



REVIEW

How Do LncRNAs Talk to miRNAs? Decoding Their Dialogue in Atherosclerosis

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ABSTRACT: Atherosclerosis, characterized by the formation of fibrofatty lesions in the arterial wall, remains a leading cause of global morbidity and mortality. Emerging evidence highlights the critical regulatory roles of long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in atherogenesis. lncRNAs can function as competing endogenous RNAs (ceRNAs) by sponging miRNAs, thereby modulating the expression of downstream target mRNAs. This review summarizes current knowledge on lncRNA-miRNA-mRNA regulatory networks and their functional roles in the three major cell types involved in atherosclerotic plaque development: endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and macrophages. In ECs, these networks are implicated in inflammation, apoptosis, proliferation, angiogenesis, pyroptosis, and autophagy. In VSMCs, they regulate proliferation, apoptosis, and migration. In macrophages, they influence lipid metabolism, inflammatory responses, oxidative stress, and autophagy. Although the ceRNA mechanism is predominant, some lncRNAs also act as primary transcripts for miRNAs. Additionally, exosome-mediated non-coding RNA delivery mediates intercellular crosstalk, further expanding the complexity of RNA-based regulation in atherosclerosis. Despite significant progress, challenges remain due to the complexity and context-specificity of these networks. Further research is essential to elucidate these mechanisms and explore their potential as therapeutic targets for atherosclerosis.

KEYWORDS: Long non-coding RNA (lncRNA); microRNA (miRNA); endothelial cells; vascular smooth muscle cells; macrophages; atherosclerosis

1 Introduction

Atherosclerosis is defined as the formation of fibrofatty lesions in the artery wall, causing high morbidity and mortality worldwide. Atherogenesis is a slowly progressive process characterized by multifocal structural alterations in the walls of large- and medium-sized arteries and the formation of atherosclerotic plaques. Endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and macrophages are the major cells in atherosclerotic plaques [1–3].



MicroRNAs (miRNAs) are endogenous small (20–22 nucleotides long) non-coding RNAs that can regulate gene expression by binding to complementary sequences on 3'-untranslated regions of their target mRNAs, thereby inhibiting mRNA translation or promoting mRNA degradation [4,5]. Long non-coding RNAs (lncRNAs) are extensively classified as transcripts > 200 nucleotides with limited coding potential [6]. A classical regulation of lncRNAs is acting as a miRNA 'sponge'. All RNA transcripts that contain miRNA-binding sites can communicate with and co-regulate each other by competing specifically for shared miRNAs. Thus, lncRNAs can serve as competing endogenous RNAs (ceRNAs) or miRNA sponges to downregulate miRNA expression and activities. The regulation mechanisms of lncRNAs are very complicated, and current research shows that lncRNAs play an important role as miRNA sponges. Although this theory has received some criticism, it is still the mainstream of current research. This research field is expected to yield great insight into the overall mechanics of lncRNAs' function [7,8]. Additionally, some lncRNAs can encode miRNAs as miRNA primary transcripts [9,10].

Emerging evidence has indicated that lncRNAs and miRNAs modulate many pathophysiological processes of atherosclerosis. For instance, lncRNA HYMAI can promote EC autophagy while inhibiting their apoptosis, thereby alleviating disease progression in As mice [11]. Adipose tissue-derived exosomes deliver miR-132/212, thereby promoting EC apoptosis as well as the proliferation and migration of VSMCs within atherosclerotic plaques *in vivo*, and exacerbating atherosclerosis progression [12]. Notably, interactions between lncRNAs and miRNAs, as exemplified by lncRNA sponging miRNA, have gained widespread attention. Some lncRNAs specifically interact with miRNAs and then influence the target mRNAs. In recent years, novel regulatory roles of lncRNA-miRNA-mRNA regulatory networks have been revealed in various pathophysiological processes [13–15]. Notably, intercellular communication is a key link in the development of atherosclerosis, and exosomes (phospholipid bilayer nanoparticles with a diameter of 30–150 nm) have been identified as critical mediators in this process. They can selectively encapsulate and deliver miRNAs, lncRNAs, and mRNA, shuttling between vascular ECs, VSMCs, and macrophages to form a regulatory layer complementary to the intracellular RNA network. This review summarizes the current research (Fig. 1) on the regulatory role of the lncRNA-miRNA-mRNA regulatory network in ECs, VSMCs, and macrophages, discusses the function of exosome-mediated non-coding RNA delivery in atherosclerosis, and explores its potential translational value in disease-specific biomarker screening and the development of targeted therapy strategies.

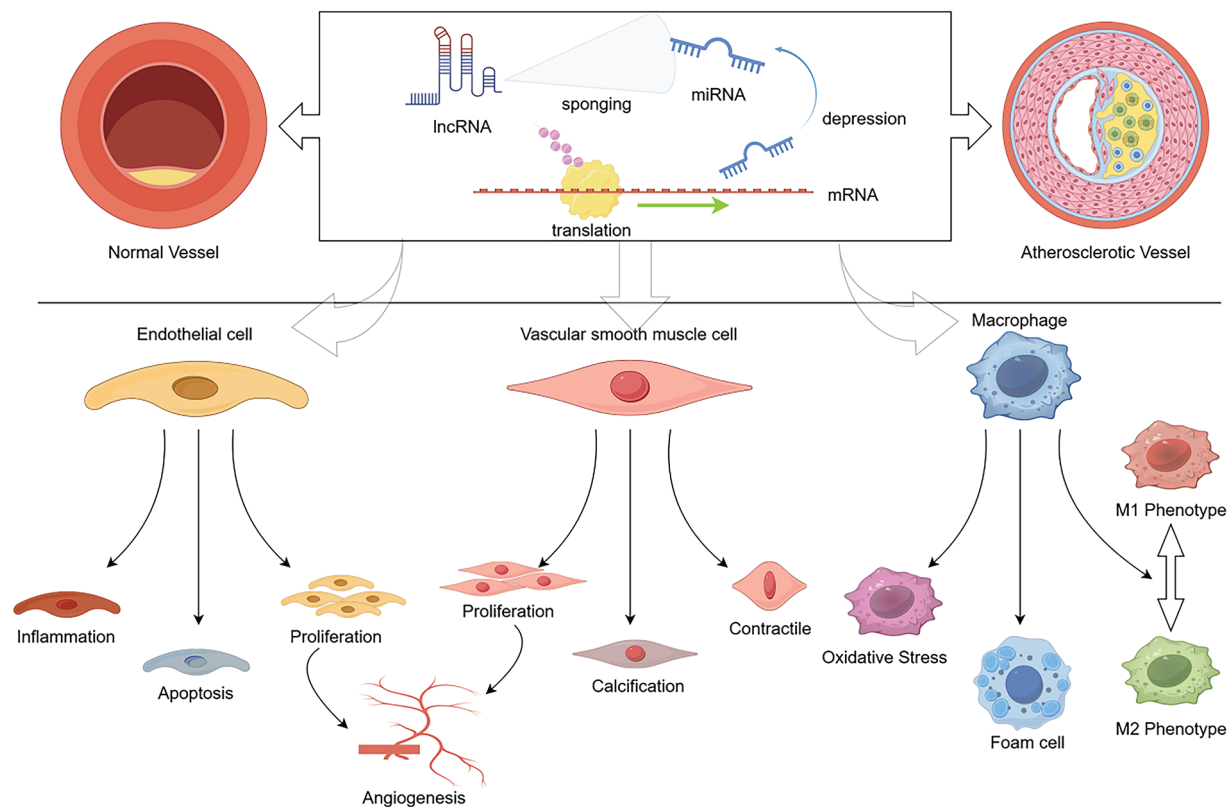


Figure 1: The lncRNA-miRNA-mRNA axis regulates atherosclerosis progression. This figure intuitively reveals the regulatory logic of the lncRNA-miRNA-mRNA regulatory axis in atherosclerosis progression, clearly presenting the functional changes of endothelial cells, vascular smooth muscle cells, and macrophages during AS progression, as well as the impact of this regulatory network on the occurrence and development of atherosclerosis. (Created with figdraw.com. ID: ORIOP4e165)

2 LncRNA-miRNA-mRNA Networks in the Regulation of Endothelial Cell Functions

2.1 Endothelial Cell Inflammation

Atherosclerosis is likely to start with dysfunction of ECs, which express adhesion molecules, attracting various mononuclear leukocytes, leading to inflammatory reactions [16,17]. Oxidized low-density lipoprotein (ox-LDL) is an important mediator involved in endothelial inflammation and atherosclerotic plaque formation and progression [18,19]. Lin et al. found that the lncRNA MKI67IP-3, the microRNA let-7e, and inhibitor of NF- κ B β ($I\kappa B\beta$) are abnormally expressed in human umbilical vein endothelial cells (HUVECs) and atherosclerotic plaques [20]. Let-7e plays pro-inflammatory roles through targeting $I\kappa B\beta$. Moreover, MKI67IP-3 can inhibit inflammatory responses in HUVECs by acting as a ceRNA against let-7e [20]. These studies suggest that modulation of the MKI67IP-3-let-7e- $I\kappa B\beta$ axis may alleviate EC inflammation and provide a potential therapeutic strategy for atherosclerosis. Another lncRNA, termed metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was previously confirmed to regulate endothelial function [21]. Recently, Li et al. demonstrated that MALAT1 exerts anti-inflammatory roles in endothelial injury [22]. The underlying mechanism is that MALAT1 contains a target site for miR-155, which can directly inhibit miR-155 expression and activity. Then, miR-155 inhibition significantly alleviated inflammation and apoptosis of ECs by increasing the level of Suppressor of Cytokine Signaling 1 (SOCS1) [22]. Another study by Cremer et al. showed that MALAT1 inhibited the activity of miR-503 by sponging it, thereby reducing the excessive

adhesion between bone marrow cells and inflammation-activated endothelial cells, and thus protected endothelial cells against inflammation-related injury [23]. These data indicate that MALAT1 can ameliorate inflammatory responses in ECs by modulating multiple miRNAs with distinct mechanisms. In addition, lncRNA small nucleolar RNA host gene 1 (SNHG1) was found to attenuate cell injury and inflammatory response in HUVECs by sponging miR-556-5p and upregulating G protein subunit alpha i2 (GNAI2) and poly(rC) binding protein 1 (PCBP1) [24]. Above lncRNA-miRNA-mRNA networks exert anti-inflammatory function in ECs.

On the contrary, lncRNA TGFB2 overlapping transcript 1 (TGFB2-OT1) plays a pro-inflammatory role in vascular ECs [25]. TGFB2-OT1 sponges miR-4459 to increase the La ribonucleoprotein domain family member 1 (LARP1) level, which ultimately promotes the production of IL-6, IL-8, and IL-1 β [25]. Similarly, by sponging miR-940 and thereby regulating the expression of inflammatory factors (IL-1 β , IL-6, TNF- α) and adhesion molecules (ICAM-1, VCAM-1), lncRNA cancer Susceptibility 15 (lncRNA CASC15) could promote ox-LDL-induced inflammatory response in vascular endothelial cells and subsequent atherosclerotic events [26]. In Zhou and Song's study, long noncoding RNA HLA complex group 11 (lncRNA HCG11) exerts its regulatory function by acting as a molecular sponge for miR-224-3p: this interaction blocks miR-224-3p from binding to its target gene JAK1, thus abrogating miR-224-3p-mediated JAK1 inhibition. Subsequent activation of endothelial cell inflammation and pyroptosis, driven by the HCG11/miR-224-3p/JAK1 axis, ultimately accelerates the pathological progression of atherosclerosis [27]. Furthermore, Hua et al. found that lncRNA ZEB1 antisense 1 (ZEB1-AS1) contributes to injury of human carotid artery ECs, via a novel miR-942-high mobility group box 1 (HMGB1) axis [28]. Blocking these inflammatory targets may contribute to the treatment of atherosclerosis.

2.2 Endothelial Cell Apoptosis

Apoptosis in ECs is closely associated with the pathogenesis of atherosclerotic cardiovascular disease [17,29]. lncRNA growth arrest-specific transcript 5 (GAS5) was found to be increased in plaques collected from patients and animal models. Exosomes derived from GAS5-overexpressing THP-1 macrophages promoted the apoptosis of ECs, while exosomes shed by GAS5 knockdown THP-1 macrophages showed the opposite effects. These results suggested some potential functions of lncRNA GAS5 in atherogenesis by regulating the apoptosis of ECs [30]. Furthermore, there is an article reporting that in ECs, lncRNA GAS5 binds to miR-21 as a ceRNA to upregulate programmed cell death 4 (PDCD4), which is a target of miR-21 and an important factor in EC apoptosis [31]. Another study revealed a pro-apoptotic role of lncRNA LINC00305 in HUVECs by sponging miR-136, but the downstream targets remain unknown [32]. Moreover, it was reported that knockdown of lncRNA X-inactive specific transcript (XIST) suppresses EC apoptosis and alleviates EC injury. Mechanistically, XIST sponges miR-320 and reduces its targeting concentration, resulting in the derepression of nucleotide-binding oligomerization domain 2 (NOD2) [33]. Similarly, a recent study revealed that depletion of lncRNA OIP5-AS1 inhibits apoptosis by sponging miR-320a targeting Lectin-like oxidized low-density lipoprotein receptor 1 (LOX1) [34].

Additionally, Chen et al. demonstrated that tanshinol (3,4-dihydroxyphenyl lactic acid) could attenuate EC apoptosis in atherosclerotic ApoE^{-/-} mice [35]. Specifically, the mRNA level of the lncRNA taurine-upregulated gene 1 (TUG1) was decreased, and the expression of miR-26a was increased by tanshinol in ECs. Further experimental results showed that TUG1 could directly sponge miR-26a. Therefore, low TUG1 expression and high levels of miR-26a are associated with the endothelial protective effect of tanshinol [35]. Transient receptor potential canonical (TRPC) has been reported to be involved in the development of atherosclerosis by promoting EC apoptosis [36,37]. Importantly, miR-26a prevents EC apoptosis during atherosclerosis by directly targeting TRPC3 and TRPC6 for repression [38,39]. Taken together, these data

highlight a possible TUG1-miR-26a-TRPC3/6 pathway in the regulation of EC apoptosis, which may be a novel therapeutic target for further research. Moreover, a recent study showed the therapeutic effect of TUG1 inhibition on atherosclerotic development by attenuating HUVEC apoptosis, possibly by sponging miR-148b targeting the insulin-like growth factor 2 (IGF2) [40].

In contrast, a novel lncRNA termed LOC100129973 had a negative effect on HUVEC apoptosis. LOC100129973 upregulated the expression of Apoptosis Inhibitor 5 (API5) and BCL2 like 12 (BCL2L12) by respectively sponging miR-4707-5p and miR-4767, ultimately relieving HUVEC apoptosis and improving endothelial function, which helps maintain vascular integrity and delay plaque formation [41]. Moreover, the newly identified ceRNA axis of SNHG1-miR-556-5p-GNAI2&PCBP1 also showed the anti-apoptotic effects in HUVECs [24]. Another lncRNA, nuclear paraspeckle assembly transcript 1 (NEAT1), altered the AKT/mTOR signaling pathway by sponging miR-638 to suppress their apoptosis [42].

Thus, these studies suggested that lncRNA-miRNA-mRNA networks play a critical role in the regulation of EC apoptosis. Further studies are expected to elucidate the specific mechanisms of these pathways in atherosclerotic EC apoptosis.

2.3 Endothelial Cell Proliferation and Angiogenesis

EC proliferation and angiogenesis significantly influence plaque growth and instability in atherosclerotic lesions [43,44]. Increasing studies have shown the involvement of lncRNA-miRNA-mRNA networks in EC proliferation and angiogenesis.

Several lncRNAs have been shown to promote EC proliferation and angiogenesis through the ceRNA mechanism. The lncRNA TCONS_00024652 was found to be overexpressed in TNF- α -stimulated HUVECs, and its dysregulated expression enhanced EC proliferation and angiogenesis. The underlying mechanisms may be that TCONS_00024652 endogenously competes with miR-21. However, the downstream target involved in the interaction of TCONS_00024652 with miR-21 remains unclear [45]. In a recent trial, lncRNA antisense non-coding RNA in the INK4 locus (ANRIL) promoted HUVEC proliferation and migration by sponging miR-399-5p targeting fibroblast growth factor receptor substrate 2 (FRS2) [46]. Huang et al. reported that the expression level of lncRNA H19 in endothelial progenitor cells (EPCs) is closely associated with cell proliferation, migration, and angiogenesis capacity. These biological effects are mediated through the pyroptosis pathway, which is regulated by the H19/miR-107/FADD axis. Transplantation of H19-overexpressing EPCs in a mouse model of limb ischemia significantly promotes angiogenesis and blood flow recovery in the ischemic region, while activating angiogenesis-related pathways. Mechanistically, H19 overexpression upregulates the expression level of the target gene Fas-associated death domain protein (FADD) through competitive binding with miR-107, thereby enhancing the proliferation, migration, and angiogenesis capacity of EPCs and inhibiting their pyroptosis, which facilitates vascular repair under ischemic conditions [47]. Similarly, Zhang et al. reported that the lncRNA SNHG1-miR-196a-mitogen activated protein kinase 6 (MAPK6) axis has the function of promoting EC proliferation and angiogenesis [48]. Additionally, the activation of hypoxia-inducible factor 1 α (HIF-1 α) is involved in angiogenesis [49]. lncRNA LINC00657 acts as a miR-590-3p sponge to attenuate the suppression of miR-590-3p on HIF-1 α , and to enhance angiogenesis [50].

However, research on the lncRNA-miRNA-mRNA pathway with anti-angiogenic effects remains relatively limited. Liang et al. found that lncRNA regulator of reprogramming (ROR) suppresses the proliferation, migration, and *in vitro* angiogenesis of human umbilical cord blood-derived EPCs. ROR may exert an anti-atherosclerotic effect by sponging microRNA-145 (miR-145). Further results of their study demonstrated that ROR, through sponging miR-145, can upregulate the expression of Smad3 (Sma- and Mad-related protein 3),

a key signaling molecule involved in endothelial-mesenchymal transition (EndMT) and angiogenic function. Thus, lnc ROR can sponge miR-145, thereby upregulating the expression of Smad3 [51].

Interestingly, an article about miRNA regulating lncRNA was reported [52]. This article reported that miR-103 inhibited the proliferation of ECs by regulating lncRNA WD Repeated Domain 59 (lncWDR59). Although the underlying mechanism is not clear yet, it suggests a new direction for researchers.

2.4 Endothelial Cell Pyroptosis

Pyroptosis is recognized as a new type of inflammatory programmed cell death. Different from apoptosis, pyroptosis responds to pathogen-associated molecular patterns and leads to the release of cytokines. Pyroptosis is initiated by the binding of intracellular pathogens to NOD-like receptors, resulting in the formation of inflammasomes, in which pro-caspase-1 becomes activated caspase-1. Activated caspase-1 can cleave the pro-inflammatory cytokines IL-1 β and IL-18, inducing their maturation [53–55]. Emerging literature suggests that EC pyroptosis has some significant impacts on atherosclerotic progression [56,57].

NOD-like receptor family pyrin domain-containing 3 (NLRP3) is crucial to EC pyroptosis, and the NLRP3 inflammasome is considered a link between lipid metabolism and inflammation in atherosclerosis [58–60]. Zhang et al. used high-fat diet-treated ApoE^{-/-} mice to demonstrate that intragastric administration of melatonin significantly alleviates atherosclerosis and suppresses the expression of pyroptosis-related genes, including the NLRP3 gene. These researchers hypothesized that melatonin prevented EC pyroptosis via lncRNA MEG3, which can enhance pyroptosis by sponging miR-223 [61]. Moreover, several studies have reported that miR-223 could negatively regulate NLRP3 [62–64]. Hence, the MEG3-miR-223-NLRP3 pathway likely accounts for the anti-atherosclerosis effects of melatonin [61]. In another study, knockdown of lncRNA MALAT1 significantly suppressed high glucose-induced pyroptosis in ECs [65]. NLRP3 expression was also significantly suppressed after MALAT1 knockdown, and miR-22 overexpression reversed the effect of MALAT1 on pyroptosis. These results highlight the involvement of MALAT1 sponging miR-22, which targets NLRP3, thereby exacerbating endothelial inflammation and pyroptosis to accelerate atherosclerosis [65]. However, this study has some limitations. First, this study only focused on EA.hy926 ECs and was not comprehensive enough to draw sufficient experimental conclusions. Second, the relationship between lncRNA MALAT1 and other potentially related genes needs further study.

2.5 Endothelial Cell Autophagy

EC injury and autophagic dysfunction occupy an important position in the atherosclerotic process. The autophagic response to ox-LDL in vascular tissue is most likely a mechanism of cell survival that protects them from dying. However, excessive autophagy in ECs may cause autophagic cell death and contribute to atherosclerosis [66,67]. Therefore, how to prevent excessive autophagy in ECs is also a direction for the treatment of atherosclerosis.

The mechanistic target of rapamycin (mTOR), a central regulator of autophagy, is involved in cardiovascular diseases, including atherosclerosis [68–70]. The urgent challenge is to discover novel mTOR downstream components [71,72]. Ge et al. identified 3-benzyl-5-((2-nitrophenoxy) methyl)-dihydrofuran-2(3h)-one (3BDO) as a new activator of mTOR, and 3BDO can inhibit autophagy in HUVECs. Their data showed that 3BDO significantly downregulated the level of lncRNA TGFB2-OT1. By sponging miR-4459, TGFB2-OT1 upregulates autophagy-related 13 (ATG13), suggesting TGFB2-OT1 as a novel promoter of autophagy [73]. Moreover, in their further study, TGFB2-OT1 sponges miR-4459 to upregulate LARP1, to elevate the levels of ATG3 and ATG7. Additionally, TGFB2-OT1 sponges miR-3960 and miR-4488, then respectively upregulates ceramide synthase 1 (CERS1) and N-acetyltransferase 8-like (NAT8L), which can both participate in autophagy by affecting mitochondrial function [25]. Collectively, TGFB2-OT1 can

promote autophagy via CERS1, NAT8L, ATG3, ATG7 and ATG13 [25,73]. A recent study showed that lncRNA GAS5 expression is increased and miR-26a is decreased in the plasma samples of atherosclerosis patients and ECs [74], which is in accordance with the previous studies [30,38,39]. In ECs, GAS5 knockdown restored impaired autophagic flux, whereas the inhibition of miR-26a reversed this effect. The authors found that the underlying molecular mechanism is GAS5 sponging miR-26a [74]. These studies suggest that TGFB2-OT1 and GAS5 may be novel therapeutic targets for further research on EC autophagy.

3 LncRNA-miRNA-mRNA Networks in the Regulation of VSMC Functions

VSMC Proliferation, Apoptosis, and Migration

Aberrant proliferation, apoptosis, and migration of VSMCs have been demonstrated to play crucial roles in atherosclerotic lesion development [75,76]. At present, most studies exploring the lncRNA-related regulation of VSMC functions only focus on the ceRNA mechanism.

Researchers found that lncRNA myocardial infarction-associated transcript (MIAT) acts as an induction factor of atherosclerosis. MIAT facilitates VSMC proliferation, accelerates cell cycle progression, and inhibits apoptosis by sponging miR-181b and upregulating its target, signal transducer and activator of transcription 3 (STAT3) [77]. Also, as a ceRNA, MIAT promotes the proliferation and migration of VSMCs via the MIAT-miR-148b-pregnancy-associated plasma protein A (PAPPA) axis [78]. There is an article reporting that lncRNA forkhead box protein C2-AS1 (FOXC2-AS1) might endogenously compete with miR-1253, whose repression increases the forkhead box F1 (FOXF1) expression, thereby enhancing VSMC proliferation [79]. The previously discussed lncRNA ANRIL-miR-399-5p-FRS2 axis also has these impacts [46]. In another trial, lncRNA XR007793 serves as a ceRNA of miR-23b to upregulate forkhead box O4 (FOXO4) [80], a promoter of smooth muscle dedifferentiation genes and an activator of VSMC migration [81]. Recently, a study revealed that depletion of lncRNA HOXA transcript at the distal tip (HOTTIP) represses proliferation and migration in VSMCs by sponging miR-490-3p targeting HMGB1 [82]. In addition, Tang et al. showed that lncRNA TUG1 sponges miR-141-3p to upregulate receptor tyrosine kinase-like orphan receptor 2 (ROR2), ultimately facilitating VSMC proliferation and migration [83]. Moreover, it was reported that the TUG1-miR-148b-IGF2 axis and TUG1-miR-133a-fibroblast growth factor 1 (FGF1) axis also show pro-proliferation effects on VSMCs [40,84]. In another study, lncRNA H19 endogenously competes with miR-148b and then enhances the WNT/ β -catenin signaling pathway, ultimately aggravating the VSMC proliferation [85]. Furthermore, by sponging microRNA let-7a and let-7b, H19 can play similar roles by respectively upregulating cyclin D1 and Ang II type 1 receptor (AT1R) [86,87]. Conversely, lncRNA UCA1 was reported to attenuate VSMC proliferation and migration against atherosclerosis by sponging miR-26a and relieving its inhibition of PTEN [88].

Interestingly, in addition to lncRNAs with the ability to downregulate the levels of miRNAs by acting as miRNA sponges, some lncRNAs can upregulate the levels of miRNAs by acting as miRNA primary transcripts. lncRNA H19 has been found to serve as the primary transcript for miR-675 [89]. H19 downregulates phosphatase and tensin homolog deleted on chromosome ten (PTEN) by encoding miR-675 and subsequently accelerates VSMC proliferation [90]. A growing body of evidence has indicated a negative correlation between PTEN and VSMC proliferation [91–93]. Similar effects were detected for lncRNA Ang362, which is regulated by angiotensin II [94]. Ang362 upregulates miR-221/222 by functioning as their primary transcripts, and these two miRNAs are both implicated in VSMC proliferation. Ang II treatment increased the levels of Ang362 and miR-221/222. Knockdown of lncRNA Ang362 downregulated the expression of miR-221/222 and minichromosome maintenance 7 (MCM7) and reduced VSMC proliferation. These results suggest that Ang362 aggravates Ang II-induced vascular dysfunction by upregulating miR-221/222, but the specific involvement of MCM7 remains unknown [94].

A novel lncRNA termed CAMK2D-associated transcript 1 (C2dat1) was highly expressed in coronary artery disease tissues and the proliferating VSMCs. C2dat1 promotes VSMC growth and migration by decreasing miR-34a expression, as well as increasing Sirtuin 1 (SIRT1) expression [95], which has been demonstrated to be an important factor in senescence and proliferation of VSMCs [96]. However, the mechanism by which C2dat1 decreases miR-34a expression remains unknown [95].

Collectively, lncRNA-miRNA-mRNA regulatory networks in VSMCs appear to be complicated. A better understanding of the VSMC-related lncRNA-miRNA axes mentioned above may provide novel tools for protection against atherosclerosis.

4 LncRNA-miRNA-mRNA Networks in the Regulation of Macrophage Functions

Macrophages can engulf modified lipoproteins and transform themselves into foam cells, leading to the formation of the necrotic core in atheromatous plaques [97]. A recent trial revealed that ox-LDL significantly increases lncRNA UCA1 expression in THP-1 macrophages, and UCA1 knockdown significantly inhibited CD36 expression, a vital biomarker in atherosclerosis. In addition, foam cell formation and the triglyceride and total cholesterol levels induced by ox-LDL were all suppressed by UCA1 knockdown. The authors hypothesized that UCA1 endogenously competes with miR-206 to exacerbate atherosclerotic events in THP-1 macrophages [98]. Another lncRNA, nuclear paraspeckle assembly transcript 1 (NEAT1), showed similar effects on macrophages by sponging miR-342-3p [99] and miR-128 [100]. The lncRNA HOX transcription antisense RNA (HOTAIR) sponging miR-330-5p axis was also demonstrated to aggravate atherosclerosis events in macrophages [101]. Moreover, it was reported that lncRNA GAS5 acts as a ceRNA of miR-221 to trigger the inflammatory response and MMP expression in THP-1 macrophages [102]. Zhang et al. reported that GAS5 knockdown suppresses inflammation and oxidative stress in macrophages by sponging miR-135a [103]. LncRNA zinc finger NFX1-type containing 1 antisense RNA 1 (ZFAS1) was identified as a functional sponge of miR-654-3p. By sponging miR-654-3p, ZFAS1 elevated ADAM10 and RAB22A expression to reduce the cholesterol efflux rate and enhance inflammatory responses in THP-1 macrophages [104]. Furthermore, the previously discussed lncRNA ZEB1-AS1 also facilitates the oxidative stress and inflammatory events of THP-1 cells via the miR-642-HMGB1 axis [28]. Thus, based on emerging evidence, there is a good reason to propose that the lncRNA sponging miRNA axis may play an important role in atherosclerosis development in macrophages.

In addition, Hu et al. reported that nuclear factor IA (NFIA) overexpression in ApoE^{-/-} mice enhances reverse cholesterol transport and decreases circulating inflammatory cytokines, thereby promoting the regression of atherosclerosis. Moreover, these researchers demonstrated that lncRNA RP5-833A20.1 suppresses NFIA expression by promoting miR-382-5p expression rather than inhibiting it [25]. Functionally, intervention targeting this pathway has been proven to improve plasma lipoprotein profiles, enhance reverse cholesterol transport, reduce systemic inflammatory cytokines, and ultimately promote the regression of atherosclerosis.

5 The Role of Exosome-Mediated Non-Coding RNA Delivery in Intercellular Communication during AS

Exosomes are nanoparticles (30–150 nm in diameter) actively secreted by cells and encapsulated by a phospholipid bilayer, capable of delivering various bioactive molecules—including proteins, DNA, RNA, and lipids—to recipient cells [105]. In the pathogenesis of AS, exosomes act as key mediators of intercellular communication, establishing a complex crosstalk network among the core cells involved in AS [106–108]. In-depth investigation of exosome-mediated ceRNA regulatory networks not only deepens the understanding of AS pathogenesis but also opens up novel avenues for the diagnosis and treatment of AS.

5.1 Exosome-Mediated Intercellular Transfer of Non-Coding RNAs: A Complex Regulatory Network

Exosomes can selectively package and deliver various non-coding RNAs (ncRNAs), such as miRNAs, lncRNAs, and circular RNAs (circRNAs) [109]. They transmit signals among AS-related ECs, VSMCs, and macrophages, establishing a sophisticated and multidirectional regulatory system characterized by distinct bidirectionality [110].

Upon exposure to pathological stimuli, the ncRNA composition of exosomes secreted by cells undergoes remodeling, thereby rendering these exosomes “amplifiers” that promote AS progression [111]. For instance, exosomes secreted by TNF- α -stimulated endothelial cells (exo-T) can be internalized by macrophages, inducing their polarization toward the pro-atherogenic M1 phenotype while exacerbating lipid deposition and apoptosis in macrophages, ultimately facilitating AS development. MiRNA-Seq analysis has identified 104 significantly differentially expressed miRNAs in exo-T, including 33 upregulated and 71 downregulated ones. Further mechanistic studies have demonstrated that these exosomes can reshape the transduction of key signaling pathways such as MAPK in macrophages through their specific miRNA profiles [112]. VSMCs also secrete exosomes involved in AS pathoregulation: under melatonin stimulation, VSMC-derived exosomes deliver miR-204/miR-211 to adjacent VSMCs, synergistically inhibiting vascular calcification and senescence in a paracrine manner by targeting BMP2 [113]. Curcumin, on the other hand, prompts VSMCs to secrete exosomes enriched in miR-92b-3p, which significantly influences vascular calcification via the exosome-miR-92b-3p/KLF4 axis [114]. Furthermore, macrophages stimulated by ox-LDL deliver miR-320b to VSMCs through exosomes. Once inside recipient cells, miR-320b directly targets and inhibits the expression of PPARGC1A, thereby activating the downstream MEK/ERK signaling pathway. This enhances VSMC viability and invasiveness, triggering their phenotypic switch from the contractile to the synthetic type—a series of changes that constitute the core pathological process underlying AS plaque progression and instability, directly driving disease deterioration [115].

In contrast, under physiological or protective signal stimulation, exosomes can deliver anti-atherogenic ncRNAs, exerting a “brake function” in disease suppression. Exosomes secreted by M2 macrophages are enriched in miR-7683-3p, which can be delivered to VSMC-derived foam cells. By directly targeting the 3' untranslated region (3' UTR) of HOXA1 mRNA, miR-7683-3p relieves the inhibitory effect of HOXA1 on the PPAR γ -LXR α -ABCG1 signaling pathway, thereby significantly activating cholesterol efflux. This mechanism effectively reduces lipid accumulation in VSMCs *in vitro*; in ApoE^{-/-} mouse models, it exhibits therapeutic effects such as reducing atherosclerotic plaque area, decreasing the necrotic core, increasing fibrous cap thickness, and enhancing plaque stability. Clinical data further show that the level of miR-7683-3p in the peripheral blood of AS patients is significantly lower, suggesting its potential as a diagnostic biomarker for AS [116]. Mesenchymal stem cell (MSC)-derived exosomes (MSC-Exos) also possess distinct anti-AS therapeutic potential. Studies have confirmed that Msc-Exos can deliver their enriched lncRNA FENDRR to ox-LDL-injured human vascular endothelial cells, significantly reducing AS plaque volume and lipid infiltration in mice. The core mechanism involves MSCs delivering FENDRR via exosomes, which regulates the miR-28/TEAD1 axis through a ceRNA mechanism, thereby protecting endothelial function and delaying AS progression [117].

5.2 Clinical Translation: From Biomarkers to Cutting-Edge Therapeutic Strategies

The core regulatory role of exosomes in intercellular communication during AS endows them with dual core values in clinical translation—serving not only as highly specific biomarkers for disease diagnosis but also as natural carriers for targeted therapy. The inherent advantages of natural exosomes, such as favorable biocompatibility, inherent targeting ability, and low immunogenicity, have provided novel breakthroughs for the clinical diagnosis and targeted treatment of AS [44,118]. In studies exploring exosome-derived ncRNAs

as biomarkers, their high stability, strong specificity, and good accessibility have made them a core research direction: the membrane structure of exosomes protects internal ncRNAs from degradation by plasma nucleases, conferring greater *in vivo* stability compared to free ncRNAs. Moreover, they can be easily obtained through liquid biopsies such as serum, plasma, and saliva, making them suitable for long-term dynamic monitoring and therapeutic effect evaluation of AS [119,120].

In specific research, Hu et al. found that the level of lncRNA LIPCAR in blood samples from AS patients was significantly higher than that in healthy individuals, and LIPCAR levels were also elevated in exosomes secreted by THP-1 stimulated with ox-LDL. These exosomes can affect the proliferation of VSMCs by regulating the levels of cyclin-dependent kinase 2 (CDK2) and proliferating cell nuclear antigen (PCNA) in VSMCs, thereby participating in AS progression [121]. Based on this, lncRNA LIPCAR is considered a potential biomarker and therapeutic target for AS. Additionally, clinical studies have confirmed that lncRNA AC100865.1 is abnormally expressed in patients with cardiovascular diseases and is closely related to macrophage adhesion and ox-LDL uptake, suggesting its potential as a therapeutic target for cardiovascular-related diseases and providing new prospects for AS treatment [122].

In the field of therapeutic translation, exosome-mediated ncRNA delivery systems have demonstrated significant clinical translation potential in AS treatment due to the inherent advantages of natural carriers [123]. Preclinical studies have shown that adipose tissue-derived mesenchymal stem cells (AD-MSCs) can stabilize atherosclerotic plaques, reduce inflammation, and promote myocardial repair through mechanisms such as regulating macrophage polarization, protecting endothelial function, and promoting angiogenesis. AD-MSCs genetically modified (overexpressing SIRT1, IGF-1, PD-L1) or pretreated with bioactive compounds exhibit superior therapeutic effects compared to unmodified cells. These modifications enhance cell survival, immune efficacy, and repair capacity, highlighting the application potential of personalized therapies. However, the clinical translation of AD-MSC therapy faces multiple obstacles. Although recent clinical trials have confirmed its safety, therapeutic efficacy remains inconsistent. Donor variability, especially in patients with complications such as type 2 diabetes and obesity, can reduce the therapeutic effect of AD-MSCs. Exosomes derived from AD-MSCs offer a promising cell-free alternative that retains therapeutic benefits while reducing associated risks, opening up new avenues for clinical translation [124].

Meanwhile, engineered exosome technology can further improve therapeutic efficiency. For example, constructing “exosome mimetics (EMs)” via bioorthogonal functionalization technology or modifying targeting ligands (e.g., hydroxyapatite-binding groups) on the exosome surface can significantly enhance tissue specificity. This property enables precise delivery of protective ncRNAs to target organs and cells, reducing off-target effects [125]. Modifying exosomal membrane proteins—such as overexpressing specific membrane proteins in mesenchymal stem cell-derived exosomes (MSC-Exos)—can enhance affinity for specific cells and further reduce off-target risks [126]. Regulating the miRNA composition of MSC-Exos through miRNA inhibitors or mimics allows for pathway-specific functions, avoiding non-specific effects. Studies have shown that specific miRNA combinations can precisely regulate immune responses or tissue regeneration [127]. Additionally, small exosomes encapsulated with off-on fluorescent complexes can real-time monitor the binding efficiency between miRNAs and target mRNAs, providing support for optimizing therapeutic doses and visualizing off-target effects [128].

6 Conclusion and Perspective

In conclusion, this review consolidates compelling evidence that intricate lncRNA–miRNA–mRNA regulatory networks are fundamentally involved in the pathogenesis of atherosclerosis by modulating the core functions of endothelial cells, vascular smooth muscle cells, and macrophages (Table 1). These networks

exert critical control over a wide spectrum of cellular processes, including inflammation, apoptosis, proliferation, migration, lipid metabolism, and autophagy, primarily through the ceRNA mechanism. Furthermore, the discovery of exosome-mediated intercellular delivery of non-coding RNAs adds a sophisticated layer of intercellular communication, amplifying and propagating pathogenic or protective signals among the key cellular players in the atherosclerotic plaque. The elucidation of these complex RNA dialogues not only significantly deepens our mechanistic understanding of atherogenesis but also firmly establishes specific lncRNAs, miRNAs, and their axes as promising candidates for novel diagnostic biomarkers and therapeutic targets, heralding a new era in RNA-based cardiovascular medicine.

Table 1: LncRNA-miRNA-mRNA regulatory networks in the pathophysiology of atherosclerosis

LncRNA	MiRNA	Mechanism	mRNA	Function	Ref.
EC inflammation					
lnc-MKI67IP-3	let-7e	ceRNA	I κ B β	Anti-inflammatory	[20]
MALAT1	miR-155	ceRNA	SOCS1	Anti-inflammatory	[22]
MALAT1	miR-503	ceRNA	FGF2 and BCL2	Anti-inflammatory	[23]
SNHG1	miR-556-5p	ceRNA	GNAI2 and PCBP1	Anti-inflammatory	[24]
TGFB2-OT1	miR-4459	ceRNA	LARP1	Pro-inflammatory	[25]
CASC15	miR-940	ceRNA	Unknown	Pro-inflammatory	[26]
HCG11	miR-224-3p	ceRNA	WNT7b/ β -catenin	Pro-inflammatory	[27]
ZEB1-AS1	miR-942	ceRNA	HMGB1	Pro-inflammatory	[28]
EC apoptosis					
GAS5	miR-21	ceRNA	PDCD4	Pro-apoptosis	[31]
LIN00305	miR-136	ceRNA	Unknown	Pro-apoptosis	[32]
XIST	miR-320	ceRNA	NOD2	Pro-apoptosis	[33]
OIP5-AS1	miR-320a	ceRNA	LOX1	Pro-apoptosis	[34]
TUG1	miR-26a	ceRNA	TRPC3 and TRPC6	Pro-apoptosis	[35,38,39]
TUG1	miR-148b	ceRNA	IGF2	Pro-apoptosis	[40]
LOC100129973	miR-4707-5p	ceRNA	API5	Anti-apoptosis	[41]
LOC100129973	miR-4767	ceRNA	BCL2L12	Anti-apoptosis	[41]
SNHG1	miR-556-5p	ceRNA	GNAI2 and PCBP1	Anti-apoptosis	[24]
NEAT1	miR-638	ceRNA	AKT/mTOR	Anti-apoptosis	[42]
EC proliferation and angiogenesis					
TCONS_00024652	miR-21	ceRNA	Unknown	Pro-proliferation Pro-angiogenesis	[45]
ANRIL	miR-399-5p	ceRNA	FRS2	Pro-proliferation	[46]
H19	miR-107	ceRNA	FADD	Pro-angiogenesis	
SNHG1	miR-196a	ceRNA	MAPK6	Pro-proliferation Pro-angiogenesis	[48]
LINC00657	miR-590-3p	ceRNA	HIF-1 α	Pro-proliferation Pro-angiogenesis	[50]
ROR	miR-145	ceRNA	Smad3	Anti-proliferation Anti-angiogenesis	[51]

(Continued)

Table 1 (continued)

LncRNA	MiRNA	Mechanism	mRNA	Function	Ref.
lncWDR59	miR-103	An unknown mechanism that miRNA regulates lncRNA	Unknown	Anti-proliferation	[52]
EC pyroptosis					
MEG3	miR-223	ceRNA	NLRP3	Pro-pyroptosis	[61]
MALAT1	miR-22	ceRNA	NLRP3	Pro-pyroptosis	[65]
EC autophagy					
TGFB2-OT1	miR-4459	ceRNA	ATG13	Pro-autophagy	[73]
		ceRNA	LARP1		
TGFB2-OT1	miR-3960	ceRNA	CERS1	Pro-autophagy	[25]
TGFB2-OT1	miR-4488	ceRNA	NAT8L		
GAS5	miR-26a	ceRNA	Unknown	Anti-autophagy	[74]
VSMC proliferation, apoptosis and migration					
MIAT	miR-181b	ceRNA	STAT3	Pro-proliferation Anti-apoptosis	[77]
MIAT	miR-148b	ceRNA	PAPPA	Pro-proliferation Pro-migration	[78]
FOXC2-AS1	miR-1253	ceRNA	FOXF1	Pro-proliferation Anti-apoptosis	[79]
ANRIL	miR-339-5p	ceRNA	FRS2	Pro-proliferation Pro-migration	[46]
XR007793	miR-23b	ceRNA	FOXO4	Pro-proliferation Pro-migration	[80]
HOTTIP	miR-490-3p	ceRNA	HMGB1	Pro-proliferation Pro-migration	[82]
TUG1	miR-148b	ceRNA	IGF2	Pro-proliferation	[40]
TUG1	miR-141-3p	ceRNA	ROR2	Pro-proliferation Pro-migration	[83]
TUG1	miR-133a	ceRNA	FGF1	Pro-proliferation Pro-migration	[84]
H19	miR-148b	ceRNA	WNT/ β -catenin	Pro-proliferation Anti-apoptosis	[85]
H19	let-7a	ceRNA	cyclin D1	Pro-proliferation	[86]
H19	let-7b	ceRNA	AT1R	Pro-proliferation	[87]
UCA1	miR-26a	ceRNA	PTEN	Anti-proliferation Anti-migration	[88]
H19	miR-675	primary miRNA transcript	PTEN	Pro-proliferation	[90]
Lnc-Ang362	miR-221 and miR-222	primary miRNA transcript	MCM7	Pro-proliferation	[94]

(Continued)

Table 1 (continued)

LncRNA	MiRNA	Mechanism	mRNA	Function	Ref.
C2dat1	miR-34a	Unknown	SIRT1	Pro-proliferation Pro-migration	[95]
Macrophages autophagy, oxidative stress, lipid metabolism and inflammation response					
UCA1	miR-206	ceRNA	Unknown	Pro-inflammatory Pro-oxidative stress Pro-lipid accumulation	[98]
NEAT1	miR-342-3p	ceRNA	Unknown	Pro-inflammatory Pro-lipid accumulation	[99]
NEAT1	miR-128	ceRNA	Unknown	Pro-inflammatory Pro-oxidative stress	[100]
HOTAIR	miR-330-5p	ceRNA	Unknown	Pro-inflammatory Pro-oxidative stress	[101]
GAS5	miR-221	ceRNA	MMP	Pro-inflammatory	[102]
GAS5	miR-135a	ceRNA	Unknown	Pro-inflammatory	[103]
ZFAS1	miR-654-3p	ceRNA	ADAM10 and RAB22A	Pro-inflammatory	[104]
ZEB1-AS1	miR-942	ceRNA	HMGB1	Pro-lipid accumulation Pro-inflammatory Pro-oxidative stress	[28]
RP5-833A20.1	miR-382-5p	Unknown	NFIA	Pro-inflammatory Pro-lipid accumulation	[25]

Note: Abbreviations: ADAM10: A disintegrin and metalloproteinase 10; ANRIL: Antisense non-coding RNA in the INK4 locus; API5: Apoptosis Inhibitor 5; AT1R: Ang II type 1 receptor; ATG13: Autophagy-related 13; BCL2L12: BCL2 like 12; Bmi-1: B-cell specific Moloney murine leukemia virus integration site 1; C2dat1: CAMK2D-associated transcript 1; CASC15: Cancer susceptibility 15; CERS1: Ceramide synthase 1; CXCR2: CXC chemokine receptor 2; DIGIT: Divergent to GSC induced by TGF- β family signaling; EC: Endothelial cells; ceRNAs: Competing endogenous RNAs; FOXC2-AS1: Forkhead box C2-AS1; FOXF1: Forkhead box F1; FOXO4: Forkhead box O4; FADD: Fas-associated death domain protein; FGF1: Fibroblast growth factor 1; FGF2: Fibroblast growth factor 2; FRS2: Fibroblast growth factor receptor substrate 2; GAS5: Growth arrest-specific transcript 5; GNAI2: G protein subunit alpha i2; HCG11: HLA complex group 11; HIF-1 α : Hypoxia-inducible factor 1 α ; HMGB1: High-mobility group box 1; HOTAIR: HOX transcription antisense RNA; HOTTIP: HOXA transcript at the distal tip; HULC: Highly upregulated liver cancer; ICAM-1: Intracellular cell adhesion molecule-1; I κ B β : Inhibitor of NF- κ B β ; IGF2: Insulin-like growth factor 2; LARP1: La ribonucleoprotein domain family member 1; LncRNA: Long non-coding RNA; LOX1: Lectin-like oxidized low-density lipoprotein receptor 1; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; MAPK6: Mitogen activated protein kinase 6; MCM7: Minichromosome maintenance 7; MEG3: Maternally expressed gene 3; MIAT: Myocardial infarction-associated transcript; Mfn2: Mitofusin-2; MMP: Matrix metalloproteinase; MiRNA: MicroRNA; NEAT1: Nuclear paraspeckle assembly transcript 1; NFIA: Nuclear factor IA; NLRP3: NOD-like receptor family pyrin domain-containing 3; NOD2: Nucleotide-binding oligomerization domain 2; NAT8L: N-acetyltransferase 8-like; PCBP1: Poly(rC) binding protein 1; PAPP: Pregnancy-associated plasma protein A; PDCD4: Programmed cell death 4; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; RAB22A: RAB22A, member RAS oncogene family; ROR: Regulator of reprogramming; ROR2: Receptor tyrosine kinase-like orphan receptor 2; ROCK1: Rho-associated protein kinase 1; SIRT1: Sirtuin 1; SNHG1: Small nucleolar RNA host gene 1; SOCS1: Suppressor of Cytokine Signaling 1; STAT3: Signal transducer and activator of transcription 3; TGFB2-OT1: TGFB2 overlapping transcript 1; TRPC: Transient receptor potential canonical; TUG1: Taurine-upregulated gene 1; UCA1: Urothelial carcinoma associated 1; VSMC: Vascular smooth muscle cell; WIPF2: WAS-interacting protein family member 2; XIST: X-inactive specific transcript; ZFAS1: Zinc finger NFX1-type containing 1 antisense RNA 1; ZEB1-AS1: ZEB1 antisense 1.

Looking ahead, several promising yet challenging avenues warrant further exploration. A primary future direction involves moving beyond correlative studies to definitively establish the causal roles of these specific ceRNA networks in atherosclerosis *in vivo*, utilizing sophisticated genetic models such as cell-specific and inducible knockout or overexpression systems. The context-specificity and sheer complexity of these networks demand the application of advanced multi-omics approaches and computational biology to map the entire “RNA interactome” within the atherosclerotic microenvironment. From a translational perspective, the potential of engineered exosomes as natural, targeted delivery vehicles for therapeutic ncRNAs (e.g., miRNA mimics or lncRNA inhibitors) represents a frontier with immense clinical potential. Overcoming challenges related to specific targeting, loading efficiency, and scalable production will be crucial. Ultimately, integrating these mechanistic insights into the development of targeted RNA therapeutics and leveraging stable exosomal ncRNAs as sensitive biomarkers for early diagnosis, risk stratification, and monitoring therapeutic responses could revolutionize the clinical management of atherosclerosis, paving the way for more precise and effective interventions.

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Abbreviations

ECs	Endothelial cells
VSMCs	Vascular smooth muscle cells
miRNA	MicroRNA
lncRNA	Long non-coding RNA
ceRNAs	Competing endogenous RNAs
ox-LDL	Oxidized low density lipoprotein
HUVECs	Human umbilical vein endothelial cells
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
SOCS1	Suppressor of Cytokine Signaling 1
SNHG1	Small nucleolar RNA host gene 1
NEAT1	Nuclear paraspeckle assembly transcript 1
GAS5	Growth arrest-specific transcript 5
XIST	X-inactive specific transcript
TUG1	Taurine-upregulated gene 1
IGF2	Insulin-like growth factor 2
ANRIL	Antisense non-coding RNA in the INK4 locus
HIF-1α	Hypoxia-inducible factor 1α
MEG3	Maternally expressed gene 3
NLRP3	NOD-like receptor family pyrin domain-containing 3

mTOR	Mechanistic target of rapamycin
MIAT	Myocardial infarction-associated transcript
PTEN	Phosphatase and tensin homolog deleted on chromosome ten
HOTAIR	HOX transcription antisense RNA
ZFAS1	Zinc finger NFX1-type containing 1 antisense RNA 1
NFIA	Nuclear factor IA
EPCs	Endothelial progenitor cells
ncRNAs	Non-coding RNAs
exo	Exosome
MSC	Mesenchymal stem cell

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