, as the absence of miRNAs that prevent vessel narrowing (such as miR-27a-3p) leaves *Dicer-deficient* mice vulnerable to neointima formation following carotid artery injury. This highlights the important role of miRNAs not only in heart function, but also in CVD.

miR-21's role in CVD has been extensively verified, especially in cases where heart problems are solely linked to inflammation, such as in sepsis. It has been observed that around half of sepsis patients experience heart complications, and for those with severe sepsis and septic cardiomyopathy, septic shock is a common complication that affects their chances of survival [80]. Wang et al. provided a detailed account of miR-21's involvement in the development of the disease. This was demonstrated through a mouse experiment in which cardiac impairment was caused by administering LPS throughout the entire body [81]. In the hearts of mice injected with LPS, there was a notable rise in miR-21 levels, which was supported by experiments involving the use of mimic and antagomir techniques. This provided evidence for the connection between miR-21 levels and impaired heart function. The researchers also proposed that miR-21 targets SORBS2, a protein that likely contribute in the development of septic cardiomyopathy [81].

Conversely, the significant impact of miR-21 in atherosclerosis has been widely recognized due to its capacity to impact diverse cells and associated signaling pathways, ultimately playing a crucial role in the development and advancement of the condition. The downregulation of *PPARα* by miR-21 has been linked to the induction of EC inflammation in response to shear stress [82]. Moreover, ECs overproducing miR-21 amplified the Akt/PKB signaling pathway, resulting in the generation of NO, increased apoptosis, and proliferation [83]. Wei et al. demonstrated that miR-21 is capable of controlling VSMC phenotype in various cell types, leading to their movement and replication from the media to the intima [84]. A recent investigation by Canfran-Duque et al. reveals that the action of miR-21 in macrophages plays a significant role in driving the progression of atherosclerosis [85]. In a mouse study, scientists used a strain of mice that did not have the LDLr gene and transplanted BM into them. The results showed that mice with a lack of miR-21 in their BM had significantly larger atherosclerotic lesions. This was due to a decrease in the expression of ABCG1, a protein known to promote the formation of foam cells, in macrophages lacking miR-21 [85].

Angiogenesis, a complex process crucial for the growth of new blood vessels, is affected by multiple factors including miR-34a. The impact of miR-34a on angiogenesis varies depending on the type of cell and surrounding environment. Research has revealed that miR-34a can trigger cell death and impede angiogenesis in microvascular cells in the heart by disrupting the Notch1 pathway [86].

During a study on induced oxygen deprivation, there was an observed elevation of miR-34a levels in cardiomyocytes. When this miRNA was silenced, there was an

increase in ZEB1 and a subsequent decrease in the occurrence of apoptosis [87].

New evidence has shown that miR-34a involve in the advancement of atherosclerosis, specifically by regulating the expression of ABCA1 in macrophages. This could potentially alter the processes of cholesterol movement and reverse cholesterol transport that take place in these cells [88]. Moreover, these researchers demonstrated that targeted elimination of miR-34a from macrophages effectively hindered the advancement of atherosclerosis in a mouse model lacking the Apo E gene [88].

Studies using experimental models in laboratories have established that miR-34a performs a crucial function in the operations of VSMCs and the development of neointima hyperplasia. This process, known as vascular remodeling, has a significant impact on the thickening of the carotid intima-media and the regulation of VSMC proliferation and migration through the modulation of the Notch1 signaling pathway. Scientists have discovered that an excess of miR-34a causes a decline in both the rate of cell growth and movement, whereas eliminating this miRNA through the process of ablation leads to a rise [89].

Studies have shown that people aged 75 and above are greatly affected by calcific aortic valve disease (CAVD), which affects a percentage of over 3% in this group. Analysis of valve tissues from individuals with CAVD revealed a heightened presence of miR-34a and other miRNAs, compared to those with aortic regurgitation. Furthermore, a decrease in Notch1 and an increase in Runx2 were also noted in CAVD samples, highlighting the differences between the two conditions [90].

MiR-33 regulates cholesterol levels by influencing key genes related to cholesterol movement, such as ABCG1 and ABCA1. It also targets various transcripts responsible for producing proteins involved in processing fatty acids through β-oxidation, including CROT, HADHB, and CPT1 A. As a result, these sites are essential controllers of cellular cholesterol metabolism [91]. The process of removing cholesterol from macrophages and hepatocytes plays a crucial role in regulating lipid levels within these cells, and is primarily controlled by the activity of *ABCA1/G1*. In short, ABCA1/G1 works in conjunction with apoA1 to initiate the production of HDL. Considering that the efficiency of HDL cholesterol removal is connected with a reduced risk of cardiovascular disease, it is reasonable to assume that lower levels of miR-33 and increased expression of ABCA1/G1 would have a protective effect against atherosclerosis [92]. Nonetheless, it is shown that the elimination of Mir33 can lead to a variety of unforeseen outcomes depending on the specific cell and surrounding conditions. Specifically, a study by Price et al. demonstrated that completely removing miR-33 in the $LDLr^{-/-}$ mouse model increased the likelihood of obesity, high levels of lipids, and insulin resistance, but did not impact the development of plaque [93]. The lack of miR-33 in macrophages in a specific mouse model resulted in a decrease in both lipid buildup and inflammatory response, ultimately leading to a smaller plaque size [93]. Shortly, these scientists proved that inducing the absence of miR-33 in the liver did not lead to weight gain in scenarios involving elevated levels of fatty substances in the bloodstream. Instead, the mice exhibited a shield against liver fibrosis and were able to withstand the impacts of insulin [94].

In addition to its connection to atherosclerosis, miR-33 has been shown to contribute to cardiac fibrosis, a condition characterized by significant inflammation that occurs after damage to the heart. In this scenario, activated cardiac fibroblasts undergo excessive proliferation and secrete inflammatory and fibrotic proteins, leading to pathological alterations in the heart [95]. Nishiga et al. conducted a research study which provided initial evidence of the correlation between miR-33 and ABCA1 with the division of cardiac fibroblasts and the adaptive response seen in the altered heart [96].

The miR-17/92 cluster is one of the most well-studied microRNA clusters, originally recognized for its role in cancer. However, its significance has expanded far beyond tumorigenesis [97]. Recent research has revealed its involvement in a wide range of biological processes, including development, immune regulation, CVDs, neurodegenerative disorders, and aging. The cluster is now known to influence both protein-coding and non-coding transcripts, highlighting its complex regulatory capabilities. Notably, it has emerged as a key player in CVDs through its impact on immune system dysfunction, underlining its broader importance in health and disease [97].

In patients with dilated cardiomyopathy (DCM), reduced levels of miR-451a-5p and elevated expression of Myc have been associated with heightened activation and proliferation of CD4 + T cells [98]. This finding highlights the critical role of T cell regulation by miRNAs in the development of heart failure (HF). Additionally, the age-related decline in immune function, known as immunosenescence, is strongly connected to the onset of HF. Age-associated miRNAs, such as those from the miR-181 family and miR-34a-5p, may influence this process by affecting lymphocyte activity [99].

In addition to microRNAs, lncRNAs have emerged as important regulatory molecules involved in various biological processes, including inflammation and cardiovascular disease [100]. LncRNAs are transcripts longer than 200 nucleotides that do not code for proteins but instead exert their effects by interacting with DNA, RNA, or

proteins to influence gene expression at transcriptional, post-transcriptional, and epigenetic levels [100]. Their roles in the immune system, especially in modulating inflammatory pathways and immune cell function, are increasingly being recognized [100].

Given their diverse mechanisms of action, lncRNAs can function as scaffolds, decoys, or guides for chromatin-modifying complexes and transcription factors, thereby influencing gene regulatory networks [100]. Recent studies have begun to uncover how specific lncRNAs contribute to cardiovascular inflammation and immune dysregulation. For instance, lincRNA-p21, lncRNA H19, and lincRNA-Cox2 have been implicated in key inflammatory responses and immune regulation relevant to cardiovascular pathology. These lncRNAs illustrate the multifaceted roles that non-coding transcripts play in the progression of cardiovascular diseases, offering potential insights into novel therapeutic targets. Spurlock et al. discovered a considerable decline in the expression of lincRNA-p21 in individuals with RA as opposed to those without the condition, indicating a distinct difference between the two groups. Interestingly, no disruption in *lincRNA-p21* levels was detected in patients with SLE or Sjögren's syndrome [100]. It is noteworthy that the levels of lincRNA-p21 could return to their typical state in individuals with rheumatoid arthritis who underwent treatment with methotrexate (MTX), the most widely prescribed anti-inflammatory medication for this condition [101]. Experiments conducted on Jurkat T cells in a laboratory setting provided evidence that MTX effectively triggers the production of a specific type of lncRNA called lincRNA-p21 [100]. Originally, studies recognized lincRNA-p21 as a potent inhibitor of p53-induced transcriptional responses. Knocking down lincRNA-p21 had a significant impact on the expression of multiple genes that are typically repressed by p53. This outcome could be counteracted by blocking p53, suggesting that lincRNA-p21 functions as a downstream suppressor for p53. The mechanism by which lincRNA-p21 achieves this repression of transcription is by binding to hnRNP-K [102]. As there is a positive association between p53 levels and lincRNA-p21 expression among RA patients, it suggests that the expression of lincRNA-p21 in PBMCs may not rely on p53. This is in contrast to its initial observation of being regulated by p53 during the response to DNA damage [102]. The objective of this investigation was to establish if the inhibition of ATM or DNA-PKcs, significant controllers of the reaction to DNA damage, can reinstate the presence of lincRNA-p21 or p53. In order to accomplish this aim, the scientists performed experiments targeting these molecules [103, 104]. The blocking of DNA-PKcs by the use of NU-7441 in Jurkat T cells effectively prevented the activation of p53 and lincRNA-p21 caused by MTX. However, there was no significant effect observed when using low levels of KU-55933, an inhibitor for ATM. Furthermore, experiments using an NF-κB luciferase reporter indicated that suppressing lincRNA-p21 reversed the inhibitory effect of MTX on NF-κB function. Similar results were seen when administering the NU-7441 inhibitor, indicating a clear correlation between lincRNA-p21 and the regulation of the NF-κB pathway through DNA-PKcs [100]. This discovery aligns with earlier observations, which indicate that DNA-PKcs controls inflammation by modifying p50, a component of the NF-κB pathway [105]. Combined, these results propose that the reduction of the NF-κB pathway by MTX is facilitated by the elevation of lincRNA-p21, a process that is dependent on DNA-PKcs [100].

Stuhlmüller et al. noted a notable increase in the expression of the long non-coding RNA H19 in both synovial macrophages and connective tissue cells collected from individuals with rheumatoid arthritis (RA), in comparison to those with no health condition. Furthermore, they observed that the production of H19 was activated in synovial fibroblasts of RA patients upon exposure to different inflammatory stimuli, including IL-1β, PDGF-BB, and TNFα. The exact significance of increased H19 levels in RA, whether it serves as a marker of inflammation or plays a role in RA pathogenesis, remains to be determined [106, 107]. Upcoming investigations will be necessary to more accurately establish the practical significance of lncRNA H19 in the progression of rheumatoid arthritis and cardiovascular disease.

LincRNA-Cox2, a type of RNA that does not code for proteins and is longer in length, was located in the immediate vicinity of the gene Ptgs2 (Cox2). Its importance has been discovered as a significant regulator of inflammatory responses, influencing the activity of different immune-related genes in both stimulatory and inhibitory ways. [108]. Treatment with LPS resulted in the activation of lincRNA-Cox2 in both dendritic cells and BMDM in a comparable manner to the expression pattern of Ptgs2 [108, 109]. LPS triggers the production of lincRNA-Cox2, which is an important regulatory molecule, by activating the MyD88 and NF-κB signaling pathways. Changing the levels of lincRNA-Cox2 in BMDM has a notable effect on the expression of crucial immune-related genes like SOCS3, IL-6, CCL5, STAT3, and TNFα [108]. Various processes have been identified for lincRNA-Cox2, such as its interaction with hnRNP A/B and A2/B1. However, there is a lack of significant information regarding these interactions [108], IKB-α is broken down in the cytosol and then combined into the SWI/SNF complex, effectively serving as a co-activator for NF-κB and stimulating the process of chromatin remodeling associated with SWI/SNF [110, 111]. New

studies have revealed that lincRNA-Cox2 has a significant role in controlling the expression of IL-12b gene, which is stimulated by TNFα. This is accomplished by promoting the assembly of a repressor complex called Mi-2/NuRD at the promoter site of IL-12b [94]. From these findings, it can be inferred that lincRNA-Cox2 may have a swift effect on various pathways involved in acute inflammation.

The lncRNA myocardial infarction-associated transcript (MIAT) has emerged as a significant regulator in cardiovascular inflammation and fibrosis [112]. Elevated levels of MIAT have been observed in patients with coronary artery disease, correlating with increased inflammatory markers such as C-reactive protein, TNF-α, IL-6, and IL-8. Mechanistically, MIAT functions as a competing endogenous RNA, sponging microRNAs like miR-29b-3p and miR-24, leading to the upregulation of pro-fibrotic and pro-inflammatory genes such as pregnancy-associated plasma protein A (PAPPA) and TGF-β1. In diabetic cardiomyopathy, MIAT-mediated silencing of miR-214-3p has been linked to increased IL-17 production and cardiac fibrosis. These interactions underscore MIAT's role in modulating inflammatory pathways and its potential as a therapeutic target in cardiovascular diseases [112].

Exosome biogenesis

The exchange of information between cells, known as intercellular communication, is essential for the proper functioning of all living organisms [113, 114]. Cell-to-cell communication happens when cells come in direct contact with each other or when they release substances, like cytokines, hormones, and chemokines, which can allow them to communicate even at a distance [113, 115]. In recent times, there has been considerable attention directed towards a form of communication between cells utilizing EVs. These are small membrane-enclosed vesicles that are created by various types of cells in various animals [116, 117]. Electric vehicles demonstrate potential for a variety of medical uses and could prove beneficial as non-intrusive indicator substances and as nanoscopic transporters for addressing a range of conditions, including cancer, neurodegeneration, and CVD [118–121]. The various forms of EVs, such as apoptotic bodies, microvesicles, exosomes, and virus-like particles, can be classified into four main groups according to their size, origin within cells, and makeup [122, 123]. The initial three classifications of electric vehicles (EVs) are produced by the extension of the cell's outer membrane, while exosomes originate from internal vesicles located within MVBs (Fig. 2) [124, 125]. Consecutive release of these tiny compartments inside the lumen by merging

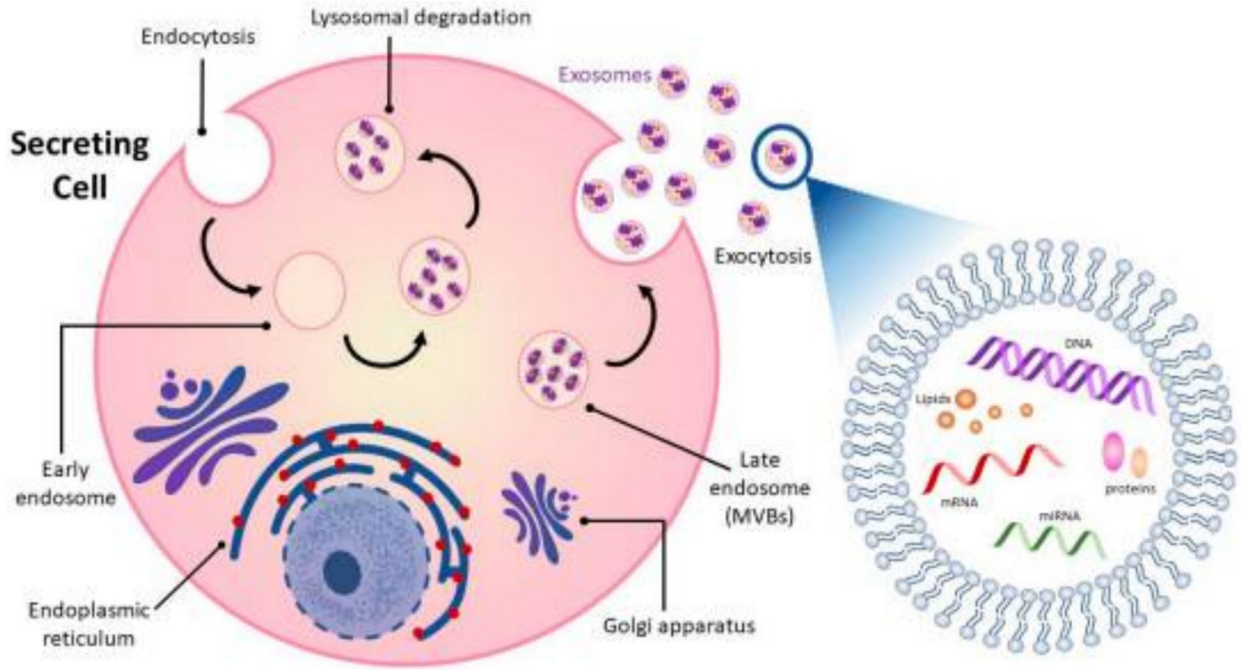

Fig. 2 The process of exosome formation and the substances they contain. Exosomes are created within MVBs as tiny vesicles and are produced by the plasma membrane's outward protrusion. The contents of exosomes are specific to each cell and include non-coding RNA like miRNA and mRNA, as well as lipids and proteins. These components are crucial for cell-to-cell communication and serve as indicators of the secreting cell's physiological condition

with the outer membrane emancipates exosomes ranging in size from approximately 40 to 160 nm into the surrounding material outside of the cell [120, 126, 127]. Small vesicles called exosomes are released into nearby bodily fluids and facilitate communication between neighboring and far-reaching cells. This is done through the transportation of cell-specific substances, including important molecules like metabolites, lipids, carbohydrates, proteins found on the cell surface and within the cytoplasm, and nucleic acids [128, 129]. Exosomes undergo a process of selective sorting, meaning their contents are carefully chosen. Exosomes carry cargo that is unique to the specific type of cell they come from, serving as a reflection of the cell's function and current state [130, 131]. Exosomes are highly concentrated in distinct proteins, including tetraspanins, which differentiate them from their originating cells and enable their detection and characterization [132]. The construction of the lipid bilayer is highly favorable for securely transporting and safeguarding its contents over extended periods and vast distances, thereby ensuring their successful delivery from the donor cell to the recipient cell and throughout various regions of the organism.

Exosomes and cardiovascular disorders

While ncRNAs such as miRNAs, lncRNAs, and circRNAs are indeed found within exosomes, the assertion that they are uniquely or specifically enriched in exosomes is subject to ongoing debate [49]. In reality, ncRNAs are also present in other types of extracellular vesicles (EVs), including microvesicles and apoptotic bodies. Multiple studies have highlighted that the RNA content of extracellular vesicles can vary widely depending on the cell type, the physiological state, and the method used for EV isolation. Notably, the current methodologies for isolating exosomes often yield a heterogeneous population of EVs, leading to inconsistent nomenclature and functional attribution [133–136]. The distinction between exosomes (30–150 nm, endosomal origin) and other EV subtypes such as microvesicles (100–1000 nm, plasma membrane-derived) remains blurred, especially given the overlap in size, density, and content. As a result, the term "exosome" is sometimes used imprecisely to describe a mixed population of EVs, which complicates interpretation of ncRNA enrichment and function. It is therefore more accurate to refer to "extracellular vesicle-associated ncRNAs" unless isolation protocols specifically characterize pure exosomal populations using accepted markers like CD63, CD81, and TSG101 [133–136]. Acknowledging this complexity is essential for accurate scientific communication and to avoid overgeneralization of EV-associated RNA functions.

Exosomes serve a remarkable function in the development of cardiovascular disease, as they aid in the transmission and exchange of signaling molecules [133–136]. Peng et al. discovered that atherosclerotic plaque-derived extracellular vesicles with exosome-like properties have the potential to propagate atherosclerosis not only in local areas, but also throughout the body [137]. The researchers isolated extracellular vesicles from carotid artery lesions in rats that lacked the LDL receptor gene and were fed a high-fat diet. These vesicles were then introduced to LDL receptor-deficient mice on a standard diet, a condition that typically does not cause atherosclerosis. As a result, the endothelial cells in the carotid arteries absorbed the extracellular vesicles, triggering an inflammatory response that ultimately contributed to the development of atherosclerotic lesions.

Various cell types within the blood vessels and heart work together to keep the body in balance. These cells, such as smooth muscle cells and endothelial, cardiomyocytes, inflammatory cells, cardiac fibroblasts, and resident stem cells, have been identified as sources of exosomes (Fig. 3) [136, 138–140]. Exosomes are integral in enabling communication between various cells, regardless of the circumstances being normal or abnormal. Their level of release and the miRNA content they contain can be altered in reaction to disease processes or administration of pharmaceuticals [141–144]. For instance, in a study using mice, the examination of exosomes from EPC revealed that the most prevalent miRNAs were all linked to the development of atherosclerosis [145]. Giving EPC-derived exosomes to mice with a genetic predisposition for atherosclerosis and high blood sugar levels resulted in a notable decrease in oxidative stress and inflammation, resulting in a smaller plaque size. This suggests that EPC exosomes have the potential to improve the health of blood vessel cells and alleviate the development of atherosclerosis in individuals with diabetes. This idea is further supported by the evidence that cardiomyocyte exosomes have a greater concentration of heat shock proteins, namely HSP-70, 60, and 20, which have been proven to contribute to the control of atherosclerosis [146–148]. HSPs hold a pivotal function in aiding the correct folding of proteins and contribute to a multitude of cellular functions including cellular expansion, inflammation, and apoptosis [149]. A greater expression of HSP-20 results in protection for the heart, possibly due to its ability to hinder the activation of IL-1β and TNF-α [147, 150]. HSP-60 is a protein found in the mitochondria that maintain mitochondrial activity and ensuring protein balance during times of stress. However, if it is release outside of the cell, it can have detrimental effects, causing cell death, inflammation, and contributing to the development of heart disease [151, 152].

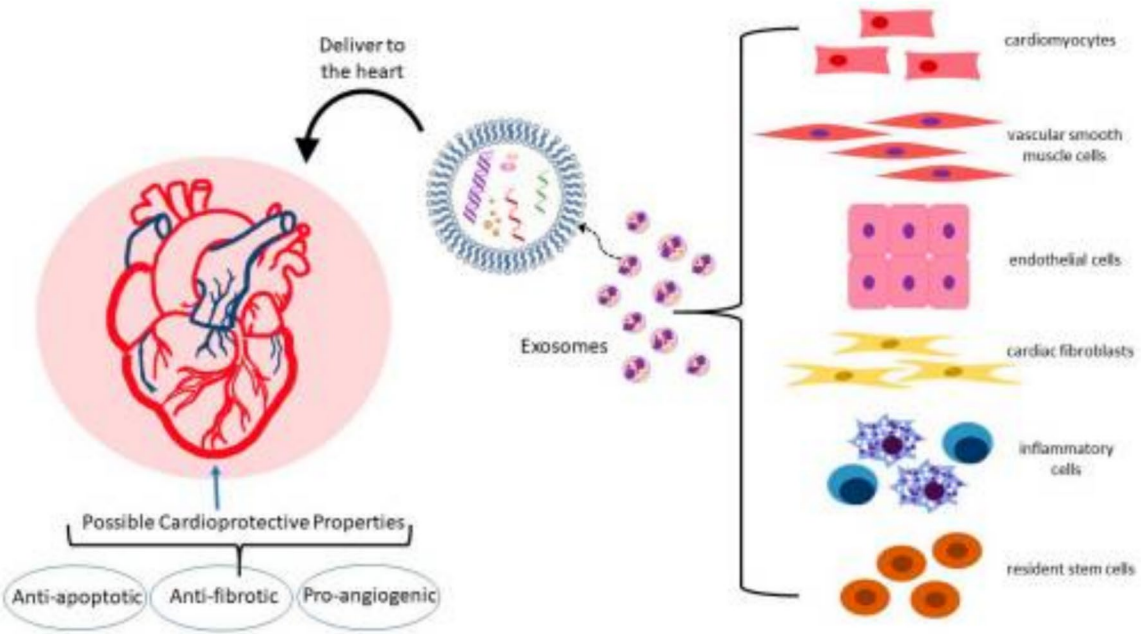

Fig. 3 The topic of exosomes and their potential to protect the heart is a complex and important one. These tiny structures, which originate from different types of cells, can impact the heart by delivering their contents of RNA, DNA, lipids, and proteins. These substances possess the capability to impact processes like angiogenesis and apoptosis in a positive manner by traveling through circulation or directly communicating between cells and entering the heart

HSP-70 molecules are present on the surface of the exosome and can initiate the MAPK/ERK1/2 signaling pathway, resulting in beneficial effects for the cardiomyocyte by interacting with toll-like receptor-4. This leads to a promotion of cell survival and protective functions [153, 154].

The release of HSP-27 through exosomes can have an impact on maintaining proper cholesterol levels in macrophages [155]. HSP-27 is classified as being protective against atherosclerosis, and individuals with reduced amounts of this protein in their blood plasma are linked to an increased risk of CVD [156]. Through their examination, Shi et al. employed both HSP-27 and an anti-HSP-27 antibody to generate immune complexes and assess its role. They determined that the application of these immune complexes to cholesterol-laden THP-1 human macrophages resulted in a notable rise in the production of exosomes. Through further analysis, it was revealed that these exosomes contained elevated concentrations of cholesterol, ultimately aiding in the expulsion of cholesterol from the macrophages [157]. It is proposed that exosomes be utilized to encase HSP-27 immune complexes in order to deliver immune therapy for atherosclerosis to macrophages.

Exosomes are small vesicles that can transport lipids, such as free fatty acids. Barcia et al. showed that exosomes have the ability to deliver these lipids to the heart in live organisms and to different types of cardiac cells grown outside the body [158, 159]. In this study, a team of scientists collected serum exosomes from a sample of healthy individuals who were either in a fasting state or had recently eaten a high-calorie meal. They discovered that these exosomes, regardless of the individual's nutritional status, exhibited the ability to take in a free fatty acid mimic. However, the researchers observed that the post-prandial exosomes contained higher levels of CD36, a scavenger receptor, as well as higher levels of lipids. Further experiments revealed that blocking CD36 reduced the uptake of the free fatty acid analogue, proving the receptor's active involvement in the exosomes'function. During experiments using cell cultures, researchers observed that cardiac endothelial cells and cardiomyocytes could effectively take in the free fatty acid analogue found in serum exosomes. They also found that when the exosomes were administered through a mouse's tail vein, the analogue was able to be absorbed by the mouse's heart. As a result, the researchers propose that exosomes may have a vital function in delivering this specific type of lipid fuel to the heart.

Exosomes separated from murine BMDM and introduced into ApoE-deficient mice on a Western diet, known for its tendency to cause atherosclerosis, demonstrate a capacity to decrease necrosis in atherosclerotic lesions and solidify atheromas [160]. In a research

experiment performed by Cheng et al., it was shown that inflamed human umbilical vein endothelial cells were shielded from cell death when exposed to exosomes derived from M2 macrophages derived from THP-1 cells. This shielding effect was attributed to the presence of miR-221-3p [161].

The proliferation, movement, and release of cytokines by VSMCs contribute in the advancement of atherosclerosis [162]. In 2016, Niu et al. showed that human aortic VSMCs'migration and adhesion abilities can be significantly enhanced by exosomes from J774a.1 macrophages that form foam cells. This demonstrates that macrophage-derived exosomes have the potential to modify VSMC actions [163]. Ren and colleagues conducted an experiment where they cultivated VSMC using a medium containing exosomes derived from macrophages that were stimulated by ox-LDL. They observed that these exosomes had a positive impact on the VSMC, enhancing their survival and promoting their ability to invade, while simultaneously inhibiting apoptosis [164].

A crucial event in the advancement of cardiovascular disorders, like heart attack and congestive heart failure, involves the deliberate demise and autophagy of cardiac muscle cells [165]. When the heart experiences a shortage of oxygen followed by a medical intervention to restore blood flow, known as ischemia–reperfusion, this causes harm and programmed cell death to cardiomyocytes during both the low oxygen period and the subsequent quick recovery period [166, 167]. Cardiac fibroblasts emit tiny vesicles known as exosomes, which play a crucial role in safeguarding cardiomyocytes from harm caused by ischemia–reperfusion disease. They achieve this by shielding against programmed cell death, and specifically pyroptosis, a type of inflammatory cell death [154, 168, 169]. Luo et al. demonstrated that the introduction of exosomes isolated from rat cardiac fibroblasts into the surrounding area of the rat heart after experiencing hypoxia and reoxygenation (as a result of the ligation and reperfusion of the left anterior descending artery) significantly decreased the extent of the myocardial damage. Upon analyzing the levels of miRNAs in these exosomes, they found that an abundance of miR-423-3p was associated with a decrease in infarct size. Further studies using cell cultures confirmed the critical role of this miRNA in sustaining cell survival and minimizing apoptosis [170].

Qiao et al. carried out a research project utilizing human exosomes, in which they obtained these particles from both healthy individuals and individuals with heart failure through the cultivation of cardiac cells in specific media. In this experiment, the exosomes were introduced into a mouse model that mimicked acute myocardial infarction through the use of ligated coronary vessels. The results demonstrated that exosomes from healthy individuals had positive impacts on healing, reduction of cell death, and preservation of tissue. Conversely, exosomes from heart failure patients hindered the cardiomyocyte proliferation, exacerbated the healing process, and inhibited angiogenesis [171].

The process of controlling the blood vessels that assist in providing oxygen and nutrients to the myocardium relies on the exchange of information between the heart muscle cells and the cells lining the myocardial blood vessels, known as exosomes [172]. Angiogenic capacity, is essential in the process of repairing and regenerating damaged heart tissue after a heart attack. Various types of cells can release small particles called exosomes, which contain specific microRNAs that stimulate angiogenesis. An exemplar of this would be the discovery that exosomes originating from mesenchymal stem cells located in the adipose tissue of humans exhibited the capability of conveying miR-125a, thereby stimulating the formation of fresh blood vessels in human umbilical vein endothelial cells [173]. EVs derived from heart muscle cells following exposure to hypoxic conditions can effectively shield endothelial cells in the cardiac microvasculature from harm caused by oxidation, as well as encourage the formation of angiogenesis, both in laboratory settings and in living organisms. This beneficial outcome is primarily orchestrated by the actions of two particular microRNAs, known as miR-143 and miR-222 [174, 175]. Gou et al. discovered that exosomes produced by infant heart muscle cells exposed to H2O2 indicated a significant increase in miR-19a-3p concentration, a known factor in cellular harm. Furthermore, a comparable surge in miR-19a-3p concentrations was observed in the blood plasma of patients who suffered a heart attack [176]. The researchers demonstrated that endothelial cells took up exosomes from mouse neonatal cardiomyocytes and observed that miR-19a-3p had inhibitory effects on angiogenesis. They also discovered that blocking this microRNA led to increased survival and multiplication of endothelial cells. The team of researchers performed experimentation on mice, inducing heart attacks through ligation on the left anterior descending coronary artery and subsequently inhibiting the function of miR-19a-3p. This resulted in a noticeable improvement in the production of new blood vessels. In addition, they identified HIF-1α as the precise target of miR-19a-3p, a regulator of numerous essential genes involved in the angiogenesis process [177].

Exosomal non-coding RNAs and inflammation in cardiovascular disorders

The interplay between endothelial cells and macrophages through the transmission of exosomes is crucial in the development of atherosclerosis [178]. Xing et al. found that exosomes derived from adipose-derived MSCs and

containing miR-342-5p provide considerable protection against atherosclerosis in endothelial cells [179]. Additionally, He et al. demonstrated that the manipulation of endothelial cells using ox-LDL or by increasing KLF2 expression leads to a remarkable increase in the levels of miR-155 in exosomes released from the cells [180]. Exosomal miR-155 has the ability to convert macrophages into M2 cells, resulting in the suppression of inflammatory responses. The study conducted by Loyer et al. and Chang et al. revealed that in cases of endothelial cell damage, there is an escalation in the release of exosomal miR-92a, which further aggravates atherosclerosis [181, 182]. In the surrounding environment, macrophages absorb exosomal miR-92a which then triggers their activation by controlling KLF4, contributing to the progression of atherosclerotic plaque. According to the findings of Zheng et al. (2017), smooth muscle cells with elevated levels of KLF5 induce miR-155 expression and its impact on neighboring endothelial cells, causing disruption of the tight junctions and compromising the integrity of the endothelial barrier.

As atherosclerosis progresses, platelets have the ability to communicate with endothelial cells by releasing exosomes. A study by Li et al. discovered that thrombin-induced platelet activation led to elevated levels of miR-223, miR-339, and miR-21 in exosomes derived from platelets [183]. A study highlighted the crucial anti-inflammatory role of miR-21-5p in the context of cardiac injury. The researchers demonstrated that exosomes derived from mesenchymal stem cells (MSCs) are enriched with miR-21-5p, which can be efficiently delivered to cardiomyocytes [184]. Once internalized, miR-21-5p directly targets and downregulates Yes-associated protein 1 (YAP1), a key regulator of cell survival and proliferation. This downregulation led to significant reduction in inflammation, as evidenced by decreased expression of pro-inflammatory cytokines such as IL-6 and TNF-α in both in vitro hypoxia models and in vivo myocardial infarction (MI) rat models. Moreover, exosomal miR-21-5p reduced cardiomyocyte apoptosis and fibrosis, ultimately leading to smaller infarct sizes and improved cardiac function. The findings suggest that modulation of post-MI inflammation through exosomal miR-21-5p delivery may represent a promising therapeutic approach for mitigating myocardial damage and enhancing recovery [184]. Exosomal microRNA-223 has the ability to trigger the production of ICAM-1 in endothelial cells when stimulated by TNF-α, ultimately suppressing the inflammatory response. Furthermore, there is evidence that dendritic cells and endothelial cells can engage in communication through the release and uptake of exosomes. For instance, according the research carried out by Zhong et al. it was demonstrated that dendritic cells release a type of small RNA called exosomal microRNA-146a. This microRNA is subsequently absorbed by endothelial cells, enabling them to control the inflammatory process by suppressing the activity of IRAK-1 [185].

According to Zhao et al., the introduction of BMSCs into the cardiac tissue after MIRI has been shown to significantly decrease the extent of myocardial infarction. Furthermore, this therapy has been found to effectively diminish the immune reaction in both the heart tissue and bloodstream [30]. The researchers discovered that miR-182, a type of exosome originating from BMSCs, facilitates the conversion of M2 macrophages through TLR4, suppresses the inflammatory response, and contributes to protecting the heart muscles. Additionally, their findings showed that MSC-Exo manages to reduce MIRI in mice by using exosomal miR-182 to alter the macrophages'polarization state. Thus, it is believed that utilizing exosomal miRNAs from CFs and BMSCs could serve as a novel approach towards mitigating MIRI.

According to Maegdefessel et al., their research revealed that miR-24 plays a crucial role in both regulating vascular inflammation and affecting the development of AAA in a mouse model of the disease. Additionally, their findings were supported by observations of increased levels of miR-24 in both human aortic tissue and plasma samples [186]. The actions of MiR-24 in M1 macrophages involve controlling the production of cytokines through its targeting of CHI3L1. Additionally, it promotes the movement of VSMCs and boosts the expression of vascular endothelial adhesive molecules. Based on their research, the authors have shown that varying levels of MiR-24 can influence the progression of AAA in animal models, and that it can also serve as a potential plasma biomarker for assessing the advancement of AAA in humans. In conclusion, targeting exosomes may offer a promising approach for counteracting the expansion of aortic aneurysms.

Recent research has indicated that the S1PR1/STAT3 signaling pathway plays a crucial role in the development of cardiac valve injury caused by rheumatic heart disease. This pathway acts by controlling the activation of Th17 cells [187]. Subsequent investigations uncovered that the pathway responsible for the development of RHD is under the influence of exosomal miRNA. The researchers, Chen et al. (2020), noted a significant correlation between the levels of exosomal miR-155-5p in the blood and the degree of valve damage [188]. In fact, the levels of exosomal miR-155-5p are elevated in a model of rheumatic heart disease (RHD) in rats. A more detailed examination demonstrated that exosomal miR-155-5p heightens the expression of S1PR1 while also inhibiting the activation of the SOCS1/STAT3 signaling pathway,

leading to a decrease in valve inflammation and fibrosis. Additionally, there is a noticeable reduction in the levels of IL-6 and IL-17 in both the valve tissue and serum. Based on these findings, it is apparent that suppressing miR-155-5p can effectively alleviate RHD-induced damage to the valve through the involvement of the S1PR1, SOCS1/STAT3, and IL-6/STAT3 signaling pathways.

Despite limited research on the impact of exosomal miRNA on RVD, it remains a valuable and significant asset in treating and identifying RVD. The malfunction of endothelial cells is heavily linked to injury in the vascular endothelium and is a crucial factor in various pathological actions. Furthermore, it is a critical trigger in the progression of atherosclerosis. The presence of ox-LDL leads to the involvement of endothelial cells and macrophages in the progression of AS [189]. The level of miR-25-3p is reduced in both vascular endothelial cells and vascular tissues when exposed to ox-LDL. Conversely, in the ApoE −/− AS mouse model, miR-25-3p expression is abundant in exosomes derived from platelets. This leads to a decrease in ADAM10 expression and subsequently hinders the inflammatory response and fat accumulation in vascular endothelial cells induced by ox-LDL. In the research conducted by Chen and colleagues, they found that exosomes derived from vascular endothelial cells treated with ox-LDL have a crucial influence on the development of atherosclerosis. This is a result of their capacity to induce the production of neutrophil extracellular traps (Nets) through the activity of miR-505 found within the exosomes [190]. Neutrophils that have been activated release Nets that have both cytotoxic and thrombogenic properties. These Nets are crucial in the development of AS [191]. The research team led by Liu discovered that paeonol has the ability to block EC signaling pathways, leading to an upregulation of miR-223 in exosomes produced by mononuclear cells. As a result, this reduces the secretion of pro-inflammatory molecules IL-6, IL-1, ICAM-1, and VCAM-1by HUVECs, ultimately preventing mononuclear cells from adhering to ECs. These findings suggest that miR-223 in exosomes from monocytes has a protective effect against inflammatory responses in vascular endothelial cells and that paeonol may have potential as a therapeutic treatment for vascular inflammatory diseases [192]. In their research, Xing and colleagues made a significant finding that exosomes derived from adipose stem cells have the ability to inhibit the expression of miR-342-5p in an injury setting. This action effectively counteracts the apoptotic effects of miR-342-5p on H2O2-treated HUVECs [179].

A recent study has revealed a notable increase in HOTAIR amounts in the exosomes of both serum and PBMCs among people with RA, while a decrease in HOTAIR levels was evident in differentiated osteoclasts and rheumatoid synoviocytes. Enhancing HOTAIR expression through lentivirus resulted in a decrease in the production of IL-23, IL-17, TNFα, and IL-1β and hindered activation of NF-κB in chondrocytes treated with LPS, controlled by miR-138 [193]. The findings are in line with an earlier initial study which found a noteworthy decline in the expression levels of HOTAIR in chondrocytes exposed to LPS and in a model of rheumatoid arthritis in mice. However, results from studies on short-term inflammatory conditions such as sepsis contradict this. In a study using mice with sepsis, it was observed that the levels of HOTAIR were significantly elevated in the cardiomyocytes. By suppressing HOTAIR expression, the cardiac function of the septic mice improved significantly, and there was a notable decrease in TNFα levels in the blood and p65 phosphorylation in the cardiomyocytes [194]. Recent investigations have uncovered that HOTAIR displays diverse roles during acute inflammation, contingent on the particular type of cell. Additional studies are imperative in order to determine and comprehend the potential compensatory mechanisms that could occur in cardiovascular cells and chondrocytes when confronted with LPS.

Chen et al. discovered the presence of the lncRNA GAS5 in exosomes released by THP-1 cells following stimulation with ox-LDL. Furthermore, when THP-1 cells were engineered to overexpress lncRNA-GAS5, the resulting exosomes were found to be taken up by vascular ECs and induce their apoptosis. Conversely, the process of disrupting lncRNA GAS5 in exosomes derived from THP-1 cells resulted in a notable decline in their capacity to initiate endothelial cell apoptosis. This suggests that lncRNA GAS5 has a significant involvement in the control of macrophage and endothelial cell death via exosomes during the progression of atherosclerosis [195].

The research conducted by Huang et al. demonstrated that the lncRNA MALAT1, found in exosomes originating from endothelial cells exposed to ox-LDL, successfully prompts the transition of macrophages to the M2 phenotype, resulting in a beneficial impact against the development of atherosclerosis [196]. Depletion of MALAT1 in exosomes derived from HUVECs and exposed to ox-LDL was shown to trigger the maturation of DCs, resulting in the advancement of atherosclerosis, as demonstrated by several studies [197, 198]. Wang et al. showed the release of circHIPK3 in exosomes is amplified in cardiomyocytes exposed to low oxygen levels. This circular RNA functions as a regulatory mechanism for miR-29a, leading to heightened levels of IGF-1 and decreased impairment of CMVEC due to oxidative stress. Furthermore, it inhibits the inflammatory reaction (174, 199).

Wehbe et al., highlighted novel regulatory networks involving circular RNAs (circRNAs) and their interaction

with microRNAs in modulating endothelial cell function and immune responses [200]. These findings are particularly relevant in the context of exosomal transfer of ncRNAs, where circRNAs act as microRNA sponges, regulating pro-inflammatory gene expression. This mechanistic insight not only supports the concept of exosomal RNA cargo as a mediator of vascular inflammation, but also positions circRNAs as potential biomarkers or therapeutic targets in cardiovascular disease. Incorporating these emerging mechanisms into our understanding of exosome-mediated signaling enriches the current landscape of RNA-based cardiovascular pathology [200].

The phenotypic switch of vascular smooth muscle cells (VSMCs) from a contractile to a synthetic phenotype is a hallmark of vascular remodeling and plays a pivotal role in the progression of atherosclerosis and other cardiovascular diseases (CVDs). This switch is characterized by increased VSMC proliferation, migration, and secretion of extracellular matrix components, contributing to plaque instability and vascular calcification. Recent studies have further delineated molecular mediators of this switch, highlighting the involvement of transcriptional regulators such as KLF4 and myocardin, as well as the influence of inflammatory microenvironments and lipid exposure on VSMC plasticity [201–203]. Notably, exosomes—nano-sized extracellular vesicles—have emerged as crucial modulators of this phenotypic transformation. Exosomes derived from various cell types, including endothelial cells, macrophages, and even VSMCs themselves, carry specific cargo such as non-coding RNAs, proteins, and lipids that can influence recipient cell behavior. For example, exosomal delivery of microRNAs such as miR-155 and lncRNAs like MALAT1 has been shown to promote or inhibit phenotypic switching depending on their cellular origin and context [204–206]. These findings underscore the dual role of exosomes as both conveyors of pathological signals and potential therapeutic vectors capable of modulating vascular remodeling in CVD. Further exploration into exosome-mediated signaling in VSMC phenotypic switching may reveal novel avenues for targeted cardiovascular interventions.

Tables 1, 2, 3 summarize the roles of key exosomal microRNAs and lncRNAs in cardiovascular inflammation, as well as their clinical and therapeutic implications.

Table 1 Key exosomal microRNAs involved in inflammation and cardiovascular disease

miRNA	Primary functions	Target pathways/genes	Associated cardiovascular conditions
miR-21	Promotes endothelial inflammation, regulates VSMC phenotype, modulates macrophage activity	PPARα, Akt/PKB, SORBS2, ABCG1	Atherosclerosis, septic cardiomyopathy
miR-34a	Inhibits angiogenesis, promotes apoptosis, impairs cholesterol efflux	Notch1, ABCA1, ZEB1	Atherosclerosis, neointima formation, CAVD
miR-33	Regulates cholesterol metabolism and fatty acid oxidation	ABCA1, ABCG1, CPT1 A, HADHB	Atherosclerosis, cardiac fibrosis
miR-155	Influences macrophage polarization and inflammatory signaling	SOCS1, KLF4, S1PR1	Atherosclerosis, rheumatic heart disease
miR-146a	Suppresses inflammatory signaling in ECs and macrophages	IRAK1, TRAF6	Endothelial dysfunction, vascular inflammation
miR-223	Reduces pro-inflammatory cytokine expression, regulates EC adhesion molecule expression	ICAM-1, IL-6, IL-1	Atherosclerosis, vascular inflammation

Table 2 Representative lncRNAs involved in cardiovascular inflammation

lncRNA	Mechanism of action	Target/interaction	Implication in CVD
lincRNA-p21	Represses NF-κB signaling, modulated by MTX and p53	hnRNP-K, DNA-PKcs	Rheumatoid arthritis-related inflammation
H19	Upregulated in response to pro-inflammatory cytokines	IL-1β, TNF-α, PDGF-BB	RA inflammation, possible cardiovascular links
lincRNA-Cox2	Dual role in promoting/repressing inflammatory genes	MyD88/NF-κB, Mi-2/NuRD	Atherosclerosis, acute inflammation
MIAT	Functions as ceRNA for miRNAs, regulates immune responses	miR-149-5p, CD47, miR-24, TGF-β1	Coronary artery disease, diabetic cardiomyopathy
MALAT1	Promotes M2 macrophage polarization, inhibits DC maturation	miR-155, STAT3, DC maturation pathways	Atherosclerosis
GAS5	Promotes EC apoptosis via exosomal transfer	Notch1, CDK6	Endothelial dysfunction in atherosclerosis

Table 3 Clinical and therapeutic implications of exosomal ncRNAs in CVD

ncRNA type	Clinical role	Potential applications	Challenges
Exosomal miRNAs	Biomarkers of inflammation and damage	Early diagnosis, disease monitoring	Isolation standardization, cargo heterogeneity
Exosomal lncRNAs	Modulators of immune response	Therapeutic targets (e.g., antisense oligos)	Limited in vivo validation, off-target effects
circRNAs (via exosomes)	miRNA sponging, gene regulation	Biomarkers, gene therapy vectors	Functional annotation, delivery specificity

Challenges and opportunities for clinical translation of ncRNA

Non-coding RNAs (ncRNAs) have emerged as promising diagnostic and therapeutic targets in cardiovascular diseases (CVDs) due to their regulatory roles in gene expression and involvement in disease pathogenesis. However, translating these findings into clinical applications presents several challenges. One major hurdle is the variability in ncRNA expression caused by technical and analytical factors, necessitating standardized and reliable isolation methods to ensure reproducibility across studies. Additionally, the lack of large-scale clinical trials hampers the validation of ncRNAs as therapeutic agents, emphasizing the need for precisely defined patient cohorts and outcome parameters to assess efficacy and safety. Despite these challenges, the unique properties of ncRNAs offer opportunities for developing novel diagnostics and therapeutics, provided that rigorous validation and standardization protocols are established.

Conclusion

The investigation of EVs and ncRNAs is a recent and highly sought-after area of research. Our focus centered on a variety of non-coding RNAs linked to EVs, which are known to have significant impacts on inflammation and cardiovascular diseases. EVs have been acknowledged as the means of transporting a variety of molecules from one cell to another in almost all living beings. These EVs are also responsible for playing intricate and significant roles in the development of CVD disorders. Furthermore, the diverse non-coding RNAs associated with EVs have been found to have critical functions in causing inflammation in CVD diseases. With the previously known roles of EVs and the growing interest in their potential clinical applications in various illnesses, this research specifically delved into the role of ncRNAs in EV-mediated inflammation in CVD diseases, in an effort to further comprehend their impact on inflammatory responses. However, the research analyzed in this evaluation is not enough to fully understand the ways in which extracellular miRNAs affect inflammation. Furthermore, the majority of the studies examined only observed alterations in ncRNA levels in various disease contexts, leaving minimal evidence for understanding how the dysfunction of specific ncRNAs contributes to those diseases. Additional research is necessary to fully examine the functions of individual ncRNAs that are involved in inflammation related to CVD. This will help validate the potential of extracellular ncRNAs as both biomarkers and a safe and effective therapeutic method. While there is still much to learn, current knowledge suggests that investigating extracellular ncRNAs as biomarkers could lead to early detection of CVDs. In addition, the use of extracellular vesicles may hold potential for utilizing gene therapy to combat inflammation in CVDs.

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