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Review Article

Non-coding RNA and Atherosclerosis

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Abstract

The overwhelming majority of genes in the human genome encode RNA molecules that are not translated into proteins. These RNA molecules are named non-coding RNAs (ncRNAs). ncRNAs play a crucial role in the regulation of gene expression and abnormalities in ncRNAs can cause disease progression, including atherosclerosis. ncRNAs regulate different stages of atherosclerosis progression, such as foam cell formation and lipid metabolism. Diverse types of ncRNAs have been studied, but the best known and widely used are small non-coding (sncRNAs), specifically microRNAs and small interfering RNAs, which are ~22 nucleotides long. The majority of drugs based on ncRNAs are composed of sncRNAs. There is strong evidence that besides sncRNAs, other types of ncRNAs, such as long ncRNAs and circular RNAs, take part in the regulation of gene expression. This review summarized recent advances in ncRNAs and atherosclerosis.

Keywords: Non-coding RNA; Atherosclerosis; Drugs; Inflammation; Epithelial-mesenchymal transition.

Abbreviations: ABC, ATP-binding cassette; ABCA1, ABC subfamily A member 1; ABCG1, ABC subfamily G member 1; ACC, acetyl-CoA carboxylase; ANGPTL3, angiopoietin-like 3; ApoE, apolipoprotein E; ASO, antisense oligonucleotide; CCND1, cyclin D1; CDC42, cell division cycle 42; circRNA, circular RNA; CVD, cardiovascular disease; CXCL10, C-X-C motif chemokine ligand 10; CXCR4, C-X-C motif chemokine receptor 4; DDX17, DEAD-box helicase 17; dsRNA, double-stranded RNA; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; EPLIN, epithelial protein lost in neoplasm beta; FGF1, fibroblast growth factor 1; HDAC, histone deacetylase; HIF-1, hypoxia inducible factor-1; IL, interleukin; IRAK1, interleukin 1 receptor associated kinase 1; KLF, Kruppel-like factor; LDL, low-density lipoprotein; lncRNA, long non-coding RNA; MEOX2, mesenchyme homeobox 2; MeXis, macrophage-expressed LXR-induced sequence; miRNA, microRNA; MMP2, matrix metallopeptidase 2; mRNA, messenger RNA; mtDNA, mitochondrial DNA; MV, microvesicle; MVB, multivesicular body; ncRNA, non-coding RNA; NF-kB, nuclear factor kappa B; NOS3, nitric oxide synthase 3; NPC1, Niemann-Pick type C1; oxLDL, oxidized LDL; PKD1, polycystic kidney disease 1; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; PTEN, phosphatase and tensin homolog; RISC, RNA-induced silencing complex; RNCR3, retinal non-coding RNA3; ROS, reactive oxygen species; SCD, stearoyl-CoA desaturase; siRNA, small interfering RNA; SMC, smooth muscle cell; sncRNA, small non-coding RNA; SOCS1, suppressor of cytokine signaling 1; SREBP, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; THBS1, thrombospondin 1; TNFα, tumor necrosis factor; TRAF6, TNF receptor associated factor 6; VEGF, vascular endothelial growth factor.

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Introduction

The end product of a gene can be either a protein or an RNA molecule. These RNAs are called non-coding RNAs (ncRNAs). They can be divided into housekeeping ncRNAs, which include ribosomal RNA, transfer RNA, small nuclear RNA, small nucleolar RNA and regulatory ncRNA.[1] Regulatory ncRNAs can be classified into small ncRNAs (sncRNAs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs); some authors refer to circRNAs as lncRNAs, while others classify them into distinct groups.[1,2]

The main groups of sncRNAs are microRNAs (miRNAs) and small interfering RNAs (siRNAs). miRNAs are generally 22 nucleotides long which participate in gene expression regulation. Their action is based on interactions with messenger RNA (mRNA) mediated by base pairing between the miRNA and complementary sequences in the target mRNA. There are three different miRNA effects on mRNA: cleavage of mRNA, translation repression or/and removal of the polyA tail and cap from mRNA ends.[3,4]

The first ever investigated miRNA was lin-4 from *Caenorhabditis elegans*. Lin-4 is responsible for the regulation of larval development timing in round worms.[3,5] Its mechanism of action is based on translation repression of the lin-14 gene, whose protein product is involved in controlling the timing of developmental events during the larval stages. Lin-4 promotes the transition from the first larval stage to the second larval stage and represses the later developmental stages. The lin-4 miRNA interacts with complementary sites in the lin-14 mRNA and acts as a negative regulator.[6]

siRNAs are also similar to miRNAs; however, there are sev-

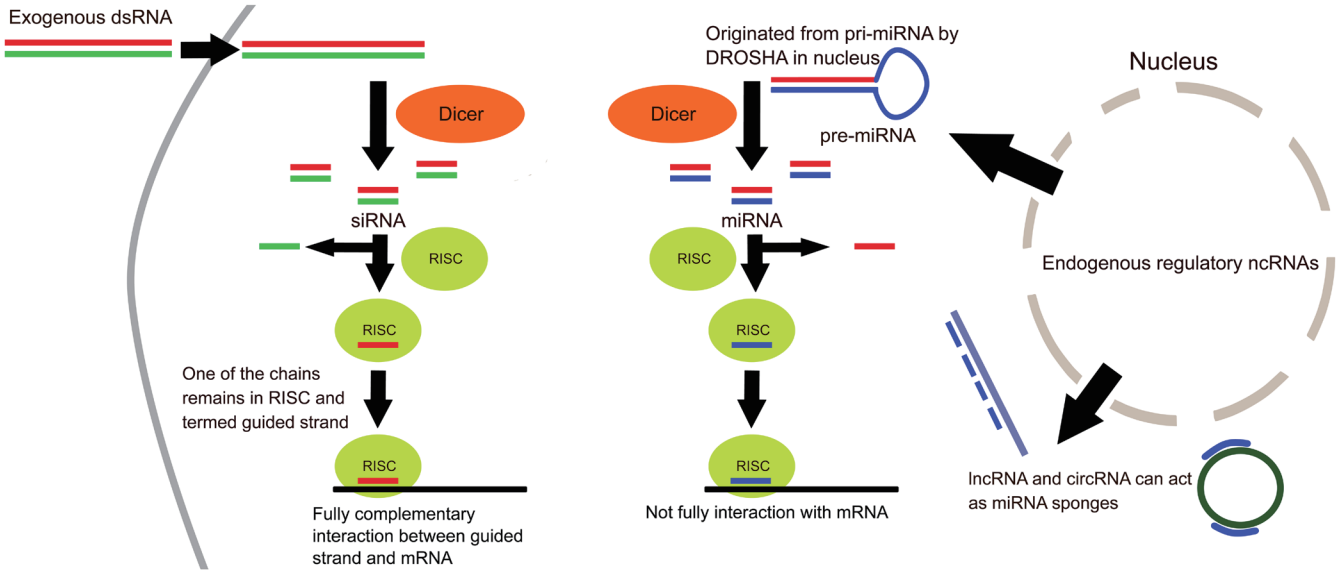

Fig. 1. Types of ncRNAs and their places of action. circRNA, circular RNA; dsRNA, double-stranded RNA; lncRNA, long non-coding RNA; mRNA, messenger RNA; miRNA, microRNA; ncRNA, non-coding RNA; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA.

eral key differences between them. siRNAs are typically derived from exogenous sources, such as viral or synthetic double-stranded RNA invading cells. In contrast, miRNAs are endogenously produced within cells from distinct genes that encode stem-loop RNA precursors. The RNase III endonuclease Dicer participates in their maturation. siRNAs typically exhibit perfect or near-perfect complementarity to their target mRNAs. This allows for highly specific gene silencing through mRNA degradation. miRNAs usually have partial complementarity to their target mRNAs and silence genes through translational repression rather than mRNA cleavage. Furthermore, siRNAs regulate only the specific gene that expresses them, while miRNAs can regulate different genes.[3,7]

LncRNAs are defined as ncRNAs longer than 200 nucleotides. They can regulate gene expression through diverse mechanisms. Generally, lncRNAs are transcribed by RNA Polymerase II. Most of these RNAs undergo post-transcriptional modifications, such as capping and polyadenylation of their ends, similar to mRNAs, which are essential for stability.[8] LncRNAs can be localized in different cellular compartments, including the nucleus, cytoplasm, and even extracellular space, but a large percentage of them are localized in the nucleus.[9] There are several mechanisms of lncRNA-mediated gene expression regulation. Due to the ability to identify complementary sequences, some lncRNAs can bind to specific DNA sequences and recruit chromatin-modifying complexes, such as histone methyltransferases, acetylases, and deacetylases or DNA methyltransferases, to regulate the epigenetic state of target genes.[10] This can lead to changes in chromatin structure and gene expression. Another mechanism involves interactions with RNA molecules, such as mRNAs, which regulate post-transcriptional processes, or with miRNAs, functioning as miRNA sponges.[8,11] According to their mechanisms of action, lncRNAs can be classified as cis-acting, which act at the site of transcription and affect the expression of neighboring genes, or trans-acting, which function beyond the site of synthesis.[12] For example, trans-acting lncRNAs can function by recruiting chromatin-modifying complexes to regulate distant genes or act as miRNA sponges.[13] The main types of ncRNAs and their potential sites of action are shown in Figure 1.

ncRNAs in lipid metabolism

The most studied miRNA involved in the regulation of cholesterol homeostasis is miR-33, which has two isoforms in humans: miR-33a and miR-33b. These miRNAs are encoded within sterol regulatory element-binding protein (SREBP) genes. SREBPs belong to a family of transcription factors that regulate the expression of genes involved in the synthesis of various lipids. Specifically, miR-33a is encoded in the intron of SREBP2, and miR33b is encoded in the intron of SREBP1.[14] SREBP1 mainly activates genes involved in fatty acid synthesis, and SREBP2 mainly activates cholesterol synthesis.[15] Excess cholesterol is removed from cells by the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1, and cholesterol is subsequently captured by high-density lipoprotein.[16] It has been revealed that the mRNAs of ABCA1, ABCG1 and NPC1 genes, which are involved in the intracellular trafficking of cholesterol, are targets of miR-33. miR-33 inhibits the expression of these proteins and thus reduces cholesterol efflux.[14,17,18]

Additionally, there are other miRNAs that target ABCA1. miR-148a binds to ABCA1 mRNA and inhibits its expression. In vivo experiments have demonstrated that the downregulation of miR-148a increases the level of cholesterol in high-density lipoprotein. miR-148a also regulates the level of low-density lipoproteins (LDLs) by targeting the mRNA of the LDL receptor. Downregulation of LDL receptor expression leads to a decrease in LDL uptake by hepatic cells and thus an increase in circulating LDL cholesterol levels, which is a risk factor for atherosclerosis.[19] miR-26 and miR-758 directly target ABCA1.[20,21]

lncRNAs also participate in the regulation of lipid metabolism. For example, the lncRNA MeXis interacts with the protein DDX17 and facilitates its action. DDX17 enhances the liver X receptor-mediated expression of ABCA1. This protein is a nuclear receptor

that stimulates cholesterol efflux in response to high cholesterol levels in cells.[22] The lncRNA uc.372 upregulates the expression of genes involved in fatty acid synthesis and uptake, such as ACC, SCD1, and CD36, which leads to lipid accumulation. This effect is caused by preventing the maturation of miR-195 and miR-4688 via uc.372. Downregulation of miR-195 and miR-4688 occurs due to the ability of uc.372 to bind with the primary miRNAs pri-miR-195 and pri-miR-4668.[23]

The role of ncRNAs in inflammation

Activation of inflammation is an important biological phenomenon in various diseases. ncRNAs are activated in inflammatory diseases, either by directly affecting components of inflammatory sites or by controlling the activity of various factors that control inflammatory activation.[24]

ncRNAs are critical in regulating the expression of genes associated with certain types of cells that cause inflammation. For example, miRNAs, such as miR-126, miR-132, miR-146, miR-155 and miR-221, are important transcriptional regulators of several mediators associated with inflammation,[25] and several lncRNAs, such as long noncoding inflammation-associated RNAs, play critical roles in inflammation—regulation of cytokines and inflammasome activation.[26] Knockdown of hLinfRNA1 has been shown to suppress the lipopolysaccharide-induced expression of cytokines and pro-inflammatory genes, such as interleukin (IL) 6, IL1β and tumor necrosis factor (TNF) α.[26]

The role of ncRNAs in vascular cell proliferation

Different ncRNAs may play different roles within the life cycle of vascular smooth muscle cells (SMCs). For instance, the overexpression of miR-130a,[27] miR-146a,[28] and the lncRNA RNCR3 promote SMC proliferation,[29] and miR-34a regulates proliferation and migration.[30] A number of studies have demonstrated a correlation between the development of atherosclerotic changes in blood vessels and the concentration of certain ncRNAs, but the underlying mechanism has not been fully elucidated.

In 2016, smooth muscle-enriched lncRNA was experimentally demonstrated as one of the drivers of vascular SMC proliferation.[31] One of the proposed mechanisms of this phenomenon is the interaction with the promoter region of the hyaluronidase 2 gene, which is a marker of atherosclerosis progression.[32] Another ncRNA, lncRNA hoxa cluster antisense RNA 3, affects the transcriptional processes by regulating histone H3K9 acetylation, leading to an increase in the number of pulmonary artery SMCs in the S+G2/M phase. Knockdown of this ncRNA leads to the opposite effect—a decrease in the number of pulmonary artery SMCs in the S+G2/M phase.[33]

On the other hand, the reverse effect of ncRNAs in the SMC life cycle is also reported. It was demonstrated that snRNA-p21 can act as an enhancer to enhance the expression of the p53 gene, which allows p53 to interact with the p300 protein, ultimately leading to the inhibition of SMC proliferation and apoptosis.[34]

The role of ncRNAs in vascular cell adhesion and migration

miR-92a increases the expression of endothelial adhesion molecules and the adhesion of leukocytes to the endothelium through targeting Kruppel-like factor 2 (KLF2) and KLF4.[35] miR-126 is expressed at high levels in endothelial cells compared to other miRNAs, and it binds to the 3′ untranslated region of vascular cell adhesion molecule 1 mRNA, leading to inhibition of its translation. This inhibition blocks the adhesion of leukocytes to vascular walls, thereby preventing their infiltration.[36] Blocking miR-126 with antisense RNA leads to an increase in vascular cell adhesion molecule 1 expression induced by TNF-α.[36] miRNA-17-3p, miRNA-141, miR-221, and miR-222 reduce the adhesion of leukocytes to endothelial cells by acting on the common target intercellular adhesion molecule-1.[37–39] miR-31 inhibits leukocyte adhesion (and rolling) on the endothelium by acting on E-selectin.[40] miR-146a/b inhibits the expression of endothelial adhesion molecules by targeting IRAK1, TRAF6.[41] miR-100 was found to suppress the expression of endothelial adhesion molecules via the attenuation of NF-kB signaling, leading to decreased interaction between leukocytes and the endothelium.[42]

Role of ncRNAs in angiogenesis

The role of ncRNAs in angiogenesis has been studied mostly in cancer research. miR-21 is upregulated in tumors and has different targets: PTEN (which leads to the induction of angiogenesis by enhancing the expression of vascular endothelial growth factor (VEGF) and HIF-1),[43] STAT3 (which leads to a decrease in VEGF levels via the knockout of STAT3),[44] and THBS1 (which leads to the inhibition of THBS1 expression in endothelial cells).[45] miR-126 is mostly downregulated in tumors, and it also has several targets related to its mostly anti-angiogenic activity: VEGF, VEGFA, LRP6 and PIK3R2.[46–49] miR-93 is upregulated in tumors because it has pro-angiogenic activity by targeting VEGF, EPLIN, LATS2, and IL8.[50–53] LncRNAs also involved in angiogenesis, with H19, HOTAIR and MVIH ncRNA being upregulated in tumors with VEGF and some specific targets for each ncRNA mentioned.[54–59] The lncRNA MANTIS has been shown to affect endothelial angiogenic function via action on BRG-1.[60] CircRNAs (circ-ATXN1, circ-SHKBP1, hsa-circ-0000515, circ-0056618, circ-PRRC2A, circRNA-MYLK, and circ-DICER1), which are upregulated in tumors, can also influence angiogenesis via different targets (MMP2, VEGFA, VEGF, CXCL10, CXCR4, TRPM3, and PI3K/AKT).[61–67]

Atherosclerosis-what is it? The basis of pathological changes occurring in atherosclerosis

Atherosclerosis is a chronic inflammatory vascular disease characterized by the formation of plaques within the intima of large- and medium-sized arteries. Multiple experimental and clinical data, including studies with animal models and humans, suggest that this disease is related to the disturbance of lipid metabolism.[68] Abnormal lipid accumulation, which causes the formation of plaques, leads to damage to the intima, inflammation and fibrosis.[69] The mouse model is the most commonly used animal model for studying atherosclerosis.[70] Mice exhibit innate resistance to atherosclerosis due to the absence of cholesteryl ester transfer protein, which contributes to the exchange of cholesteryl ester and triglycerides between different lipoproteins.[71] However, knockout of specific genes involved in lipid metabolism, such as the apolipoprotein E (ApoE) gene or LDL receptor,[72,73] leads to the development of atherosclerosis-like changes in these mice.

Over time, atherosclerosis can cause narrowing of the arteries, which can restrict blood flow and potentially lead to severe complications, such as myocardial infarction and cerebrovascular disease, leading to stroke and other complications.

Plaques are multicomponent structures that include lipids,

cholesterol, calcium, connective-tissue elements, cells and their remains. Plaque development can be divided into several stages. Initially, isolated macrophages transform into foam cells. As the number of foam cells increases, intracellular lipid accumulation starts, which subsequently results in the formation of a lipid core. As the plaque progresses, SMCs migrate from the arterial wall to the developing plaque. These SMCs produce collagen and other extracellular matrix proteins, contributing to the formation of the fibrous cap. The fibrous cap provides structural support to protect the plaque. Sometimes different parts of plaques are mineralized by calcium, which makes the structure harder.[74,75]

LDLs (another important player in atherosclerosis development) transport cholesterol from the liver to cells. Modified LDLs, such as desialylated and oxidized ones, initiate excessive lipid accumulation in artery walls and trigger an inflammatory response in the artery. Modified LDLs trigger endothelial cells to synthesize leukocyte adhesion molecules,[76–78] such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1.[79,80] This leads to the recruitment of immune cells, such as monocytes, to the intima, representing one of the earliest events in atherosclerosis development.[81] Monocytes then differentiate into macrophages that engulf the modified LDLs via scavenger receptors. Excessive lipid uptake leads to lipid droplets accumulation in macrophages, which are subsequently transformed into foam cells, contributing to the formation of the lipid core within the plaque.[82]

The main source of foam cells is macrophages, although a small portion of these cells may originate from endothelial and vascular SMCs.[83] The process by which epithelial cells transform into mesenchymal cells is called epithelial-mesenchymal transition (EMT). EMT plays a crucial role in early embryonic development, contributing to the formation of germ layers: ectoderm, mesoderm, and endoderm.[84] During EMT, epithelial cells lose their features such as cell polarity and cell-cell adhesion and acquire mesenchymal characteristics, allowing them to migrate and invade surrounding tissues.[85] EMT occurs not only during embryonic development but also in adulthood, contributing to processes such as tissue regeneration and the development of different diseases.[86] The EMT subcategory in which endothelial cells undergo this transition is called endothelial-mesenchymal transition (EndMT). Studies have shown that, besides atherosclerosis, cardiac fibrosis is also linked with EndMT.[87] Research indicates a correlation between the severity of coronary atherosclerosis and decreased endothelial expression of FGF receptor 1, endothelial activation of TGF-β signaling, and the degree of EndMT.[88] It has been found that histone deacetylases (HDACs), particularly HDAC9, play an important role in EndMT upon atherosclerosis development, and knock-out endothelial cell-specific HDAC9 leads to reduced plaque size and increased plaque stability in atherosclerosis-prone mice.[89]

More attention gets attracted to the role of immune cells other than macrophages (for example, T- and B-cells) in the development and progression of atherosclerosis.[90] Atherosclerotic plaques contain significantly high amounts of CD4+ T cells.[91] B cells can regulate atherosclerosis development by producing cytokines and antibodies.[92] It has been found that the quantity of the chemokine receptor CXCR4 residing on human CD20+CD27+CD43+ B1 cells is associated with the level of circulating IgM antibodies recognizing MDA-LDL, and the higher expression of CXCR4 in B1 cells corresponds to reduce coronary artery plaque burden in patients.[93]

Mitochondrial dysfunction could well be one of the pathological factors contributing to atherosclerosis development.[94,95] Certain mutations of mitochondrial DNA (mtDNA) in white blood cells of patients were shown to be associated with cardiac angina (G14459A and C5178A), with carotid atherosclerosis or the presence of coronary heart disease (C3256T, T3336C, G12315A, G13513A, G14459A, G14846A, and G15059A).[96,97] Additionally, atherosclerotic lesions in the human aorta contain mtDNA mutations like A1555G, C3256T, T3336C, G13513A, and G15059A.[98] The accumulation of mtDNA mutations may lead to mitochondrial dysfunction, increased reactive oxygen species (ROS) production, oxidative stress and pro-inflammatory cytokine release.[99] Mitochondrial damage-associated molecular patterns can trigger sterile inflammation via different signaling pathways, including NF-kB, Toll-like receptors, and NLRP3,[100] and damaged mtDNA itself may serve as a damage-associated molecular pattern, causing an inflammatory response.[101]

Interestingly, mitochondrial DNA mutations and mitochondrial dysfunction are associated with other diseases, including neurological disorders,[102] diabetes,[103] muscle atrophy and non-alcoholic fatty liver disease.[104–106]

Atherosclerosis can also be considered an autoimmune disease; thus, certain approaches related to the treatment of such diseases can potentially be applied.[107,108] The autoimmune nature of atherosclerosis can be demonstrated by the presence of autoantibodies against oxidized LDL (oxLDL), β2 glycoprotein I and heat shock proteins.[109] oxLDL binds to β2 glycoprotein I to form a complex capable of triggering autoimmune reactions.[110] The binding of C-reactive protein to ox-LDL, enhances its interaction with Fcγ receptors in macrophages, which may augment oxLDL uptake by macrophages (a process not observed with native LDL).[111]

Atherosclerosis and amyloid-related diseases are closely associated with aging. Opinions about the possible interconnection between these two different pathologies have appeared relatively recently.[112] For example, deposits of Apo-AI-based amyloid were found in the intima and atherosclerotic plaques of carotid artery specimens from a significant portion of atherosclerotic patients.[113] The number of stenoses was higher in Alzheimer's disease patients than in the control population, as well as the number and degree of atherosclerosis in certain cerebral arteries.[114] There is a certain connection between vascular amyloidosis and the following factors, some of which can also be associated with atherosclerosis: MMP-2/9, Ang II, Medin, MFG-E8, and MCP-1.[112] However, the exact mechanism underlying the connection between atherosclerotic changes and amyloid deposition has yet to be determined. One could hypothesize that amyloid deposition further exacerbates chronic inflammation in the vessel wall since, for example, systemic amyloidosis can be associated with chronic inflammation.[115]

This hits at potential benefits (for the prevention or reduction of severity of atherosclerosis development) through early diagnosis and treatment of amyloid-related diseases.[116] Thus, the development of new approaches to target amyloid-caused diseases holds significant importance, and yeast could serve as an important model organism for new insights for the development of such therapies (for example, based on findings about yeast anti-prion/amyloid/aggregate systems or about amyloid properties in general).[117,118] The main pathological factors contributing to atherosclerosis development are shown in Figure 2.

Initial stages of atherosclerosis development

Understanding the main pathological factors contributing to atherosclerosis development allows us to guess the sequence of events during the initial stages of atherosclerosis development.[119] Pre-atherosclerotic lesions in humans are believed to be diffuse thickening of the artery intima in atherosclerosis-prone areas of arteries where

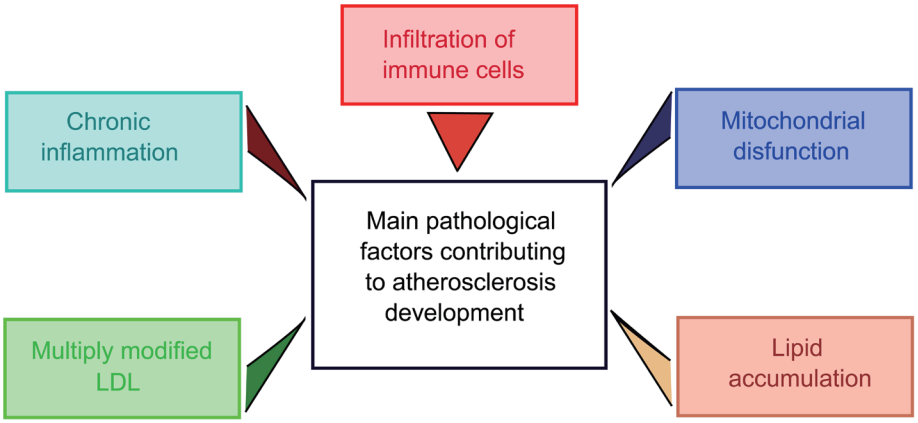

Fig. 2. Main pathological factors contributing to atherosclerosis development. LDL, low-density lipoprotein.

there is disturbed blood flow even at a very early age.[120] Vascular SMCs migrate from the media into the intima, leading to the production of a negatively charged extracellular matrix that can bind to positively charged ApoB-based lipoproteins.[121] This leads to the retention of lipids in the subendothelial space following endothelial dysfunction and activation of endothelial cells, resulting in the production of pro-inflammatory cytokines and adhesion molecules, and increased permeability of the endothelium.[122] Accumulated lipids in the intima can be further modified (for example, oxidized), activating the innate immune response.[123] Monocytes from the circulation are attracted to initial atherosclerotic lesions and reach the intima, where they differentiate into macrophages. These macrophages accumulate lipids and change into foam cells, accumulating in the intima.[124] During the abovementioned processes, the migration (and proliferation) of vascular SMCs into the intima continues, and the production of collagen by these cells eventually leads to the formation of a fibrous cap.[125]

ncRNAs can affect atherosclerosis development at different stages. For example, the expression of miR-155-5p in the case of early atherosclerosis restricts lesion formation by reducing the proliferation of macrophages, but the formation of advanced lesions is increased by miR-155-5p by impairing efferocytosis induced by inflammation.[126]

The connection of atherosclerosis and cardiovascular diseases with ncRNAs

ncRNAs take part in the regulation of gene expression and can act not only inside the cell where they were synthesized but also outside it. Generally, donor cells can secrete ncRNAs into the extracellular space through extracellular vesicles, which reach the recipient cell and regulate internal processes. Secretion of ncRNAs can occur in various ways. Extracellular vesicles are not a name for one type of vesicles; this term includes three different types of vesicles: exosomes, microvesicles (MVs) and apoptotic bodies. This classification is based on the way those vesicles were generated.[127]

Exosomes originate from the multivesicular body (MVB), which is a component of the endosomal-lysosomal system, and fuse with the cell membrane. The MVB contains vesicles up to 100 nm in diameter. These vesicles are termed intraluminal vesicles.[128] Upon fusion with the membrane, the MVB releases these intraluminal vesicles in the extracellular space, known as exosomes.[129]

MVs (40–1,000 nm in diameter), which are also called ectosomes, microparticles or shedding vesicles, are formed through outward budding of the cell membrane mediated by actin and myosin interactions.[130]

Apoptotic bodies, also known as apoptotic vesicles, are released from cells undergoing programmed cell death (apoptosis) and contain cellular components, including organelles, proteins and nucleic acids. They have a larger size than exosomes and MVs, ranging from 50 nm up to 5,000 nm in diameter.[127]

ncRNAs are secreted inside the cell through various ways, including exosomes, MVs, and apoptotic bodies, and can also be components of lipoproteins or ribonucleoproteins.[131]

ncRNAs are involved in various cellular processes, including gene expression regulation and cell communication. In various cardiovascular diseases (CVDs), alterations in ncRNA levels occur. For example, it was demonstrated that miRNAs are necessary for cardiovascular system development.[132] In this study, mice with cardiac-specific knockout of the Dicer gene, crucial for miRNA maturation showed decreased mature miRNA levels, causing changes in gene expression in the heart, particularly in genes that are involved in regulating the structure and function of heart muscle cells. These changes ultimately led to the development of dilated cardiomyopathy and heart failure, causing the death of the mutant mice.[132]

Alterations in the quantities of different miRNAs have been revealed during CVD. For example, the expression of miR-126 is significantly lower in patients with coronary artery disease than in healthy individuals.[133] Another study revealed that miR-122 and miR-370 levels are greater in patients with high levels of lipids in the blood and that high levels of these miRNAs are associated with a high risk of coronary artery disease.[134]

The first report on the association of miRNAs with CVD was published in 2006. This study demonstrated correlations between miRNA expression patterns and heart failure and cardiac hypertrophy in mice and humans. Numerous studies describing alterations in miRNA levels during CVD have been published.[135]

Quantitative changes during various CVD types have also been observed in lncRNAs and circRNAs.[136]

Why can we use ncRNAs as biomarkers? ncRNAs can exhibit tissue-specific or cell-specific expression patterns; thus, they can act as indicators of specific pathological processes. These molecules can be detected in bodily fluids, and their levels can be measured.[136]

The first description of morphological changes in CVD was provided by van Rooij *et al*. They reported that the overexpression of specific miRNAs, such as miR-195 and miR-199a, resulted in

Table 1. ncRNAs associated with atherosclerosis

ncRNA	Targets	Effects	Reference
miR-33a, miR-33b	ABCA1, ABCG1, NPC1	Reduces efflux of cholesterol from cell	14
miR-148a	ABCA1	Reduces efflux of cholesterol from cell, increases the level of LDL	19
miR-26	ABCA1	Reduces efflux of cholesterol from cell	20
miR-758	ABCA1	Reduces efflux of cholesterol from cell	21
MeXis	DDX17	Promotes enhancement of *ABCA1* expression	22
uc.372	pri-miR-195, pri-miR-4668	Increases lipid accumulation	23
miR-130a	MEOX2	Stimulates SMC proliferation	27
miR-146a	KLF4	Stimulates SMC proliferation	28
miR-155	SOCS1	Promotes inflammation	145
miR-195	CDC42, CCND1, FGF1	Inhibits SMC proliferation, migration	146
miR-199a-5p	VEGFA, NOS3	Represses vascularization, represses nitric oxide synthesis	147
RNCR3	miR-185-5p	Prevents inflammation	29
H19	miR-199a-5p, PKD1, miR-29a, miR-29c	Promotes proliferation, inhibits apoptosis, stimulates vascularization	148

ABC, ATP-binding cassette; ABCA1, ABC subfamily A member 1; ABCG1, ABC subfamily G member 1; CCND1, cyclin D1; CDC42, cell division cycle 42; DDX17, DEAD-box helicase 17; FGF1, fibroblast growth factor 1; KLF4, Kruppel-like factor 4; LDL, low-density lipoprotein; MEOX2, mesenchyme homeobox 2; MeXis, macrophage-expressed LXR-induced sequence; miRNA, microRNA; ncRNA, non-coding RNA; NPC1, Niemann-Pick type C1; NOS3, nitric oxide synthase 3; PKD1, polycystic kidney disease 1; pri-miRNA, primary miRNA; RNCR3, retinal non-coding RNA3; SMC, smooth muscle cell; SOCS1, suppressor of cytokine signaling 1; VEGFA, vascular endothelial growth factor A.

changes in the phenotypes of myocytes.[135] In endothelial cells, the expression of several miRNAs depends on hemodynamic conditions, specifically the shear stress exerted by blood flow on the endothelial surface. These miRNAs, also called flow-sensitive miRNAs, are termed mechano-miRNAs.[137] For example, the mechano-miRNA miR-92a affects inflammatory signaling pathways. Overexpression of miR-92a led to a significant decrease in KLF4 and KLF2. Conversely, inhibition of miR-92a increases the levels of KLF4 and KLF2, both possessing anti-inflammatory properties.[138] Research in mice with deficient miR-92a showed a significant decrease in macrophage and T lymphocyte accumulation, leading to reduced inflammatory responses.[138,139]

Interestingly, ncRNAs are significantly involved in the control of T-cell function. For example, deletion of the components involved in the processing of miRNAs (DGCR8, Drosha, and Dicer) leads to a decrease in the proliferation of T cells.[140–142] Additionally, CD4+ T cells with miRNA deficiency exhibit increased Th1 differentiation and cytokine production after activation.[143] lncRNAs, such as IFNG-AS1, which is specific for Th1 cells, can be associated with a certain stage of T cells.[144]

In macrophages, miR-155 increases during atherosclerosis and promotes inflammation. In a study with two mouse groups: apolipoprotein E-deficient ($ApoE^{-/-}$) and $ApoE^{-/-}$ combined with miR-155 deficient ($miR155^{-/-}$), findings showed that $ApoE^{-/-}$ mice deficient in miR-155 exhibited reduced macrophage inflammation compared to those with normal miR-155 levels.[145]

The list of ncRNAs potentially involved in atherosclerosis pathogenesis is shown in Table 1.[14,19-23,27-29,145-148]

Therapy with ncRNAs

Therapeutic approaches involving ncRNA include the use of RNA interference effectors, such as siRNAs or miRNAs, as well as DNA short antisense oligonucleotides (ASOs) or miRNA sponges.

An advantage of ncRNAs-based drugs is that they can target various locations, unlike protein-based drugs, whose targets are mainly extracellular proteins.[149]

In contrast to miRNAs, which can silence many genes because they do not require full complementary interactions, siRNA mechanism of action is based on full complementarity with the target mRNA; hence siRNA affects the expression of a single gene.

The first clinically approved siRNA, patisiran in 2018, targeted transthyretin mRNA for hereditary transthyretin amyloidosis.[150]

Another siRNA-based drug, Oplasiran developed by Amgen, has shown promise in decreasing lipoprotein (a) levels by preventing translation of the apo(a) protein. Additionally, Oplasiran has demonstrated reductions in LDL cholesterol and apolipoprotein B levels, though the underlying mechanisms warrant further clinical exploration.[151]

Another siRNA drug is inclisiran (brand name Leqvio). It was approved for use in the EU in 2020 and in the USA in 2021.[152] Inclisiran decreases the serum levels of LDL by silencing PCSK9 mRNA in the liver. PCSK9 facilitates the degradation of LDL receptors; by reducing PCSK9 levels, the uptake of LDL by hepatocytes increases, consequently lowering the serum levels of LDL.[153,154]

ASOs are oligonucleotides that are complementary to specific RNAs including mRNAs, miRNAs, etc. ASOs were initially single-stranded DNA, termed antisense oligodeoxynucleotides.[155,156] Modern ASOs generally comprise DNA nucleotides and modified nucleotide regions. To protect these oligonucleotides from cellular nucleases and improve their efficacy, they are chemically modified. All three parts of the nucleotide can be modified: phosphorothioate, instead of a regular phosphate group, can have a 2′ hydroxyl group (ribose usage), which will be methylated or have a 2′-4′ bond. ASOs function through several mechanisms, including triggering RNase H to cleave DNA/RNA hybrids.[157]

The first approved ASO drug, fomivirsen (brand name: Vit-

ravene) in 1998, was used against human cytomegalovirus.[158]

It has been demonstrated that suppressing miR-33 by miR-33 ASOs, which are delivered to macrophages by pH low-insertion peptides, decreases lipid accumulation in vascular lesions in mice.[159]

Vupanorsen, also known as AKCEA-ANGPTL3-LRx, is an ASO that targets and inhibits the production of angiopoietin-like 3 (ANGPTL3) in the liver by binding to ANGPTL3 mRNA. The ANGPTL3 protein inhibits lipoprotein lipase and endothelial lipase, and inhibition of this protein has been shown to reduce triglyceride and non-high-density lipoprotein cholesterol levels.[160] However, these reductions were not sufficient. Additionally, vupanorsen was associated with elevated liver fat, aminotransferase and aspartate aminotransferase levels. Due to these discouraging outcomes, it was announced on January 31, 2022, that the development of vupanorsen was discontinued.[161]

miRNA sponges contain complementary sites to specific miRNAs. Moreover, they suppress the levels of target miRNAs that are complementary to them. It has been shown that lncRNAs and circRNAs can act as miRNA sponges.[162,163]

Different delivery systems, including dendrimers, exosomes, polymeric nanoparticles, PEG/PEI nanoparticles, and rod nanocrystals, have been utilized for delivering ncRNAs to corresponding targets.[164] Despite the potential of ncRNAs as therapeutic agents against atherosclerosis, challenges persist in their application. These challenges encompass the chemical instability of a particular ncRNA, extracellular and intracellular barriers for the delivery of ncRNAs, immunogenicity problems (pro-inflammatory cytokine production, NF-kB activation, RNA interference), and off-target effects.[164]

Conclusions

The study of ncRNAs has gained significant attention in the last decade due to their involvement in different processes, including the progression of various diseases. ncRNAs hold great promise as therapeutic targets for a wide range of diseases. Various ncRNAs crucial in regulating different cellular processes have been identified, and mutations or abnormal expression of ncRNAs can result in the development of diseases, including atherosclerosis. ncRNAs regulate different aspects of atherosclerosis, such as lipid metabolism, inflammation, and SMC proliferation. Numerous studies have demonstrated the therapeutic potential of targeting ncRNAs through various approaches. However, despite the promise, there are currently limited approved drugs against atherosclerosis based on ncRNAs. Many RNA therapeutics are either under development or have been discontinued. Drugs based on siRNAs and ASOs have been successfully used because they can target specific genes effectively. LncRNAs and circRNAs also play important roles in atherosclerosis development and present potential as treatment targets.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

Searched the literature and prepared draft (AA), figures preparation (AA, EG), reviewed the literature and improved the manuscript (AA, EB, EG, AG, DB), conceived, designed, and edited the manuscript and supervised the study (EB). All authors have read and approved the manuscript.

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