Molecular Diagnosis & Therapy (2019) 23:735–749
https://doi.org/10.1007/s40291-019-00427-9

REVIEW ARTICLE

The Long Non-Coding RNA Landscape of Atherosclerotic Plaques

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Published online: 10 October 2019

Abstract
Currently, cardiovascular diseases continue to be the leading cause of death worldwide; therefore, atherosclerosis remains one of the most crucial public health problems. This chronic and complex disease is considered to be a result of aberrant lipid homeostasis and inflammation of the inner wall of arteries that leads to plaque development. In recent years, a specific class of non-coding RNAs that are characterised by transcript lengths longer than 200 nucleotides, called long non-coding RNAs (lncRNAs), has emerged. Moreover, a growing body of evidence indicates that deregulation of lncRNA expression may contribute to the development of many diseases. Despite continuous efforts in deciphering the molecular basis of atherosclerotic plaque (AP) formation, many aspects of this process remain elusive. Therefore, continuing efforts in this area should remain the highest priority in the coming years. Establishment of a standardised experimental pipeline and validation of lncRNAs as possible relevant biomarkers for cardiovascular disease would enable the translation of gathered findings into clinical practice.

Key Points

1. Recent studies suggest that long non-coding RNAs (lncRNAs) could have pivotal role in the development of many diseases.

2. Deciphering the functions of lncRNAs associated with atherosclerotic plaque formation could lead to finding new therapeutic targets or even biomarkers for arthrosclerosis.

1 Introduction

1.1 Aetiology of Atherosclerosis

Atherosclerotic plaque (AP) formation in the inner walls of the arteries is a leading trigger of cardiovascular diseases (CVDs), including coronary artery disease (CAD) and myocardial infarction (MI), and therefore constitutes a significant health threat to modern society [1]. The interplay of multiple genetic and environmental factors underlies atherosclerosis development. Moreover, the list of these factors is continuously expanding [2]. From the traditional point of view, atherosclerosis is a disease connected with a chronic inflammatory state of the arterial walls accompanied by aberrant lipid metabolism [3, 4]. According to the endothelial injury–response theory, initial lesion formation is a result of endothelial cell (EC) pro-inflammatory activation and phenotypic changes that could be elicited by either chemical agents or physical injuries [5]. Through the course of this process, increased permeability of the endothelium along with the production of cell surface adhesion molecules leads to infiltration of monocytes or other molecules, e.g. lipoproteins into the intima. Subsequently, monocytes differentiate into macrophages that take up these lipoproteins to finally become foam cells, whereas smooth muscle cells proliferate and migrate from the media to the intima. Additionally, synthesis of extracellular matrix components is increased. As a result, atherogenesis progression leads to the accumulation of cellular, extracellular, and lipid material within the arterial wall, forming APs [3, 5]. During atherosclerosis development, plaques exhibit different histological compositions and structures and are therefore classified into eight categories according to a report by the American Heart Association (AHA), reflecting the stages of the disease [6].

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At the molecular level, bioinformatic analysis indicated that 5784 messenger RNAs (mRNAs) and 654 transcripts identified as long non-coding RNAs (lncRNAs) were differentially expressed in early plaques versus advanced APs [7].

1.2 Biology of Long Non-Coding RNAs (lncRNAs)

Interestingly, a whole range of studies indicates that lncRNAs contribute considerably to the development of various diseases, including atherosclerosis. The data accumulated thus far show that lncRNAs encompass 270,044 transcripts in the human genome [8], constituting one of the most abundant groups of non-coding RNAs (ncRNAs) [9]. The transcripts comprising lncRNAs are mainly characterised by a strand length longer than 200 nucleotides and a low protein-coding capacity [10]. Since many ncRNAs do not have a thoroughly investigated annotation, there are several approaches for classifying lncRNAs. One of these approaches is based on their location and direction of transcription according to the protein-coding gene, and thus divides lncRNAs into different classes: antisense (transcribed in the antisense orientation to the protein-coding genes), bidirectional (transcribed in the opposite direction of the protein-coding genes), overlapping (transcribed in the same direction as the protein-coding genes and sharing the same sequence), sense intronic (transcribed in the same direction as the protein-coding gene but from an intronic sequence) and intergenic (transcribed from an intergenic region of the genome, > 10 kb from protein-coding genes) [11]. lncRNA transcripts can be localised in the nucleus or cytosol [12] and are derived from both the nuclear and mitochondrial genomes [13, 14]. The abundance and diversity of lncRNAs reflect their range of functions, which encompass lncRNA:RNA, lncRNA:protein and lncRNA:chromatin interactions [15] and can be categorised into four different archetypes describing their molecular mode of action: signalling archetype-lncRNAs that can serve as molecular signals, being transcribed only during specific cell processes; decoy archetype-lncRNAs that bind to and titrate away proteins and other regulatory RNAs; guide archetype-lncRNAs that bind to and direct ribonucleoprotein complexes to the proper localization; and scaffold archetype-lncRNAs that function as a platform to molecular components, allowing them to be assembled together [16]. A more detailed description of lncRNA classification, structure, biogenesis and function can be found in recently published articles (for detailed information, see Amin et al. [17] and Ransohoff et al. [18]). Many lncRNAs exhibit cell type-specific expression patterns, providing an excellent opportunity to investigate the relevance of their aberrant expression in different diseases [19]. However, low conservation of lncRNAs across species impedes the use of animal models to investigate their function in humans [20].

In this article, we summarise the recent findings in the study of lncRNA in human APs. Rather than discussing the relevance of lncRNAs in all models used in atherosclerosis research, we focus only on human tissues and cells.

2 Utility of Plaques for Studies Regarding lncRNA Relevance in Atherosclerosis

With the advent of novel technologies, especially next-generation sequencing and microarrays, it has become possible to employ global transcriptome profiling to identify RNAs that are dysregulated in many diseases [21]. Scientists use various strategies to elucidate the biological function and mode of action of lncRNAs in atherosclerosis. Many of the strategies apply in vitro experiments using cell lines to reflect specific processes in atherosclerosis. There is an approach based on APs that provides an opportunity to investigate complex and multilayer cell environments; however, several ambiguities and technical obstacles limit its usage for lncRNA study. First, there are ethical as well as technical restrictions regarding obtaining specimens because they can be collected only from patients subjected to the specific types of invasive surgical treatments (e.g. endarterectomy, bypass grafting, amputation, transplantation or autopsy). A comparison between gene expression levels in advanced APs obtained from surgery and autopsy showed that 500 genes were differentially expressed at the mRNA level [22], which could cast doubts on the suitability of autopsy material for lncRNA analysis. Some research, despite combining different kinds of plaque sources (i.e. cadavers and patients), still faces the issue of small sample size (Table 1). In this context, it could be reasonable to use the collections deposited in biobanks, e.g. the Biobank of Karolinska Endarterectomy whose resources also allows the results of the investigation to be related to additional clinical parameters [23]. In addition, the demographic and clinical characteristics of the study patients could have a profound contribution to the interpretation of the lncRNA expression data; for example, results from expression profiling study have demonstrated altered gene expression associated with statin (HMG-CoA reductase inhibitor) treatment [23]. Given that, it would be reasonable to validate the influence of medical treatment on the expression of lncRNA. Second, analysis of the cellular origin of lncRNAs may be hindered by an insufficient amount of harvested tissue sample to allow simultaneous gene expression analysis and fluorescent in situ hybridization (FISH) [24]. Third, the choice of control non-atherosclerotic samples is even more strictly limited and varies from using the peripheral end of the same lesion to choosing independently from the sample and could also be derived from the same patients as well as from different donors with no evidence of atherosclerosis (Table 1). However, different

Table 1 Characteristics of atherosclerotic plaques and controls used in a few examples of long non-coding RNA studies

lncRNA	Source of plaques	Evaluation of plaques	Number of plaques	Source of controls	Number of controls	References
GAS5	Carotid artery	ICA stenosis > 70%	8	Healthy aortic tissue surrounding the plaque	8	[61]
	Aorta from patients	Not described	11	Aorta from cadavers	11	[62]
HOTAIR	ECs of coronary artery plaque from patients and cadavers	Coronary angiography	40	Corresponding vascular wall from patients and cadavers	40	[115]
MALAT1	Coronary artery	CA stenosis > 50%	20	Internal mammary artery of plaque donors	20	[24]
	Coronary artery	CA stenosis > 50%	127	Aorta and iliac artery from organ donors	10	[87]
RP11-7146181	Carotid artery	Histopathological confirmation of atherosclerosis	12	Renal artery of non-atherosclerotic patients	12	[122]
	Carotid artery or abdominal artery	Grade V or VI atherosclerosis according to AHA classification	3	An artery from a cadaver and a healthy artery of an AP donor	3	

AHA the American Heart Association, *AP* atherosclerotic plaque, *CA* coronary artery, *ECs* endothelial cells, *GAS5* growth arrest-specific 5, *HOTAIR* HOX transcript antisense RNA, *ICA* internal carotid artery, *lncRNA* long non-coding RNA, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1

localisation of the control and APs may have an influence on the research results due to variations in individual gene expression [24]. Fourth, plaques exhibit composition variability, even along the length of the same lesion, and their evaluation in the study is performed in many different ways (Table 1), e.g. by histological assessment and classification [6]. Due to the previously mentioned restrictions and several difficulties that limit detection by non-invasive methods of the early stages of the disease [25], mainly advanced types of lesions are included in the studies, impeding investigation concerning the mechanisms underlying the progression of atherosclerosis.

3 lncRNAs in Atherosclerotic Plaques (APs)

Among the lncRNAs with altered expression in APs, there are newly identified lncRNAs as well as lncRNAs with previously characterised functions or mechanisms of action (Table 2), in many cases not yet associated with atherosclerosis or any other CVDs. Taking this into account, in this review, we provide comprehensive insight into the current knowledge regarding lncRNAs with aberrant expression in APs compared to healthy arteries (Fig. 1).

3.1 LncRNAs Upregulated in APs in Comparison with Healthy Tissue

3.1.1 H19

Imprinted maternally expressed transcript (*H19*) is one of the first described lncRNAs. *H19* expression is thought to be upregulated during embryogenesis and downregulated postnatally in most tissues [26]. Its re-expression has been observed in human APs, especially in actin-enriched cells with smooth muscle characteristics; however, some cells with probably endothelial origin also exhibited expression of *H19* [27]. Interestingly Hofmann et al. [28] indicated that expression of *H19* was higher in endothelium of healthy arteries than in APs. Moreover, in APs its expression was mainly restricted to ECs from intraplaque vessels [28]. The abovementioned discrepancy in the results obtained suggests a need for further investigations concerning the cell type-specific pattern of *H19* expression in AP. Subsequent research has shown that the *H19* gene polymorphism among the Chinese population is associated with CAD [29]. Moreover, the elevated expression of *H19* observed in blood samples of atherosclerotic patients [30–32] indicates that this lncRNA could serve as a potential biomarker for CAD [32]. It is possible that the role of *H19* in lesion development is connected with homocysteine, elevated levels of which in the bloodstream may be a risk factor for atherosclerosis [34]. Of note, homocysteine facilitated vascular smooth muscle cell (VSMC) proliferation in vitro [35, 36]. Stimulation of VSMCs with homocysteine led to increased *H19* expression

Table 2 Summary of long non-coding RNAs with altered expression in atherosclerotic plaques

Approved symbol	Gene ID	Expression	Regulated cellular processes	Expression in cell lines /types related to atherosclerosis	References
ANRIL	100048912	↑	Adhesion, apoptosis, inflammation, migration, nucleolar stress, transmigration, proliferation, viability	Adventitial fibroblasts, CD68-positive macrophages, EA.hy926, iPSC-derived macrophages, MonoMac, HCAECs, HCSMs, HMEC, HuAoVSMCs, HUVECs, human monocyte-derived macrophages, PBMCs, VSMCs	[24, 46–48, 51, 52, 55, 56, 126]
BANCR	100885775	↑	Migration, proliferation	VSMCs	[81]
CHROME	ENSG00000223960	↑	Cholesterol efflux	B cells CD19, CD14 monocytes, PBMCs, regulatory T cells, smooth muscle cells, CD3 T cells, CD8 T cells, CD4 T helper cells, THP-1-derived macrophages	[74]
GAS5	60674	↑	Activation, angiogenesis, apoptosis, autophagy, inflammation migration, phenotypic switching, proliferation, tube formation, vasoconstrictors production, viability	HAECs, HCAECs, HUVE-12, HUVECs, THP-1-derived macrophages, U937, VSMCs	[61–64, 66–69]
H19	283120	↑ or ↓	Apoptosis, autophagy, inflammation, mineralisation, proliferation, senescence	HA-VSMCs, hCoAECs, HUVECs, PBMCs, T/G HA-VSMCs, VSMCs	[27, 28, 30, 32, 33, 38–40, 125]
HOTTIP	100316868	↑	Migration, proliferation	HUVECs	[83]
HYMAI, *KIAA1656*, *LOC339803*, *LOC730101*	57061 (*HYMAI*), 85371 (*KIAA1656*), 339803 (*LOC339803*), 730101 (*LOC730101*)	↑	Probably a role in the cellular response to hypoxia	HUVECs	[85]
LINC00305	221241	↑	Apoptosis, inflammation, phenotypic switching, proliferation	HASMCs, HUVECs, PBMCs, THP-1	[77, 78]
LINC00968	100507632	↑	Migration, proliferation	ECs	[84]
MIAT	440823	↑	Apoptosis, proliferation	EA.hy926, HA-VSMCs, HMVECs, HUVECs, U937	[24, 73, 127]
RNCR3	157627	↑	Apoptosis, migration, proliferation	HUVECs, VSMCs	[79]
SMILR	ENSG00000255364	↑	Maintenance of synthetic phenotype, proliferation	CASMCs, HCASMCs, HSVECs, HSVSMCs	[75, 76]
SNHG6, *Zfas1*	641638 (*SNHG6*), 441951 (*Zfas1*)	↑	Unknown	Unknown	[61]
APPAT	ENSG00000230606	↓	Probably maintaining the contractile phenotype of VSMCs	VSMCs	[123]
FENDRR	400550	↓	Unknown	Unknown	[112]
HOTAIR	100124700	↓	Apoptosis, ox-LDL uptake, inflammation, migration, oxidative stress, proliferation	ECs, HAECs, HUVECs, PBMCs, THP-1-derived macrophages	[115, 116, 119]
lincRNA-p21	102800311	↓	Apoptosis, proliferation	PBMCs, VSMCs	[112, 113]
MALAT1	378938	↓	Apoptosis, endothelial-to-mesenchymal transition, inflammation, lipid uptake, migration, proliferation, pyroptosis	EA.hy926, HAECs, HCAECs, HCMEC-C, HMVEC-L, HUVECs, HPAECs, HPASMCs, THP1-derived macrophages, VSMCs	[24, 85, 89, 91, 93–95, 97, 99–101]

Table 2 (continued)

Approved symbol	Gene ID	Expression	Regulated cellular processes	Expression in cell lines /types related to atherosclerosis	References
NEXN-AS1	374987	↓	Adhesion, inflammation, migration	HUVECs, THP-1, VSMCs	[120]
RP11-714G18.1	ENSG00000250410.1	↓	Adhesion, apoptosis, migration, NO production, proliferation, tube formation	HA-VSMCs, HUVECs	[122]
SENCR	100507392	↓	Angiogenesis, cell adherence, embryonic stem cells differentiation to ECs, maintenance of contractile phenotype, migration, proliferation	HCAECs, HCASMCs, hESC-derived EC, hESCs, HPAECs, HUVECs, PBMC	[103–105, 107]

ANRIL antisense ncRNA in the INK4 locus, *APPAT* atherosclerotic plaque pathogenesis-associated transcript, *BANCR BRAF*-regulated lncRNA 1, *CASMCs* human coronary artery vascular smooth muscle cells, *CECs* circulating endothelial cells, *CHROME* cholesterol homeostasis regulator of microRNA expression, *EA.hy926* human umbilical vein cell line, *ECs* endothelial cells, *EPCs* endothelial progenitor cells, *FENDRR* Forkhead box protein F1 (FOXF1) adjacent non-coding developmental regulatory RNA, *GAS5* growth arrest-specific 5, *iPSC* induced pluripotent stem cell, *H19* imprinted maternally expressed transcript, *HAECs* human aortic endothelial cells, *HASMCs* human aortic smooth muscle cells, *HA-VSMCs* human aorta vascular smooth muscle cells, *HCAECs* human coronary artery endothelial cells, *HCASMCs* human coronary artery smooth muscle cells, *HCMEC-C* cardiac microvasculature, *hCoAECs* human coronary artery endothelial cells, *HCSMs* human coronary artery smooth muscle, *hESC* human embryonic stem cells, *HMEC* human microvascular endothelial cell line, *HMVECs* human microvascular endothelial cells,*HMVEC-L* lung microvasculature, *HOTAIR* HOX transcript antisense RNA, *HOTTIP* HOXA transcript at the distal tip, *HPAECs* human pulmonary artery endothelial cells, *HSVSMCs* human saphenous vein smooth muscle cells, *HSVECs* human saphenous vein endothelial cells, *HPASMCs* human pulmonary artery smooth muscle cells, *HuAoVSMCs* human aortic vascular smooth muscle cells, *HUVECs* human umbilical vein endothelial cells, *HUVE-12* human umbilical vein endothelial cells-12, *HYMAI* hydatidiform mole-associated and imprinted transcript, *linc-p21* long intergenic non-coding RNA p21, *lncRNA* long non-coding RNA, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *MIAT* myocardial infarction-associated transcript, *MonoMac* monocytic cell line, *NEXN-AS1* NEXN antisense RNA 1, *NO* nitric oxide, *ox-LDL* oxidised low-density lipoprotein, *PBMCs* peripheral blood mononuclear cells, *RNCR3* retinal non-coding RNA3, *SENCR* smooth muscle and endothelial enriched lncRNA, *SMILR* smooth muscle-induced lncRNA enhances replication, *SNHG6* small nucleolar RNA host gene 6, *T/G HA-VSMC* human aortic vascular smooth muscle cell line, *THP-1* human leukaemic monocyte, *U937* human mononuclear cells, *VSMCs* vascular smooth muscle cells, *Zfas1* ZNFX1 antisense RNA 1, ↑ indicates upregulated, ↓ indicates downregulated

while decreasing the level of insulin-like growth factor 2 (*IGF2*) transcript; therefore, it was proposed that homocysteine may promote proliferation by inducing hypomethylation of the sixth CCCTC-binding factor (*CTFC*) binding sites located upstream of *H19* [37]. In case of ECs, *H19* may facilitate cell proliferation while impeding cell senescence and inflammatory activation by inhibition of signal transducer and activator of transcription (STAT) 3 signalling [28]. Recently, published research has shed light on the mechanisms of action by which *H19* may regulate cell function. Pan [30] has shown that overexpression of *H19* in both VSMCs and human umbilical vein ECs (HUVECs) resulted in increased levels of p38 and p65, suggesting possible facilitation of proliferation and apoptosis suppression by the mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB pathway [30]. Sun et al. [38] found that *H19* may act as a competing endogenous RNA (ceRNA) through an interaction with let-7a, which results in the promotion of *cyclin D1* expression and at the cellular level also leads to VSMC proliferation [38]. Additionally, Zhang et al. [32] indicated a role for *H19* in modulating the Wnt/β-catenin signalling pathway in oxidised low-density lipoprotein (ox-LDL)-treated human aorta VSMCs (HA-VSMCs). *H19* may promote proliferation and decrease apoptosis by sponging microRNA (miR)-148b to enhance Wnt family member 1 (*Wnt1*) expression [32]. In another study, Huang et al. [39] showed that the acid phosphatase 5 (*ACP5*) gene could be a potential target of *H19*. Overexpression of *H19* in HUVECs and VSMCs resulted in increased ACP5 levels, facilitated cell proliferation and inhibited apoptosis [39]. Song et al. [40] showed that astragaloside IV might affect autophagy by modulating *H19* expression. This pharmacological stimulant elicited an increased expression of *H19*, phosphorylated ERK1/2 nuclear phosphatase (p-ERK1/2), and phosphorylated mammalian target of rapamycin (p-mTOR) while inhibiting dual specificity protein phosphatase 5 (DUSP5) expression, which resulted in reduced mineralization and autophagy in VSMCs [40].

3.1.2 ANRIL

Antisense ncRNA in the INK4 locus (*ANRIL*) is an lncRNA derived from the chromosome 9p21 region [41], which comprises several single nucleotide polymorphisms (SNPs) associated with an increased risk of CAD and atherosclerosis development [42]. Furthermore, some of the identified SNPs lay within the *ANRIL* gene sequence (see Hu et al. [43] and Xie et al. [44]). The data gathered so far have suggested that

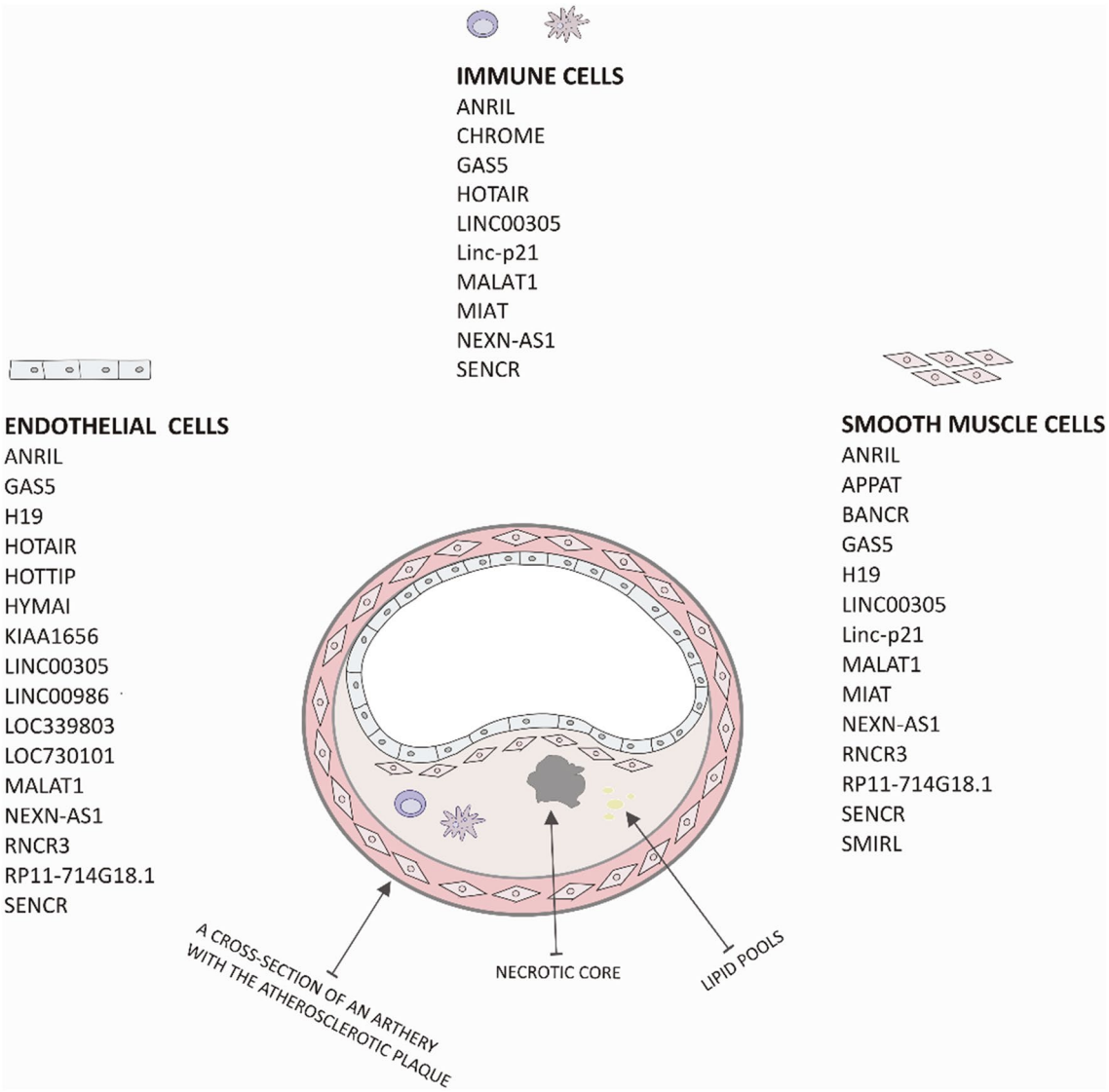

Fig. 1 List of long non-coding RNAs (lncRNAs) with aberrant expression in the atherosclerotic plaque reported in this review. lncRNAs are divided according to their association with immune cells, endothelial cells and smooth muscle cells. *ANRIL* antisense ncRNA in the INK4 locus, *APPAT* atherosclerotic plaque pathogenesis-associated transcript, *BANCR BRAF*-regulated lncRNA 1, *CHROME* cholesterol homeostasis regulator of microRNA expression, *GAS5* growth arrest-specific 5, *H19* imprinted maternally expressed transcript, *HOTAIR* HOX transcript antisense RNA, *HOTTIP* HOXA transcript at the distal tip, *HYMAI* hydatidiform mole-associated and imprinted transcript, *Linc-p21* long intergenic non-coding RNA p21, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *MIAT* myocardial infarction-associated transcript, *NEXN-AS1* NEXN antisense RNA 1, *RNCR3* retinal non-coding RNA3, *SENCR* smooth muscle and endothelial enriched lncRNA, *SMILR* smooth muscle-induced lncRNA enhances replication

there are many linear or even circular transcripts of *ANRIL*. Importantly, linear *ANRIL* is connected with pro-atherogenic cell function while circular *ANRIL* has shown the opposite, atheroprotective effects; moreover, CAD risk SNPs up- and downregulate the expression levels of linear and circular *ANRIL* transcripts [45], respectively. A more detailed summary of the current knowledge regarding the association of *ANRIL* with genetic polymorphism of the 9p21 locus in the context of atherosclerosis can be found in the review article by Holdt et al. [45]. Therefore, we focused on the relevance of *ANRIL* for cardiovascular cell function because its expression was detected in ECs, VSMCs and different immune cells [46, 47]. Researchers have shown that *ANRIL* splicing variants could affect the expression of distinct genes involved in pathways linked with atherosclerosis [48] and potentially this regulation could be exerted by cis- or trans-regulatory mechanisms (for detailed review, see Chi et al. [49] and Aarabi et al. [50]). Stress factors could elicit different expression patterns of *ANRIL* transcripts. For example, stimulation of ECs by tumour necrosis factor (TNF)-α or

ox-LDL cholesterol led to upregulation of the full-length *ANRIL* transcript (*NR_003529*) but downregulation of the *ANRIL* transcript *DQ485454*. Interestingly, the *DQ485454* transcript was most abundant in EC lines and decreased in the coronary artery of CAD patients. Gain-and loss-of-function experiments revealed that *ANRIL DQ485454* affects monocyte adhesion to ECs and transmigration across ECs along with EC migration, probably via regulation of the expression of *CLIP1*, *EZR*, and *LYVE1* [51]. Guo et al. [52] have shown that human coronary artery ECs (HCAECs) viability, survival and apoptosis, and the production of proteins specific for the epithelial–mesenchymal transition along with the release of inflammatory factors and vascular-protective factors might be regulated by the *ANRIL*/miR-181b/NF-κB signalling pathway [52]. Zhou et al. [53] previously demonstrated the upregulation of interleukin (*IL*)*-6/IL-8* expression in TNF-α-stimulated ECs through *ANRIL* binding to the transcriptional factor Yin Yang 1 (YY1). Another investigation revealed that distinct *ANRIL* splicing variants can affect the expression of atherosclerosis-related genes in VSMCs [54]. For instance, *ANRIL* affects VSMC proliferation probably via the regulation of cyclin-dependent kinase (CDK) inhibitor 2A/B expression [55]. The circular transcript of *ANRIL* (circANRIL) is claimed to exert atheroprotective function through binding to pescadillo homologue 1 (PES1), which results in an impairment of pre-ribosomal RNA (rRNA) maturation and an induction of nucleolar stress along with p53 activation. In line with that, overexpression of *circANRIL* in VSMCs and macrophages led to an induction of apoptosis and a reduction in proliferation, which was accompanied by increased numbers of nucleoli and an accumulation of pre-rRNAs in these cells [56]. Several studies have established the expression of both circular and linear *ANRIL* transcripts in APs and human blood [56–59], indicating the importance of an expression pattern of linear and circular *ANRIL* transcripts in atherosclerosis development [45].

3.1.3 GAS5

Growth arrest-specific 5 (*GAS5*) has gained attention as an lncRNA that could potentially be utilised as a diagnostic biomarker for atherosclerosis. Its gene is located on chromosome 1, and the ins/del polymorphism (rs1452042) of the promoter region is linked to the risk of disease development [60]. Moreover, the level of *GAS5* was upregulated in APs [61, 62] and plasma of atherosclerosis patients [63], while it was downregulated in the plasma [64] or serum of CAD patients [65]. This lncRNA is involved both in the regulation of vascular cell function in vitro, such as cell activation, viability, apoptosis, proliferation, migration, tube formation, vasoconstrictor production and phenotypic switching, and in the response to stress conditions such as hypoxia or H_2O_2 stimulation [66]. Of note, *GAS5* could participate in cell communication, being transmitted in exosomes [66, 67]. The molecular mechanism underlying *GAS5* function in HUVECs and VSMCs may be linked to β-catenin signalling, as *GAS5* was proved to interact with β-catenin protein and affect its nuclear translocation [66]. In a subsequent study, Yin et al. [64] showed that in HCAEC *GAS5* might be engaged in the mTOR signalling pathway through inhibition of its activation. Interestingly, ox-LDL stimulation of human leukaemic monocyte (THP-1)-derived macrophages triggers elevated expression of *GAS5*. A possible model describes *GAS5* acting via sponging miR-221, which results in the production of pro-inflammatory molecules and matrix metalloproteinase (MMP) secretion by macrophages [62]. Recently, Yang et al. [68] have shown that *GAS5* is also involved in other inflammatory pathways activated in *Porphyromonas gingivalis*-stimulated macrophages. Another study found that ox-LDL-treated macrophages release exosomes enriched in *GAS5*, which could be taken up by HUVECs, subsequently leading to increased apoptosis of the ECs [67]. Liang et al. [63] reported that *GAS5* interaction with miR-26a could contribute to ox-LDL-induced apoptosis and defective autophagy in human aortic ECs (HAEC). Previously, regulation of *GAS5* along with other ncRNA expression was also observed in ECs in vitro during angiogenesis promoted by isoprenaline—a synthetic catecholamine [69].

3.1.4 MIAT

MI-associated transcript (*MIAT*) was discovered and characterised as a result of investigations concerning SNP association with heart diseases in the Japanese population [70, 71]. Further studies have shown that *MIAT* was upregulated in APs [24] as well as in the serum of patients suffering from symptoms of vulnerable APs [72]. In a recently published article, Zhong et al. [73] shed light on a role of MIAT in atherosclerosis, indicating that elevated expression of *MIAT* was found in atherosclerosis patients' serum as well as in ox-LDL-treated smooth muscle cells and mononuclear cells in vitro, whereas miR-181b exhibited the opposite expression pattern [73]. Functional assays have shown that *MIAT* augmented the proliferation of, while hindering apoptosis in, HA-VSMCs and human mononuclear cells (U937) by sponging miR-181b, resulting in enhanced *STAT3* expression [73].

3.1.5 CHROME

lncRNA cholesterol homeostasis regulator of miR expression (*CHROME*) is a primate-specific lncRNA that exerts a role in cholesterol homeostasis in humans. This lncRNA is transcribed from a locus situated on chromosome 2 and has seven splice variants that contain Alu transposable repeat elements. Elevated *CHROME* expression was found in infiltrating inflammatory cells in the APs and plasma of patients

with CAD. Subsequent analysis has shown that in THP-1-derived macrophages, *CHROME* expression may be regulated by the sterol-activated liver X receptor transcription factor LXR, and its increased level was elicited by stimulation with acetylated LDL. Moreover, *CHROME* may play a role in the cholesterol efflux pathway in macrophages via interactions with miR-27b, miR-33a, miR-33b and miR-128. Notably, *CHROME* silencing led to a decreased level of ATP-binding cassette transporter A1 (ABCA1) protein, which regulates cellular cholesterol homeostasis [74].

3.1.6 SMILR

The expression of smooth muscle-induced lncRNA enhances replication (*SMILR*) was initially found in VSMCs stimulated with IL-1α or platelet-derived growth factor (PDGF). The genomic localisation of this lncRNA is in proximity to the hyaluronan synthase 2 (*HAS2*). Of note, elevated *SMILR* levels were observed in unstable APs as well as in the plasma of patients suffering from inflammation where *SMILR* levels exhibited a positive correlation with C-reactive protein levels. VSMCs in vitro were able to release *SMILR* into the medium but, interestingly, it was not detected in the exosomes or microvesicles. The subsequent functional assays have shown that *SMILR* overexpression leads to increased proliferation of VSMCs, and this effect may be exerted by the regulation of *HAS2* expression [75]. It was further reported that increased *SMILR* expression is strongly associated with a synthetic phenotype of VSMCs in vitro [76].

3.1.7 LINC00305

Long intergenic ncRNA 00305 (*LINC00305*) was found to be associated with atherosclerosis as a result of the genome-wide association study (GWAS) that had uncovered two disease-associated SNPs, rs2850711 and rs2676671, located in an intron of the *LINC00305* gene. Moreover, APs, along with CD14-positive cells from atherosclerosis patients, exhibited an increased expression level of *LINC00305*. A subsequent functional investigation revealed that *LINC00305* overexpression facilitates inflammation THP-1 cells by associating with lipocalin-1 interacting membrane receptor (LIMR), thus enhancing the LIMR-AHRR (aryl-hydrocarbon receptor repressor) interaction and AHRR protein expression along with its nuclear localisation, which results in inhibition of AHR signalling and NF-κB activation. At the cellular level, overexpression of *LINC00305* may promote switching from a contractile to a synthetic phenotype in human aortic smooth muscle cells (HASMCs) co-cultured with THP-1 cells [77]. Another study demonstrated that *LINC00305* plays a role during EC impairment, promoting apoptosis by acting as a miR-139 sponge. In hypoxia-induced HUVECs, *LINC00305* upregulation resulted in augmented apoptosis and suppressed proliferation [78].

3.1.8 RNCR3

In APs as well as in ox-LDL-treated ECs and VSMCs, retinal ncRNA3 (*RNCR3*) expression levels are significantly increased, which could be a part of an atheroprotective mechanism. Of interest, exosomes could transfer *RNCR3* between ECs and VSMCs. This lncRNA plays a role in promoting proliferation and migration while suppressing apoptosis in both cell lines. It is possible that *RNCR3* may exert its biological function as a ceRNA in the Kruppel-like factor 2 (KLF2)/miR-185-5p regulatory network by sponging miR-185-5p to regulate the *KLF2* gene expression level [79].

3.1.9 BANCR

BRAF-regulated lncRNA 1 (*BANCR*) was discovered in melanoma cells as a transcript regulating the expression of genes involved in cell migration [80]. The AP tissues, along with proliferating VSMCs, exhibited upregulated *BANCR* expression. Further functional assays have revealed that elevated *BANCR* expression in VSMCs led to increased cell proliferation and migration, probably via modulation of c-Jun N-terminal kinase (JNK) expression [81].

3.1.10 HOTTIP

HOXA transcript at the distal tip (*HOTTIP*) is a 3764 bp lncRNA derived from the *HOTTIP* gene located near *HOXA13* [82]. Recently, scientists discovered that *HOTTIP* expression levels were upregulated in CAD tissue as well as in ECs stimulated by TNF-α or PDGF-BB in vitro. Subsequent gain- and loss-of-function assays have revealed possible promotion of EC proliferation and migration through the Wnt/β-catenin pathway activation [83].

3.1.11 LINC00968

Long intergenic non-protein coding RNA 968 (*LINC00968*) has emerged as a novel atherosclerosis-associated lncRNA since Wang et al. [84] found its upregulated expression in atherosclerosis tissue obtained from CAD patients. Of note, ox-LDL treatment of ECs leads to increased expression of *LINC00968* and inhibited expression of miR-9-3. Interestingly, a decreased level of miR-9-3 was also found in CAD patient samples. Further functional analysis has shown that elevated expression of *LINC00968* may augment the proliferation and migration of ECs through modulation of miR-9-3p expression [84].

3.1.12 *SNHG6*, *Zfas1*, *HYMAI*, *LOC730101*, *KIAA1656* and *LOC339803*

To date, the contribution of small nucleolar RNA host gene 6 (*SNHG6*) and ZNFX1 antisense RNA 1 (*Zfas1*) to AP development remains unknown [61]. Recently, bioinformatics analysis has showed co-expression of *Zfas1* with 358 mRNAs, which are dysregulated in atherosclerosis progression, indicating its potential function in atherosclerosis [7]. Hydatidiform mole-associated and imprinted transcript (*HYMAI*), lncRNA *LOC730101*, lncRNA *KIAA1656* and lncRNA *LOC339803* are other examples of newly identified lncRNAs in APs. It has been shown that they are upregulated in primary and restenosis plaques, and their expression in HUVECs is modulated under hypoxic conditions; however, the exact molecular mechanisms require further characterisation [85].

3.2 LncRNAs Downregulated in APs in Comparison with Healthy Tissue

3.2.1 MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) was identified in lung cancer cells as well as various healthy tissues [86]. In the AP, the *MALAT1* expression level was downregulated [24, 87]. The same expression pattern, as mentioned earlier, was found in both primary and restenotic APs [85]. Of note, in the blood of CAD patients and endothelial progenitor cells (EPCs), *MALAT1* expression was increased [88]. The previous analysis revealed that higher expression levels of *MALAT1* in plaques might be correlated with plaque stability and good prognosis, suggesting that this lncRNA could be used as a predictive marker of atherosclerosis progression [87]. Interestingly, microvascular, venous and arterial ECs in vitro exhibited high expression of *MALAT1* [89]. Further functional assays showed that at the cellular level, *MALAT1* promoted the proliferation but decreased the migration of ECs. Several studies have shown its upregulated expression in response to different stressful stimuli, e.g. a hypoxic condition in which hypoxia-inducible factor 1α (HIF1α) [90] causes elevated expression of *MALAT1* in ECs [89]. During oxidative stress in ECs, *MALAT1* exerts a protective function, attenuating cell death and apoptosis. Mechanistically, *MALAT1* contributes to the downregulation of Kelch-like ECH-associated protein 1 (*Keap1*), thereby indirectly activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway [91]. In ox-LDL-stimulated ECs, *MALAT1* reduces apoptosis and pro-inflammatory cytokine release probably by acting as a ceRNA, and, to date, scientists have found two possible molecular mechanisms. Tang et al. [92] indicated that *MALAT1* interacts with miR-22-3p, leading to the upregulation of C-X-C chemokine receptor type 2 (*CXCR2*) and RAC-α serine/threonine-protein kinase (*AKT*) expression, while, more recently, Li et al. [93] found that *MALAT1* may bind to miR-155, leading to an increase in the suppressor of cytokine signalling 1 (SOCS1), which results in JAK-STAT signalling pathway repression. In contrast, the upregulation of *MALAT1* induced by high glucose levels in ECs was linked to increased expression of inflammatory mediators [94] and resulted in the promotion of pyroptosis partly by sponging miR-22, which led to the increased expression of the NLRP3 inflammasome [95]. All of the aforementioned stress agents can induce endothelial-to-mesenchymal transition (endMT), a process that commonly appears in APs [96]. In ox-LDL-stimulated HUVECs, *MALAT1* could affect endMT by the activation of the Wnt/β-catenin axis [97], while in transforming growth factor (TGF)-β1-stimulated human circulating EPCs by the regulation of the miR-145-TGFBR2/SMAD3 pathway [98]. In macrophages, ox-LDL or lipopolysaccharide (LPS) treatment could induce the elevated expression of *MALAT1* [99, 100]. Dissecting the function of MALAT1 during ox-LDL stimulation showed that its interaction with β-catenin led to the promotion of *CD36* transcription, which augments lipid uptake in macrophages via scavenger receptors [100]. In response to LPS stress stimuli, *MALAT1* inhibits the binding of NF-κB to target promoters leading to the attenuated production of TNF-α and IL-6 through interaction with NF-κB subunits p65 and p50 [99]. In pumonary smooth muscle cells, *MALAT1* augments proliferation by affecting CDK inhibitor expression but also facilitates migration. Similar to what has been reported for ECs, hypoxia is a factor that results in the upregulation of *MALAT1*, and HIF1α may be engaged in the modulation of *MALAT1* expression [101], while extracellular matrix stiffness is associated with decreased levels of *MALAT1* [102].

3.2.2 SENCR

Smooth muscle and endothelial enriched lncRNA (*SENCR*) is transcribed from the antisense strand of the first intron of a protein-coding gene called Friend leukaemia virus Integration 1 and exists in two isoforms: *SENCR_V1* (a full-length transcript) and *SENCR_V2* (an alternative splice variant). Interestingly, *SENCR* was expressed in endothelial and smooth muscle cells with solely cytoplasmic spatial distribution and therefore may play its biological role by acting in trans. Subsequent investigation revealed its role in maintaining the contractile phenotype of smooth muscle cells, probably via the regulation of myocardin (*MYOCD*), a contractile and pro-migratory gene, expression; nevertheless, the exact molecular mechanism of action remains elusive [103]. More recently, scientists have shown that *SENCR* could play a role in EC development and facilitates

the proliferation, migration and angiogenesis of HUVECs. Additionally, *SENCR* expression levels were decreased in patients with EC dysfunction and atherosclerotic vascular disease [104]. Lyu et al. [105] demonstrated elevated expression of *SENCR* in vitro in human ECs subjected to laminar stress, indicating its role in maintaining EC membrane integrity via stabilization of cell adherens junctions. Binding of *SENCR* to a non-canonical RNA binding domain of cytoskeletal-associated protein 4 (CKAP4) entails promoting an interaction of vascular endothelial (VE)-catenin with p120-cadherin instead of CKAP4, thereby indirectly enabling VE-catenin placement at the adherens junctions of ECs [105]. While *SENCR* gene polymorphism does not constitute a potential genetic risk factor for CAD [106], its altered expression in circulating ECs (CECs) and monocytes is associated with early-onset CAD (EOCAD); therefore, it could serve as an endothelial dysfunction biomarker [107]. Downregulation of *SENCR* in CECs and upregulation in monocytes along with increased surface/intracellular levels of CD146 in CECs and CD14 in monocytes were found in blood samples of EOCAD patients. Further analysis showed a positive correlation between *SENCR* expression and the surface/intracellular level of CD14 protein in monocytes. Theoretically, there may be an interaction between sequences localised in the second exon of *SENCR* and the 5' untranslated region of *CD14* (transcript variant 1 or 3) mRNA, indicating that *SENCR* could exert a role in stabilizing mRNAs or enhancing *CD14* transcription in monocytes [107].

3.2.3 linc-p21

Long intergenic ncRNA p21 (*linc-p21*) is situated 15 kb upstream of the *CDKN1A* gene-encoding protein p21 that regulates the cell cycle [108]. Structurally, it is a single-exon lncRNA, which exists in two isoforms containing two inverted repeat Alu elements that can form secondary structures [109]. Various studies have confirmed the significance of *linc-p21* for development of CVDs. It was shown that polymorphism of *linc-p21* is associated with risk of CAD and MI among the Chinese Han population [110] and its transcript level was decreased in peripheral blood mononuclear cells (PBMCs) obtained from CAD patients [111]. Moreover, the expression of *linc-p21* was found to be downregulated in APs [111, 112]. Functional analysis has shown that *linc-p21* promotes apoptosis and reduces the proliferation of VSMCs [111, 113]. At the molecular level, *linc-p21* may modulate p53 activity by interacting with mouse double minute 2 (MDM2), resulting in the release of p53 from MDM2 and p53 binding to p300 [111]. Recently Hu et al. [113] showed that *linc-p21* could exert a biological role in VSMCs through activation of the TGF-β1 axis.

3.2.4 HOTAIR

HOX transcript antisense RNA (*HOTAIR*) is an lncRNA derived from the transcription of the antisense strand of the *HoxC* gene, located on chromosome 12 [114]. ECs isolated from APs had a decreased level of *HOTAIR* transcript [115]. Previous studies demonstrated elevated expression of thymic stromal lymphopoietin (TSLP) in APs, especially in layers containing smooth muscle cells [116]. Of note, Peng et al. [115] found a positive correlation between the serum level of TSLP and *HOTAIR* expression in the ECs of atherosclerosis patients and proved that TSLP regulates *HOTAIR* transcription via the PI3K (phosphoinositide 3-kinase)/AKT-IRF1 (interferon regulatory factor 1) pathway. Further functional assays have shown the role of *HOTAIR* in a protection against ox-LDL-induced injury, promoting proliferation and migration, and suppressing apoptosis in ECs in vitro [115]. Recently, the function of *HOTAIR* was also investigated in macrophages, showing that in ox-LDL-treated THP-1 cells, its overexpression led to increase in apoptosis, di-ox-LDL uptake, oxidative stress and inflammation. At the molecular level, *HOTAIR* may exert its role as a ceRNA for miR-330-5p [117]. Some research indicates that *HOTAIR* could be a potential biomarker for atherosclerosis. Pang et al. [118] found that *HOTAIR* expression was downregulated in lymphocytes derived from atherosclerosis patients, while Avazpour et al. [119] demonstrated the opposite result: elevated *HOTAIR* expression in PBMCs from patients suffering from severe coronary artery stenosis.

3.2.5 NEXN-AS1

NEXN antisense RNA 1 (*NEXN-AS1*) has been shown to play a role in atherosclerosis since the discovery that this lncRNA along with the transcript of *NEXN* has decreased levels in human APs. Both the *NEXN-AS1* and *NEXN* genes share a location on chromosome 1 and even have a partially overlapping sequence [120]. Previously, *NEXN* gene polymorphism was found to be linked with susceptibility to CAD in Han Chinese [121]; furthermore, CAD patients exhibited decreased levels of nexilin F-actin binding protein (NEXN) in the blood [120]. The comparison of *NEXN-AS1* and *NEXN* expression patterns between three different stages of plaque development has shown that in the early plaque (types I–III according to the AHA classification) *NEXN-AS1* and *NEXN* expression levels were higher than those in advanced plaques (types IV–VIII). Among advanced plaque types, higher levels were found in advanced stable plaques (types VII and VIII) than in advanced vulnerable plaques (types IV–VI). *NEXN-AS1* may upregulate *NEXN* expression in cultured vascular ECs via interaction with the

chromatin remodeller BAZ1A and *NEXN* gene 5'-flanking region. Other functional assays showed that elevated expression of *NEXN-AS1* in monocytes in vitro inhibited monocyte adhesion to vascular ECs, while in VSMCs this phenomenon resulted in reduced migration. In HUVECs, enhanced expression of *NEXN-AS1* suppressed LPS-induced expression of adhesion molecules, cytokines and extracellular matrix-degrading enzymes. Moreover, *NEXN-AS1* was shown to exert a role on monocyte chemoattractant protein-1 (MCP1), TNF-α, and IL-6 expression though NEXN. Investigations of specific mechanisms revealed that *NEXN-AS1* and NEXN might suppress the TLR4-NFκB signalling pathway in HUVECs [120].

3.2.6 RP11-714G18.1

lncRNA *RP11-714G18.1* is a newly identified lncRNA, which shows downregulated expression in the APs. Its genomic locus is located adjacent to the protein-coding gene for lipoprotein-related receptor 2 binding protein (LRP2BP) on chromosome 4. Moreover, these two genes have opposite transcription directions and share a conserved 89 bp sequence; therefore, *RP11-71418.1* could potentially interact with *LRP2BP*. Interestingly, further investigation implied that overexpression of *RP11-71418.1* and LRP2BP may suppress cell migration in HA-VSMCs and HUVECs partly via downregulation of *MMP1* expression. The results of gain-of-function experiments demonstrated that at a cellular level *RP11-71418.1* also inhibits cell adhesion and tube formation and promotes nitric oxide production in HUVECs while suppressing apoptosis and augmenting proliferation in HA-VSMCs [122].

3.2.7 APPAT

The intergenic lncRNA-AP pathogenesis-associated transcript (*APPAT*) was first identified in human blood. Importantly, in the AP, it exhibited downregulated expression and was stable in the bloodstream; therefore, a change in the *APPAT* expression pattern could potentially serve as a biomarker reflecting disease progression. The spatial distribution of *APPAT* within the human coronary artery was detected mainly in the cytoplasm of tunica media contractile smooth muscle cells, suggesting that its biological function may be exerted by acting as a ceRNA for miR. Subsequent investigation has shown that miR-647 could be a potential target for *APPAT* as the two molecules exhibited opposite expression patterns in arteriostenosis samples [123].

3.2.8 FENDRR

Forkhead box protein F1 (FOXF1) adjacent non-coding developmental regulatory RNA (*FENDRR*) was first reported as an lncRNA that plays role during heart and body wall development in mice. Nevertheless, there was no clear evidence indicating *FENDRR* involvement in CVD [124] until recently conducted research showed downregulation of this lncRNA in an AP [112]. The exact role of *FENDRR* in atherosclerosis development requires further investigation.

4 Future Perspective and Conclusions

In summary, recent studies have uncovered the altered expression of many lncRNAs in APs. They have indicated that these transcripts participate in the regulation of a broad spectrum of cellular processes; however, for most of them, the molecular mode of action remains elusive. Further exploration of the functions of atherosclerosis-related lncRNAs would require a focus on differently expressed splice variants and genetic polymorphisms alongside single-cell expression analysis. To date, multiple lines of evidence have implicated lncRNAs as potential targets for detecting initiation and progression as well as for treating of atherosclerosis and predicting outcomes; therefore, continuing efforts in this area should remain the highest priority in the coming years. In this context, there is a pressing need to establish a standardised experimental pipeline and validation of lncRNAs as possible relevant biomarkers for CVD that would enable the translation of gathered findings into clinical practice.

Compliance with Ethical Standards

Conflict of Interest Weronika Kraczkowska Paweł Piotr Jagodziński declare they have no conflicts of interest that are directly relevant to the content of this review.

Funding No financial support was received in relation to this article.

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