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Long Non-coding RNAs in Atherosclerosis: *JACC* Review Topic of the Week

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Abstract

Atherosclerosis is a complex and chronic disease characterized by lipid deposition in the vessel wall that leads to an inflammatory and proliferative cascade involving smooth muscle, endothelial and immune cells. Despite substantial improvements in our understanding of mechanisms contributing to atherosclerosis and overall reduction in cardiovascular mortality, the absolute disease burden remains substantially high. The recent discovery of a new group of mediators known as long noncoding RNAs (lncRNAs) offers a unique opportunity for the development of novel diagnostic and therapeutic tools in atherothrombotic disease. A number of studies suggest that lncRNAs are important mediators in health and disease and rapidly accumulating evidence implicates lncRNAs in regulatory circuits controlling atherosclerosis. In this review, we outline important contributions of lncRNAs to atherosclerosis and its associated risk factors including hypercholesterolemia, diabetes, hypertension and obesity.

Condensed Abstract:

Atherosclerosis is the single most devastating cause of worldwide mortality forming the epicenter of major efforts to mitigate cardiovascular disease. Understanding how genetic sequences control function has substantially improved our understanding of common cardiovascular problems including atherosclerosis. Galvanized by evidence from the human genome project, an expanded genetic catalog has led to the discovery of new players in biology known as long noncoding RNAs (lncRNAs). In this review, we discuss the contributions of lncRNAs to atherosclerosis risk factors and key cells involved in plaque formation. The identification of lncRNAs offers newly recognized opportunities for cardiovascular risk mitigation.

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Keywords

Non-coding RNA; Arteriosclerosis; genetic, knockout models; genetics, bioinformatics; Atherosclerosis; Lipids and Cholesterol; Genetics; Gene expression and regulation

Introduction

Although a precise cause for how atherosclerosis develops is not fully understood, it is well established that a number of traits increase the propensity for disease development and progression. Major modifiable risk factors for atherosclerosis development often occur in concert and include dyslipidemia, hypertension, diabetes as well as lifestyle factors such obesity and smoking. These risk factors do not equally impact disease progression, but a cornerstone of cardiovascular risk reduction includes mitigating the influence of all the above traits using lifestyle interventions or pharmacotherapy. A few of the drugs commonly used today for cardiovascular risk reduction, such as PCSK9 inhibitors, have been inspired by population genetics and complementary mechanistic studies that have dissected the relationship between gene variants and disease phenotype (1). Recently a more expanded catalog of functional genetic material has been identified with the discovery of unique set of genes referred to as long noncoding RNAs (lncRNAs). Modulation of lncRNA genes has been shown to play important roles in various stages of plaque development and may potentially offer novel diagnostic and therapeutic strategies to reduce atherosclerosis burden.

Fifty years after the term “junk DNA” became popular (2) evidence from the human genome project showed that the vast majority of human DNA bases are associated with at least one RNA transcript. Furthermore, most of these transcripts do not appear to code for functional proteins (3). These findings have helped catalyze the promulgation of the field of lncRNA biology. Today, lncRNAs are defined as noncoding transcripts >200 bp, in order to distinguish them from other types of noncoding RNA such as microRNAs. In just over a decade, there have been >10,000 studies characterizing important biological roles for these novel mediators and strongly implicating them in human disease. Although the bulk of these studies have focused on the contribution of lncRNAs in cellular development and differentiation, rapidly accumulating evidence suggests an additional contribution of lncRNAs in cardiovascular disease.

A remarkable feature of lncRNAs is that they are expressed with potent specificity. For example, roughly 80% of lncRNAs are highly tissue-specific which in theory suggests that may serve as disease markers or therapeutic targets (4). Indeed, a small number of studies have shown that lncRNAs could serve as disease markers in cancer states and cardiovascular disease (5,6). Although the precise mode of action of lncRNAs remains mysterious, diverse mechanisms have been proposed and extensively outlined elsewhere (7,8). A summary of these mechanisms is provided in Figure 1. In brief, lncRNAs can function by acting as decoys or guides to chromatin modifying and transcriptional machinery thus directly influencing gene expression. LncRNAs have also been shown to impact mRNA splicing, nuclear to cytoplasmic shuttling, and translation. Some lncRNAs may impact post-translational protein modification while others have been shown to buffer other regulatory

mediators such as microRNAs. Regardless of proposed mechanism, however, functional relevance has been established for a large repertoire of lncRNAs in cardiovascular disease (9). In this review, we will highlight important contributions of lncRNAs in cardiometabolic risk factors such as dyslipidemia, hypertension, obesity and diabetes as well as lncRNAs that directly contribute to the development and propagation of atherothrombotic events (Figure 2). A summary of lncRNAs and interacting partners are provided in Table 1.

LncRNAs modulating atherosclerosis risk factors

Dyslipidemia

Abnormal cholesterol accumulation is a hallmark of atherosclerosis lesion development. Although the contributions of lncRNAs in sterol regulation is not well studied, multiple lines of evidence revealed important contributions of lncRNAs in sterol regulatory circuits. The vast majority of this evidence, however, comes from mechanistic animal studies. At the level of systemic lipid metabolism, Li and colleagues showed that loss of the lncRNA lncLSTR in mice markedly reduced plasma triglyceride levels (10). LncLSTR is thought to regulate expression of Cyp8b1, a rate-limiting enzyme in the bile acid biosynthesis, via interaction with the RNA-binding protein TDP-43. The change in bile acid pool alters the activity of the bile acid receptor FXR and leads to enhanced ApoC2 lipoprotein, an important component of very low-density lipoproteins and chylomicrons. Our previous work has shown that the lncRNA *LeXis* acts as important conduit between the nutrient-sensing nuclear receptor liver X receptor (LXR) and the master cholesterol regulator Srebp2. Under conditions where sterols accumulate in liver, *LeXis* is robustly induced with LXR activation, which in turn reduces *de novo* cholesterol synthesis by blocking the DNA binding of the transcriptional activator Raly at Srebp2-regulated genes including Hmgcr, the target of statin drugs (11). Loss of *LeXis* has a strong impact on serum cholesterol levels and hepatic sterol content. More recently, a gene therapy strategy utilizing *LeXis* was shown to reduce atherosclerosis burden in an animal model of familial hypercholesterolemia (12). Although a putative human *LeXis* transcript has been identified, the relevance of the *LeXis* pathway in humans remains undefined.

Using evidence from human hepatoma samples, a recent study showed that that the lncRNA HULC modulates the activity of the acyl-CoA synthetase subunit ACSL1, an enzyme responsible for fatty acid synthesis, through activation of the nuclear receptors PPARA and RXRA(13). The authors go on to show that HULC promotes lipogenesis in an *in vivo* murine model substantiating the contributions of lncRNAs in integrating metabolic signaling with cellular proliferation. Finally, lncRNAs play important roles in lipid transport. An endogenous antisense transcript, APOA1-AS, acts as a negative transcriptional regulator of APOA1 (14). Antisense oligonucleotides targeting APOA1-AS increase ApoA1 levels in primates.

Collectively these studies suggest that dysregulation in lncRNA regulatory circuits can alter sterol balance in vitro and in vivo. Despite these interesting observations, however, it should be noted that human functional conservation for the majority of these lncRNAs has not been established. In addition, it is unclear whether any of the above of the lncRNAs can be readily detected in blood or other accessible compartments. Thus, a major question moving forward

is whether the lncRNAs described above have any relevance to human disease or potential diagnostic and therapeutic applications.

Obesity

Obesity, an established independent risk factor for heart disease, is a worsening health hazard in most parts of the world (6). Not surprisingly, substantial efforts have recently been devoted to dissecting pathways that influence the development of obesity, such as the role of lncRNAs in fat formation and maintenance of energy balance. Some of the earliest evidence implicating noncoding genes in metabolic phenotypes comes from studies linking the Igf2 locus with obesity (15). Epidemiological data from human blood leukocytes suggests that differences in methylation at the Igf2 gene and neighboring noncoding gene are associated with paternal obesity (15). Intriguingly, deletion of a noncoding region between Igf2 and the noncoding gene H19 in animal models was accompanied by increased fat deposition and obesity through poorly understood mechanisms (16). Similar genetic evidence suggests that the noncoding RNA LINC00237 is directly implicated in MOMO Syndrome, a rare autosomal recessive disease characterized by macrosomia, obesity, macrocephaly, and ocular abnormalities (17). Interestingly, LINC00237 is expressed in the brain; suggesting it may play a role in social disorders and feeding behavior (17). Prader-Willi syndrome (PWS) is a genetic disorder characterized by a loss of a noncoding RNA from chromosome 15q11-q13 leading to obesity from hyperphagia and intellectual disability (18). Using iPSC cells derived from PWS patients, a recent study showed that that expression of the chromatin-modifying lncRNA IPW is associated with abnormal expression of maternally expressed genes responsible for the PWS phenotype (19).

In addition to inherited obesity syndromes, systematic interrogation of lncRNAs revealed important clues to the role of these molecules in normal adipose tissue development. Work from the Rinn group showed, on a genome-wide scale, that 175 lncRNAs are specifically regulated during murine adipogenesis and that knockdown of some of these lncRNAs led to abnormal adipose tissue formation *in vitro* (20). A role for lncRNAs in energy homeostasis has also been corroborated *in vivo*. Using integrative transcriptome approaches, Yang and colleagues identified lncRNAs in diverse organs involved in energy metabolism. Using this framework, they showed that one of these lncRNAs, LncMS, acts as a suppressor of lipogenesis by modulating the activity of the master metabolic regulator srebp1c in liver (21). Finally, RNA-seq data from human tissues suggests that certain lncRNAs such as linc-DMRT2 and linc-TP53I13 may be dysregulated in human adipose tissue from obese patients compared with normal controls (22).

Since lncRNAs have been shown to directly influence transcriptional outputs, it is not surprising that a number of lncRNAs have been found to act as coactivators for important adipogenic transcription factors. For example, the SRA noncoding RNA has been shown to function as a transcriptional coactivator of PPARγ, the master regulator of adipogenesis (22). Knockout of SRA in mice is associated with decreased fat mass and enhanced insulin sensitivity.

Overall a preponderance of evidence supports the notion that lncRNAs are differentially regulated during obesity and that perturbations of lncRNAs may be causally linked to human

adiposity. More recently, an area that has attracted growing attention is the contribution of lncRNAs to brown adipose tissue function, a critical determinant of energy expenditure. Recent evidence suggests that the conserved lncRNA Blnc1 enhances the activity of the browning adipose transcription factor EBF-2 to stimulate thermogenesis (23). Given the substantial interest in developing therapies that enhance thermogenesis as means of treating obesity, continued interrogation of lncRNAs in this setting may lead to fruitful results.

Diabetes

The first evidence suggesting that non-coding transcripts play important metabolic roles came from systematic interrogation of human pancreatic islet and β cells (24). This work catalogs over 1000 dynamically regulated lncRNAs in type I diabetes and reinforces the tissue-specific expression of some of these lncRNAs. In addition, a number of lncRNAs have been shown to be important for human islet cell function by acting in concert with pancreatic lineage specific transcription factors. For example, the lncRNA PLUTO influences the β cell transcription factor PDX1 by regulating chromatin architecture. PLUTO levels are downregulated in islets from donors with type 2 diabetes or impaired glucose tolerance (25). Similar unbiased high throughput studies analyzing human pancreatic islets revealed that certain lncRNAs are highly enriched when comparing patients with hyperglycemia to normal glucose controls (26). In addition, mechanistic evidence has linked dysregulation of lncRNAs with serum glucose levels. For example, the conserved lncRNA Betalinc1 is involved in normal islet cell formation knockout of this lncRNA in a murine model resulted in glucose intolerance through regulation of β-cell rich genes (27). Given the strong influence of autoimmunity in type I diabetes, it is not surprising that lncRNAs have been implicated in organ-specific immune activation. *Flicr* (*Foxp3* long intergenic noncoding RNA) is a *cis*-acting noncoding RNA in human and mouse regulatory T cells which acts as negative regulator of *Foxp3* expression by modifying chromatin accessibility (28). *Flicr* promotes autoimmune diabetes whereas its loss of function is associated with improved glucose control in mice. Taken together, the above studies strongly suggest that lncRNAs directly contribute to the regulation of systemic glucose homeostasis by modulating islet cell function as well as priming immune pathways and impacting disease progression.

Unbiased population genetic studies found a strong association between SNPs at intergenic noncoding regions or intronic transcripts with diabetes risk. For example, a SNP in the first intron of ABO at the putative promoter of an antisense lncRNA was significantly associated with elevated fasting glucose levels (29). Mechanistically, how this noncoding region may be conferring disease risk or whether biological effects could be attributed to other genes in the vicinity remains largely unexplored. A number of clinical studies investigating the potential of lncRNAs to serve as diabetes clinical disease markers have shown promising initial results (30). For example, profiling of human serum samples revealed that the lncRNA Gas5 strongly correlates with type 2 diabetes risk (31). However, more robust clinical evidence systematically validating these results is required. In summary, the weight of evidence suggests that lncRNAs play important roles in human diabetes development but additional insight into the pathophysiology of these lncRNAs remains lacking.

Hypertension

A limited number of studies have also demonstrated a role for lncRNAs in hypertension. It is well established that dysregulation in the renin angiotensin system is causally associated with hypertension and heart disease risk. Using unbiased transcriptional profiling coupled with epigenetic interrogation, one study identified differentially regulated lncRNAs in vascular smooth muscle cells in response to angiotensin II (32). Loss of one these lncRNAs, Lnc-Ang362, resulted in reduced proliferation of VSMC thereby corroborating an important role for lncRNAs in molecular mechanisms driving the development of hypertension. Similarly, a number of studies profiling lncRNAs in rat models of hypertension have observed unique transcriptional signatures (33,34). Recently, an elegant report implicated the nuclear lncRNA MANTIS in modulating human endothelial function through direct interactions with brg1, an important component of chromatin modifying machinery (35). Finally, GWAS has provided further evidence linking noncoding regions with hypertension. Variants at the lncRNA ANRIL locus have been strongly associated with systemic hypertension and vascular aneurysms (36–38) . Although ANRIL is a commonly studied lncRNA, its precise role in impacting a number of cardiovascular traits including hypertension remains poorly understood. Remarkably, very few studies have investigated the contributions of lncRNAs to systemic blood pressure in humans.

LncRNAs inside the lesion

Genome wide association studies have shed important light on disease regulatory circuits controlling heart disease. An astonishing finding validated by the multiple groups is that the strongest GWAS hit associated with risk of heart disease in humans by far is the noncoding RNA ANRIL located at chromosome 9p21 region (39,40). The function of this lncRNA has been completely puzzling but a number of studies suggest an important role in cellular proliferative responses within lesions (41). This is particularly timely since growing evidence suggests that regulation of smooth muscle or macrophage proliferation has a profound impact on lesion progression (42,43). A number of studies directly measuring lncRNAs in human atherosclerosis lesions including carotid plaque have found a number of lncRNAs, including GAS5, SNHG6 and Zfas1, to be dramatically increased in this context (44). More recently, several lncRNAs, such as ANRIL and KCNQ1OT1, have been measured in blood from patients with myocardial infarction and their levels have been found to predict left ventricular dysfunction in multivariable analysis models (45). Given that atherosclerosis development involves an orchestrated interplay between endothelial, immune and smooth muscle cells, we review the contributions of lncRNAs in each of these cells below.

Immune Cells

A number of studies have shown important contributions of lncRNAs to sterol regulation in macrophages, key drivers of atherogenesis and integrators of metabolic and inflammatory signaling. The lncRNA *RP5–833A20.1* is an intronic lncRNA that regulates the transcription factor NFIA in human foam-cell macrophages by modulating microRNA hsa-miR-382–5p (46). Recent work identified the lncRNA *MeXis* as an important contributor to cellular responses to cholesterol overload in macrophages (47). *MeXis* influences chromatin

architecture at the locus of critical cholesterol efflux regulator Abca1 to enhance Abca1 expression. This effect requires the transcriptional coactivator DDX17. Loss of *MeXis* from immune cells using a genetic deletion approach markedly enhances foam cell formation and accelerates atherosclerosis in a murine model. In addition, perturbing a human orthologue of *MeXis* influences Abca1 levels and function in human macrophages. A SNP overlapping the human *MeXis* orthologue is associated with coronary artery disease risk, hinting at functional conservation of this lncRNA. In addition, deep sequencing of human-derived macrophage transcriptomes corroborates dynamic regulation of macrophage lncRNAs in response to exogenous stimuli and loss of one these lncRNAs influenced IFN-γ signaling (48).

A number of lncRNAs have been shown to play important roles in other immune cell subtypes thought to be highly relevant to lesion development; although their effects on atherosclerosis have not been directly tested. Lnc-DC is a noncoding transcript expressed with potent specificity in human dendritic cells. This STAT3 binding noncoding RNA promotes STAT3 phosphorylation and enhances T cell activation (49). LincCox2 and LincRNA EPS are two conserved lncRNAs found to be induced by TLR ligands in BMDMs leading to activation or repression of a subset of inflammatory genes *in vivo*(50) (51). Similarly, the murine lncRNA NeST alters chromatin methylation patterns at the interferon gamma locus in T cells (52).

Since most of the lncRNAs described here have been shown to modulate inflammatory signaling in vivo, it would be intriguing to directly test their contribution to lesion development since this has only been tested in a few studies. Furthermore, a number of lncRNAs described in this section have been shown to potently modulate IL-1B, a key target of anti-inflammatory therapy shown to reduce cardiovascular disease burden in the CANTOS trial (53). Given the growing interest in developing novel strategies that target lesions directly, interrogation of lncRNAs may be one promising approach. However, it cannot be overstated that future studies need to directly delineate the role of lncRNAs in human lesions and immune-subsets from disease patients and matching controls.

Endothelial Cells

Dysfunction of endothelial lining of blood vessels is a key inciting event in atherosclerosis initiation. Multiple lines of evidence corroborate important roles for lncRNAs in endothelial cell function. Interrogation of human umbilical vein endothelial cells (HUVECs) responses to oxidized LDL loading revealed dysregulation of hundreds of lncRNAs (54). More recently, a number of studies have shown that commonly used cardiovascular drugs may function through modulation of lncRNA activity. For example, clopidogrel reduces cell death and promotes proliferation of human vascular endothelial cells through the expression of LncRNA HIF 1 alpha-antisense RNA 1 (HIF1A-AS1) (55). In fact, knockdown of HIF1A-AS1 is sufficient to promote proliferation and suppress apoptosis of HUVECs. Another antisense transcript to the tyrosine kinase Tie1 (tie-1AS) has been shown to modulate tie1 protein activity and is differentially regulated in samples from infants and children with various vascular malformations (56).

More recently, various lncRNA regulatory circuits have been shown to impact autophagy, proliferation and inflammation in vascular endothelial cells (57,58). MALAT1 is a notable conserved lncRNA shown to influence proliferation of endothelial cells *in vivo* and neonatal retina vascularization (59). An interesting report suggests that the lncRNA Meg3 is also important in controlling endothelial function (60). Inhibition of Meg3 in HUVECs prevented aging-mediated inhibition of angiogenic sprouting, and *in vivo* silencing led to improved blood flow in an ischemic hindlimb mouse model. It is tempting to speculate that inhibition of Meg3 may represent a therapeutic strategy for mitigating age-related endothelial dysfunction. Overall, the rapidly growing evidence presented here highlights the important contributions of lncRNAs to endothelial cell function, particularly in human endothelial cell models. However, the relevance of these lncRNAs to whole organism development and function is less well understood.

Vascular Smooth Muscle Cells

A number of studies have cataloged lncRNAs in human vascular smooth muscle cells. Bell and colleagues identified a number of lncRNAs in human coronary artery smooth muscle cells including *ENCR* (Smooth muscle and Endothelial cell enriched migration/differentiation-associated long Non-Coding RNA), which is thought to influence smooth muscle contractile machinery and inflammatory mediators (61). Lincp21 a well-characterized lncRNA that is conserved between mice and humans and was originally identified as a noncoding transcript regulated by p53 and required for p53 mediated transcriptional repression by interacting with hnRNP-K (62). Recent evidence suggests that inhibition of lincRNA-p21 results in neointimal hyperplasia in a mouse carotid disease model and that lincRNA-p21 expression is decreased in patients with coronary artery disease (63). Lately, the novel lncRNA SMILR was shown to be induced in proliferating smooth muscle cells in response to interleukin-1α and PDGF stimulation (64). Remarkably, SMILR expression was more enhanced in serum samples from patients with unstable atherosclerotic plaques. Considerable interest lately has also been devoted to understanding cardiovascular progenitor to disease transitions. A recent study identified 3 novel lncRNAs, *TERMINATOR*, *ALIEN,* and *PUNISHER,* in cardiovascular development (65). Given the substantial recent interest in linking proliferative pathways and plaque development, lncRNAs such lincRNA-p21 and SMILR may be viable targets for disease modulation. In addition, it is also plausible that lineage tracing of lncRNA expression patterns can provide clues to the origin and fates of smooth muscle cells within lesions a topic of much debate in scientific circuits (42).

Conclusions and Future Perspective

The study of lncRNAs has undoubtedly changed the way we think about health and disease, yet a number of important questions remain unresolved. The expression level of many lncRNAs remains quite low, which brings some uncertainty to the reliability and reproducibility of large-scale lncRNA interrogations. Protein-coding transcripts are transported to the cytoplasm and bound by ribosomes whereas most non-coding transcripts are retained in the nucleus? Understanding the molecular basis of why seemingly structurally similar transcripts are destined for different cellular fates remains unresolved. A

few studies reported that lncRNAs can be detected in exosomes, extracellular transport vesicles that carry biologic mediators, but the triaging of some lncRNAs to the circulation remains poorly understood (66,67). More importantly, *de novo* discovery of lncRNAs is costly and often requires extensive sequencing with no established standards regarding data analysis methodologies. Another major challenge in studying lncRNAs is the lack of predictive function based on sequence or structural features. One can predict the function of a protein-coding gene based on known homology domains and the function of a micoRNA gene based on bioinformatic target prediction sites, but the primary sequence of a lncRNA offers almost no clues into the function of the transcript.

Perhaps the most important outstanding question is how do we convert these recent discoveries in lncRNA biology from being merely interesting observations into viable therapeutic and diagnostic options. The fact that the vast majority of noncoding transcripts are not conserved remains a challenge; hence functional relevance of many identified lncRNAs to human disease is often questioned. This underscores the importance of a "patient-centric" discovery approach. Finally, the potent tissue-specific expression pattern of lncRNAs is a double-edge sword. On the one hand, it implies that one must strive to find the right context, a key to accurate cataloging of lncRNAs. On the flipside, however, this specificity imparts exciting potential gains even with lack of mechanistic detail. Fifty-five years since the identification of troponin, perhaps the ultimate biomarker in cardiovascular disease, we are still searching for the next big one. It is tempting to speculate that more rigorous studies of lncRNAs may offer breakthroughs on that front.

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Abbreviations and Acronyms

LncRNA	Long noncoding RNA
hnRNP	Heterogeneous nuclear ribonucleoproteins
SREBP	Sterol regulatory element-binding protein
PPARA	Peroxisome proliferator-activated receptor alpha
RXRA	Retinoid X receptor alpha
APOA1	Apolipoprotein A1
BMDM	Bone marrow derived macrophages

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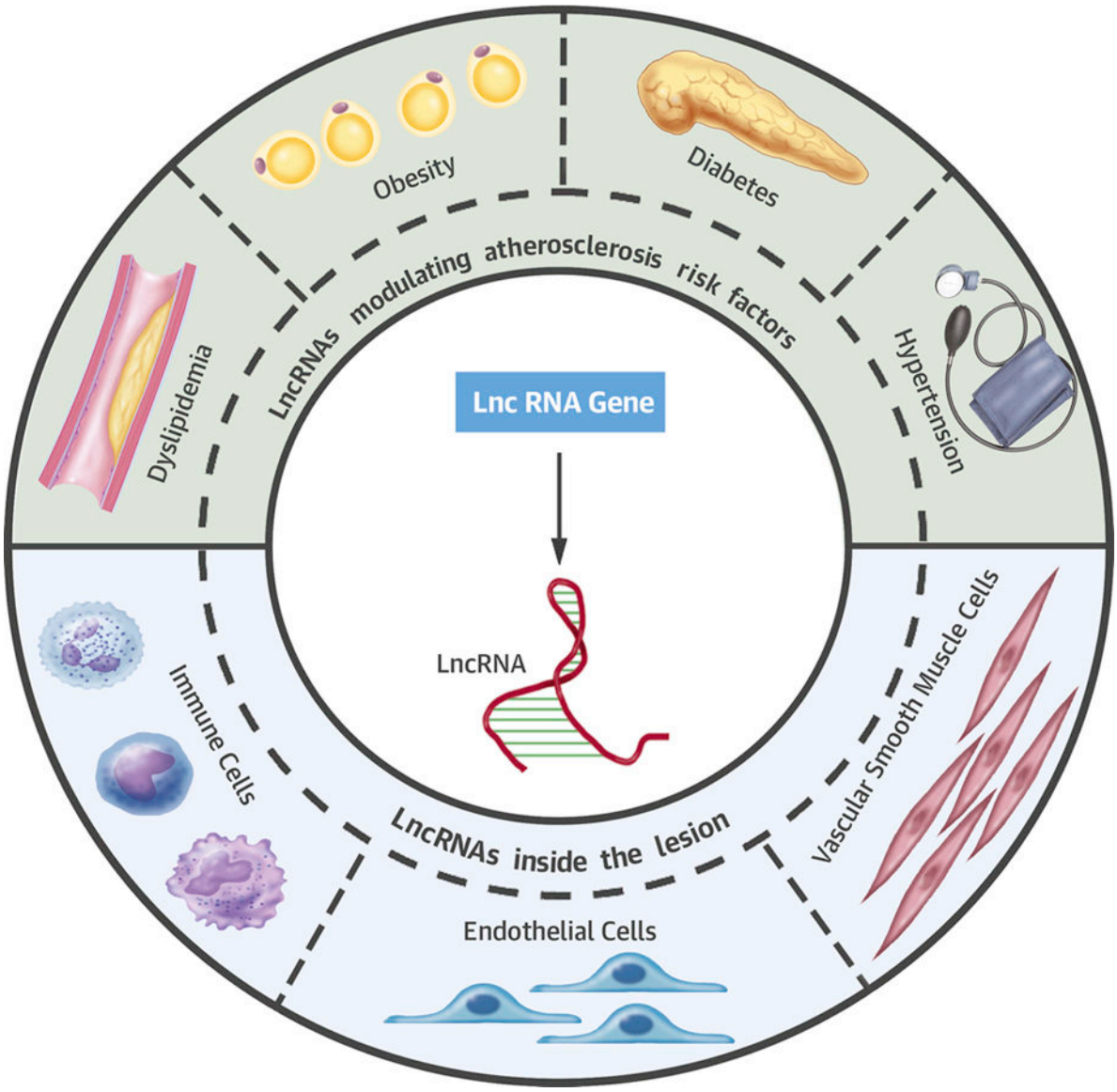

Central Illustration: Long non-coding RNAs in Atherosclerosis.

Long non-coding RNAs are actively transcribed genes that do not “appear” to code for proteins. Emerging evidence suggests that lncRNAs serve as key regulators of atherosclerosis and related risk factors.

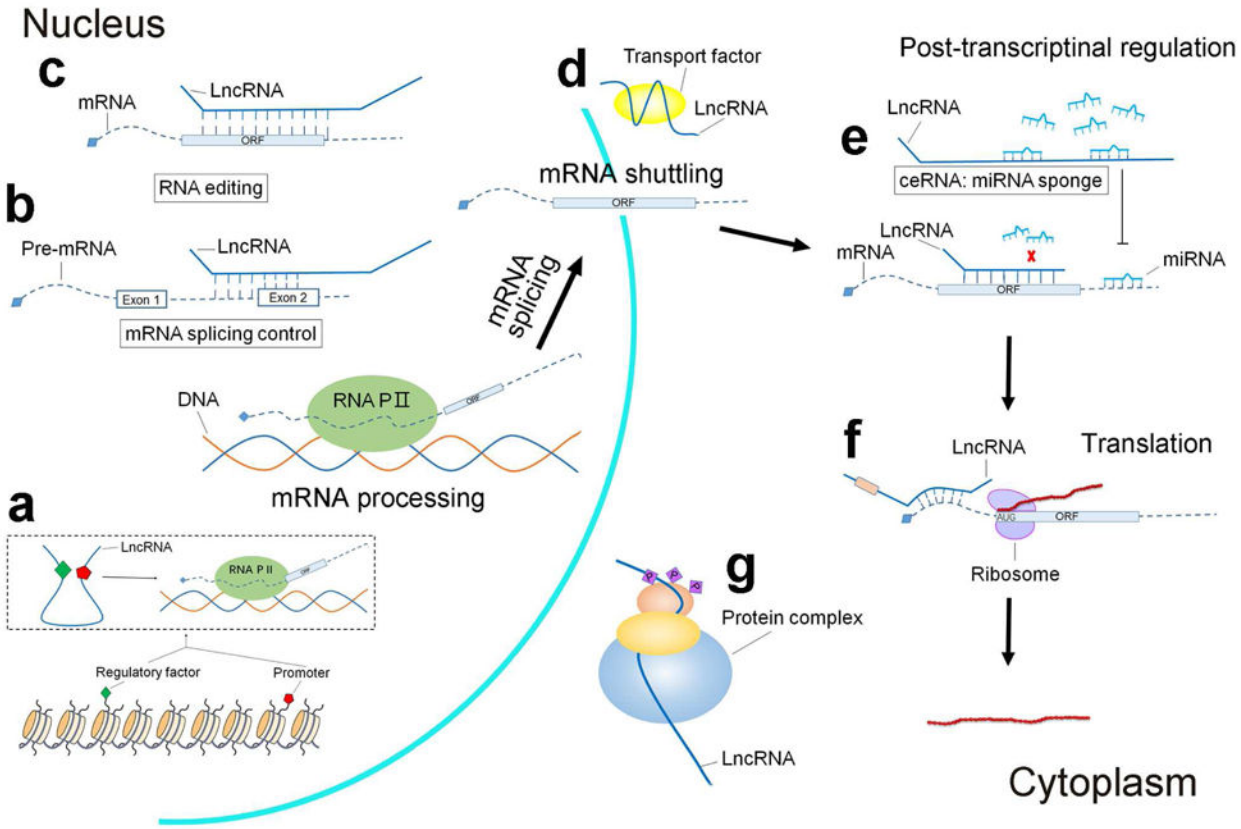

Figure 1. Long non-coding RNAs (lncRNAs) regulatory mechanisms.

a. LncRNAs modulate chromatin architecture and enhancer-promoter looping at cognate genes to influence transcription. **b.** LncRNAs can regulate mRNA splicing by interfering with pre-mRNA processing. **c.** LncRNAs, in particular antisense lncRNAs, may direct mRNA editing through base paring interaction. **d.** By acting as decoys, lncRNAs influence the folding of complex three-dimensional structures affecting mRNA cytoplasmic shuttling and localization. **e.** LncRNAs regulate mRNA stability by acting as sponges to sequester microRNAs. **f.** LncRNAs may influence protein translation through interactions with binding of translation co-factors and regulators. **g.** LncRNAs may influence post-translational protein modification.

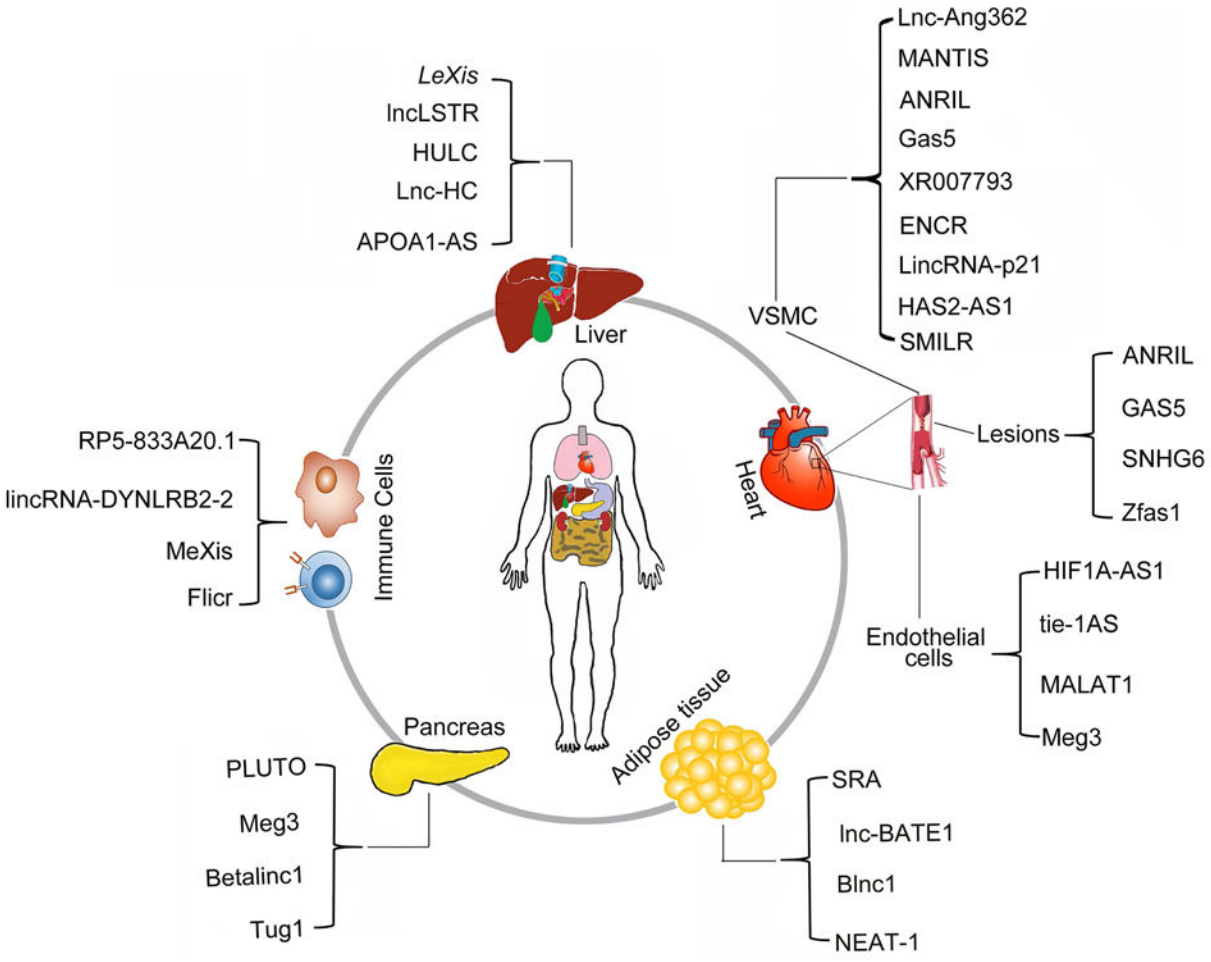

Figure 2: LncRNAs involved in mammalian atherothrombotic disease.

Summary of mammalian lncRNAs expressed from various tissues or cell-types involved in atherosclerosis pathways.

Table 1.

LncRNAs and their partners involved in the atherothrombotic disease

LncRNAs/ partners	Phenotype	Putative human orthologue identified	Data on functional conservation	ref
lncLSTR/TDP-43	Plasma triglyceride levels, bile acid biosynthesis	No	No	10
Lexis/Raly	Serum cholesterol levels, hepatic sterol content	Yes	No	11, 12
HULC	Lipogenesis	Yes	Yes	13
APOA1-AS	lipid transport	Yes	Yes	14
Noncoding region between Igf2 and H19	fat deposition and obesity			16
LINC00237	MOMO Syndrome	Yes	Yes	17
Noncoding RNA from chromosome 15q11-q13	Prader-Willi syndrome Obesity	No	No	17 18
IPW	PWS	Yes	Yes	19
SRA/ PPARγ	adipogenesis	Yez	Yes	22
Blnc1/EBF-2	thermogenesis	Yes	Yes	23
PLUTO/PDX1	type 2 diabetes, glucose tolerance	Yes	Yes	25
Betalinc1	normal islet cell formation	No	No	27
Flicr	promoting autoimmune diabetes	Yes	Yes	28
Gas5	correlating with type 2 diabetes risk, regulating vascular remodeling in hypertensive rats	Yes	Yes	31
Lnc-Ang362	Regulation of proliferation of VSMC	No	No	32
MANTIS/brg1	Modulating endothelial function	Yes	Yes	35
ANRIL	Systemic hypertension and vascular aneurysms	Yes	Yes	36–38
KCNQ1OT1	Myocardial infarction	Yes	Yes	45
RP5-833A20.1/NFIA	Function in foam-cell macrophages	Yes	Yes	46
MeXis/ Abca1	foam cell formation and atherosclerosis	Yes	Yes	47, 48
Lnc-DC/ STAT3	enhancing T cell activation	Yes	Yes	49
Linc-Cox2	Regulation of inflammatory genes	No	No	50
LincRNA-EPS	Regulation of inflammatory genes	Yes	No	51
NeST	Altering chromatin methylation pattern at interferon gamma locus in T cells	Yes	Yes	52
HIF1A-AS1	Promoting proliferation and suppressing apoptosis of HUVECs	Yes	Yes	55
tie-1AS	Differentially regulated in samples from infants and children with various vascular malformations	Yes	Yes	56
MALAT1	Influencing proliferation of endothelial cells *in vivo* and neonatal retina vascularization	Yes	Yes	59

LncRNAs/ partners	Phenotype	Putative human orthologue identified	Data on functional conservation	ref
Meg3	Controlling endothelial function	Yes	Yes	60
ENCR	Influence smooth muscle contractile machinery and inflammatory mediators	Yes	Yes	61
lincRNA-p21/hnRNP-K	Neointimal hyperplasia, coronary artery	Yes	Yes	62, 63
SMILR	In response to interleukin-1α and PDGF stimulation	Yes	Yes	64
TERMINATOR	Cardiovascular development	Yes	Yes	65
ALIEN	Cardiovascular development	Yes	Yes	65
PUNISHER	Cardiovascular development	Yes	Yes	65

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