MicroRNAs and Long Noncoding RNAs in Coronary Artery Disease

New and Potential Therapeutic Targets

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KEYWORDS

• Atherosclerosis • miRNAs • microRNA • lncRNAs • Long noncoding RNA • miR-155 • miR-33 • miR-92a

KEY POINTS

- Noncoding RNAs (ncRNAs) including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) play an important role in CAD onset and progression.
- The ability of ncRNAs to simultaneously regulate many target genes allows them to modulate various key processes involved in AS, including lipid metabolism, smooth muscle cell proliferation, autophagy, and foam cell formation.
- Both lncRNAs and miRNAs may have potential as novel therapeutics in CAD.

INTRODUCTION

Atherosclerosis (AS), the major underlying cause of coronary artery disease (CAD), is a chronic progressive inflammatory state that leads to plaque buildup inside arteries. An important trigger in AS is hypercholesterolemia, which induces endothelial injury allowing entry of lipids, such as low-density lipoprotein (LDL) particles, into the subendothelial space of the intimal layer of arteries, where they are then oxidized and act as strong chemoattractants. Macrophages also play a key role in AS; they engulf oxidized LDL (ox-LDL) and transform into foam cells, the prototypical cells in atherosclerotic plaques. Macrophages additionally increase proinflammatory cytokines, which induce the recruitment and proliferation of smooth muscle cells (SMCs). Vulnerable plaques are the leading cause of coronary thrombosis and are usually characterized by thin fibrous caps, few or absent SMCs, and increased number of inflammatory cells.[1] These processes are of particular importance in the pathology of AS and are often targeted in AS therapy.

The incidence and progression of CAD are closely linked with modulatory noncoding RNAs (ncRNAs), such as microRNAs (miRNAs) and

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long noncoding RNAs (lncRNAs).[2] miRNAs regulate gene expression at the post-transcriptional level by inhibiting gene translation or promoting messenger RNA degradation.[3–6] lncRNAs, however, are relevant in fundamental processes of gene regulation, such as chromatin modification and transcriptional regulation.[7]

The role of miRNAs in the pathophysiology of various diseases, especially cardiovascular diseases, was broadly reported.[4–6] They are involved in lipid metabolism, inflammation processes, SMCs proliferation, and foam cell formation, which demonstrates their importance in AS development. Nowadays, there is growing evidence that lncRNAs affect the onset and progression of cardiovascular diseases. lncRNAs have been identified as important regulators of complex biologic processes linked to the proper functioning of the cardiovascular system, including cardiac muscle development and in case of disrupted regulatory functions also multiple cardiovascular pathologies.[7] The multistage involvement of lncRNAs and miRNAs in the development of cardiovascular diseases makes them promising therapeutic targets.

We review current literature knowledge about miRNAs and lncRNAs involvement in CAD progression and their potential as novel therapeutic approach.

MicroRNA-155

miR-155 is coded by *BIC* gene and expressed in hematopoietic stem-progenitor and mature hematopoietic cells. It is known to be elevated during monocytic cell differentiation toward macrophages. miR-155 can target *SOCS1*, and *TNF-α*, related to inflammatory processes and pathogenesis of AS.[8] Various inflammatory mediators, such as tumor necrosis factor (TNF)-α, may enhance miR-155 expression in monocytes and macrophages.[9] miR-155 stimulates inflammatory gene expression through inhibition of *BCL6* gene, which is a negative regulator of nuclear factor (NF)-κB, thus its suppression leads to enhanced expression of NF-κB. As a result, miR-155 causes overexpression of NF-κB and plays a key role in inflammatory responses and regulates expression of proinflammatory cytokines, leukocytes recruitment, and cell survival.[8,10,11] However, miR-155 may alleviate inflammation by targeting *CARHSP1*, which impacts the stability of TNF-α. TNF-α directly activates NF-κB in response to injury and inflammation. The loss of its stability leads to decreased levels of TNF-α causing less activation of NF-κB pathway. Consequently, miR-155 may have a protective role in AS-associated foam cell formation via miR-155-*CARHSP1*-TNF-α pathway.[9]

Under physiologic conditions macrophages express scavenger receptors (SR), including SR-A1, CD36, and LOX-1. All the of listed SR present affinity to ox-LDL, which causes the transformation of macrophages to the foam cells. Increased levels of ox-LDL along with proinflammatory cytokines results in upregulation of LOX-1 expression. This process leads to lipid accumulation and foam cell formation.[12] Additionally, ox-LDL is responsible for enhanced miR-155 expression in macrophages. Surprisingly, miR-155 may alleviate inflammation and foam cells formation acting through *CARHSP1*.[9] However, several studies documented that miR-155 is associated with proinflammatory processes.[13,14] lncRNA, MALAT1, is known to sponge miR-155. MALAT1 can elevate the proliferation and repress the proinflammatory cytokine secretion and cell apoptosis via sponging miR-155 and increasing the anti-inflammatory protein SOCS1 concentration.[13] Additionally, miR-155 directly inhibits SOCS1 expression and enhances p-STAT3 and PDCD4 expression. PDCD4 improves inflammatory response through the activation of NF-κB and inhibition of anti-inflammatory interleukin (IL)-10.[14]

Ox-LDL not only initiates inflammation but also stimulates apoptosis of macrophages. It acts through different pathways; among them p85α/*AKT* pathway was identified. miR-155 directly targets p85α gene, which leads to p85α suppression. This action results in inhibition of *AKT* activation and antiapoptotic effect.[15] Moreover, miR-155 is also involved in macrophage differentiation; it promotes macrophage transition into M1 phenotype and increases proinflammatory cytokines and chemokine secretion.[16] There is evidence of miR-155 involvement in foam cell formation by targeting *HBP1*.[17] Furthermore, upregulated miR-155 sensitized macrophages to inflammatory activation by abrogating *BCL6*-mediated inhibition of NF-κB signaling.[10] In contrary, miR-155 can inhibit the transformation of macrophages into foam cells by enhancing *CEH* signaling pathway in macrophages.[18]

miR-155 also contributes to the autophagy process, which is important for regeneration of vascular intimal wall injury. It promotes autophagy in vascular endothelial cells (VECs) by suppressing phosphorylated *PI3K/Akt/mTOR* pathway. *PI3K/Akt/mTOR* pathway plays an important role in the regulation of autophagy in AS. The activation of this pathway resulted in autophagy inhibition.[19] Moreover, in vitro analysis showed that miR-155 enhances ox-LDL-induced autophagy.[20] It indicates that miR-155 upregulation may have a

protective effect in atherosclerotic lesions by promoting autophagy.

The role of miR-155 in AS development is ambiguous. Upregulation of miR-155 might contribute to the prevention of AS by inhibiting apoptosis and altering the inflammation process in atherosclerotic lesions.[9,15] However, downregulation of miR-155 shows a therapeutic effect by attenuating ox-LDL-mediated inflammation signaling, stimulating M2 macrophage phenotype and decreasing foam cell formation.[10,11,13,14,17] Furthermore, animal studies showed that antagomir-155 (miR-155 inhibitor) attenuated AS development and progression in mice.[10,17,21] Therefore, antagomir-155 should be considered as a potential therapeutic agent against AS. Several clinical trials are testing antagomir-155 safety and tolerability; however, none of them are registered for AS treatment. MRG-106 is a locked nucleic acid–modified oligonucleotide inhibitor of miR-155, which had promising preliminary results in a phase 1 clinical trial with cutaneous T-cell lymphoma.[22,23] Further investigations are needed to elucidate clinical effect of antagomir-155 in AS treatment.

MicroRNA-33

miR-33 family consists of miR-33a and miR-33b, which are encoded within the introns of the *SREBP2* and *SREBP1* genes, respectively. miR-33a and its host gene are transcriptionally upregulated under conditions of low sterol concentration. SREBP2 protein induces the expression of genes involved in cholesterol synthesis, whereas miR-33a inhibits genes involved in hydrolysis and export of cholesterol from the cell, including intracellular trafficking and cholesterol efflux.[24] miR-33 targets *ABCA1*, *ABCG1*, *CPT1A*, *IRS2*, *AMPK*, and *CROT* in hepatic cells and *ABCA1* and *ABCG1* in macrophages.[16,25] These genes are involved in glucose and lipid metabolism, both of which are impaired during AS development.

miR-33 has been shown to modulate *ABCA1* and *ABCG1* expression in macrophages.[26,27] These proteins mediate cholesterol efflux, and they are responsible for decreasing cholesterol concentration in many types of cells including macrophages. In AS, proinflammatory stimulation induces deposition of cholesterol in macrophages, triggering the formation of foam cells.[28] Several studies showed that downregulation of miR-33 in vivo increased cholesterol efflux in peripheral macrophages including arterial macrophages in atherosclerotic lesions.[26,29–31] Moreover, miR-33 modulates target genes *PDK4* and *PGC-1α*.[32] PDK4 is responsible for regulation of mitochondrial respiration, whereas PGC-1α participates in mitochondrial biogenesis and regulation of carbohydrate and lipid metabolism.[33] miR-33 inhibition increased the expression of PDK4 and PGC-1α proteins, which resulted in boosted mitochondrial respiration and production of ATP in macrophages. This effect in combination with increased *ABCA1* expression resulted in promoting macrophage cholesterol efflux.[32]

Proinflammatory phenotype of macrophages in arterial wall lesions contributes to the formation of foam cells and atherosclerotic plaque development. miR-33 plays an important role in macrophage activation by promoting phenotype shift into proinflammatory M1. Inhibition of miR-33 expression resulted in an increased level of anti-inflammatory M2 markers (Arginase-1, IL-10) and reduced expression of proinflammatory M1 markers (inducible nitric oxide synthase and TNF-α).[30] Moreover, miR-33 modulates an expression of proinflammatory cytokines. The deficiency of miR-33 suppressed the secretion of IL-1β, IL-6, and TNF-α in ox-LDL-treated THP-1 macrophages.[34] Moreover, lack of miR-33 expression leads to the inhibition of NF-κB and TLR4 mediated pathways resulting in a reduction in arterial macrophage activation and polarization in vivo.[31] In contrast, miR-33 inhibition resulted in the elevation of M2 markers, such as anti-inflammatory IL-10, and M1 markers, such as IL-6. These results indicate a more complex role of miR-33 in the inflammatory regulation.[26]

miR-33 is involved in the regulation of autophagy by targeting genes engaged in autophagy pathways including *LAMP1*, *ATG5*, and *ATG12*. Moreover, it modulates AMPK-dependent activation of *TFEB* and *FOXO3*.[24,35] FOXO3 promotes autophagy, whereas TFEB is involved in the regulation of autophagy and lysosome biogenesis.[36] Inhibition of miR-33 resulted in increased expression of *LAMP1*, *ATG5*, and *ATG12*, and promoted AMPK-dependent activation of the *TFEB* and *FOXO3* in macrophage foam cells, and thus enhanced the autophagy process.[24,35]

Additionally, miR-33 contributes to the overall number of macrophages within the arterial wall. The inhibition of miR-33 expression results in decreased arterial macrophage content and decrease in atherosclerotic plaque size.[31]

miR-33 inhibition was shown to increase *ABCA1* expression. *ABCA1* has a role in mediating cholesterol efflux and transports it to lipid-poor apolipoproteins that consequently form nascent high-density lipoproteins (HDL). Activation of miR-33 was shown to inhibit the expression of *ABCA1* in mouse and human cells limiting cholesterol efflux to ApoA1 and therefore reducing lipid

molecules accepted by nascent HDL.[37] The relationship between miR-33 inhibition and increased plasma HDL levels was also demonstrated in two nonhuman primate studies.[38] Furthermore, another study revealed that the difference in measured HDL cholesterol (HDL-C) levels in plasma was only significant in mice fed a chow diet receiving anti-miR-33 oligonucleotides therapy compared with control mice. In contrast, anti-miR-33 oligonucleotides-treated mice fed a western diet did not show a significant change in HDL-C plasma levels compared with control mice.[25] Therefore, the efficacy of miR-33 therapy in HDL elevation is controversial and must be further investigated to determine its true effect.

However, long-term inhibition of miR-33 by using anti-miR-33 oligonucleotides increased the expression of genes involved in fatty acid synthesis, such as ACC and FAS in the liver. Anti-miR-33 therapy resulted in elevated circulating triglyceride levels and caused lipid accumulation in the liver of mice fed with a high-fat diet.[39]

Taken together, miR-33 inhibition has been demonstrated as a promising therapeutic approach for delaying the development and enhancing the regression of AS. miR-33 inhibition achieves these effects by inducing cholesterol efflux from macrophages, decreasing the proinflammatory macrophage phenotype, inducing autophagy, and reducing macrophage content in atherosclerotic plaques. Rayner and colleagues[30] reported that anti-miR-33-treated mice showed reductions in plaque size and lipid content; increased markers of plaque stability; and decreased inflammatory genes expression, such as *TNF-*α, *TLR6*, and *TLR13*. However, the effects of miR-33 inhibition on HDL-C levels are still debated. The influence of miR-33 on glucose and lipid metabolism is important to recognize because it may contribute to complications and adverse effects of the treatment. miR-33 inhibition in LDL receptor–deficient mice promoted obesity, insulin-resistance, and hyperlipidemia.[31] Currently, no clinical trials on miR-33 are being conducted but effects and safety of antagomiR-33 treatment should be assed in the future.

MicroRNA-92A

The miR-92a family consists of miRNAs including miR-25, miR-92a, and miR-363 and is a part of the miR-17∼19 cluster.[40] miR-17∼9 cluster is involved in heart development and has numerous effects on the cardiovascular system. miR-92a-3p, a component of miR-17∼19 cluster, stimulates cardiomyocytes metabolism through targeting the fatty acid translocase *CD36* and *ABCA8b* genes. CD36 is a transporter of fatty acids in the heart.[41] Its upregulation is mainly associated with increased free fatty acid uptake from cardiomyocytes that leads to enhanced β-oxidation process of free fatty acids, which is a process responsible for cellular energy production.[42] In contrast, ABCA8b main role is to transport HDL in cardiac cells. Depletion of miR-92a in myocardial infarction (MI) leads to enhanced activity of CD36, which maintains proper energy homeostasis of the heart under pathologic conditions.[41]

miR-92a is involved in vascular pathologies, including AS. Overexpression of miR-92a promotes macrophage participation in AS formation and atherosusceptibility through targeting *KLF4*.[43] *KLF4* can promote macrophages differentiation into anti-inflammatory M2 type, and increase the expression of *Ch25h* and *LXR*, which causes cholesterol transport back to the liver and regulates vascular smooth muscle cell (VSMC).[44] Thus, miR-92a-induced downregulation of *KLF4* leads to ECs injury, PDGF-BB-mediated proliferation, and migration of VSMCs and atherosclerotic plaque formation.[45] Additionally, overexpression of miR-92a enhances LDL uptake and proinflammatory cytokines expression in ECs, which enhances the plaque buildup.[43]

In contrary, overexpression of miR-92a downregulates *ITAG5* gene expression. *ITAG5* is responsible for the accumulation of proangiogenic factors, including vascular endothelial growth factor or endothelial nitric oxide synthase, and thus has influence on vascular tone and platelet aggregation. Moreover, *ITAG5* is able to activate *ERK1/2* and *PI3K/AKT* signaling pathways.[46] Both *ERK1/2* and *PI3K/AKT* are involved in angiogenesis by promoting EC survival and migration. *PI3K/AKT* axis is also involved in MI progression and regulation of oxidative stress in CAD.[47] Thus, both can influence the progression of CAD and its long-term complications.

Consequently, miR-92a acts as a proatherogenic through targeting *KLF4* and antiatherogenic via *ITAG5*. Moreover, miR-92a downregulation acts cardioprotectively via CD36, ABCA8b on post-MI heart.[41,43,46]

miR-92a shows the highest expression among all members of the miR-17∼92 cluster in human ECs. Its overexpression causes inhibition of proangiogenic factor expression, such as ITGA5, impairment of ECs, and promotion of AS lesions. Inhibition of miR-92a expression may lead to increased angiogenesis and revascularization in injured hearts and reduction in AS severity. Moreover, in vivo study has shown the therapeutic effect of miR-92a downregulation in AS mice by preventing AS development.[48] Altogether,

inhibition of miR-92a is a promising approach in CAD treatment. Currently, no clinical trials with miR-92a in CAD are being conducted. However, MRG-110 (a locked nucleic acid modified oligonucleotide inhibitor of miR-92), is currently being tested for angiogenesis induction to improve healing of chronic cutaneous wounds.[49,50] Positive results of that trial would pave the way to further applications of miR-92a inhibition in patients with ischemic heart disease or peripheral artery disease.

OTHER microRNAs AS A POTENTIAL THERAPEUTIC TARGET

VSMCs are the main source of plaque cells and extracellular matrix in all stages of AS. Inflammation enhances the proliferation of VSMCs and stimulates production of dense extracellular matrix, which leads to the development of more advanced atherosclerotic lesions. One of the genes responsible for regulation of the proliferation and migration of VSMC is *HMGB1*. This gene also enhances inflammation in atherosclerotic plaques via stimulation of expression of proinflammatory IL-1β in VSMCs.[51] miR-126-5p targets *HMGB1* and inhibits its expression, which causes the alleviation of AS. In patients with AS significant downregulation of miR-126-5p was observed.[52]

AS initiation and its severity is highly dependent on vascular inflammatory response, including proinflammatory cytokines and signaling pathways. Also, inflammatory macrophages play a crucial role in formation of atherosclerotic plaque. One of the genes responsible for inflammation regulation is *PDCD4*. It plays a role in regulation of apoptosis in VSMCs, promotion of inflammation by activation of NF-κB signaling pathway and inhibition of IL-10. miR-16 targets *PDCD4* expression and through downregulation decreases levels of proinflammatory cytokines, increases levels of anti-inflammatory factors, and reduces the *NF-KB* signaling pathway. Moreover, through targeting *PDCD4*, miR-16 can also reduce the activity of *MAPK* axis, which activates inflammatory macrophages.[53] In addition, miR-16 is released by ischemic peripheral muscle and exerts a proinflammatory action on remote vascular beds, increasing the expression of TNF-α and reducing the production of endothelial nitric oxide synthase and vascular endothelial growth factor.[54] Hence, blocking blood-borne miR-16 might reveal an easy and useful strategy to prevent endothelial dysfunction especially in patients with severe multibed AS.

Foam cells have great contribution to an atherosclerotic plaque formation. Development of those cells is caused by excessive lipid uptake by macrophages via SR receptors.[12] LOX-1 is one of the glycoproteins responsible of ox-LDL uptake in macrophages, which results in foam cells formation and plays a role in the development of AS. miR-98 directly targets and inhibits LOX-1 messenger RNA expression in macrophages. In the macrophages treated with ox-LDL, miR-98 expression is decreased, and LOX-1 synthesis is increased. Thus, miR-98 could repress the AS development acting through LOX-1.[55]

The activity of macrophages in formation of atherosclerotic plaque is also regulated by *MAML1*. *MAML1* is a component of Notch axis, which contributes to progression of AS mainly via regulation of inflammation. miR-133b can regulate Notch signaling pathway via targeting *MAML1*. Inhibition of either miR-133b or Notch axis can reduce plaque size, reduce macrophages proliferation and migration, and enhance their apoptosis. Moreover, Zheng and colleagues[56] reported that mice with AS treated with miR-133b antagomir showed wider lumen of the vessels, more stable plaque shape, smaller lipid core, and thicker fibrous cap of the plaque compared with those treated with miR-133b antagomir.

Impairment of autophagy plays a key role in the AS development. Both autophagy and AS are triggered by a few common factors, such as inflammation, reactive oxygen species, and shear stress. Impairment of autophagy leads to greater accumulation of lipids, increased death of VSMC, and, as a consequence, increased vulnerability of atherosclerotic plaque and AS progression.[1,12] ox-LDL, an important factor in foam cells formation, increases the levels of LC3, Beclin 1, and P63, markers of autophagy in human umbilical vascular endothelial cells (HUVECs). Additionally, ox-LDL upregulated the expression of *PI3K*, *Akt*, and *mTOR*. *PI3K/Akt/mTOR* pathway was proved to block autophagy in AS. miR-126 is a molecule specific for ECs. Its levels are reduced in ECs treated with ox-LDL. Upregulation of miR-126 expression in HUVECs leads to inhibition of ox-LDL activated *PI3K/Akt/mTOR* pathway and improvement of the autophagy. Thus, miR-126 can serve as a potential target in AS treatment.[57]

Not only inflammation and macrophages activity are promising targets in CAD treatment, but also EC pathologies and apoptosis. XIAP can inhibit apoptosis by binding to caspase-3. *XIAP* is a target of miR-122, which is able to suppress its expression. It was reported that the expression of miR-122 was upregulated in ox-LDL-induced

apoptotic human aortic ECs. Thus, overexpression of miR-122 promotes apoptosis via *XIAP* suppression.[58]

Additionally, *Ets-1* gene and its downstream target p21 are responsible for angiogenesis and vascular remodeling and inflammation. *Ets-1* is a target gene of miR-221/222, which can suppress its expression. Even though miR-221/222 have antiapoptotic effect on ECs with excessive accumulation of ox-LDL, its expression in those cells is reduced. Thus, upregulation of miR-221/222 can potentially reduce the ox-LDL-induced cell death via inhibition of *Ets-1*.[59]

miR-29 is involved in vascular remodeling and aneurysm formation.[60,61] In this regard, a trial is already ongoing to test MRG-201, a miR-29 mimic to prevent keloid formation in individuals with predisposition to develop keloid scars.[62] Positive results of this trial might anticipate further therapeutic applications, including vascular remodeling to counteract AS or aneurysm formation and inhibition of myocardial fibrosis with heart failure (**Table 1**).

The prevalence of CAD in modern society constitutes a growing challenge for medical professionals. miRNAs offer a wide range of potential treatment approaches. Consequently, drugs acting on miRNAs could influence the processes crucial for the development and progression of AS and CAD (**Figs. 1** and **2**).

LONG NONCODING RNAs

lncRNAs have been demonstrated to play a key role in the pathogenesis of AS, by regulating the functions of ECs, inflammation, and cholesterol accumulation. lncRNAs can act as miRNA sponges, meaning that they prevent the regulatory functions of miRNAs by binding to them and hindering interactions with their target.[7]

lncRNA GAS5 is a 5′-terminal oligopyrimidine class of genes that control cell growth, proliferation, and survival. Notably, GAS5 knockdown in THP-1 cells alleviated apoptosis of ECs, an important factor in preventing atherosclerotic plaque necrosis, which could lead to plaque instability.[63] Silencing of GAS5 was shown to attenuate inflammation in atherosclerotic mice by first upregulating miR-135a, which increased the alleviating effects of GAS5 silencing, and second by reducing proinflammatory cytokines including IL-1β, IL-6, and TNF-α in macrophages through sponging miR-221.[64,65] lncRNA GAS5 was also identified to restrain the reverse-transportation of cholesterol, a key process in the progression of AS, by binding to EZH2, which inhibits the expression of ABCA1.[66] Collectively, lncRNA GAS5 inhibition could alleviate apoptosis of ECs, inflammation, and increase reverse transportation of cholesterol, making it a potential therapeutic approach for AS.

The lncRNA MALAT1 was initially found in non–small cell lung cancer but has now been proven to be an important factor in AS.[67] The protective effect of MALAT1 in inflammation was demonstrated in knockout animal models, which showed increased adhesion to ECs and elevated levels of proinflammatory mediators partly by the reduction of miR-503.[68] Similarly, MALAT1 decreased ox-LDL-induced proinflammatory cytokines via regulating miR-155/SOCS1 pathway.[13] MALAT1 promoted autophagy, a protective mechanism in AS, in HUVECs by sponging miR-216a-5p and consequently upregulating Beclin-1 expression, and by inhibiting the PI3K/AKT pathway.[69,70] However, another study found that MALAT1 inhibited autophagy in endothelial progenitor cells.[71] Altogether, MALAT1 may be a useful target in AS treatment because it has been demonstrated to inhibit ox-LDL-induced inflammation and potentially induce autophagy.

lncRNA H19 regulates lipid metabolism, inflammation, apoptosis, and autophagy during development of AS. It was shown that H19 knockdown resulted in decreased WNT1 expression, which led to suppressed proliferation and increased apoptosis of VSMCs.[72] Moreover, H19 upregulation promoted the expression of ERK1/2 and mTOR proteins and inhibited the expression of autophagy-related proteins, such as LC3, p62, and Beclin1 in VSMCs.[73] ERK1/2 is responsible for increased proliferation and migration of VSMCs, whereas mTOR mediates hypoxia-induced proliferation of VSMCs.[74,75] Furthermore, H19 overexpression resulted in increased ACP5 protein expression in VECs, which promoted cell proliferation and suppressed apoptosis.[76] Additionally, H19 knockdown effectively decreased lipid accumulation and expression of proinflammatory factors, such as TNF-α and IL-1, by promoting the expression of miR-130b in ox-LDL-treated macrophage cells.[77] These findings indicate that lncRNA H19 contributes in the progression of AS by stimulating an excessive activation of VSMCs and VECs and promoting the lipid accumulation in macrophages. The ultimate effects of H19 on AS are still not fully understood. Nevertheless, the inhibitor of lncRNA H19 may help to attenuate AS and should be considered as a target for future animal and clinical studies.

lncRNA MIAT was found to activate PI3K/Akt signaling pathway and STAT3 in mice aortic cells and human aortic VSMCs, respectively.[78,79] PI3K/Akt regulates VSMCs proliferation and induces inflammatory response, whereas STAT3

Table 1
Role of miRNA in CAD development

miRNA	Upregulation/ Downregulation of the miRNAs	Target/Signaling Pathway	Effect	Data Source (Reference Number)
miR-155	↑	BCL6	Proinflammatory effect by activating NF-κB signaling pathway and macrophages.	10
	↑			11
	↑	CARHSP1	Anti-inflammatory effect by impairing TNF-α stability and thus NF-κB inhibition.	9
	↓	SOCS1	Repression of ox-LDL-mediated inflammation and apoptosis in ECs.	13
	↑		Enhancement of STAT3 and NF-κB signaling. Promotion of inflammatory cytokine and chemokine production and atherosclerosis progression.	21
	↑		Increase of the expression of p-STAT and PDCD4, and the production of proinflammation mediators IL-6 and TNF-α.	14
	↑	*p85α*	Antiapoptotic effect by AKT inhibiting.	15
	↓	HBP1	Decrease of lipid accumulation in macrophages and reduction of atherosclerotic plaques.	17
	↑	CEH	Inhibition of foam cell formation.	18
	↑	PI3K/Akt/mTOR	Induction of autophagy.	19
miR-33	↓	ABCA1, ABCG1	Induction of cholesterol efflux.	26,37
	↓	ABCA1	Induction of cholesterol efflux.	30
	↓	ABCA1	Induction of cholesterol efflux.	29
	↓	PDK4, PGC-1α	Induction of mitochondrial respiration and production of ATP.	32
	↓	Tnfa, Tlr6, Tlr13	Promotion of anti-inflammatory M2 phenotype in lesional macrophages.	30
	↓		Decrease of IL-1β, IL-6, and TNF-α secretion in ox-LDL-induced macrophages.	34
	↓		Restoration of autophagy function in atherosclerotic plaques.	24
	↓	ATG5, ATG12, LAMP1, FOXO3, TFEB	Enhanced autophagy.	35
	↓	ACC, FAS	Modulation of lipid accumulation in the liver.	39

(*continued on next page*)

Table 1
(*continued*)

miRNA	Upregulation/ Downregulation of the miRNAs	Target/Signaling Pathway	Effect	Data Source (Reference Number)
miR-92a	↓	CD36	FFA uptake to cardiomyocytes.	41
	↓	ABCA8B	Transport of HDL to cardiomyocytes.	41
	↑	ITAG5	Accumulation of proangiogenic factors, activation of proangiogenic ERK1/2 and PI3K/AKT signaling pathways.	46
	↑	KLF4	Promotion of macrophage participation in AS formation, enhancement of LDL uptake and proinflammatory cytokines expression in ECs.	43
	↑	KLF4	Promotion of PDGF-BB-mediated proliferation and migration of VSMCs.	45
↑miR-34		PNUTS	Favors vascular aging.	91
		SIRT-1	Favors vascular aging.	92
↑miR-23b		FoxO4, SIRT1	Induced differentiation of VSMCs, prevented from neointimal hyperplasia and adverse vascular remodeling.	93
miR-29		ADAM12, ADAMTS9, COL1A1/2, COL2A1, COL3A1, COL4A1/2, COL5A1/3, COL6A2, COL7A1, COL15A1, COL21A1, ELN, FBN1, FN1, MCL1, MMP2, MMP9, MMP15, MMP-24, TGFB1-3	Inhibited collagen synthesis and prevented from fibrosis.	60,61
↑ miR-126-5p		HMGB1	Reduced proliferation and migration of VSMC. Reduced expression of proinflammatory cytokine IL-1β in VSMCs.	52
↑ miR-98		LOX-1	Reduced uptake of ox-LDL in macrophages.	55
↑ miR-126		PI3K/Akt/mTOR	Inhibition of ox-LDL activated PI3K/Akt/mTOR pathway and improvement of the autophagy.	57
↑miR-125a		ETS-1	Inhibits proliferation and migration of VSMCs by inhibition of the PDGF-BB pathway.	94
		PinX1		95
↑miR-122		XIAP	Promoted apoptosis in ox-LDL ECs.	58

↑miR-221/222	Ets-1	Reduced ox-LDL-induced apoptosis in ECs.	[59]
↓ miR-133b	MAML1	Downregulation of Notch signaling pathway can reduce plaque size, macrophages proliferation, and migration.	[56]
↑ miR-16	PDCD4	Decreased proinflammatory cytokines levels, increased levels of anti-inflammatory factors, and reduced NF-κB and MAPK signaling pathways.	[53]
	RhoA/RhoGDIα	Increased activation of RhoA by targeting RhoGDIα reduced eNOS and VEGF expression and increases TNF-α in endothelial cells.	[54]

Abbreviations: ABCA1, adenosine triphosphate binding cassette subfamily A member 1; ABCA8b, ATP-binding cassette subfamily A member 8-B; ABCG1, ATP binding cassette subfamily G member 1; ACC, Acetyl-CoA carboxylase; Akt, protein kinase B; ATG, autophagy related gene; BCL6, B-cell lymphoma 6; CARHSP1, calcium-regulated heat stable protein 1; Ch25h, cholesterol-25-hydroxylase; ECM, extracellular matrix; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; Ets-1, ETS proto-oncogene 1; FAS, fatty acid synthase; FFA, free fatty acid; FOXO3, forkhead box O3; HBP1, high-mobility group box-transcription protein 1; HMGB1, high mobility group box 1; ITAG5, integrin subunit alpha 5; KLF, Krüppel-like factor; LAMP1, lysosomal associated membrane protein 1; LOX-1, lectin-like ox-LDL receptor-1; LXR, liver X receptor; MAML1, mastermind-like protein 1; MAPK, mitogen-activated protein kinase; MLCK, myosin light-chain kinase; mTOR, mammalian target of rapamycin; PDCD4, programmed cell death protein 4; PDK4, pyruvate dehydrogenase kinase 4; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphorylated phosphoinositide 3-kinase; SOCS1, suppressor of cytokine signaling 1; STAT3, signal transducer and activator of transcription 3; TFEB, transcription factor EB; Tsp-1, antiangiogenic trombospondin-1; XIAP, X chromosome-linked inhibitor of apoptosis.

Data from Refs.[9–19,21,24,26,27,29,30,32,34,35,39,41,43,45,46,52–61,91–95]

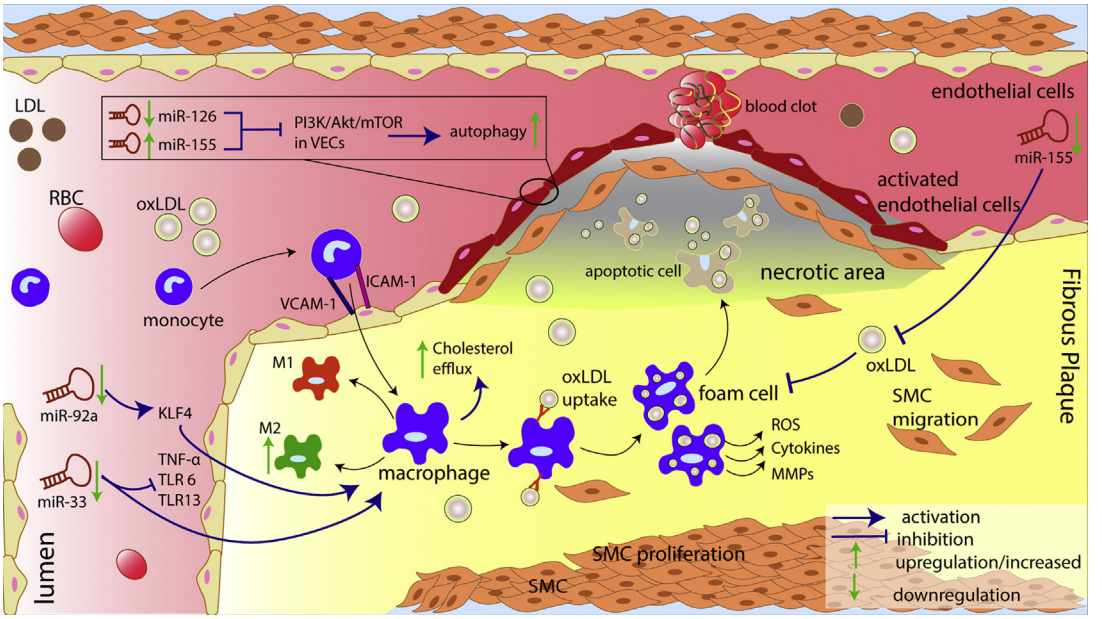

Fig. 1. MicroRNAs in atherosclerotic plaque initiation, progression, and rupture. (*Data from* Refs.[1,2,18–20,30,43,57])

promotes VSMCs proliferation.[80] Overexpression of MIAT facilitated proliferation, accelerated cell cycle progression, and hindered apoptosis in ox-LDL-induced VSMCs.[78] Moreover, MIAT upregulation promoted atherosclerotic plaque formation in mice models.[79] These findings indicate a potential role of MIAT as a therapeutic approach in AS. lncRNA MIAT inhibitor should be considered in AS treatment and needs to be further investigated.

lncRNA XIST was shown to simulate *PTEN* and *NOD2* signaling by sponging miR-30a-5p and miR-320, respectively, in HUVECs.[81,82] The knockdown of XIST suppressed cell apoptosis,

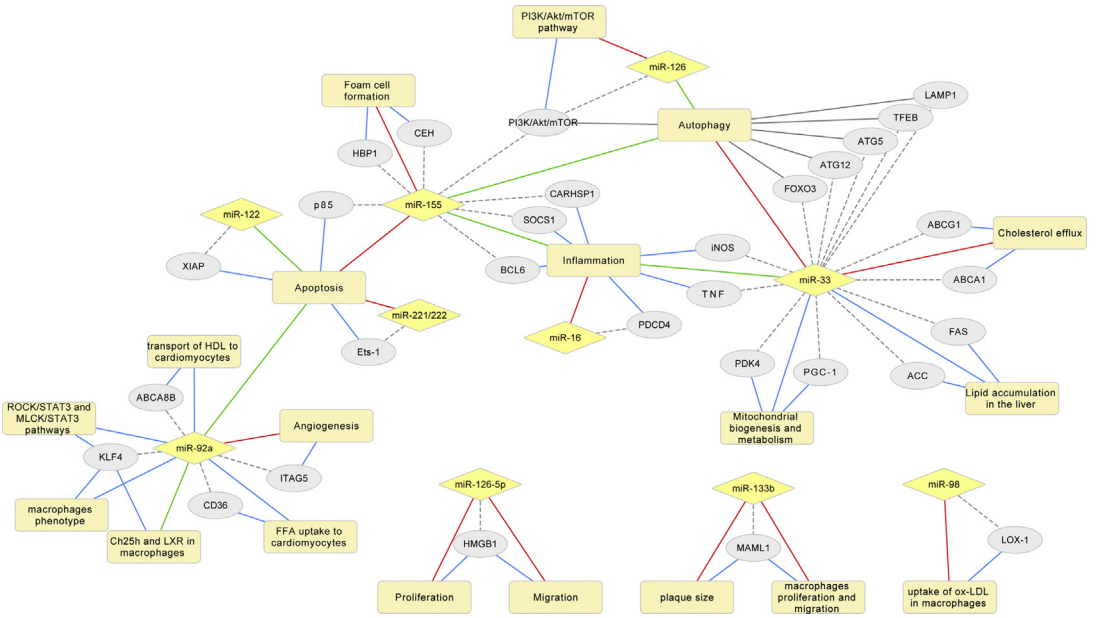

Fig. 2. Network of microRNA regulation by targeting genes in atherosclerosis and coronary artery diseases. *Blue*, *green*, and *red edges* represent modulation, activation, and inhibition, respectively. (*Data from* Refs.[9–19,21,26,29,30,32,35,37,39,41,43,45,46,52,53,55–59])

Table 2
Role of lncRNAs in CAD development

lncRNA	Target	miRNA Sponging	Effect	Data Source (Reference Number)
GAS5 ↓			Alleviated apoptosis	63
		miR-135a ↑	Decreased inflammation	64
		miR-221 ↓	Reduced the expression of proinflammatory cytokines	65
	EZH2 ↓		Increased reverse-transportation of cholesterol	66
MALAT1 ↓		miR-503 ↓	Increased adhesion to ECs and elevated expression of proinflammatory mediators	68
MALAT1 ↑	SOCS1 ↑	miR-155 ↓	Decreased ox-LDL induced proinflammatory cytokines	13
	Beclin 1 ↑	miR-216a-5p ↓	Promoted autophagy	69
	PI3K/AKT pathway		Promoted autophagy	70
			Inhibition of autophagy	71
H19 ↑	WNT1	miR-148b (competition to target binding)	Promoted proliferation and suppressed apoptosis of VSMCs	72
	ERK1/2, mTOR			73
	ACP5		Promoted proliferation and suppressed apoptosis of VECs	76
H19 ↓		miR-130b ↑	Increased expression of anti-inflammatory factors in macrophage	77
MIAT ↑	PI3K/Akt, STAT3	miR-181b ↓	Promoted proliferation, accelerated cell cycle progression, and suppressed apoptosis of VSMCs	79, 78
XIST ↑	PTEN	miR-30a-5p ↓	Promoted cell apoptosis and inflammation response in HUVECs	81
	NOD2	miR-320 ↓		82
HOTAIR ↑			Promoted proliferation and migration of ECs	83
RNCR3 ↓	KLF2	miR-185-5p↑	Reduced proliferation and migration of ECs and VSMCs	85
CASC11 ↑	IL-9↓		Supressed proliferation and induced apoptosis of VSMCs	96

(*continued on next page*)

Table 2
(*continued*)

lncRNA	Target	miRNA Sponging	Effect	Data Source (Reference Number)
ENST00113 ↓	PI3K/Akt/mTOR		Decreased proliferation, survival, and migration of VSMCs and HUVECs	86
lncRNA 430945 ↑	ROR2/RhoA		Promoted proliferation and migration of VSMCs	87
RAPIA ↑		miR-183-5p↓	Promoted proliferation and suppressed apoptosis of macrophages	97
AF131217.1↓	KLF4	miR-128-3p–target competition	Regulation of HUVECs under shear stress	98
ATB ↑			Promoted apoptosis and inhibited proliferation of HUVECs	88
TUG1 ↑	FGF1	miR-133a↓	Improved inflammatory factor expression and inhibited apoptosis in macrophages	90
LINC00657 ↑		miR-590-3p↓	Promotes angiogenesis	99
AC096664.3 ↓	PPAR-γ/ABCG1		Induced cholesterol accumulation in VSMCs	100
SNHG16 ↑	Smad2	miR-205–target competition	Regulation of HSMCs migration and proliferation	89
OIP5-AS1 ↓		miR-320a ↑	Enhanced cell viability and repressed apoptosis of HUVECs	84

Abbreviations: ABCG1, ATP binding cassette subfamily G member 1; ACP5, acid phosphatase 5 protein; AKT, protein kinase B; ATB, long noncoding RNA activated by TGF-Beta; CASC11, cancer susceptibility 11 gene; ECs, endothelial cells; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; EZH2, enhancer of zeste homolog 2; FGF1, fibroblast growth factor 1; GAS5, growth-arrest specific transcript 5; HOTAIR, HOX transcript antisense RNA; HSMCs, human mesenchymal stem cells; KLF, Krüppel-like factor; MALAT1, metastasis associated lung adenocarcinoma transcript 1; mTOR, mammalian target of rapamycin; NOD2, nucleotide-binding oligomerization domain 2; OIP5-AS1, OIP5 antisense RNA 1; PI3K, phosphorylated phosphoinositide 3-kinase; PPAR-γ, peroxisome proliferator-activated receptor gamma; PTEN, phosphatase and tensin homolog; RAPIA, lncRNA associated with the progression and intervention of atherosclerosis; RhoA, Ras homolog family member A; RNCR3, retinal noncoding RNA; ROR2, receptor tyrosine kinase like orphan receptor 2; Smad2, SMAD family member 2; SNHG16, small nucleolar RNA host gene 16; SOCS1, suppressor of cytokine signaling 1; STAT3, signal transducer and activator of transcription 3; TUG1, taurine-upregulated gene 1; VECs, vascular endothelial cells; WNT1, Wnt family member 1.

Data from Refs.[13,63–66,68–73,76–78,81–90,96–100]

increased cell viability, and decreased inflammatory response in HUVECs under ox-LDL stimuli. Endothelial cell proliferation and viability are highly impaired during AS development, thus inhibition of XIST may act protectively and should be considered as a therapeutic strategy in AS.

Several different lncRNAs may participate in the development of AS. lncRNAs HOTAIR, RNCR3, ENST00113, lncRNA 430945, ATB, SNHG16, and OIP5-AS1 are involved in the regulation of VSMC or VEC viability, proliferation, and migration.[83–89] Moreover, lncRNAs RAPIA and TUG1 enhance macrophage viability and reduce apoptosis.[87,90]

An increasing number of studies show lncRNAs as emerging important modulators of AS, making them promising targets for drug development. Further studies are needed to elucidate the mechanisms of their action and estimate their potential benefits and risks in clinical application (**Table 2**).

SUMMARY

Numerous studies have shown that miRNAs and lncRNAs might be promising therapeutic targets in CAD. miR-155 inhibitor has been described to be the most promising novel therapeutic strategy against progression of CAD. Moreover, inhibition of miR-33 and miR-92a has also been demonstrated as a promising therapeutic approach by delaying the development and enhancing the regression of CAD. No data about their safety in clinical trials have been available so far. In addition, lncRNAs, such as GAS5 and H19, were shown to have a relevant impact on CAD progression, thus their inhibition could be a potential therapeutic approach for CAD. Various limitations of ncRNAs used for CAD exist, including the lack of registered clinical trials and the incomplete understanding of the specific mechanism by which ncRNAs modulate CAD development on a molecular level. In addition, many ncRNAs have yet to be studied. Recent studies are promising, but further research is required to investigate ncRNA potential in clinical application.

HIGHLIGHTS OF THE ARTICLE

1. MiRNAs and lncRNAs could be a target of novel treatment as many studies showed promising results.
2. MiRNAs and lncRNAs have an important role both in regulation and pathophysiology of atherosclerosis in coronary artery disease.

CONTRIBUTORS

L. Zareba, C. Eyileten, and M. Postula contributed to the data collection and elaboration, writing, and approval of article; and is guarantor of the article. Z. Fitas, M. Wolska, and E. Junger contributed writing, editing, discussion, and approval of article. S. De Rosa and J.M. Siller-Matula contributed to revising and approval of the article. C. Eyileten and Z. Wicik contributed valuable graphical designs. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONFLICTS OF INTEREST

The authors state there are no conflicts of interest.

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