HHS Public Access

Author manuscript

Vascul Pharmacol. Author manuscript; available in PMC 2019 March 26.

Published in final edited form as:

Vascul Pharmacol. 2019 March ; 114: 64–75. doi:10.1016/j.vph.2018.03.001.

Non-coding RNA regulation of endothelial and macrophage functions during atherosclerosis

Binod Aryal and **Yajaira Suárez**

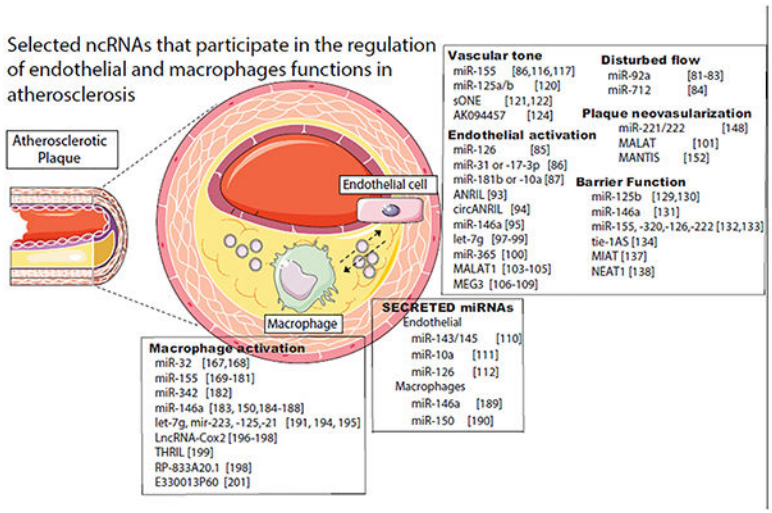
Program in Integrative Cell Signaling and Neurobiology of Metabolism, Department of Comparative Medicine, Department of Pathology and the Vascular Biology and Therapeutics Program, Yale University School of Medicine, New Haven, CT 06520, USA.

Abstract

The endothelial lining can be viewed as the first line of defense against risk factors of vascular disease. Endothelial dysfunction is regarded as an initial event for atherogenesis since defects in vascular integrity and homeostasis are responsible for lipid infiltration and recruitment of monocytes into the vessel wall. Monocytes-turned-macrophages, which possess astounding inflammatory plasticity, perpetuate chronic inflammation and growth of atherosclerotic plaques and, are therefore central for the pathogenesis of atherosclerosis. Because endothelial cells and macrophages are key players during atherogenesis, it is crucial to understand the regulation of their functions in order to develop strategies to intervene disease progression. Interestingly, non-coding RNAs (ncRNAs), broad class of RNA molecules that do not code for proteins, are capable of reprogramming multiple cell functions and, thus, can be used as target agents. MicroRNAs are small ncRNAs whose roles in the regulation of vascular functions and development of atherosclerosis through post-transcriptional manipulation of gene expression have been widely explored. Recently, other ncRNAs including long noncoding RNAs (lncRNAs) have also emerged as potential regulators of these functions. However, given their poor-genetic conservation between species, much work will be needed to elucidate the specific role of lncRNAs in vascular biology. This review aims to provide a comprehensive perspective of ncRNA, mostly focusing in lncRNAs, mechanism of action and relevance in regulating lipid metabolism-independent endothelial and macrophages functions in the pathogenesis of atherosclerosis.

Graphical abstract

Correspondence: Yajaira Suárez, PhD, Yale University School of Medicine, 10 Amistad Street, Amistad Research Building 301-B, New Haven, CT 06520. Phone (203) 737-8858. Fax (203) 737-2290. yajaira.suarez@yale.edu.



Keywords

Atherosclerosis; noncoding RNAs; miRNAs; lncRNAs; endothelial cells; macrophages

Introduction

Atherosclerosis underlines the leading cause of death in industrialized societies [1]. Atherosclerosis is a chronic disease characterized by lipid retention, vascular inflammation and accumulation of fibrous elements in the artery wall [2, 3]. The pathogenesis of the disease is directly linked to hypercholesterolemia, indeed increased plasma levels of circulating low density lipoproteins (LDLs) favors their entry into focal areas of the artery wall, bends and branch points, characterized by disturbed laminar flow[4, 5]. The retention of these ApoB containing lipoproteins in the subendothelial proteoglycan-rich layer of the arterial wall intima[6] favors a series of modifications that mimic pathogen-and /or damage-associated molecular patterns (DAMPs) that trigger a low-grade inflammatory response, this leads to the activation of the endothelial cells (ECs) which is mainly characterized by the induced expression of cell adhesion molecules and a number of chemokines that promote the recruitment of leukocytes into the vessel wall[3, 7, 8]. Influx of monocytes is usually considered an initial step in the development of the atherosclerotic plaque. At the lesion site, monocytes differentiate to macrophages where they encounter and internalize the retained and modified LDLs giving rise to macrophage foam cells and thus triggering the activation of chronic inflammatory pathway that is critical for the atherogenic process[9–11]. At this stage, macrophages contribute to the maintenance of the local inflammatory response by secreting proinflammatory cytokines and chemokines and producing reactive oxygen species (ROS). As such, these areas display an exacerbated endothelial dysfunction becoming more proinflammatory, prothrombotic and with impaired barrier function [12–14]. Additionally, macrophages populating the atherosclerotic plaques exhibit reduced ability to migrate and, to efferocytose dead cells and therefore to fail to resolve inflammation. Moreover, dying macrophages are responsible for necrotic core formation in progressing plaques[9, 15].

The pathogenesis of atherosclerosis is a result of various changes and interactions in and between multiple cell types in the artery wall which mainly include lipid deposition, inflammation, endothelial dysfunction, macrophage activation and smooth muscle cell (SMC) alteration. Throughout the last three decades, the cardiovascular community has made great progress in understanding the process of atherosclerosis, identifying the risk factors for atherosclerotic vascular disease, and developing, testing, and implementing effective therapies such as statins[16, 17]. However, atherosclerosis remains as one of the largest deadly diseases, as such new cellular and molecular mechanisms are urgent to provide novel therapeutic targets. Relatively recent work has shown that microRNAs (miRNAs), a class of short non-coding RNAs (ncRNAs) play an important role in the pathogenesis of atherosclerosis [18–25]. Interestingly, recent advances in the high-throughput RNA sequencing has greatly improved our knowledge of the mammalian transcriptome [26]. As such, novel classes of gene modulators known as long ncRNAs (lncRNAs) have been identified and only recently we have started to appreciate the diverse biological functions of these lncRNAs.

While several cell types are clearly involved in the pathogenesis of atherosclerotic plaques, endothelial cells and macrophages play a key role in the pathogenesis of atherosclerosis and makes them an attractive target for therapy development. As such, the major focus of this review will be to highlight the contribution of ncRNAs in the regulation of EC and macrophage functions during atherosclerosis. Nevertheless, ncRNAs are also critical in all other aspects of cardiovascular biology. For instance, the vascular cell–enriched cytoplasmic lncRNA, SENCR, has been described to stabilize the SMC contractile phenotype [27]. Another lncRNA human vascular SMC-selective and serum response factor/CArG-dependent lncRNA, MYOSLID, has been described as a modulator of vascular SMC (VSMC) differentiation program, likely through feed-forward actions of both MKL1 and transforming growth factor-β/SMAD pathways [28]. Interestingly, lnc-Ang362, an Angiotensin II–regulated lncRNA, is responsible for the production of microRNAs miR-221 and −222, which are implicated in the regulation of VSMC proliferation [29]. Additionally, lncRNAs have also been involved in regulating lipid metabolism. For example, DYNLRB-2 and RP5–833A20.1 have been described to participate cholesterol homeostasis and vascular inflammation [30, 31]. Similarly, AT102202 is involved in the biosynthesis of cholesterol acting on hydroxy-methyl glutaryl CoA reductase (HMGCR) [32], Moreover, APOA1-AS regulates the formation of high density lipoproteins (HDL) through the inhibition of the expression of APOA1[33]. Recently identified lncRNA LeXis (liver-expressed LXR-induced sequence) that lies in close proximity to the canonical LXR target gene Abca1 in mice, is markedly induced in response to LXR agonists and high fat diet [34]. Hepatic LeXis overexpression inhibits the expression of cholesterol biosynthetic genes and reduces cholesterol biosynthesis and circulating cholesterol. Altogether, these reports demonstrate that lncRNAs are capable of regulating physiological processes including VSMC functions and cholesterol metabolism which are closely associated with the pathogenesis of cardiovascular diseases including atherosclerosis [35–39].

Since there is ample bibliography describing the role of miRNAs in atherosclerosis [18–23, 40], in the present review, we summarize the role of ncRNAs, mostly focusing on the recent advances on lncRNAs while we will only highlight the action of most relevant miRNAs, in

regulating endothelial function and dysfunction as well as macrophage inflammatory responses linked to atherosclerosis and discuss their potential therapeutic applicability.

1. General overview to ncRNA biology.

ncRNAs are RNA molecules that are not translated into protein products. Only 2% of the entire human genome represents protein coding genes containing 20,000 genes and the vast portion of the genome is comprised of ncRNAs [41]. They accomplish a remarkable variety of biological functions [42]. Different classes of ncRNAs participate in different cellular processes; for example, gene expression regulation (miRNAs, piRNAs, lncRNAs), RNA maturation (snRNAs, snoRNAs) and protein synthesis (rRNAs, tRNAs)[42].

The rRNA, tRNA, snRNA, and snoRNA were among the first ncRNAs to be identified and characterized to have a role in mRNA translation and RNA processing events such as nucleotide modification and splicing[41, 42]. Later the discovery of the first two miRNAs - *lin-4* and *let-7* [43, 44] opened up a new era of novel regulatory functions of ncRNAs thas was followed by identification of lncRNAs[45, 46]. Whereas it is well accepted that miRNAs participate in the regulation of gene expression post-transcriptionally, we are only beginning to understand how lncRNAs work, mainly because of their low sequence conservation, weak expression and variable functions. However, their most established functions include regulation of both post-transcriptional and transcriptional gene regulation, predominantly through RNA-guided (dependent) mechanisms[42, 45, 46].

The current classification of ncRNAs is based primarily on transcript size as small ncRNAs (<200 nucleotides) and lncRNAs (>200 nucleotides). A notable family in the class of ncRNAs is the evolutionary conserved family of miRNAs, which are 20–25 nucleotides in length that mediate post-transcriptional silencing of specific target genes[47, 48]. They generally repress target mRNAs through an antisense mechanism. In animals, miRNAs typically target sequences in the transcript 3′ untranslated regions (3′UTR) that are only partially complementary to the miRNA, causing a repression of the protein synthesis[49, 50]. miRNAs are generally produced as RNA polymerase II–transcribed primary transcript, namely pri-miRNA. The biogenesis of primiRNA transcript occurs either through the canonical pathway involving Drosha and Dicer or through various non-canonical pathways that are Drosha and even Dicer-independent[51–54].

As introduced above, the emergence of high-throughput sequencing technologies coupled with mass spectrometry and bioinformatics techniques has led to the discovery of lncRNAs and hence expanded the field of ncRNAs dramatically. lncRNAs range in size from 200 bp to a hundred kb. To date, lncRNAs are broadly classified on the basis of their genomic localization, modes of action, and function[55]. Intronic lncRNAs originate from the introns of protein-coding genes; intergenic lncRNAs (lincRNA) originate from the region between two protein-coding genes; enhancer lncRNAs (elncRNA) originate from the promoter enhancer regions; bidirectional lncRNAs are localized within the vicinity of a coding transcript of the opposite strand; sense-overlapping lncRNAs overlap with one or more introns and exons of different protein-coding genes in the sense strand of the DNA; antisense transcripts originate from the anti- sense strands of the DNA, and they may or may not be

complementary to protein coding sequences in the sense-strand[42, 45, 46]. lncRNAs are transcribed by RNA polymerase II, and most of them undergo alternative splicing, 5′-capping, and polyadenylation. They could also serve as a template for transcription of small ncRNAs [46, 55]. Most, transcribed mature lncRNAs are thought to have low protein coding potential, because they lack known protein coding domains or open reading frames, display random codon usage, and have no significant bias toward silent nucleotide substitutions[55]. However, some lncRNAs might indeed contain small open reading frames and encode functional peptides that have been shown to exhibit interesting biological functions [56, 57].

Overall, lncRNAs are under less selective pressure and, therefore, show less sequence conservation [55, 58], that precludes comprehensive homology-based surveys and makes them nearly impossible to align. The rapid development of sequencing technology has made it feasible to obtain high coverage transcriptome data sets for a wide variety of cell and tissue types. As a consequence, comparative transcriptomics approaches become feasible [59]. Indeed, a recent study demonstrated that 30%–40% of nearly 2000 human lncRNAs show conserved expression in rodents or ungulates[60], based on direct comparison of transcriptome sequencing data for six mammalian species. A maximum likelihood approach to estimate the number of lncRNAs from publicly available data resulted in an estimate of 40,000–50,000 lncRNAs of which ~60%–70% are conserved between man and mouse [61]. It appears likely that thousands of transcriptome evolutionarily conserved functional roles of lincRNAs remain to be characterized.

lncRNAs might function either in *cis* or *trans* to modulate the expression of their target genes by using an array of different molecular mechanisms, such as serving as a scaffold for recruitment of chromatin modifiers or transcription factors, or as decoys for protein sequestration and miRNA sponges to activate or silence genes [45, 58, 62, 63]. The competing endogenous RNA hypothesis is controversial, due to the low level of expression of the lncRNA relative to the molecule to be sponged out. Thus, the physiological relevance in an *in vivo* setting may be difficult to be confirmed [64]. lncRNAs have also been reported to influence mRNA splicing, translation, and turnover[65–67].

Another class of lncRNAs that are emerging as a novel class of endogenous ncRNAs are circular RNAs (circRNA) that form covalently closed continuous loops instead of traditional linear forms[68]. CircRNAs are conserved across species and are found to be associated with a variety of important biological processes and human diseases. CircRNAs appear to function as miRNA sponges and are involved in the regulation of mRNA splicing, transcription, and gene expression [68, 69]. circRNAs are classified as exonic, intronic, and retained-intronic circRNAs. They may be derived from exons, introns, untranslated regions, antisense transcripts, and intergenic regions. CircRNA biogenesis is the result of back splicing [70]. Because of their unique structure, circRNAs are resistant to nucleases and are stable with a relatively long half-life [70, 71]. They may exist in tissues, serum, and urine, indicating their potential as novel biomarkers for human diseases including atherosclerosis.

2. Endothelial ncRNAs and Atherosclerosis

The endothelial lining can be viewed as the first line of defense between risk factors and vascular disease [13]. Endothelial dysfunction is deemed of particular importance as it is a necessary and initiating occurrence for atherogenesis to proceed. The natural predisposition of the disease has its basis in the vulnerability of the endothelium in sites of turbulent arterial flow in bifurcated arteries [4, 5]. The damaged endothelial layer at arterial branches, characterized by decreased endothelial Nitric Oxide Synthase (eNOS) expression [72–74] and increased nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity is more prone to infiltration of low-density lipoproteins (LDLs), leukocyte adhesion and inflammation[8, 14, 75]. The infiltration of LDL causes the recruitment of immune cells, mostly monocytes, to the sites of the lesions and is accompanied by secretion of inflammatory cytokines and recruitment of other immune cells into the intima which further promotes activation of ECs[76].

2.1 Shear stress, disturbed flow and ncRNAs.

As discussed above, most atherosclerotic lesions occur at the site of arterial bifurcation, where the flow exhibits turbulent dynamics. A considerable amount of the genes regulated in physiological laminar shear stress are modulated by the transcription factor Krüppel-like factor 2 and 4 (KLF2 and KLF4), which are induced by the same stimuli (e.g., flow and statins) and that both regulate similar key endothelial targets (e.g., *Nos3* and *Thbd*) to confer antiinflammatory and antithrombotic effects to the vessel wall [4, 77–79]. Additionally, hemodynamics itself has a profound effect on miRNA expression, and differentially regulated miRNAs contribute to the regulation of shear stress-mediated transcriptional programs[19]. These flow-sensitive microRNAs, known as “mechano-miRs”, modulate endothelial gene expression, and can regulate endothelial dysfunction and atherosclerosis. MiRNAs such as, miR-10a, −19a, −23b, −17~92, −21, −663, −92a, −143/145, −101, −126, −712, −205, and −155, have been identified as mechano-miRs[80]. Many of these miRNAs were initially identified as flow-sensitive *in vitro* and were later found to play a critical role in endothelial function and/or atherosclerosis *in vivo* through either gain-of-function or loss-of-function approaches. The key signaling pathways that are targeted by these mechano-miRs include the endothelial cell cycle, inflammation, apoptosis, and nitric oxide signaling [80]. miR-92a is upregulated in atherogenic sites in LDL receptor-deficient mice ($Lldr^{-/-}$) fed a high fat diet and in swine inner aortic arch endothelium[81, 82]. miR-92a directly downregulates the anti-inflammatory gene suppressor of cytokine signaling 5 (SOCS5), and it also affects the expression of the transcription factors KLF2- and KLF4, thereby decreasing the activation of NF-kB and the expression of cell adhesion molecules, and stimulating the production of NO in arteries[81–83]. Interestingly, inhibition of miR-92a in a murine model of atherosclerosis blunts inflammatory cytokine secretion in aortas, decreases leukocyte recruitment and adhesion and prevents endothelial dysfunction, overall decreasing atherosclerotic lesions[82]. miR-712 is another miRNA stimulated in conditions of disturbed flow *in vitro* and *in vivo* in murine endothelium. This miRNA inhibits the expression of tissue inhibitor of metalloproteinase 3 (TIMP3), therefore activating matrix metalloproteinases (MMP2 and MMP9) and a disintegrin and metalloproteases (especially ADAM10/17) [84]. The overall effect of disturbed flow-induced expression miR-712 is pro-

atherogenic, as it promotes endothelial inflammation and permeability. Consistently, *in vivo* silencing of miR-712 prevents atherosclerotic lesions in murine models of atherosclerosis[84].

2.2 Endothelial inflammatory activation and ncRNAs

Multiple pathophysiological factors contribute the endothelial activation such altered shear stress, as discussed above, physical damage, hypoxia and cytokine inflammatory stimulation. In response to inflammatory stimuli mainly mediated by NF-kB activation, the vascular endothelium expressed adhesion molecules including vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and intercellular adhesion molecule 1 (ICAM-1) that mediate leukocyte recruitment from the blood into extravascular tissues [8, 76]. Additionally, low-density lipoproteins are oxidized (ox-LDL), contributing to sustain an inflammatory response and to induce apoptosis in ECs. Both inflammatory cytokines and ox-LDL contribute to the regulation of ncRNAs, which in turn regulate cellular responses to these insults. miR-126, an endothelial-specific miRNA, was the first miRNA described to play a role in vascular inflammation through the negatively regulation of VCAM-1 in ECs[85]. Later, miR-17–3p and miR-31 were described to provide a negative feedback control of inflammation in response to tumor necrosis α (TNFα) via the downregulation of ICAM-1 and E-selectin expression, respectively[86]. miR-181b and miR-10a affect EC activation by negatively modulating NF-kB signaling, therefore promoting an anti-inflammatory phenotype both *in vitro* and *in vivo*. The expression of miR-181b has been shown to be regulated by is regulated by TNFα. This miRNA controls endothelial cell activation by targeting importing-α3, a protein required for nuclear translocation of NF-kB. By indirectly targeting, miR-181b inhibits TNFα-induced expression of adhesion molecules and antagonizes the binding of leukocytes to ECs[87]. On the other hand, miR-10a contributes to the regulation of proinflammatory endothelial phenotypes in athero-susceptible regions *in vivo* by targeting mitogen-activated 3 kinase 7 (MAP3K7) and β-transducin repeat containing gene (βTRC), which are main regulators of IkBα degradation[88].

Several studies in the past decade identified chromosome arm 9p21 locus as a strong genetic risk factor for coronary artery disease [89, 90]. This region contains antisense ncRNA in the INK4 locus (ANRIL, also known as CDKN2B antisense RNA 1) lncRNA which is transcribed in an antisense direction with respect to the primary INK4 and ARF transcripts. SNPs in 9pq21 locus risk increase the expression of ANRIL in both atherosclerotic plaques and circulating blood. Moreover, ANRIL expression is closely associated with severity of atherosclerosis. ANRIL binds to and recruits polycomb repression complexes PRC-1 and PRC-2 to the INK4 locus, leading to the transcriptional repression of p15 and p16, two of the genes encoded by the INK4 locus [91, 92]. In human ECs, ANRIL expression is induced by TNFα. In turn, ANRIL also mediates inflammatory responses by interacting with transcription factor Yin Yang1 (YY1) and regulating the expression of cytokines IL-6 and IL-8 suggesting its pro-inflammatory role [93]. In addition to its linear form, a recent report shows that circularization of ANRIL (circANRIL) confers atheroprotection by controlling ribosomal RNA (rRNA) maturation and modulating pathways of atherogenesis. CircANRIL impairs ribosomal biogenesis in VSMCs and macrophages resulting in proliferation

inhibition and apoptosis in these cells. In addition, cANRIL expression could prevent coronary AS by reducing vascular EC apoptosis and inflammatory factor expression [94].

In addition to TNFα, interleukin 1β (IL1 β) induce the expression of miR-146a and miR-146b in ECs[95]. miR-146a/b upregulation favors the downregulation of adhesion molecules and pro-inflammatory genes, by suppressing NF-κB and MAP kinase/early growth response (EGR) pathways by direct targeting of TNF receptor associated factor 6 (TRAF6) and IRAK1[95]. In addition to its direct effect on inflammatory pathways, miR-146a targets human antigen R (HuR) and, loss of this protein decreases cell adhesion molecules and inhibits endothelial activation by releasing the suppression on eNOS, probably by stabilization of the transcription factor KLF2[95].

ECs can also be activated by oxidized lipoproteins. Lipid deposition in the sub-intimal layer does not only affect foam cell formation of macrophages and inflammation, but it has been shown to induce pro-inflammatory activation and apoptosis in ECs [96]. Ox-LDL induces the downregulation of let-7g in ECs through the binding of OCT-1 to the let-7g promoter [97]. Interestingly, let-7g, as well as let-7a and let-7b [98], target the lectin-like low-density lipoprotein receptor 1 (LOX-1), which is the receptor for ox-LDL in ECs. While overexpression of let-7a and let-7b decreases the production of ROS and reduce ox-LDL-mediated EC apoptosis and NF-κB activation, let-7g indirectly decreases senescence by upregulating SIRT1 [99]. Administration of let-7g in ox-LDL treatment, results in a downregulation of LOX-1 and in decreased EC proliferation and increased migration [97]. These data suggest that the members of the let-7 family are protective against endothelial dysfunction. On the other hand, one of the most upregulated miRNAs in ECs treated with ox-LDL is miR-365[100]. It is well known that ox-LDL increases inflammation and apoptosis in ECs through the downregulation of the anti-apoptotic gene B-cell CLL-lymphoma 2 (Bcl2). Interestingly, miR-365 targets Bcl2, and, consistently, delivery of anti-miR-365 rescues the ox-LDL-mediated apoptosis.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is an lncRNA highly expressed in different types of ECs and is further induced by stressful conditions such as hypoxia, hyperglycemia and oxidative stress [101]. MALAT1 was first described to be associated with metastasis of lung tumors and via interaction with polycomb 2 (CBX4) regulate histone modifications to control cellular proliferation [102]. MALAT1 depletion ameliorates diabetic retinopathy and endothelial dysfunction in rats and mice as shown by pericyte loss, microvascular leakage and retinal inflammation. Liu et al showed that silencing of MALAT1 in diabetic rats significantly reduces the levels of diabetic retinopathy induced ICAM-1, vascular endothelial growth factor (VEGF) and TNFα in retinal cells and promotes their viability [103]. Another study reported that MALAT1 regulates glucose-induced upregulation of inflammatory mediators interleukin-6 (IL-6) and TNFα through activation of inflammatory ligand serum amyloid antigen 3 SAA3 in ECs [104]. Together, these studies indicate a pro-inflammatory function of MALAT1 and suggest that it might contribute to atherogenesis. In contrast, Tang et al reported an anti-inflammatory role for MALAT1 whereby it protects the endothelium against ox-LDL induced dysfunction by sponging miR-22–3p and derepressing target genes CCR2 and AKT [105].

Unlike MALAT1, maternally expressed gene 3 (MEG3) is a lncRNA downregulated under diabetic stress. However, it is induced under hypoxia [106]. MEG3 is an important tumor suppressor in several types of human cancers that regulates gene expression through transcriptional regulation and microRNA sponging [107]. Depletion of MEG3 in diabetic mice results in increased vascular proliferation, vascular leakage and inflammation as assessed by levels of inflammation markers VEGF, TNFα, IL-1, IL-6 and CCL2. The EC dysfunction in the absence of MEG3 seems to be mediated through PI3K/Akt signaling [108]. Follow up studies show that suppression of EC proliferation and angiogenesis by MEG3 is mediated through sponging miR-9[109].

Interestingly, it has been recently shown that ECs secrete extracellular vesicles [110]. They may have potent anti-inflammatory activities that can be attributable in part to the transfer of miR-10a to monocytes/macrophages and suppression of several components of the NF-κB pathway, including Interleukin-1 Receptor-Associated Kinase 4 (IRAK4), β-TRC, and MAP3K7[111].

Apoptotic bodies produced by ECs during atherosclerosis contain miRNA-126. By targeting the regulator of G protein signaling 16 (Rgs16), an inhibitor of G protein-coupled receptor signaling (GPCR), miR-126 increases the expression of chemokine receptor type 4 (CXCR4), which in turn increases chemokine receptor type 12 (CXCL12) that counteracts apoptosis and recruits progenitor cells in mice with atherosclerosis [112].

2.3 Vascular tone and ncRNAs

Hypercholesterolemia has been associated with an increase in vascular tone, mainly because of an impairment of endothelium-dependent relaxation. This endothelial dysfunction occurs before any definite atherosclerotic lesion is demonstrated. In both animal models and humans, the correction of hypercholesterolemia has been associated with hemodynamic improvement. ECs control the secretion of two potent short-lived mediators that influence vascular hemodynamincs in the physiological state and therefore contribute to the regulation of blood pressure and blood flow by releasing vasodilators, such as NO and prostacyclin or prostagladin I2 (PGI2), as well as vasoconstrictors, including endothelin1 (ET-1) and platelet activating factor (PAF)[113]. The specific blood-mediators released by ECs vary depending on the vascular bed, but the principal vasorelaxant is NO [114].

Regarding the role of miRNAs in the regulation of the vascular tone, initial studies demonstrated that knockdown of Dicer, the enzyme necessary for miRNA maturation, increases eNOS expression in ECs[115]. Several reports provide evidence that miR-155 downregulate eNOS expression through decreasing eNOS mRNA stability by binding to its 3-UTR[116]. Interestingly, TNF increases miR-155 expression in ECs[86] and knockdown of miR-155 prevents cytokine-induced downregulation of eNOS expression, increases NO production, and improves endothelium-dependent vascular relaxation[117]. These findings indicate that miR-155 is an essential regulator of eNOS expression and endothelium-dependent vasorelaxation.

In addition to producing the potent vasodilator NO, ECs also synthesize ET-1, one of the most potent and long-lasting vasoconstrictive peptides[118]. In non-stimulated physiological

conditions ET-1 mRNA levels are very low, while its expression and secretion from ECs is stimulated by hypoxia and shear stress. Upon release, ET-1 binds to ET-A receptor on vascular SMCs, resulting in an increase in calcium concentration and vascular SMC tone. NO controls the duration of these effects by accelerating the restoration of intracellular basal calcium levels. Therefore, in states of EC dysfunction where NO levels are reduced, ET-1 promotes vasoconstriction[119]. miR-125a/b is upregulated in response to ox-LDL[120] and its involved in the regulation ET-1 expression. However, it is not known whether this effect is indirect or through direct targeting of the ET-1 3'UTR. Interestingly, aortas in stroke-prone spontaneously hypertensive rats compared to normotensive rats have an inverse correlation between the levels of miR-125a/b and the precursor protein ET-1 (preproET-1) [120].

In addition to miRNAs, handful of lncRNAs are associated with regulation of vascular tone. An antisense lncRNA sONE derived from a transcription unit on the opposite strand from which eNOS mRNA is transcribed is expressed reciprocally compared to eNOS. Unlike eNOS, sONE expression is low in ECs and high in VSMCs. While the depletion of sONE in VSMCs led to decrease in levels of eNOS, its overexpression in ECs blunted eNOS expression through post transcriptional regulation[121]. Interestingly, hypoxia induces the expression and enrichment of otherwise nucleus-localized sONE in cytoplasm of ECs through transcript stabilization and negatively regulates the expression of eNOS[122]. Whether the regulation of eNOS and NO levels by sONE in ECs contributes to atherogenesis has not been investigated. In addition to eNOS, NO is also generated by inducible nitric oxide synthase (iNOS) which is highly expressed in VSMCs and macrophages in atherosclerotic plaques[123]. Yang et al showed that notoginsenoside R1 stimulates phosphorylation of iNOS and NO production and reduces blood pressure in spontaneously hypertensive rat model through the induction of lncRNA AK094457 expression[124]. Through knockdown studies they found that depletion of lncRNA AK094457 results in increase of iNOS expression and NO production in rat vascular ECs. Altogether these studies suggest that lncRNA may partake in atherosclerosis process through influencing the expression of eNOS and iNOS as well as endothelial functions.

2.4 Control of barrier function by endothelial ncRNAs

ECs form a monolayer, within the blood vessel, through which the cells are linked to each other by different types of adhesive structures or cell-cell junctions (i.e. tight junctions, adherens junctions and gap junctions). The EC monolayer forms a selective barrier for the transport of molecules between blood and tissue[125, 126]. Changes in endothelial permeability are associated with redistribution of surface cadherins or occludins, stabilization of focal adhesion bonds and the progressive activation of matrix metalloproteases[127]. Loss of barrier function in pathophysiological situations can lead to extracellular edema. Different stimuli, such as histamine and thrombin, induce a rapid and short-lived increase in vascular permeability while others, like TNF or VEGF, induced a more sustained response. Of interest, most of these agonists are produced in situations of acute or chronic inflammation[128].

MiR-125b expression has been shown to be transiently induced in ECs stimulated with VEGF. This miRNA inhibited the translation of vascular endothelial (VE)-cadherin mRNA[129]. Because miR-125b induction in ECs is transient after VEGF stimulation, prolonged overexpression of miR-125b could result in blood vessel regression due to loss of normal barrier function[129, 130]}. More recently, miR147b have been described to regulate endothelial barrier function by targeting ADAM15 expression[131]. Additionally, miR-155, miR-320, miR-126 and miR-222 have been shown to regulate adherens junction disassembly, cell migration, and cell morphology, which contribute to changes in vascular permeability[132, 133].

Tie-1AS lncRNA, a natural antisense transcript for tie-1 gene, has been described to bind tie-1 mRNA and regulate the expression of tie-1, leading to specific defects in contact junctions of endothelial cells[134]. Higher levels of tie-1AS lncRNA as well as imbalance between tie-1 and tie-1AS lncRNA are suggested to associate with vascular anomaly diseases. However, despite clear possibilities, role of tie-1AS in atherosclerosis has not been explored and needs to be further investigated.

Myocardial-infarction-associated transcript (MIAT) is one of the earliest lncRNAs identified as a risk factor for cardiovascular disease. Particularly, through a large-scale case–control association study, it was shown that altered expression of MIAT by one particular SNP confers susceptibility to myocardial infarction[135, 136]. Biao Yan et al demonstrated that MIAT knockdown ameliorates diabetes mellitus–induced retinal microvascular dysfunction in vivo, and inhibits endothelial cell proliferation, migration, and tube formation in vitro[137]. This study shows that depletion of MIAT reduces vascular leakage in diabetic rats and alleviates vascular inflammation. In particular, expression of ICAM-1, TNFα and VEGF were reduced in the retinal cells from diabetic rats injected with shRNA against MIAT. Mechanistically, MIAT acts as a competing endogenous RNA to sponge miR-150–5p and alleviate the expression of miR-150–5p targets, in particular, VEGF and exert its vascular effects[137].

A recent study has reported a role for lncRNA NEAT1 in permeability in glioma endothelial cells where it is highly expressed. NEAT1 binds to miR-181d-5p and inhibit its targeting activity. Specifically, depletion of NEAT1 in ECs results in downregulation of miR-181d-5p target SOX5 and its subsequent tight junction protein targets ZO-1, occludin and claudin-5 and increase permeability[138]. This observation suggests the possibility that NEAT1 might regulate vascular permeability in the context of atherosclerosis. Altogether, ncRNAs are important regulators of vascular permeability. However, further investigation is necessary to determine the significance of ncRNAs, particularly lncRNAs, mediated regulation in vascular homeostasis in the progression of atherosclerosis.

2.4 Control of neovascularization during atherosclerosis by ncRNAs

During adulthood, the quiescent endothelium has a low turnover rate and proliferates only following angiogenic activation[139]. The loss of quiescence and barrier functions are common features of atherosclerosis[140]. As introduced above, one factor responsible for loss of quiescence in ECs is inflammation. In atherosclerosis, inflammation and angiogenesis are intertwined. Chronic inflammatory activation of ECs of large blood vessels

induces increased proliferation of vasa vasorum, positively supporting lesion progression[141]. Advanced human atherosclerotic plaques are characterized by neovascularization. In the atherosclerotic intima layer neovascularization proceeds with irregular but ubiquitous distribution of blood vessels, which are immature and leaky therefore contributing to disease progression. As the intima thickens, the hypoxic areas of the plaque further promote angiogenesis[142]. Newly formed blood vessels deliver more inflammatory leukocytes to the plaque, which in turn produce cytokines, chemokines and growth factors that positively support cytokine-induced angiogenesis programs in a positive feedback fashion[143]. MiRNAs do not only control the angiogenic response, but their expression may also be regulated by pro-angiogenic factors VEGF to promote the angiogenic response of ECs[144–147].

IL-3 and bFGF down-regulate the expression of miR-221–222. Interestingly, STAT5, transcription factor that regulate the expression of genes involved in proliferation and migration, was identified as a target of miR-222. The upregulation of STAT5A mediated by IL-3-bFGF-induces down-regulation of miR-222 controls proliferation and migration in ECs and therefore facilitates intraplaque neovascularization during atherosclerosis. Moreover, diminished expression of miR-222 in advanced lesions correlates with an increased proliferation rate of ECs lining vessels[148].

Hypoxia also regulates miRNAs[149], which in turn modulate the angiogenic properties of ECs. The classical hypoxamiR miR-210 is induced in a HIF-1a dependent manner is upregulated in atherosclerotic plaques[150]. Intriguingly, miR-424, which is also upregulated in hypoxic ECs, downregulates Cullin2, a protein responsible for HIF-1a and HIF-2a destabilization resulting in an increase proliferation and migratory capabilities in ECs[151]. Overall miRNAs that are induced in hypoxia contribute to the activation of angiogenic properties of ECs and promoting angiogenesis in atheromas[149].

As introduced before, MALAT1 is a LncRNA significantly increased by hypoxia and reported to control phenotypic switch in endothelial cells. Silencing of MALAT1 induces a promigratory response and increases basal sprouting and migration, whereas proliferation of endothelial cells is inhibited. In vivo studies show that genetic ablation of MALAT1 inhibit proliferation of endothelial cells and reduced neonatal retina vascularization. Gene expression profiling followed by confirmatory quantitative reverse transcriptase-polymerase chain reaction demonstrated that silencing of MALAT1 impaired the expression of various cell cycle regulators[101].

MANTIS is a recently described lncRNA which is highly expressed in the carotid arteries of monkeys subjected to atherosclerosis regression diet or humans with glioblastoma whereas downregulated in patients with idiopathic pulmonary hypertension. Deletion of MANTIS inhibited angiogenic sprouting and alignment of endothelial cells in response to shear stress. Mechanistically, MANTIS interacts with Brg1, the catalytic subunit of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex and regulates SOX18, SMAD6, and COUP-TFII, which are all implicated in angiogenesis modulation[152].

3. ncRNAs in inflammatory activation of macrophages

The mechanisms and consequences of macrophage-mediated inflammation comprise a central topic in atherosclerosis research[10, 11, 153]. Macrophages in atherosclerotic lesions actively participate in modified lipoproteins ingestion and accumulation giving rise to lipid-rich foam cell which is a hallmark feature of atherosclerosis and leads to lesion expansion[154]. Macrophage activation results in the excretion of proinflammatory and cytotoxic substances, including peroxynitrite, an early inducer of atherosclerosis through the endoplasmic reticulum (ER) stress pathway[155]. Dying macrophages are responsible for necrotic core formation in progressing plaques[156]. Cytokine release from macrophages augments the inflammatory response and increases lesion size. Cytotoxic substances, including proinflammatory cytokines, chemokines and ROS released by the macrophage results in cell death of lesion-resident endothelial and smooth muscle cells, thereby disrupting vessel structure. Macrophages populating the atherosclerotic plaque have a decreased ability to migrate, which leads to failure in inflammation resolution and to further progression of the lesion into complicated atherosclerotic plaque[157]. ncRNAs, and in particular miRNAs, can impact each of these key macrophage processes to influence the progression of atherosclerosis including regulating monocyte/macrophage recruitment to growing lesions, cholesterol efflux and lipid storage, as well as modulating macrophage plasticity and their ability to polarize towards pro- or anti-inflammatory phenotypes[10]. Here we summarize the involvement of ncRNAs in macrophage functions that do not involve the regulation of macrophage cholesterol homeostasis since it is the focus of another review in these series.

miR-33 has been reported to be involved in a number of biological processes and regulate inflammation and lipid accumulation in macrophages[158–166]. Ouimet et al. showed that miR-33 depletion from macrophages promoted induction of M2 polarization-associated gene profile. Moreover, miR-33 associated M2 polarization was required for miR-33 targeting of the energy sensor AMPK but not cholesterol efflux. Overall, miR33 antagonism was atheroprotective through the induction of M2 macrophages and Treg induction[167]. In contrast, a recent report by Price et al failed to see any real differences in macrophage polarization in miR-33 deficient macrophages. The differences in these studies might have resulted from different approaches used to deplete macrophages- the former used inhibitors of miR-33 while the latter used genetically depleted miR-33 deficient macrophages. Although the classical markers were not changed, RNA sequencing data showed that there was an overall decrease in inflammatory pathways including NFκB and TLR4 in *in vivo* foam cells (macrophages from mice fed a western diet) from miR-33 deficient mice, indicating a pro-inflammatory role of miR-33[168].

miR-155 is one of the most prominent genes that has been implicated in inflammatory activation of macrophages and atherosclerosis progression although there is no consensus on its actual role. It is induced by inflammatory stimuli, including mild-oxLDL, IFNγ or activation of toll-like receptor (TLR) signaling. In response, miR-155 represses suppressor of cytokine signaling 1 (SOCS-1) and B-cell lymphoma 6 (Bcl-6) and promotes pro-inflammatory cytokines CCL2, IL-5, NOS2 and TNFα to mediate macrophage inflammation[169–173]. miR-155/SOCS1 axis mediated classical activation of macrophages

have been reported in the context of host defense against bacterial pathogens and adaptive immune responses in periphery during pulmonary infection and in the central nervous system during multiple sclerosis[174, 175]. In addition, miR-155 promotes macrophages activation by targeting Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1), a negative regulator of TLR pathways[176]. Conversely, miR-155 suppresses anti-inflammatory alternative activation of macrophages by targeting CCAAT/enhancer-binding protein (C/EBP), a hallmark of alternative activation of macrophages, and by targeting IL-13Ra1 and resulting in diminished activation of STAT6 in human macrophages[177, 178]. Importantly, miR-155 is highly expressed in atherosclerotic plaques in mouse and human indicating its promise as a therapeutic potential[179]. However, in contrast to aforementioned studies, miR-155 has been reported to reduce inflammation in macrophages and atherogenesis by targeting calcium-regulated heat stable protein 1 (CARHSP1), which regulates the stability of TNFα mRNA[180]. Supporting this anti-atherogenic role of miR-155, hematopoietic miR-155 deficiency enhanced atherosclerosis and decreases plaque stability in $Ldlr^{-/-}$ mice by increasing CD11b+Ly6Chi monocyte inflammatory subset[181]. On the contrary, whole body knockout of miR-155 and bone marrow transplantation of $miR\text{-}155^{-/-}$ cells into $Apoe^{-/-}$ decreased lesional macrophages and reduced atherosclerosis deficient indicating a pro-atherogenic role of miR-155[170, 171]. Importantly, the ability of macrophage miR-155 in atherosclerosis may greatly depend on the stage of atherosclerotic development (i.e. early versus advanced) when the expression of key target genes is stage-specific[179].

Similar to miR-155, miR-342–5p is also highly expressed in lesional macrophages. Interestingly, miR-342–5p enhances the inflammatory stimulation of macrophages by suppressing the Akt-1 mediated expression of miR-155 and induction of inflammatory mediators such as nitric oxide synthase 2 (Nos2) and IL6[182]. Supporting these observations, systemic inhibition of miR-342–5p decreased atherosclerosis in the aorta of $Apoe^{-/-}$ mice.

miR-146a was first identified as a negative feedback regulator in macrophage activation by directly targeting the downstream signaling molecules of TLRs signaling, such as IRAK1 and TRAF6[183]. It is highly upregulated in human atherosclerotic plaques[150]. Apoe induces miR-146 expression in monocytes and macrophages via increasing expression of transcription factor purine-rich PU-box-binding protein 1. In turn, miR-146 represses NF-$_k$B signaling cascades by targeting IRAK1 and TRAF6, reduces inflammatory activation of macrophages and consequently reduces atherosclerosis[184]. Several other studies have shown that miR-146 inhibits inflammatory M1 polarization by targeting IRAK2, STAT1 and IRF5[185–187]. Interestingly, a recent study showed that despite an increase in circulating pro-inflammatory cytokines, mice deficient in miR-146a in the bone marrow have reduced atherosclerosis as a result of defect in hematopoietic stem cell function contributing to extramedullary hematopoiesis, decreased level of circulating pro-atherogenic cells and reduction in cholesterol levels[188]. Interestingly, during inflammation, macrophages secrete vesicles carrying RNA, protein, and lipids as a form of extracellular communication. In the vessel wall, extracellular vesicles have been shown to be transferred between vascular cells during atherosclerosis[110]. In response to an atherogenic stimulus (ox-LDL) mouse and human derived macrophages are enriched in miR-146a, miR-128, miR-185, miR-365, and

miR-503. In particular miR-146a, may accelerate the development of atherosclerosis by decreasing cell migration and promoting macrophage entrapment in the vessel wall[189]. MiR-150 is contained in monocyte-derived microvesicles, both from the monocytic cell line, THP1, and from human peripheral blood monocytes[190]. The miRNA can be transferred to ECs and induce downregulation of c-Myb, which is responsible for the increased migratory capabilities of ECs.

In addition to above mentioned microRNAs, several other microRNAs including miR-let7a, miR-21, miR-223 and miR-125a among others have been implicated in inflammatory activation of macrophages. miR-223, which regulates lipid metabolism-related genes in liver, can suppress M1 proinflammatory pathways and enhance alternative activation by targeting Pknox1[191]. In addition, miR-223 also controls the infiltration of myeloid cells in lesions through directly targeting chemoattractants, such as chemokine C-X-C motif ligand 2 (CXCL2) and CCL3[192]. Similarly, miR-125a-5p, a microRNA induced by TLR2 and TLR4 in macrophages, suppresses classical activation while and promoting alternative activation of macrophage by targeting KLF13, a transcription factor important in T lymphocyte activation[193]. In contrast, miR-21, which is regulated by prostaglandin E2 (PGE2) in macrophages suppresses alternative activation, in part, by targeting STAT3 and SOCS1[194]. Consistent with this, it has recently reported that in the absence of miR-21, macrophages exhibit a pro-inflammatory phenotype and promote atherogenesis[195]. In particular, bone marrow derived macrophages (BMDMs) from *miR-21*$^{-/-}$ mice express more inflammatory markers upon LPS treatment. Additionally, miR-21 deficient peritoneal macrophages have reduced phagocytic activity associated with reduced MERTK protein levels and are more susceptible to ER stress mediated apoptosis via enhanced MKK3/p38 and JNK signaling pathways which are direct targets of miR-21[195].

Recently, lncRNAs have also emerged as important regulators of inflammatory activation of macrophages. However, the direct involvement of macrophage lncRNAs in the context of atherosclerosis has rarely been explored. LincRNA-Cox2 was identified in RNA-Seq studies as a differentially expressed lncRNA in mouse BMDMs treated with TLR2 ligand Pam3CSK4[196]. This study demonstrated that lincRNA-Cox2 interacts with heterogeneous ribonulcleoprotein A/B and A2/B1 and controls inflammatory response by regulating expression of various immune genes including Ccl5 and IL-6. Another study showed that lincRNA-Cox2 is induced by TNFα in NF-$_k$B dependent manner and mediates immune response as its knockdown resulted in enhanced transcription of Il12b upon TNFα treatment[197]. A recent study reported that lincRNA-Cox2 acts as coactivator of NF-kB for the transcription of late inflammatory genes through modulating SWI/SNF-mediated chromatin remodeling in macrophages in response to LPS[198]. Despite numerous reports indicating direct involvement of lincRNA-Cox2 in macrophages activation, its role in atherosclerosis has not been investigated. Through a custom microarray to identify lincRNAs associated with activation of the innate immune response, THRIL (TNFα and hnRNPL related immunoregulatory LincRNA) was identified to be highly expressed in THP1 macrophages upon Pam3CSK4 treatment. THRIL bound with heterogeneous nuclear ribonucleoprotein L (hnRNPL) and regulated the expression of many immune-response genes including TNFα[199]. In another study characterizing the lncRNA transcriptome in human monocytes identified several lncRNAs, enhancer RNAs (eRNAs), and regions of

bidirectional transcriptions (TBT) that were differentially expressed upon treatment with LPS. In particular, knockdown of two thus identified lncRNAs IL1βeRNA and IL1β-RBT46 attenuated LPS-induced mRNA transcription and release of inflammatory mediators IL1β and CXCL8 indicating that these lncRNAs might be involved in inflammatory activation of macrophages[200]. Hu et al identified the increased expression of lncRNA RP5–833A20.1 in human foam cells which led to decrease in expression of nuclear factor IA (NFIA) by inducing miR-382–5p expression. lncRNA RP5–833A20.1/miR-382–5p/NFIA pathway was essential for the regulation cholesterol homeostasis and inflammatory response and atherosclerosis development[31]. Another lncRNA E330013P60 that was highly induced in macrophages of diabetic mice promoted the classical activation of macrophages and stimulated the expression of proinflammatory genes and foam cell formation[201]. As we discussed, despite the increasing number of studies implicating the quintessential role of lncRNAs in macrophages activation, the direct association of this role in the development of atherosclerosis is relatively unexplored. Further investigations are warranted to identify lncRNAs as novel class of molecules in the therapeutic intervention against cardiovascular disorders.

Concluding remarks

Overall, work over the last two decades has identified multiple new levels of regulatory networks, and the discovery of miRNAs and lncRNAs has entirely transformed the way we view the genetic code and the regulation of gene expression. Much work is still needed to properly understand the regulation, impact, and mechanistic functions of these new gene expression modulators ongoing work clearly indicates that including ncRNAs are potential therapeutic targets as they possess biological potential to be used as non-traditional regulatory molecules and strong biomarkers for the diagnosis of cardiovascular diseases including atherosclerosis. The elucidation of the mechanism of ncRNAs requires physiological and systematic study. However, the establishment of RNA profiling using bioinformatics tools and development databases is also very important. LncRNAs are major regulators of chromatin dynamics and gene regulation, associated with a variety of cell signaling pathways, and their expressions are influenced by a variety of factors including hormones, cytokines, nutrients, age, and sex. Aberrant expression, mutations and SNPs of miRNAs have been associated with atherosclerosis while that of lncRNAs still remains to be linked. The latter is likely due to their weak expression and the poor-genetic conservation between species. However, comparative transcriptomics approaches demonstrated that 30%–40% of nearly 2000 human lncRNAs show conserved expression in rodents. It appears likely that thousands of transcriptome evolutionarily conserved functional roles of lincRNAs remain to be characterized and some that are already characterized need to be revisited. Thus, much work will be needed to elucidate the specific role of lncRNAs in controlling atherosclerosis.

Given their regulation of endothelial and macrophage functions, lncRNAs are likely associated with vascular diseases as well more than what is acknowledged. On the other hand, in addition to their established roles in vascular diseases, miRNAs have also been recently shown to be differentially present in biofluids of patients with different vascular disease and shown to participate in cell-cell communication during atherosclerosis

suggesting their wider functions in cardiovascular diseases. Future perspectives which are based upon lncRNA localization, their genetic profiles and their mechanism will undoubtedly help to elucidate their key roles in regulation of EC and macrophages functions relevant to atherosclerosis.

Acknowledgements

The authors apologize to the many scientists whose contributions to the field could not be acknowledged owing to space limitations. YS laboratory is supported by grants from the National Institutes of Health (R01HL105945 and R01HL135012) and the American Heart Association (16GRNT26420047).

Abbreviations

3'UTR	3' untranslated region
AMPK	AMP-activated protein kinase
ANRIL	antisense ncRNA in the INK4 locus
circRNA	circular RNA
EC	endothelial cell
eNOS	endothelial nitric oxide synthase
ET-1	endothelin 1
ICAM-1	intercellular adhesion molecule 1
iNOS	inducible nitric oxide synthase
IRAK	interleukin-1 receptor-associated kinase
KLF2	Krüppel-like factor 2
LDL	low density lipoproteins
lincRNA	long intergenic RNA
lncRNA	long noncoding RNA
MALAT1	Metastasis-associated lung adenocarcinoma transcript
miRNA	microRNA
MMP	matrix metalloproteinase
ncRNA	non-coding RNA
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
ox-LDL	oxidized LDL
PAF	platelet activating factor

ROS	reactive oxygen species
rRNA	ribosomal RNA
SOCS	suppressor of cytokine signaling
THRIL	TNFα and hnRNPL related immunoregulatory LincRNA
TLR	toll-like receptor
TNFα	tumor necrosis factor alpha
TRAF6	TNF receptor associated factor 6
VCAM-1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor THRIL (TNFα and hnRNPL related immunoregulatory LincRNA)

References

[1]. Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, Soliman MA-T, Frohlich B, Mininberg DT, Monge JM, Vallodolid CM, Cox SL, Abd el-Maksoud G, Badr I, Miyamoto MI, el-Halim Nur el-din A, Narula J, Finch CE, Thomas GS, Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations, The Lancet 381(9873) (2013) 1211–1222.

[2]. Glass CK, Witztum JL, Atherosclerosis. the road ahead., Cell 104(4) (2001) 503–516. [PubMed: 11239408]

[3]. Tabas I, Garcia-Cardena G, Owens GK, Recent insights into the cellular biology of atherosclerosis, J Cell Biol 209(1) (2015) 13–22. [PubMed: 25869663]

[4]. Dai G, Vaughn S, Zhang Y, Wang ET, García-Cardeña G, Gimbrone MA, Biomechanical forces in atherosclerosis-resistant vascular regions regulate endothelial redox balance via phosphoinositol 3-kinase/Akt-dependent activation of Nrf2., Circulation Research 101(7) (2007) 723–733. [PubMed: 17673673]

[5]. Krauss RM, Lipoprotein subfractions and cardiovascular disease risk, Curr Opin Lipidol 21(4) (2010) 305–11. [PubMed: 20531184]

[6]. Sima AV, Stancu CS, Simionescu M, Vascular endothelium in atherosclerosis, Cell Tissue Res 335(1) (2009) 191–203. [PubMed: 18797930]

[7]. Galkina E, Ley K, Leukocyte influx in atherosclerosis, Curr Drug Targets 8(12) (2007) 1239–48. [PubMed: 18220701]

[8]. Mestas J, Ley K, Monocyte-endothelial cell interactions in the development of atherosclerosis, Trends Cardiovasc Med 18(6) (2008) 228–32. [PubMed: 19185814]

[9]. Tabas I, Macrophage death and defective inflammation resolution in atherosclerosis, Nat Rev Immunol 10(1) (2010) 36–46. [PubMed: 19960040]

[10]. Moore KJ, Sheedy FJ, Fisher EA, Macrophages in atherosclerosis: a dynamic balance, Nat Rev Immunol 13(10) (2013) 709–21. [PubMed: 23995626]

[11]. Moore KJ, Tabas I, Macrophages in the pathogenesis of atherosclerosis, Cell 145(3) (2011) 341–55. [PubMed: 21529710]

[12]. Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, Pober JS, Wick TM, Konkle BA, Schwartz BS, Barnathan ES, McCrae KR, Hug BA, Schmidt AM, Stern DM, Endothelial cells in physiology and in the pathophysiology of vascular disorders, Blood 91(10) (1998) 3527–61. [PubMed: 9572988]

[13]. Davignon J, Ganz P, Role of endothelial dysfunction in atherosclerosis, Circulation 109(23 Suppl 1) (2004) III27–32. [PubMed: 15198963]

[14]. Hanson M, Gluckman P, Endothelial dysfunction and cardiovascular disease: the role of predictive adaptive responses, Heart 91(7) (2005) 864–6. [PubMed: 15958346]

[15]. Thorp E, Tabas I, Mechanisms and consequences of efferocytosis in advanced atherosclerosis, J Leukoc Biol 86(5) (2009) 1089–95. [PubMed: 19414539]

[16]. Cooke JP, Mechanisms of Atherosclerosis: New Insights and Novel Therapeutic Approaches, Methodist Debakey Cardiovasc J 11(3) (2015) 154–5. [PubMed: 26634021]

[17]. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, C. Cholesterol Treatment Trialists, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366(9493) (2005) 1267–78. [PubMed: 16214597]

[18]. Araldi E, Chamorro-Jorganes A, van Solingen C, Fernandez-Hernando C, Suarez Y, Therapeutic Potential of Modulating microRNAs in Atherosclerotic Vascular Disease, Curr Vasc Pharmacol 13(3) (2015) 291–304. [PubMed: 26156264]

[19]. Araldi E, Suarez Y, MicroRNAs as regulators of endothelial cell functions in cardiometabolic diseases, Biochim Biophys Acta (2016).

[20]. Chamorro-Jorganes A, Araldi E, Suárez Y, MicroRNAs as pharmacological targets in endothelial cell function and dysfunction, Pharmacological Research 75 (2013) 15–27. [PubMed: 23603154]

[21]. Fernández-Hernando C, Ramirez CM, Goedeke L, Suárez Y, MicroRNAs in metabolic disease., Arteriosclerosis, thrombosis, and vascular biology 33(2) (2013) 178–185.

[22]. Moore KJ, Rayner KJ, Suárez Y, Fernández-Hernando C, microRNAs and cholesterol metabolism, Trends in Endocrinology & Metabolism 21(12) (2010) 699–706. [PubMed: 20880716]

[23]. Madrigal-Matute J, Rotllan N, Aranda JF, Fernandez-Hernando C, MicroRNAs and atherosclerosis, Curr Atheroscler Rep 15(5) (2013) 322. [PubMed: 23512606]

[24]. Feinberg MW, Moore KJ, MicroRNA Regulation of Atherosclerosis, Circ Res 118(4) (2016) 703–20. [PubMed: 26892968]

[25]. Schober A, Weber C, Mechanisms of MicroRNAs in Atherosclerosis, Annu Rev Pathol 11 (2016) 583–616. [PubMed: 27193456]

[26]. Telenti A, Pierce LC, Biggs WH, di Iulio J, Wong EH, Fabani MM, Kirkness EF, Moustafa A, Shah N, Xie C, Brewerton SC, Bulsara N, Garner C, Metzker G, Sandoval E, Perkins BA, Och FJ, Turpaz Y, Venter JC, Deep sequencing of 10,000 human genomes, Proc Natl Acad Sci U S A 113(42) (2016) 11901–11906. [PubMed: 27702888]

[27]. Bell RD, Long X, Lin M, Bergmann JH, Nanda V, Cowan SL, Zhou Q, Han Y, Spector DL, Zheng D, Miano JM, Identification and initial functional characterization of a human vascular cell-enriched long noncoding RNA, Arterioscler Thromb Vasc Biol 34(6) (2014) 1249–59. [PubMed: 24578380]

[28]. Zhao J, Zhang W, Lin M, Wu W, Jiang P, Tou E, Xue M, Richards A, Jourd'heuil D, Asif A, Zheng D, Singer HA, Miano JM, Long X, MYOSLID Is a Novel Serum Response Factor-Dependent Long Noncoding RNA That Amplifies the Vascular Smooth Muscle Differentiation Program, Arterioscler Thromb Vasc Biol 36(10) (2016) 2088–99. [PubMed: 27444199]

[29]. Leung A, Trac C, Jin W, Lanting L, Akbany A, Saetrom P, Schones DE, Natarajan R, Novel long noncoding RNAs are regulated by angiotensin II in vascular smooth muscle cells, Circ Res 113(3) (2013) 266–78. [PubMed: 23697773]

[30]. Hu YW, Yang JY, Ma X, Chen ZP, Hu YR, Zhao JY, Li SF, Qiu YR, Lu JB, Wang YC, Gao JJ, Sha YH, Zheng L, Wang Q, A lincRNA-DYNLRB2–2/GPR119/GLP-1R/ABCA1-dependent signal transduction pathway is essential for the regulation of cholesterol homeostasis, J Lipid Res 55(4) (2014) 681–97. [PubMed: 24493833]

[31]. Hu YW, Zhao JY, Li SF, Huang JL, Qiu YR, Ma X, Wu SG, Chen ZP, Hu YR, Yang JY, Wang YC, Gao JJ, Sha YH, Zheng L, Wang Q, RP5–833A20.1/miR-382–5p/NFIA-dependent signal transduction pathway contributes to the regulation of cholesterol homeostasis and inflammatory reaction, Arterioscler Thromb Vasc Biol 35(1) (2015) 87–101. [PubMed: 25265644]

[32]. Liu G, Zheng X, Xu Y, Lu J, Chen J, Huang X, Long non-coding RNAs expression profile in HepG2 cells reveals the potential role of long non-coding RNAs in the cholesterol metabolism, Chin Med J (Engl) 128(1) (2015) 91–7. [PubMed: 25563320]

[33]. Halley P, Kadakkuzha BM, Faghihi MA, Magistri M, Zeier Z, Khorkova O, Coito C, Hsiao J, Lawrence M, Wahlestedt C, Regulation of the apolipoprotein gene cluster by a long noncoding RNA, Cell Rep 6(1) (2014) 222–30. [PubMed: 24388749]

[34]. Sallam T, Jones MC, Gilliland T, Zhang L, Wu X, Eskin A, Sandhu J, Casero D, Vallim TQ, Hong C, Katz M, Lee R, Whitelegge J, Tontonoz P, Feedback modulation of cholesterol metabolism by the lipid-responsive non-coding RNA LeXis, Nature 534(7605) (2016) 124–8. [PubMed: 27251289]

[35]. Aryal B, Rotllan N, Fernandez-Hernando C, Noncoding RNAs and atherosclerosis, Curr Atheroscler Rep 16(5) (2014) 407. [PubMed: 24623179]

[36]. Freedman JE, Miano JM, L. National Heart, P. Blood Institute Workshop, Challenges and Opportunities in Linking Long Noncoding RNAs to Cardiovascular, Lung, and Blood Diseases, Arterioscler Thromb Vasc Biol 37(1) (2017) 21–25. [PubMed: 27856459]

[37]. Gurha P, Marian AJ, Noncoding RNAs in cardiovascular biology and disease, Circ Res 113(12) (2013) e115–20. [PubMed: 24311620]

[38]. Li H, Zhu H, Ge J, Long Noncoding RNA: Recent Updates in Atherosclerosis, Int J Biol Sci 12(7) (2016) 898–910. [PubMed: 27314829]

[39]. Leung A, Natarajan R, Noncoding RNAs in vascular disease, Curr Opin Cardiol 29(3) (2014) 199–206. [PubMed: 24614861]

[40]. Aryal B, Singh AK, Rotllan N, Price N, Fernandez-Hernando C, MicroRNAs and lipid metabolism, Curr Opin Lipidol 28(3) (2017) 273–280. [PubMed: 28333713]

[41]. Collins LJ, Penny D, The RNA infrastructure: dark matter of the eukaryotic cell?, Trends Genet 25(3) (2009) 120–8. [PubMed: 19171405]

[42]. Cech TR, Steitz JA, The noncoding RNA revolution-trashing old rules to forge new ones, Cell 157(1) (2014) 77–94. [PubMed: 24679528]

[43]. Lee RC, Feinbaum RL, Ambros V, The C elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14, Cell 75(5) (1993) 843–54. [PubMed: 8252621]

[44]. Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G, The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans, Nature 403(6772) (2000) 901–6. [PubMed: 10706289]

[45]. Batista PJ, Chang HY, Long noncoding RNAs: cellular address codes in development and disease, Cell 152(6) (2013) 1298–307. [PubMed: 23498938]

[46]. Schmitz SU, Grote P, Herrmann BG, Mechanisms of long noncoding RNA function in development and disease, Cell Mol Life Sci 73(13) (2016) 2491–509. [PubMed: 27007508]

[47]. Ambros V, The functions of animal microRNAs., Nature, 2004, pp. 350–355.

[48]. Bartel DP, MicroRNAs: genomics, biogenesis, mechanism, and function., Cell, 2004, pp. 281–297.

[49]. Bartel DP, MicroRNAs: target recognition and regulatory functions., Cell, 2009, pp. 215–233.

[50]. Filipowicz W, Bhattacharyya SN, Sonenberg N, Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight?, Nature reviews. Genetics 9(2) (2008) 102–14.

[51]. Cai X, Hagedorn CH, Cullen BR, Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs, RNA 10(12) (2004) 1957–66. [PubMed: 15525708]

[52]. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ, Processing of primary microRNAs by the Microprocessor complex, Nature 432(7014) (2004) 231–5. [PubMed: 15531879]

[53]. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN, MicroRNA genes are transcribed by RNA polymerase II, The EMBO journal 23(20) (2004) 4051–60. [PubMed: 15372072]

[54]. Ruby JG, Jan CH, Bartel DP, Intronic microRNA precursors that bypass Drosha processing, Nature 448(7149) (2007) 83–6. [PubMed: 17589500]

[55]. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhattar R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J, Guigo R, The GENCODE v7 catalog of human long noncoding RNAs:

analysis of their gene structure, evolution, and expression, Genome Res 22(9) (2012) 1775–89. [PubMed: 22955988]

[56]. Magny EG, Pueyo JI, Pearl FM, Cespedes MA, Niven JE, Bishop SA, Couso JP, Conserved regulation of cardiac calcium uptake by peptides encoded in small open reading frames, Science 341(6150) (2013) 1116–20. [PubMed: 23970561]

[57]. Kondo T, Plaza S, Zanet J, Benrabah E, Valenti P, Hashimoto Y, Kobayashi S, Payre F, Kageyama Y, Small peptides switch the transcriptional activity of Shavenbaby during Drosophila embryogenesis, Science 329(5989) (2010) 336–9. [PubMed: 20647469]

[58]. Ulitsky I, Bartel DP, lincRNAs: genomics, evolution, and mechanisms, Cell 154(1) (2013) 26–46. [PubMed: 23827673]

[59]. Hashimshony T, Yanai I, Revealing developmental networks by comparative transcriptomics, Transcription 1(3) (2010) 154–158. [PubMed: 21326891]

[60]. Washietl S, Kellis M, Garber M, Evolutionary dynamics and tissue specificity of human long noncoding RNAs in six mammals, Genome Res 24(4) (2014) 616–28. [PubMed: 24429298]

[61]. Managadze D, Lobkovsky AE, Wolf YI, Shabalina SA, Rogozin IB, Koonin EV, The vast, conserved mammalian lincRNome, PLoS Comput Biol 9(2) (2013) e1002917. [PubMed: 23468607]

[62]. Cesana M, Cacchiarelli D, Legnini I, Santini T, Sthandier O, Chinappi M, Tramontano A, Bozzoni I, A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA, Cell 147(2) (2011) 358–69. [PubMed: 22000014]

[63]. Wang Y, Xu Z, Jiang J, Xu C, Kang J, Xiao L, Wu M, Xiong J, Guo X, Liu H, Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal, Dev Cell 25(1) (2013) 69–80. [PubMed: 23541921]

[64]. Denzler R, Agarwal V, Stefano J, Bartel DP, Stoffel M, Assessing the ceRNA hypothesis with quantitative measurements of miRNA and target abundance, Mol Cell 54(5) (2014) 766–76. [PubMed: 24793693]

[65]. Gong C, Maquat LE, lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3' UTRs via Alu elements, Nature 470(7333) (2011) 284–8. [PubMed: 21307942]

[66]. Yoon JH, Abdelmohsen K, Srikantan S, Yang X, Martindale JL, De S, Huarte M, Zhan M, Becker KG, Gorospe M, LincRNA-p21 suppresses target mRNA translation, Mol Cell 47(4) (2012) 648–55. [PubMed: 22841487]

[67]. Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF, Sharma A, Bubulya PA, Blencowe BJ, Prasanth SG, Prasanth KV, The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation, Mol Cell 39(6) (2010) 925–38. [PubMed: 20797886]

[68]. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J, Natural RNA circles function as efficient microRNA sponges, Nature 495(7441) (2013) 384–8. [PubMed: 23446346]

[69]. Dong Y, He D, Peng Z, Peng W, Shi W, Wang J, Li B, Zhang C, Duan C, Circular RNAs in cancer: an emerging key player, J Hematol Oncol 10(1) (2017) 2. [PubMed: 28049499]

[70]. Vicens Q, Westhof E, Biogenesis of Circular RNAs, Cell 159(1) (2014) 13–14. [PubMed: 25259915]

[71]. Zhang XO, Dong R, Zhang Y, Zhang JL, Luo Z, Zhang J, Chen LL, Yang L, Diverse alternative back-splicing and alternative splicing landscape of circular RNAs, Genome Res 26(9) (2016) 1277–87. [PubMed: 27365365]

[72]. Lefer AM, Nitric oxide: nature's naturally occurring leukocyte inhibitor, Circulation 95(3) (1997) 553–4. [PubMed: 9024134]

[73]. Sessa WC, eNOS at a glance, J Cell Sci 117(Pt 12) (2004) 2427–9. [PubMed: 15159447]

[74]. Wilcox JN, Subramanian RR, Sundell CL, Tracey WR, Pollock JS, Harrison DG, Marsden PA, Expression of multiple isoforms of nitric oxide synthase in normal and atherosclerotic vessels, Arterioscler Thromb Vasc Biol 17(11) (1997) 2479–88. [PubMed: 9409218]

[75]. Hansson GK, Libby P, The immune response in atherosclerosis: a double-edged sword, Nature reviews Immunology 6(7) (2006) 508–519.

[76]. Pober JS, Sessa WC, Evolving functions of endothelial cells in inflammation, Nat Rev Immunol 7(10) (2007) 803–15. [PubMed: 17893694]

[77]. Atkins GB, Jain MK, Role of Krüppel-like transcription factors in endothelial biology., Circulation Research 100(12) (2007) 1686–1695. [PubMed: 17585076]

[78]. Parmar KM, Larman HB, Dai G, Zhang Y, Wang ET, Moorthy SN, Kratz JR, Lin Z, Jain MK, Gimbrone MA, Jr, García-Cardeña G, Integration of flow-dependent endothelial phenotypes by Kruppel-like factor 2, Journal of Clinical Investigation 116(1) (2006) 49–58. [PubMed: 16341264]

[79]. Zakkar M, Van der Heiden K, Luong LA, Chaudhury H, Cuhlmann S, Hamdulay SS, Krams R, Edirisinghe I, Rahman I, Carlsen H, Haskard DO, Mason JC, Evans PC, Activation of Nrf2 in endothelial cells protects arteries from exhibiting a proinflammatory state., Arteriosclerosis, thrombosis, and vascular biology 29(11) (2009) 1851–1857.

[80]. Kumar S, Kim CW, Simmons RD, Jo H, Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis: mechanosensitive athero-miRs, Arterioscler Thromb Vasc Biol 34(10) (2014) 2206–16. [PubMed: 25012134]

[81]. Fang Y, Davies PF, Site-specific microRNA-92a regulation of Kruppel-like factors 4 and 2 in atherosusceptible endothelium., Arteriosclerosis, thrombosis, and vascular biology 32(4) (2012) 979–987.

[82]. Loyer X, Potteaux S, Vion A-C, Guérin CL, Boulkroun S, Rautou P-E, Ramkhelawon B, Esposito B, Dalloz M, Paul J-L, Julia P, Maccario J, Boulanger CM, Mallat Z, Tedgui A, Inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice., Circulation Research 114(3) (2014) 434–443. [PubMed: 24255059]

[83]. Wu W, Xiao H, Laguna-Fernandez A, Villarreal G, Wang K-C, Geary GG, Zhang Y, Wang W-C, Huang H-D, Zhou J, Li Y-S, Chien S, García-Cardeña G, Shyy JYJ, Flow-Dependent Regulation of Kruppel-Like Factor 2 Is Mediated by MicroRNA-92a., Circulation 124(5) (2011) 633–641. [PubMed: 21768538]

[84]. Son DJ, Kumar S, Takabe W, Kim CW, Ni C-W, Alberts-Grill N, Jang I-H, Kim S, Kim W, Kang SW, Baker AH, Seo JW, Ferrara KW, Jo H, The atypical mechanosensitive microRNA-712 derived from pre-ribosomal RNA induces endothelial inflammation and atherosclerosis, Nature Communications 4 (2013) 3000.

[85]. Harris TA, Yamakuchi M, Ferlito M, Mendell JT, Lowenstein CJ, MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1, Proc Natl Acad Sci U S A 105(5) (2008) 1516–21. [PubMed: 18227515]

[86]. Suárez Y, Wang C, Manes TD, Pober JS, Cutting edge: TNF-induced microRNAs regulate TNF-induced expression of E-selectin and intercellular adhesion molecule-1 on human endothelial cells: feedback control of inflammation., The Journal of Immunology 184(1) (2010) 21–25. [PubMed: 19949084]

[87]. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, Hunninghake GM, Vera MP, Blackwell TS, Baron RM, Feinberg MW, MicroRNA-181b regulates NF-kappaB-mediated vascular inflammation, The Journal of clinical investigation 122(6) (2012) 1973–90. [PubMed: 22622040]

[88]. Fang Y, Shi C, Manduchi E, Civelek M, Davies PF, MicroRNA-10a regulation of proinflammatory phenotype in athero-susceptible endothelium in vivo and in vitro, Proc Natl Acad Sci U S A 107(30) (2010) 13450–5. [PubMed: 20624982]

[89]. Jarinova O, Stewart AF, Roberts R, Wells G, Lau P, Naing T, Buerki C, McLean BW, Cook RC, Parker JS, McPherson R, Functional analysis of the chromosome 9p21.3 coronary artery disease risk locus, Arterioscler Thromb Vasc Biol 29(10) (2009) 1671–7. [PubMed: 19592466]

[90]. Gschwendtner A, Bevan S, Cole JW, Plourde A, Matarin M, Ross-Adams H, Meitinger T, Wichmann E, Mitchell BD, Furie K, Slowik A, Rich SS, Syme PD, MacLeod MJ, Meschia JF, Rosand J, Kittner SJ, Markus HS, Muller-Myhsok B, Dichgans M, C. International Stroke Genetics, Sequence variants on chromosome 9p21.3 confer risk for atherosclerotic stroke, Ann Neurol 65(5) (2009) 531–9. [PubMed: 19475673]

[91]. Yap KL, Li S, Munoz-Cabello AM, Raguz S, Zeng L, Mujtaba S, Gil J, Walsh MJ, Zhou MM, Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a, Mol Cell 38(5) (2010) 662–74. [PubMed: 20541999]

[92]. Kotake Y, Nakagawa T, Kitagawa K, Suzuki S, Liu N, Kitagawa M, Xiong Y, Long non- coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene, Oncogene 30(16) (2011) 1956–62. [PubMed: 21151178]

[93]. Zhou X, Han X, Wittfeldt A, Sun J, Liu C, Wang X, Gan LM, Cao H, Liang Z, Long non-coding RNA ANRIL regulates inflammatory responses as a novel component of NF-kappaB pathway, RNA Biol 13(1) (2016) 98–108. [PubMed: 26618242]

[94]. Holdt LM, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, Kohlmaier A, Herbst A, Northoff BH, Nicolaou A, Gabel G, Beutner F, Scholz M, Thiery J, Musunuru K, Krohn K, Mann M, Teupser D, Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans, Nat Commun 7 (2016) 12429. [PubMed: 27539542]

[95]. Cheng HS, Sivachandran N, Lau A, Boudreau E, Zhao JL, Baltimore D, Delgado-Olguin P, Cybulsky MI, Fish JE, MicroRNA-146 represses endothelial activation by inhibiting pro-inflammatory pathways, EMBO Molecular Medicine 5(7) (2013) 1017–1034. [PubMed: 23733368]

[96]. Napoli C, Quehenberger O, De Nigris F, Abete P, Glass CK, Palinski W, Mildly oxidized low density lipoprotein activates multiple apoptotic signaling pathways in human coronary cells., FASEB journal : official publication of the Federation of American Societies for Experimental Biology 14(13) (2000) 1996–2007. [PubMed: 11023984]

[97]. Chen K-C, Hsieh I-C, Hsi E, Wang Y-S, Dai C-Y, Chou W-W, Juo S-HH, Negative feedback regulation between microRNA let-7g and the oxLDL receptor LOX-1., Journal of Cell Science 124(Pt 23) (2011) 4115–4124. [PubMed: 22135361]

[98]. Bao M-H, Zhang Y-W, Lou X-Y, Cheng Y, Zhou H-H, Protective effects of let-7a and let-7b on oxidized low-density lipoprotein induced endothelial cell injuries., PLoS ONE 9(9) (2014) e106540. [PubMed: 25247304]

[99]. Liao Y-C, Wang Y-S, Guo Y-C, Lin W-L, Chang M-H, Juo S-HH, Let-7g improves multiple endothelial functions through targeting transforming growth factor-beta and SIRT-1 signaling., Journal of the American College of Cardiology 63(16) (2014) 1685–1694. [PubMed: 24291274]

[100]. Qin B, Xiao B, Liang D, Xia J, Li Y, Yang H, MicroRNAs expression in ox-LDL treated HUVECs: MiR-365 modulates apoptosis and Bcl-2 expression., Biochemical and biophysical research communications 410(1) (2011) 127–133. [PubMed: 21640710]

[101]. Michalik KM, You X, Manavski Y, Doddaballapur A, Zornig M, Braun T, John D, Ponomareva Y, Chen W, Uchida S, Boon RA, Dimmeler S, Long noncoding RNA MALAT1 regulates endothelial cell function and vessel growth, Circ Res 114(9) (2014) 1389–97. [PubMed: 24602777]

[102]. Yang L, Lin C, Liu W, Zhang J, Ohgi KA, Grinstein JD, Dorrestein PC, Rosenfeld MG, ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs, Cell 147(4) (2011) 773–88. [PubMed: 22078878]

[103]. Liu JY, Yao J, Li XM, Song YC, Wang XQ, Li YJ, Yan B, Jiang Q, Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus, Cell Death Dis 5 (2014) e1506. [PubMed: 25356875]

[104]. Puthanveetil P, Chen S, Feng B, Gautam A, Chakrabarti S, Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the endothelial cells, J Cell Mol Med 19(6) (2015) 1418–25. [PubMed: 25787249]

[105]. Tang Y, Jin X, Xiang Y, Chen Y, Shen CX, Zhang YC, Li YG, The lncRNA MALAT1 protects the endothelium against ox-LDL-induced dysfunction via upregulating the expression of the miR-22–3p target genes CXCR2 and AKT, FEBS Lett 589(20 Pt B) (2015) 3189–96. [PubMed: 26364720]

[106]. Voellenkle C, Garcia-Manteiga JM, Pedrotti S, Perfetti A, De Toma I, Da Silva D, Maimone B, Greco S, Fasanaro P, Creo P, Zaccagnini G, Gaetano C, Martelli F, Implication of Long noncoding RNAs in the endothelial cell response to hypoxia revealed by RNA-sequencing, Sci Rep 6 (2016) 24141. [PubMed: 27063004]

[107]. Zhou X, Ji G, Ke X, Gu H, Jin W, Zhang G, MiR-141 Inhibits Gastric Cancer Proliferation by Interacting with Long Noncoding RNA MEG3 and Down-Regulating E2F3 Expression, Dig Dis Sci 60(11) (2015) 3271–82. [PubMed: 26233544]

[108]. Qiu GZ, Tian W, Fu HT, Li CP, Liu B, Long noncoding RNA-MEG3 is involved in diabetes mellitus-related microvascular dysfunction, Biochem Biophys Res Commun 471(1) (2016) 135–41. [PubMed: 26845358]

[109]. He C, Yang W, Yang J, Ding J, Li S, Wu H, Zhou F, Jiang Y, Teng L, Yang J, Long Noncoding RNA MEG3 Negatively Regulates Proliferation and Angiogenesis in Vascular Endothelial Cells, DNA Cell Biol 36(6) (2017) 475–481. [PubMed: 28418724]

[110]. Hergenreider E, Heydt S, Tréguer K, Boettger T, Horrevoets AJG, Zeiher AM, Scheffer MP, Frangakis AS, Yin X, Mayr M, Braun T, Urbich C, Boon RA, Dimmeler S, Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs., Nature Cell Biology 14(3) (2012) 249–256. [PubMed: 22327366]

[111]. Njock MS, Cheng HS, Dang LT, Nazari-Jahantigh M, Lau AC, Boudreau E, Roufaiel M, Cybulsky MI, Schober A, Fish JE, Endothelial cells suppress monocyte activation through secretion of extracellular vesicles containing antiinflammatory microRNAs, Blood 125(20) (2015) 3202–12. [PubMed: 25838349]

[112]. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, Hristov M, Köppel T, Jahantigh MN, Lutgens E, Wang S, Olson EN, Schober A, Weber C, Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection., Sci Signal, 2009, p. ra81. [PubMed: 19996457]

[113]. Busse R, Fleming I, Vascular endothelium and blood flow, Handb Exp Pharmacol (176 Pt 2) (2006) 43–78.

[114]. Moncada S, Higgs EA, Nitric oxide and the vascular endothelium, Handb Exp Pharmacol (176 Pt 1) (2006) 213–54.

[115]. Suarez Y, Fernandez-Hernando C, Pober JS, Sessa WC, Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells, Circ Res 100(8) (2007) 1164–73. [PubMed: 17379831]

[116]. Kuehbacher A, Urbich C, Zeiher AM, Dimmeler S, Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis, Circ Res 101(1) (2007) 59–68. [PubMed: 17540974]

[117]. Sun HX, Zeng DY, Li RT, Pang RP, Yang H, Hu YL, Zhang Q, Jiang Y, Huang LY, Tang YB, Yan GJ, Zhou JG, Essential role of microRNA-155 in regulatingendothelium-dependent vasorelaxation by targeting endothelial nitric oxide synthase, Hypertension 60(6) (2012) 1407–14. [PubMed: 23108656]

[118]. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T, A novel potent vasoconstrictor peptide produced by vascular endothelial cells, Nature 332(6163) (1988) 411–5. [PubMed: 2451132]

[119]. Bohm F, Pernow J, The importance of endothelin-1 for vascular dysfunction in cardiovascular disease, Cardiovasc Res 76(1) (2007) 8–18. [PubMed: 17617392]

[120]. Li D, Yang P, Xiong Q, Song X, Yang X, Liu L, Yuan W, Rui Y-C, MicroRNA-125a/b- 5p inhibits endothelin-1 expression in vascular endothelial cells., Journal of hypertension 28(8) (2010) 1646–1654. [PubMed: 20531225]

[121]. Robb GB, Carson AR, Tai SC, Fish JE, Singh S, Yamada T, Scherer SW, Nakabayashi K, Marsden PA, Post-transcriptional regulation of endothelial nitric-oxide synthase by an overlapping antisense mRNA transcript, J Biol Chem 279(36) (2004) 37982–96. [PubMed: 15234981]

[122]. Fish JE, Matouk CC, Yeboah E, Bevan SC, Khan M, Patil K, Ohh M, Marsden PA, Hypoxia-inducible expression of a natural cis-antisense transcript inhibits endothelial nitric-oxide synthase, J Biol Chem 282(21) (2007) 15652–66. [PubMed: 17403686]

[123]. Depre C, Havaux X, Renkin J, Vanoverschelde JL, Wijns W, Expression of inducible nitric oxide synthase in human coronary atherosclerotic plaque, Cardiovasc Res 41(2) (1999) 465–72. [PubMed: 10341846]

[124]. Yang Y, Xi P, Xie Y, Zhao C, Xu J, Jiang J, Notoginsenoside R1 reduces blood pressure in spontaneously hypertensive rats through a long non-coding RNA AK094457, Int J Clin Exp Pathol 8(3) (2015) 2700–9. [PubMed: 26045775]

[125]. Dejana E, Del Maschio A, Molecular organization and functional regulation of cell to cell junctions in the endothelium, Thromb Haemost 74(1) (1995) 309–12. [PubMed: 8578477]

[126]. Schnittler HJ, Structural and functional aspects of intercellular junctions in vascular endothelium, Basic Res Cardiol 93 Suppl 3 (1998) 30–9.

[127]. Alexander JS, Elrod JW, Extracellular matrix, junctional integrity and matrix metalloproteinase interactions in endothelial permeability regulation, J Anat 200(6) (2002) 561–74. [PubMed: 12162724]

[128]. Dejana E, Corada M, Lampugnani MG, Endothelial cell-to-cell junctions, FASEB J 9(10) (1995) 910–8. [PubMed: 7615160]

[129]. Muramatsu F, Kidoya H, Naito H, Sakimoto S, Takakura N, microRNA-125b inhibits tube formation of blood vessels through translational suppression of VE-cadherin, Oncogene 32(4) (2013) 414–21. [PubMed: 22391569]

[130]. Pepini T, Gorbunova EE, Gavrilovskaya IN, Mackow JE, Mackow ER, Andes virus regulation of cellular microRNAs contributes to hantavirus-induced endothelial cell permeability, J Virol 84(22) (2010) 11929–36. [PubMed: 20844033]

[131]. Chatterjee V, Beard RS, Jr., Reynolds JJ, Haines R, Guo M, Rubin M, Guido J, Wu MH, Yuan SY, MicroRNA-147b regulates vascular endothelial barrier function by targeting ADAM15 expression, PLoS One 9(10) (2014) e110286. [PubMed: 25333931]

[132]. Nicoloso MS, Spizzo R, Shimizu M, Rossi S, Calin GA, MicroRNAs--the micro steering wheel of tumour metastases, Nat Rev Cancer 9(4) (2009) 293–302. [PubMed: 19262572]

[133]. Cichon C, Sabharwal H, Ruter C, Schmidt MA, MicroRNAs regulate tight junction proteins and modulate epithelial/endothelial barrier functions, Tissue Barriers 2(4) (2014) e944446. [PubMed: 25610754]

[134]. Li K, Blum Y, Verma A, Liu Z, Pramanik K, Leigh NR, Chun CZ, Samant GV, Zhao B, Garnaas MK, Horswill MA, Stanhope SA, North PE, Miao RQ, Wilkinson GA, Affolter M, Ramchandran R, A noncoding antisense RNA in tie-1 locus regulates tie-1 function in vivo, Blood 115(1) (2010) 133–9. [PubMed: 19880500]

[135]. Ishii N, Ozaki K, Sato H, Mizuno H, Saito S, Takahashi A, Miyamoto Y, Ikegawa S, Kamatani N, Hori M, Saito S, Nakamura Y, Tanaka T, Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction, J Hum Genet 51(12) (2006) 1087–99. [PubMed: 17066261]

[136]. Vausort M, Wagner DR, Devaux Y, Long noncoding RNAs in patients with acute myocardial infarction, Circ Res 115(7) (2014) 668–77. [PubMed: 25035150]

[137]. Yan B, Yao J, Liu JY, Li XM, Wang XQ, Li YJ, Tao ZF, Song YC, Chen Q, Jiang Q, lncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA, Circ Res 116(7) (2015) 1143–56. [PubMed: 25587098]

[138]. Guo J, Cai H, Zheng J, Liu X, Liu Y, Ma J, Que Z, Gong W, Gao Y, Tao W, Xue Y, Long non-coding RNA NEAT1 regulates permeability of the blood-tumor barrier via miR-181d-5p-mediated expression changes in ZO-1, occludin, and claudin-5, Biochim Biophys Acta 1863(9) (2017) 2240–2254.

[139]. Carmeliet P, Angiogenesis in health and disease, Nature medicine 9(6) (2003) 653–660.

[140]. Carmeliet P, Angiogenesis in life, disease and medicine., Nature 438(7070) (2005) 932–936. [PubMed: 16355210]

[141]. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, Wrenn SP, Narula J, Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage, Arterioscler Thromb Vasc Biol 25(10) (2005) 2054–61. [PubMed: 16037567]

[142]. Moulton KS, Plaque angiogenesis and atherosclerosis, Curr Atheroscler Rep 3(3) (2001) 225–33. [PubMed: 11286644]

[143]. Ramji DP, Davies TS, Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets, Cytokine Growth Factor Rev 26(6) (2015) 673–85. [PubMed: 26005197]

[144]. Chamorro-Jorganes A, Araldi E, Penalva LO, Sandhu D, Fernandez-Hernando C, Suarez Y, MicroRNA-16 and microRNA-424 regulate cell-autonomous angiogenic functions in endothelial cells via targeting vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1, Arterioscler Thromb Vasc Biol 31(11) (2011) 2595–606. [PubMed: 21885851]

[145]. Chamorro-Jorganes A, Araldi E, Rotllan N, Cirera-Salinas D, Suarez Y, Autoregulation of glypican-1 by intronic microRNA-149 fine tunes the angiogenic response to FGF2 in human endothelial cells, J Cell Sci 127(Pt 6) (2014) 1169–78. [PubMed: 24463821]

[146]. Chamorro-Jorganes A, Lee MY, Araldi E, Landskroner-Eiger S, Fernandez-Fuertes M, Sahraei M, Quiles Del Rey M, van Solingen C, Yu J, Fernández-Hernando C, Sessa WC, Suárez Y, VEGF-Induced Expression of miR-17~92 Cluster in Endothelial Cells is Mediated by ERK/ELK1 Activation and Regulates Angiogenesis., Circulation Research (2015) CIRCRESAHA. 115.307408.

[147]. Suárez Y, Suarez Y, Fernandez-Hernando C, Fernández-Hernando C, Yu J, Yu J, Gerber SA, Gerber SA, Harrison KD, Harrison KD, Pober JS, Pober JS, Iruela-Arispe ML, Iruela-Arispe ML, Merkenschlager M, Merkenschlager M, Sessa WC, Sessa WC, Dicer-dependent endothelial microRNAs are necessary for postnatal angiogenesis., Proceedings of the National Academy of Sciences of the United States of America 105(37) (2008) 14082–14087. [PubMed: 18779589]

[148]. Dentelli P, Dentelli P, Rosso A, Rosso A, Orso F, Orso F, Olgasi C, Olgasi C, Taverna D, Taverna D, Brizzi MF, Brizzi MF, microRNA-222 Controls Neovascularization by Regulating Signal Transducer and Activator of Transcription 5A Expression, Arteriosclerosis, thrombosis, and vascular biology 30(8) (2010) 1562–1568.

[149]. Ivan M, Harris AL, Martelli F, Kulshreshtha R, Hypoxia response and microRNAs: no longer two separate worlds, J Cell Mol Med 12(5A) (2008) 1426–31. [PubMed: 18624759]

[150]. Raitoharju E, Lyytikainen LP, Levula M, Oksala N, Mennander A, Tarkka M, Klopp N, Illig T, Kahonen M, Karhunen PJ, Laaksonen R, Lehtimaki T, miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study, Atherosclerosis 219(1) (2011) 211–7. [PubMed: 21820659]

[151]. Ghosh G, Subramanian IV, Adhikari N, Zhang X, Joshi HP, Basi D, Chandrashekhar YS, Hall JL, Roy S, Zeng Y, Ramakrishnan S, Hypoxia-induced microRNA-424 expression in human endothelial cells regulates HIF-alpha isoforms and promotes angiogenesis, The Journal of clinical investigation 120(11) (2010) 4141–54. [PubMed: 20972335]

[152]. Leisegang MS, Fork C, Josipovic I, Richter FM, Preussner J, Hu J, Miller MJ, Epah J, Hofmann P, Gunther S, Moll F, Valasarajan C, Heidler J, Ponomareva Y, Freiman TM, Maegdefessel L, Plate KH, Mittelbronn M, Uchida S, Kunne C, Stellos K, Schermuly RT, Weissmann N, Devraj K, Wittig I, Boon RA, Dimmeler S, Pullamsetti SS, Looso M, Miller FJ, Jr., Brandes RP, Long Noncoding RNA MANTIS Facilitates Endothelial Angiogenic Function, Circulation 136(1) (2017) 65–79. [PubMed: 28351900]

[153]. Tall AR, Yvan-Charvet L, Cholesterol, inflammation and innate immunity, Nat Rev Immunol 15(2) (2015) 104–16. [PubMed: 25614320]

[154]. Greaves DR, Gordon S, Thematic review series: the immune system and atherogenesis. Recent insights into the biology of macrophage scavenger receptors, J Lipid Res 46(1) (2005) 11–20. [PubMed: 15548472]

[155]. Dickhout JG, Hossain GS, Pozza LM, Zhou J, Lhotak S, Austin RC, Peroxynitrite causes endoplasmic reticulum stress and apoptosis in human vascular endothelium: implications in atherogenesis, Arterioscler Thromb Vasc Biol 25(12) (2005) 2623–9. [PubMed: 16210571]

[156]. Seimon T, Tabas I, Mechanisms and consequences of macrophage apoptosis in atherosclerosis, J Lipid Res 50 Suppl (2009) S382–7. [PubMed: 18953058]

[157]. Randolph GJ, Mechanisms that regulate macrophage burden in atherosclerosis, Circ Res 114(11) (2014) 1757–71. [PubMed: 24855200]

[158]. Herrera-Merchan A, Cerrato C, Luengo G, Dominguez O, Piris MA, Serrano M, Gonzalez S, miR-33-mediated downregulation of p53 controls hematopoietic stem cell self-renewal, Cell Cycle 9(16) (2010) 3277–85. [PubMed: 20703086]

[159]. Rotllan N, Ramirez CM, Aryal B, Esau CC, Fernandez-Hernando C, Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in Ldlr−/− mice--brief report, Arterioscler Thromb Vasc Biol 33(8) (2013) 1973–7. [PubMed: 23702658]

[160]. Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, Fisher EA, Moore KJ, Fernández-Hernando C, MiR-33 contributes to the regulation of cholesterol homeostasis., Science, 2010, pp. 1570–1573.

[161]. Ramirez CM, Goedeke L, Rotllan N, Yoon JH, Cirera-Salinas D, Mattison JA, Suarez Y, de Cabo R, Gorospe M, Fernandez-Hernando C, MicroRNA 33 Regulates Glucose Metabolism, Mol Cell Biol 33(15) (2013) 2891–902. [PubMed: 23716591]

[162]. Price NL, Holtrup B, Kwei SL, Wabitsch M, Rodeheffer M, Bianchini L, Suarez Y, Fernandez-Hernando C, SREBP-1c/miR-33b genomic loci control adipocyte differentiation, Mol Cell Biol (2016).

[163]. Goedeke L, Vales-Lara FM, Fenstermaker M, Cirera-Salinas D, Chamorro-Jorganes A, Ramirez CM, Mattison JA, de Cabo R, Suarez Y, Fernandez-Hernando C, A regulatory role for microRNA 33* in controlling lipid metabolism gene expression, Mol Cell Biol 33(11) (2013) 2339–52. [PubMed: 23547260]

[164]. Goedeke L, Salerno A, Ramirez CM, Guo L, Allen RM, Yin X, Langley SR, Esau C, Wanschel A, Fisher EA, Suarez Y, Baldan A, Mayr M, Fernandez-Hernando C, Long-term therapeutic silencing of miR-33 increases circulating triglyceride levels and hepatic lipid accumulation in mice, EMBO Mol Med 6(9) (2014) 1133–41. [PubMed: 25038053]

[165]. Davalos A, Goedeke L, Smibert P, Ramirez CM, Warrier NP, Andreo U, Cirera-Salinas D, Rayner K, Suresh U, Pastor-Pareja JC, Esplugues E, Fisher EA, Penalva LO, Moore KJ, Suarez Y, Lai EC, Fernandez-Hernando C, miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling, Proc Natl Acad Sci U S A 108(22) (2011) 9232–7. [PubMed: 21576456]

[166]. Cirera-Salinas D, Pauta M, Allen RM, Salerno AG, Ramirez CM, Chamorro-Jorganes A, Wanschel AC, Lasuncion MA, Morales-Ruiz M, Suarez Y, Baldan A, Esplugues E, Fernandez-Hernando C, Mir-33 regulates cell proliferation and cell cycle progression, Cell Cycle 11(5) (2012) 922–33. [PubMed: 22333591]

[167]. Ouimet M, Ediriweera HN, Gundra UM, Sheedy FJ, Ramkhelawon B, Hutchison SB, Rinehold K, van Solingen C, Fullerton MD, Cecchini K, Rayner KJ, Steinberg GR, Zamore PD, Fisher EA, Loke P, Moore KJ, MicroRNA-33-dependent regulation of macrophage metabolism directs immune cell polarization in atherosclerosis, The Journal of clinical investigation 125(12) (2015) 4334–48. [PubMed: 26517695]

[168]. Price NL, Rotllan N, Canfran-Duque A, Zhang X, Pati P, Arias N, Moen J, Mayr M, Ford DA, Baldan A, Suarez Y, Fernandez-Hernando C, Genetic Dissection of the Impact of miR-33a and miR-33b during the Progression of Atherosclerosis, Cell Rep 21(5) (2017) 1317–1330. [PubMed: 29091769]

[169]. O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D, MicroRNA-155 is induced during the macrophage inflammatory response, Proc Natl Acad Sci U S A 104(5) (2007) 1604–9. [PubMed: 17242365]

[170]. Nazari-Jahantigh M, Wei Y, Noels H, Akhtar S, Zhou Z, Koenen RR, Heyll K, Gremse F, Kiessling F, Grommes J, Weber C, Schober A, MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages, The Journal of clinical investigation 122(11) (2012) 4190–202. [PubMed: 23041630]

[171]. Du F, Yu F, Wang Y, Hui Y, Carnevale K, Fu M, Lu H, Fan D, MicroRNA-155 deficiency results in decreased macrophage inflammation and attenuated atherogenesis in apolipoprotein E-deficient mice, Arterioscler Thromb Vasc Biol 34(4) (2014) 759–67. [PubMed: 24504735]

[172]. Tian FJ, An LN, Wang GK, Zhu JQ, Li Q, Zhang YY, Zeng A, Zou J, Zhu RF, Han XS, Shen N, Yang HT, Zhao XX, Huang S, Qin YW, Jing Q, Elevated microRNA-155 promotes foam cell formation by targeting HBP1 in atherogenesis, Cardiovasc Res 103(1) (2014) 100–10. [PubMed: 24675724]

[173]. Jablonski KA, Gaudet AD, Amici SA, Popovich PG, Guerau-de-Arellano M, Control of the Inflammatory Macrophage Transcriptional Signature by miR-155, PLoS One 11(7) (2016) e0159724. [PubMed: 27447824]

[174]. Xu F, Kang Y, Zhang H, Piao Z, Yin H, Diao R, Xia J, Shi L, Akt1-mediated regulation of macrophage polarization in a murine model of Staphylococcus aureus pulmonary infection, J Infect Dis 208(3) (2013) 528–38. [PubMed: 23613163]

[175]. Moore CS, Rao VT, Durafourt BA, Bedell BJ, Ludwin SK, Bar-Or A, Antel JP, miR-155 as a multiple sclerosis-relevant regulator of myeloid cell polarization, Ann Neurol 74(5) (2013) 709–20. [PubMed: 23818336]

[176]. O'Connell RM, Chaudhuri AA, Rao DS, Gibson WS, Balazs AB, Baltimore D, MicroRNAs enriched in hematopoietic stem cells differentially regulate long-term hematopoietic output, Proc Natl Acad Sci U S A 107(32) (2010) 14235–40. [PubMed: 20660734]

[177]. He M, Xu Z, Ding T, Kuang DM, Zheng L, MicroRNA-155 regulates inflammatory cytokine production in tumor-associated macrophages via targeting C/EBPbeta, Cell Mol Immunol 6(5) (2009) 343–52. [PubMed: 19887047]

[178]. Martinez-Nunez RT, Louafi F, Sanchez-Elsner T, The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor alpha1 (IL13Ralpha1), J Biol Chem 286(3) (2011) 1786–94. [PubMed: 21097505]

[179]. Wei Y, Zhu M, Corbalan-Campos J, Heyll K, Weber C, Schober A, Regulation of Csf1r and Bcl6 in macrophages mediates the stage-specific effects of microRNA-155 on atherosclerosis, Arterioscler Thromb Vasc Biol 35(4) (2015) 796–803. [PubMed: 25810298]

[180]. Li X, Kong D, Chen H, Liu S, Hu H, Wu T, Wang J, Chen W, Ning Y, Li Y, Lu Z, miR-155 acts as an anti-inflammatory factor in atherosclerosis-associated foam cell formation by repressing calcium-regulated heat stable protein 1, Sci Rep 6 (2016) 21789. [PubMed: 26899994]

[181]. Donners MM, Wolfs IM, Stoger LJ, van der Vorst EP, Pottgens CC, Heymans S, Schroen B, Gijbels MJ, de Winther MP, Hematopoietic miR155 deficiency enhances atherosclerosis and decreases plaque stability in hyperlipidemic mice, PLoS One 7(4) (2012) e35877. [PubMed: 22558252]

[182]. Wei Y, Nazari-Jahantigh M, Chan L, Zhu M, Heyll K, Corbalan-Campos J, Hartmann P, Thiemann A, Weber C, Schober A, The microRNA-342–5p fosters inflammatory macrophage activation through an Akt1- and microRNA-155-dependent pathway during atherosclerosis, Circulation 127(15) (2013) 1609–19. [PubMed: 23513069]

[183]. Taganov KD, Boldin MP, Chang KJ, Baltimore D, NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses, Proc Natl Acad Sci U S A 103(33) (2006) 12481–6. [PubMed: 16885212]

[184]. Li K, Ching D, Luk FS, Raffai RL, Apolipoprotein E enhances microRNA-146a in monocytes and macrophages to suppress nuclear factor-kappaB-driven inflammation and atherosclerosis, Circ Res 117(1) (2015) e1–e11. [PubMed: 25904598]

[185]. Hou J, Wang P, Lin L, Liu X, Ma F, An H, Wang Z, Cao X, MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2, J Immunol 183(3) (2009) 2150–8. [PubMed: 19596990]

[186]. He X, Tang R, Sun Y, Wang YG, Zhen KY, Zhang DM, Pan WQ, MicroR-146 blocks the activation of M1 macrophage by targeting signal transducer and activator of transcription 1 in hepatic schistosomiasis, EBioMedicine 13 (2016) 339–347. [PubMed: 27780686]

[187]. Peng L, Zhang H, Hao Y, Xu F, Yang J, Zhang R, Lu G, Zheng Z, Cui M, Qi CF, Chen C, Wang J, Hu Y, Wang D, Pierce S, Li L, Xiong H, Reprogramming macrophage orientation by microRNA 146b targeting transcription factor IRF5, EBioMedicine 14 (2016) 83–96. [PubMed: 27825654]

[188]. Cheng HS, Besla R, Li A, Chen Z, Shikatani EA, Nazari-Jahantigh M, Hammoutene A, Nguyen MA, Geoffrion M, Cai L, Khyzha N, Li T, MacParland SA, Husain M, Cybulsky MI, Boulanger CM, Temel RE, Schober A, Rayner KJ, Robbins CS, Fish JE, Paradoxical Suppression of Atherosclerosis in the Absence of microRNA-146a, Circ Res 121(4) (2017) 354–367. [PubMed: 28637783]

[189]. Nguyen MA, Karunakaran D, Geoffrion M, Cheng HS, Tandoc K, Perisic Matic L, Hedin U, Maegdefessel L, Fish JE, Rayner KJ, Extracellular Vesicles Secreted by Atherogenic Macrophages Transfer MicroRNA to Inhibit Cell Migration, Arterioscler Thromb Vasc Biol (2017).

[190]. Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, Sun F, Lu J, Yin Y, Cai X, Sun Q, Wang K, Ba Y, Wang Q, Wang D, Yang J, Liu P, Xu T, Yan Q, Zhang J, Zen K, Zhang C-Y, Secreted monocytic miR-150 enhances targeted endothelial cell migration., Mol. Cell, 2010, pp. 133–144. [PubMed: 20603081]

[191]. Zhuang G, Meng C, Guo X, Cheruku PS, Shi L, Xu H, Li H, Wang G, Evans AR, Safe S, Wu C, Zhou B, A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation, Circulation 125(23) (2012) 2892–903. [PubMed: 22580331]

[192]. Dorhoi A, Iannaccone M, Farinacci M, Fae KC, Schreiber J, Moura-Alves P, Nouailles G, Mollenkopf HJ, Oberbeck-Muller D, Jorg S, Heinemann E, Hahnke K, Lowe D, Del Nonno F, Goletti D, Capparelli R, Kaufmann SH, MicroRNA-223 controls susceptibility to tuberculosis by regulating lung neutrophil recruitment, The Journal of clinical investigation 123(11) (2013) 4836–48. [PubMed: 24084739]

[193]. Banerjee S, Cui H, Xie N, Tan Z, Yang S, Icyuz M, Thannickal VJ, Abraham E, Liu G, miR-125a-5p regulates differential activation of macrophages and inflammation, J Biol Chem 288(49) (2013) 35428–36. [PubMed: 24151079]

[194]. Wang Z, Brandt S, Medeiros A, Wang S, Wu H, Dent A, Serezani CH, MicroRNA 21 is a homeostatic regulator of macrophage polarization and prevents prostaglandin E2-mediated M2 generation, PLoS One 10(2) (2015) e0115855. [PubMed: 25706647]

[195]. Canfran-Duque A, Rotllan N, Zhang X, Fernandez-Fuertes M, Ramirez-Hidalgo C, Araldi E, Daimiel L, Busto R, Fernandez-Hernando C, Suarez Y, Macrophage deficiency of miR-21 promotes apoptosis, plaque necrosis, and vascular inflammation during atherogenesis, EMBO Mol Med 9(9) (2017) 1244–1262. [PubMed: 28674080]

[196]. Carpenter S, Aiello D, Atianand MK, Ricci EP, Gandhi P, Hall LL, Byron M, Monks B, Henry-Bezy M, Lawrence JB, O'Neill LA, Moore MJ, Caffrey DR, Fitzgerald KA, A long noncoding RNA mediates both activation and repression of immune response genes, Science 341(6147) (2013) 789–92. [PubMed: 23907535]

[197]. Tong Q, Gong AY, Zhang XT, Lin C, Ma S, Chen J, Hu G, Chen XM, LincRNACox2 modulates TNF-alpha-induced transcription of Il12b gene in intestinal epithelial cells through regulation of Mi-2/NuRD-mediated epigenetic histone modifications, FASEB J 30(3)(2016) 1187–97. [PubMed: 26578685]

[198]. Hu G, Gong AY, Wang Y, Ma S, Chen X, Chen J, Su CJ, Shibata A, Strauss-Soukup JK, Drescher KM, Chen XM, LincRNA-Cox2 Promotes Late Inflammatory Gene Transcription in Macrophages through Modulating SWI/SNF-Mediated Chromatin Remodeling, J Immunol 196(6) (2016) 2799–2808. [PubMed: 26880762]

[199]. Li Z, Chao TC, Chang KY, Lin N, Patil VS, Shimizu C, Head SR, Burns JC, Rana TM, The long noncoding RNA THRIL regulates TNFalpha expression through its interaction with hnRNPL, Proc Natl Acad Sci U S A 111(3) (2014) 1002–7. [PubMed: 24371310]

[200]. Ilott AJ, Trease NM, Grey CP, Jerschow A, Multinuclear in situ magnetic resonance imaging of electrochemical double-layer capacitors, Nat Commun 5 (2014) 4536. [PubMed: 25082481]

[201]. Reddy MA, Chen Z, Park JT, Wang M, Lanting L, Zhang Q, Bhatt K, Leung A, Wu X, Putta S, Saetrom P, Devaraj S, Natarajan R, Regulation of inflammatory phenotype in macrophages by a diabetes-induced long noncoding RNA, Diabetes 63(12) (2014) 4249–61. [PubMed: 25008173]

[202]. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, Hristov M, Koppel T, Jahantigh MN, Lutgens E, Wang S, Olson EN, Schober A, Weber C, Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection, Sci Signal 2(100) (2009) ra81. [PubMed: 19996457]

[203]. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, Hunninghake GM, Vera MP, Registry M, Blackwell TS, Baron RM, Feinberg MW, MicroRNA-181b regulates NF-kappaB-mediated vascular inflammation, J Clin Invest 122(6) (2012) 1973–90. [PubMed: 22622040]

[204]. Son DJ, Kumar S, Takabe W, Kim CW, Ni CW, Alberts-Grill N, Jang IH, Kim S, Kim W, Won Kang S, Baker AH, Woong Seo J, Ferrara KW, Jo H, The atypical mechanosensitive microRNA-712 derived from pre-ribosomal RNA induces endothelial inflammation and atherosclerosis, Nat Commun 4 (2013) 3000. [PubMed: 24346612]

[205]. Li D, Yang P, Xiong Q, Song X, Yang X, Liu L, Yuan W, Rui YC, MicroRNA-125a/b-5p inhibits endothelin-1 expression in vascular endothelial cells, J Hypertens 28(8) (2010) 1646–54. [PubMed: 20531225]

[206]. Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, Sun F, Lu J, Yin Y, Cai X, Sun Q, Wang K, Ba Y, Wang Q, Wang D, Yang J, Liu P, Xu T, Yan Q, Zhang J, Zen K, Zhang CY, Secreted monocytic miR-150 enhances targeted endothelial cell migration, Mol Cell 39(1) (2010) 133–44. [PubMed: 20603081]

Table 1.

Regulation of endothelial non-coding RNAs in atherosclerosis

ncRNA	Target	Function	Atherosclerosis outcome	References
miR-10a	MAP3K7, βTRC	↓EC activation	Anti	[88]
miR-17–3p, miR-31	ICAM-1, SELE	↓EC activation	Anti	[86]
miR-126	RGS16, VCAM1	↓Apoptosis, EC activation	Anti	[85, 202]
miR-143/145	eNOS, ETS-1	↑EC activation	Pro	[80]
miR-146a	TRAF6, IRAK1, HuR	↓EC activation	Anti	[95, 150]
miR-181b	KPNA4	↓EC activation	Anti	[87, 203]
miR-365	BCL2	↓EC activation	Anti	[100]
ANRIL	CDKN2A, CDKN2B	↑EC activation	Pro	[93]
circANRIL	PES1	↓EC activation/ apoptosis	Anti	[94]
let-7g	LOX-1	↓EC activation/ cell senescence	Anti	[97–99]
MALAT1	ICAM-1, VEGF, TNFα	↑Inflammatory activation	Unknown	[101, 104]
MALAT1	miR-22–3p, CCR2, AKT	Anti-inflammatory	Unknown	[105]
MEG3	miR-9	Deficiency ↓EC leakage and inflammation	Unknown	[108, 109]
miR-92a	SOCS5, KLF2/KLF4	↑Inflammation and EC activation	Pro	[81, 82]
miR-712	TIMP3	Disturbed flow/ EC activation	Pro	[84, 204]
miR-221/222	STAT5A	Neovascularization/ barrier function	Anti	[148]
MANTIS	BRG1	Angiogenic modulaton	Unknown	[152]
miR-125a/b	CDH5, ET-1	Barrier function, vascular tone	Unknown	[120, 129, 205]
miR-147b	ADAM15	Improves barrier function	Unknown	[131]
miR-155	eNOS	↓Barrier function/ vascular tone/ adherens junction assembly	Pro	[116, 117]
TieAS	Tie-1	Worsens barrier function	Unknown	[134]
MIAT	miR150–5p, ICAM-1, VEGF	Improves barrier function and reduces inflammation	Unknown	[137]
NEAT1	miR-181d/ SOX5, ZO-1	Increases barrier function	Unknown	[138]
sONE	eNOS	Vascular tone	Unknown	[122]
AK094457	iNOS	↓NO production and vascular tone	Unknown	[124]

Table 2.

Regulation of macrophage non-coding RNAs in atherosclerosis

ncRNA	mRNA target	Function	Regulation	Atherosclerosis outcome	References
miR-21	STAT3, SOCS1, MKK3	↓Lipid uptake and inflammation	Induced in plaques	Anti	[194, 195]
miR-33	AMPK,	↑Inflammation		Pro	[167, 168]
miR-125	KLF13	↓TH1 response	Induced by TLRs	Anti	[193]
miR-146	IRAK1, TRAF6	↓Inflammation	Up in athero plaques	Anti	[150, 184]
miR-150	c-Myb	↑EC migration	Secreted, ↑with inflammatory stimuli	Pro	[206]
miR-155	SOCS-1, BCL6, IL-13Ra1, CARHSP1	↑Inflammation through SOCS-1, BCL6 ↓Inflammation through CARHSP1	Induced by oxLDL, TLRs	Pro and anti	[176–179]
miR-223	PKNOX, CXCL2, CCL3	Suppress M1 activation		Anti	[191, 192]
miR-342–5p	AKT-1	↑Inflammation	↑in athero plaques	Pro	[182]
LncRNACox2	hnRNPAB, SWI/SNF	Inflammatory activation	Induced by proinflammatory cytokines	Unknown	[196–198]
THRIL	hnRNPL	↑TNFα induction	Induced by Pam3CSK4	Unknown	[199]
RP-833A20.1	miR-382–5p	Suppresses cholesterol and inflammation	↑ in human foam cells	Unknown	[31]
E330013	Unknown	Promotes M1 activation	Up in macrophages of diabetic mice	Unknown	[201]