

LncRNA-modulated autophagy in plaque cells: a new paradigm of gene regulation in atherosclerosis?

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ABSTRACT

The development of atherosclerosis is accompanied by the functional deterioration of plaque cells, which leads to the escalation of endothelial inflammation, abnormal vascular smooth muscle cell phenotype switching and the accumulation of lipid-laden macrophages within vascular walls. Autophagy, a highly conserved homeostatic mechanism, is critical for the delivery of cytoplasmic substrates to lysosomes for degradation. Moderate levels of autophagy prevent atherosclerosis by safeguarding plaque cells against apoptosis, preventing inflammation, and limiting the lipid burden, whereas excessive autophagy exacerbates cell damage and inflammation and thereby accelerates the formation of atherosclerotic plaques. Increasing lines of evidence suggest that long noncoding RNAs can be either beneficial or detrimental to atherosclerosis development by regulating the autophagy level. This review summarizes the research progress related to 1) the significant role of autophagy in atherosclerosis and 2) the effects of the lncRNA-mediated modulation of autophagy on the plaque cell fate, inflammation levels, proliferative capacity, and cholesterol metabolism and subsequently on atherogenesis.

INTRODUCTION

Cardiovascular disease (CVD) is among the leading causes of morbidity and mortality around the world. The critical pathological foundation of CVD is atherosclerosis, which is characterized by the formation of atheromatous plaques in large- and medium-sized

arteries, a damaged endothelium, fatty deposits and the build-up of fibrous caps [1, 2]. The development of strategies for the prevention of atherosclerosis will facilitate a decrease in the incidence of CVD.

Autophagy, an evolutionarily conserved catabolic process, is the orderly turnover of cellular components

that deliver harmful pathogens, damaged protein aggregates and organelles to the lysosome for degradation [3]. Basal autophagy protects cells against the accumulation of cytosolic metabolic waste or other dysfunctional constituents. Under environmentally critical conditions, autophagy-mediated nutrient recycling is crucial for the maintenance of energy sources and cell viability [4]. Specifically, the entire process involves more than 30 types of autophagy-related genes (ATGs) and can generally be divided into the following three steps: (1) cytoplasmic materials are sequestered into an expanding membrane sac, called the phagophore, which matures into a characteristic double-membrane vesicle, known as the autophagosome; (2) autophagosomes fuse with lysosomes to form autolysosomes, where dysfunctional organelles and cellular substances are degraded; and (3) the degraded components are delivered to the cytoplasm for anabolism or recycling [5]. To date, three different forms of autophagy have been delineated: macroautophagy, chaperone-mediated autophagy, and micro-

autophagy. In this review, macroautophagy is referred to as autophagy.

Autophagy occurs in all major atherosclerotic plaque cells present around the necrotic core and in the fibrous cap, e.g., endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and macrophages [6]. In the normal vessel wall, basal/moderate levels of autophagy function as cytoprotective and antiatherogenic mechanisms [7], as illustrated in Figure 1. The sequestosome 1 (SQSTM1/p62) levels are considered as a negative indicator of autophagic flux [8, 9]. In Western diet-fed apoE-deficient (apoE^{-/-}) mice, the SQSTM1/p62 levels are clearly amplified in the atherosclerotic aortae, and increases in the age/plaque burden are associated with further enhancements in these levels [10], which suggests that plaque progression is accompanied by defective autophagy. The conundrum of how reparative, life-sustaining machinery, such as autophagy, becomes dysfunctional in atherosclerosis has attracted the attention of researchers. In contrast to basal autophagy,

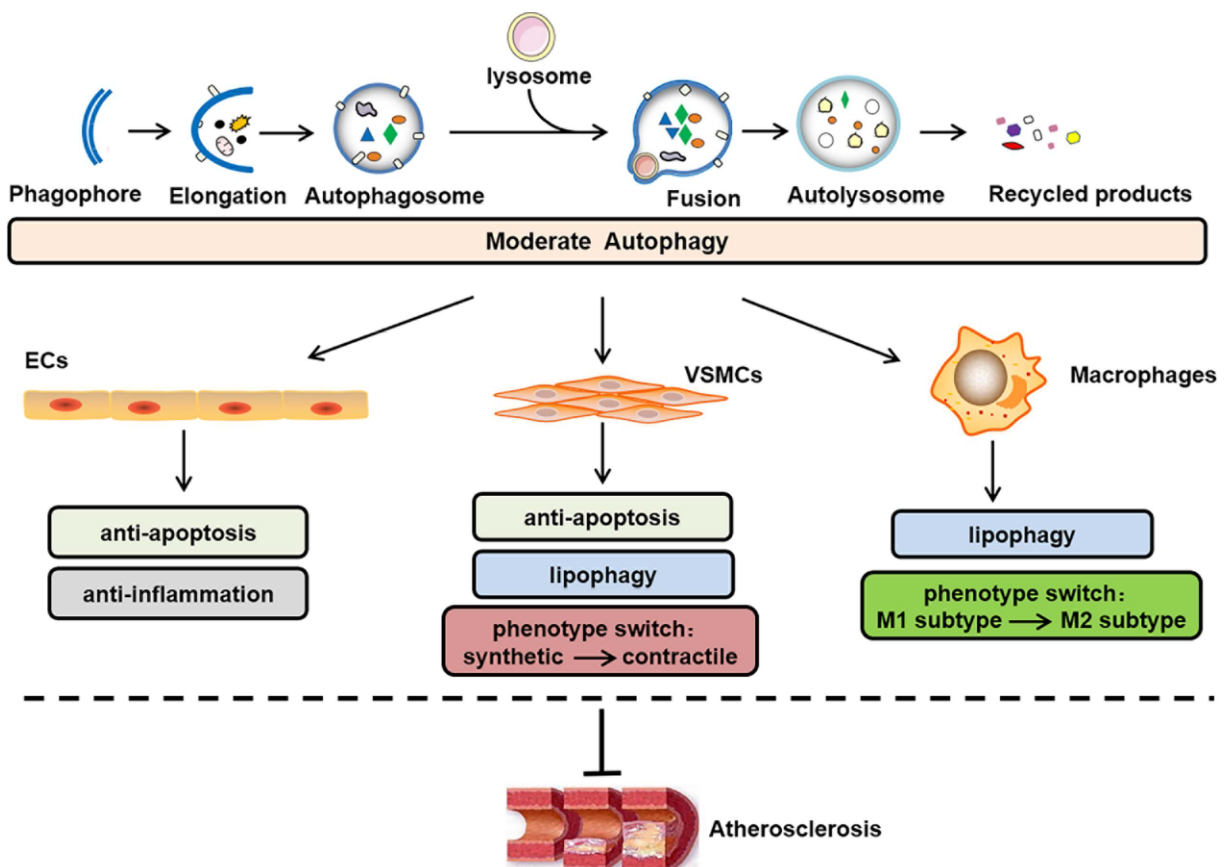


Figure 1. Role of moderate autophagy in atherosclerosis. The process of autophagy primarily involves the following steps: phagophore elongation, autophagosome formation, autophagosome-lysosome fusion, autolysosome formation, acidic hydrolase-mediated degradation of the autophagosome cargo and recycling of constituent macromolecules. In addition, moderate autophagy can inhibit atherosclerosis by protecting plaque cells (i.e., ECs, VSMCs, and macrophages) against apoptosis, inflammation, lipid accumulation, and abnormal phenotype switching. ECs, endothelial cells; VSMCs, vascular smooth muscle cells.

the available evidence also shows that certain stimuli can induce excessive autophagy, which exerts cytotoxic effects on plaque cells and is detrimental for atherogenesis [11]. In general, the disruption of “autophagic homeostasis”, which can be reflected as either insufficient autophagy or overstimulated autophagy, is common during atherogenesis.

Long noncoding RNAs (lncRNAs) are defined as non-protein-coding transcripts longer than 200 nucleotides [12]. According to their genomic location, lncRNAs can be classified into several broad subclasses, including sense/antisense, intronic, intergenic, divergent/convergent, promoter-/enhancer-associated and upstream promoter lncRNAs (Figure 2). In addition, lncRNAs can exhibit various functions, which include serving as molecular signals, decoys, guides and scaffolds (Figure 3) [13]. Despite their poor conservation among species, lncRNAs serve as molecular switches that determine the cell viability, inflammatory response and lipid metabolism in the vasculature by governing the autophagic flux [14, 15]. This review aims to provide a better overall picture of the relationships among lncRNAs, autophagy and atherosclerosis (Table 1).

AUTOPHAGY IN ATHEROSCLEROSIS

EC autophagy in atherogenesis

Based on the available evidence, the defective autophagy occurs in ECs during atherogenesis. ECs isolated from high-fat diet (HFD)-fed apoE^{-/-} mice exhibit significantly lower levels of ATG-6/Beclin-1

protein and a decreased ratio of microtubule-associated protein 1 light chain 3 II to I (LC3-II/I) [16]. In addition, low shear stress (LSS) can decrease the LC3-II/I ratio and the formation of autophagic vacuoles in human umbilical vein endothelial cells (HUVECs). The rapamycin-induced activation of autophagy promotes endothelial alignment in the flow direction, whereas the LSS-induced defects in autophagy disrupt this alignment and accelerate atherosclerotic plaque formation [17]. Nevertheless, Chen et al. reported that LC-3 and ATG-13 are highly expressed in aortic ECs of severe atherosclerotic patients, which indicates that the intimal ECs of advanced plaques might exhibit overactivated autophagy [18].

Effects of autophagy on EC apoptosis

EC apoptosis contributes to atherogenesis [19]. Lunasin reportedly protects EAhy926 ECs against H₂O₂-induced cytotoxicity and mitochondrial-dependent apoptosis by repressing the generation of reactive oxygen species (ROS), which results in inhibition of the formation of thick plaques and increases in the collagen content in atherosclerotic lesions [20].

The role of endothelial autophagy in cell survival and atherosclerosis progression depends on the autophagy intensity levels. Wang et al. reported that the levels of ATG-5 and ATG-12 are decreased in ECs from the aortae of atherosclerotic mice. An *in vitro* study suggested that lower levels of ATG-5, ATG-12 and LC3-II proteins and enhanced SQSTM1/p62 accumulation are concomitant with an impaired cell

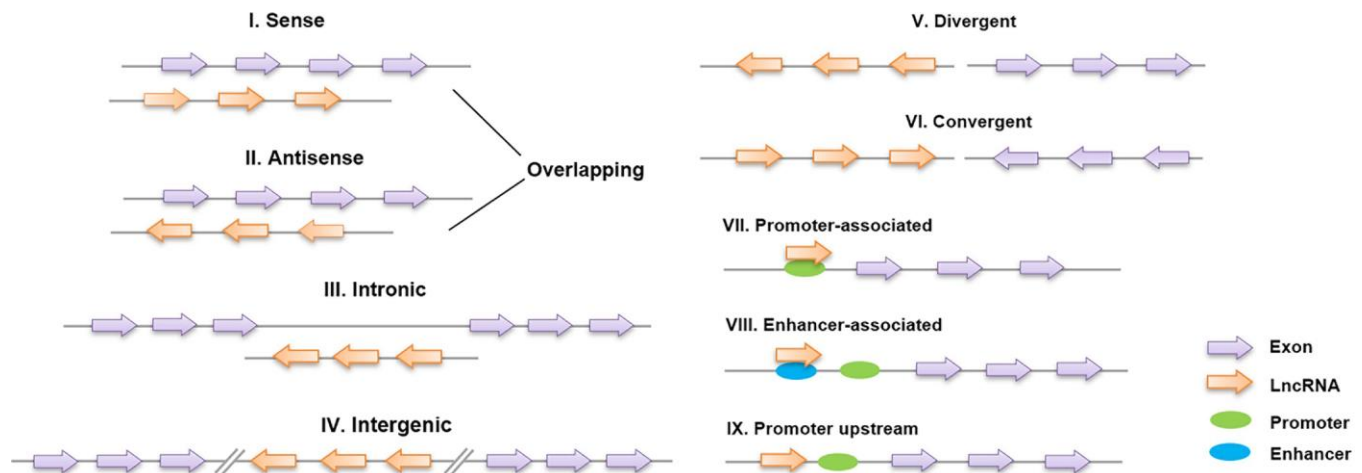


Figure 2. Classification of lncRNAs based on their genomic region. I, II: Sense lncRNAs and antisense lncRNAs are located on the same and opposite strands, respectively, and overlap with neighboring genes; III: intronic lncRNAs are transcribed entirely from the introns of protein-encoding genes; IV: intergenic lncRNAs lie within the genomic interval between two genes; V, VI: divergent/convergent lncRNAs are transcribed in the opposite/same direction as nearby protein-encoding genes; VII, VIII: promoter/enhancer-associated lncRNAs originate from the promoter/enhancer regions of protein-encoding genes; and IX: lncRNAs are situated upstream of the promoter.

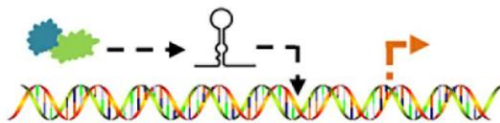
viability of young HUVECs [21]. The injection of 6-amino-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine (ABO) into apoE^{-/-} mice substantially promotes autophagy and ameliorates apoptosis in the aortic endothelium. Furthermore, ABO robustly decreases the atherosclerotic plaque size and improves the stability of plaques [22]. Nevertheless, because autophagy is a process of self-cannibalization, it is reasonable to propose that under proatherosclerotic conditions, high levels of specific stimulators, such as oxidized low-density lipoproteins (ox-LDL) or lipopolysaccharides (LPS), might induce excessive “self-eating” and autophagic cell death [18, 23]. Peng et al. found that the treatment of HUVECs with 3BDO, a novel activator of mammalian target of rapamycin (m-TOR), can significantly reverse ox-LDL-induced autophagy. The administration of 3BDO to apoE^{-/-} mice decreases the ATG-13 protein level in the plaque endothelium, prevents EC death and stabilizes atherosclerotic lesions [24]. Similarly, recombinant thrombomodulin can exert antiatherogenic effects by inhibiting ox-LDL-induced

EC apoptosis through the repression of overactivated autophagy [18].

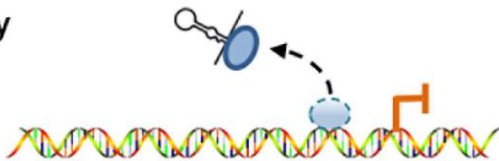
Effects of autophagy on EC-related inflammation

Pankratz et al. observed that miR-100 can suppress mTOR complex 1 (mTORC1) signaling, enhance endothelial autophagy and decrease the expression of adhesion molecules *in vivo* and *in vitro*. In LDL receptor-deficient (LDLR^{-/-}) mice, systemic miR-100 overexpression reduces the plaque area by 45% [25]. Additionally, apoE^{-/-} mice treated with morin hydrate exhibit attenuated atherosclerosis development, decreased serum levels of pro-inflammatory factors (TNF- α , ICAM-1) and enhanced autophagy in plaques. *In vitro* studies have revealed that morin hydrate-treated HUVECs display decreased inflammation, and these effects can be counteracted by the autophagy blocker 3-MA, which suggests that the anti-atherogenic and anti-inflammatory effects of morin hydrate are largely associated with the induction of autophagy [26].

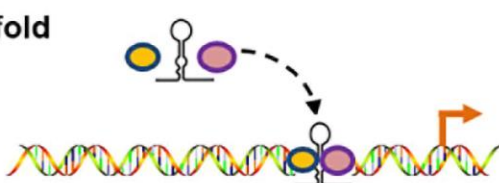
I. Signal



II. Decoy



III. Scaffold



IV. Guide

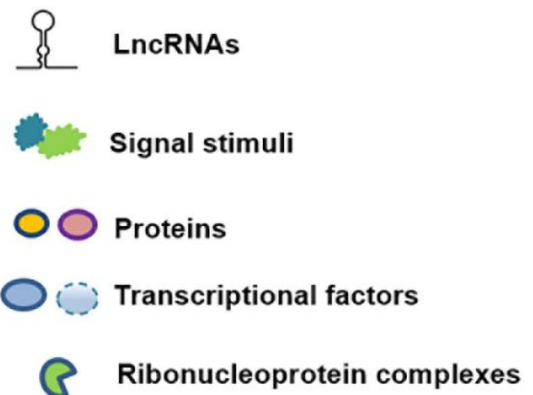
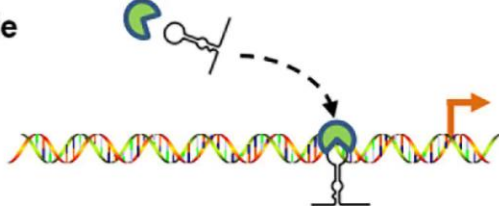


Figure 3. Schematic diagram of the four mechanisms of action of lncRNAs. (I) As molecular signals, lncRNAs are involved in gene transcription in response to various stimuli; (II) as decoys, lncRNAs can repress gene transcription by titrating transcription factors; (III) as scaffolds, lncRNAs can recruit different proteins to target genes; and (IV) as guides, lncRNAs can localize particular ribonucleoprotein complexes to specific chromatin targets.

Table 1. Take-home messages of this review.

Non-coding RNAs	Cell type	Autophagy activity	As
LncRNAs	Plaque cells (ECs, VSMCs, macrophages)	Basal/moderate level	↓
		Insufficient level	↑
		Excessive level	↑

Notes: LncRNAs can mitigate atherosclerosis development by inducing basal/moderate autophagy in plaque cells (ECs, VSMCs, macrophages) and instigate atherogenesis by inducing insufficient or excessive autophagy. EC, endothelial cell; VSMC, vascular smooth muscle cell; As, atherosclerosis. ↓, inhibitory effects; ↑, stimulatory effects.

VSMC autophagy in atherogenesis

Effects of autophagy on VSMC phenotype switching and proliferation

During atherosclerosis, VSMCs can switch from a differentiated, “contractile” phenotype to a dedifferentiated, “synthetic” phenotype, which is characterized by high proliferative and migratory capacities [27]. Injection of the DNA methyltransferase inhibitor (DNMT) 5-aza-2'-deoxycytidine into apoE^{-/-} mice can profoundly reduce the plaque size, and the underlying mechanisms are related to inhibition of the VSMC switch to a synthetic phenotype [28].

Autophagy suppresses the synthetic phenotype in VSMCs and cell proliferation [29]. Grootaert et al. showed that ATG-7 deficiency in VSMCs induces clear defects in autophagy and augments the proliferative capacity of the cells. In VSMC-specific ATG-7^{-/-} mice, the medial thickness of the aorta and the size of atherosclerotic plaques are significantly increased [30]. However, a positive correlation among autophagy, the synthetic VSMC phenotype and atherosclerosis has also been reported. The incubation of VSMCs with nicotine significantly promotes a switch from the contractile phenotype to the synthetic phenotype through the induction of autophagy. Injections of nicotine into HFD-fed apoE^{-/-} mice increase the LC3-II/I ratio, decrease the SQSTM1/p62 levels in plaque VSMCs and enlarge the lesion area in the aortic root [31]. The mechanisms underlying this contradiction merit further study.

Autophagy in VSMCs prevents cell death and attenuates the instability of atheromatous plaques [32]. VSMCs isolated from ATG-7^{-/-} mice exhibit a higher apoptotic death rate, and the mice had larger stenosis areas and intraplaque hemorrhage regions in their carotid arteries [33, 34]. Nevertheless, some factors can induce excessive VSMC autophagy and impair cell viability. The treatment of VSMCs isolated from human atherosclerotic plaques with TNF- α markedly enhances autophagic cell death by increasing the number of vacuolated cells and the expression of the autophagy

marker LC3 [35]. In addition, human VSMCs treated with osteopontin exhibit marked increases in the autophagosome numbers, the LC3-II/I ratio and the expression of several ATGs, which results in accelerated cell death [36]. Altogether, the results show that moderate and overactivated autophagy most likely exert opposite effects on VSMC fate and atherosclerosis.

Effects of autophagy on lipid accumulation in VSMCs

Autophagy can also impede atherogenesis by preventing excessive lipid loading in VSMCs. Li et al. observed that the downregulation of sterol regulatory element-binding cleavage-activating proteins (SREBPs) rescues dysfunctional autophagy in VSMCs, which leads to decreased accumulation of lipid droplets (LDs), free cholesterol (FC) and cholesteryl ester (CE). Furthermore, the VSMC-specific knockdown of SREBPs in apoE^{-/-} mice enhances cell autophagy and alleviates lipid deposition in plaques [37]. Similarly, the treatment of lipid-laden VSMCs with spermidine increases cholesterol efflux, and this effect is substantially attenuated in ATG-7-deficient VSMCs. *In vivo* studies have shown that spermidine significantly increases the LC3-II/I ratio, decreases the levels of SQSTM1/p62, and diminishes lipid deposition and necrotic core formation in aortic atherosclerotic plaques [38].

Macrophage autophagy in atherogenesis

Lipophagy

Lipophagy, a special type of autophagy, refers to an important acidic cholesterol hydrolysis pathway through which cytoplasmic LD-associated CE is transported to lysosomes [39]. This lipophilic flux consists of the following steps: (1) ATG-6/Beclin-1 mediates the formation of vesicle nucleation and subsequent LD-sequestered autophagosomes, which fuse with lysosomes to promote autolysosome production, and (2) lysosomal acid lipase (LAL) in the autolysosome hydrolyzes LD-associated CE to liberate FC [40]. Moreover, ATP-binding cassette transporter A1 (ABCA1) mediates the efflux of FC from macrophages,

which is a key step in the formation of high-density lipoprotein (HDL) and reverse cholesterol transport (RCT) [40, 41]. RCT can increase the clearance of circulating low-density lipoprotein cholesterol (LDL-C), an independent risk factor for atherosclerosis [42, 43]. Thus, the activation of lipophagy is a viable therapeutic target for preventing lipid deposition and atherogenesis.

Jeong et al. observed dysfunctional lipophagy and an increased number of macrophage foam cells in plaques of peroxiredoxin-1^{-/-} apoE^{7/-} mice. In peroxiredoxin-1-deficient murine peritoneal macrophages, the ratio of autolysosomes to autophagosomes is decreased, which leads to impaired lipophagic flux and increased levels of total cholesterol (TC) and CE [44]. In addition, miR-33 antagonism exerts antiatherogenic effects by promoting the ABCA1-mediated efflux of cholesterol from plaque macrophages [45]. These effects are related to enhanced lipophagy, as demonstrated by the finding that hypercholesterolemic mice treated with miR-33 inhibitors show markedly increased LC3 levels, substantially higher autophagosome formation and less LD accumulation in macrophage foam cells [46]. These findings highlight the critical role of macrophage lipophagy in alleviating lipid overload and preventing atherogenesis.

Effects of autophagy on macrophage polarization and inflammation

Liu et al. showed that ATG-5 deficiency suppresses anti-inflammatory M2 macrophage generation [47], which indicates that autophagy inhibits macrophage inflammation. Additionally, the cellular repressor of E1A-stimulated genes (CREG) can ameliorate macrophage inflammation by promoting lysosomal maturation and autolysosome formation. The treatment of HFD-fed apoE^{-/-} mice with recombinant CREG significantly decreases the plaque areas by reducing the number of macrophages and inhibiting inflammation in aortae [48]. Moreover, autophagy induced by tanshinone IIA promotes macrophage polarization towards the M2 phenotype. The administration of tanshinone IIA to apoE^{-/-} mice increases the CD206⁺ macrophage (M2) numbers, and this effect is accompanied by augmented autophagy, weakened inflammatory responses and smaller atherosclerotic lesion areas in the aorta [49].

LNCRNAs INVOLVED IN ATHEROGENESIS THROUGH AUTOPHAGY

EC

The downregulation of GAS5 prevents atherosclerosis progression in apoE^{-/-} mice [50]. In cardiac microvascular

endothelial cells (CMECs), the overexpression of GAS5 significantly elevates the activity of the apoptosis-related protein caspase-3 and promotes the formation of incomplete nuclei [51]. Moreover, in ox-LDL-treated human aortic ECs, the knockdown of GAS5 substantially augments the LC3-II/I ratio, decreases the SQSTM1/p62 levels and reduces cell apoptosis, and these effects are reversed by miR-26a suppression. Therefore, impaired autophagic flux and exacerbated EC apoptosis might be involved in the pro-atherogenic effects of GAS5 [52].

MALAT1 mitigates atherosclerotic plaque formation by decreasing myeloid cell adhesion to ECs and reducing proinflammatory cytokine production [53]. *In vitro* studies have shown that the downregulation of MALAT1 notably enhances the secretion of interleukin-6 (IL-6) and IL-8 from human aortic ECs [54]. The overexpression of MALAT1 significantly increases the LC3-II protein levels and facilitates the formation of autophagosomes and autolysosomes in HUVECs [55]. Similarly, the downregulation of MALAT1 in brain microvascular endothelial cells (BMECs) significantly decreases LC3-II expression and increases the SQSTM1/p62 levels by targeting the miR-200c-3p/sirtuin 1 (SIRT-1) axis [56]. Other studies have revealed that MALAT1 can also exert pro-autophagic effects through the miR-26b/ULK-2 axis [57] or the miR-216-5p/Beclin-1 axis [58]. MALAT1-induced autophagy in ECs might contribute to the inhibition of inflammation and atherogenesis.

Both LPS and ox-LDL can induce excessive autophagy and increase the TGFB2-OT1 levels [59]. TGFB2-OT1 can increase the production of IL-6 and IL-8 in HUVECs likely due to the overactivation of autophagy through the miR-4459/La ribonucleoprotein domain family member 1 pathway (LARP1) [59]. Whether TGFB2-OT1 accelerates atherogenesis by promoting autophagy and inflammation in ECs is unclear.

VSMC

MALAT1 can inhibit atherosclerosis development through several mechanisms [60–62]. In siMALAT1-transfected VSMCs, the expression of SMC-specific contraction-related genes, including α -smooth muscle actin, SM-22, myocardin and serum response factor (SRF), was significantly enhanced. Furthermore, VSMC proliferation and migration are inhibited by the knockdown of MALAT1. Mechanistically, MALAT1 acts as a miR-142-3p sponge to enhance the expression of ATG-7 and LC3-II and decrease the SQSTM1/p62 levels [63]. Thus, in addition to its beneficial role in atherogenesis, MALAT1 might have the potential to accelerate atherosclerosis by inhibiting the contractile phenotype of VSMCs via autophagy stimulation.

The expression of the lncRNA BANCR is significantly increased in human atherosclerotic plaques. The overexpression of BANCR in VSMCs clearly increases the LC3-II/I ratio and promotes cell proliferation, and these effects are counteracted by the JNK inhibitor SP600125 [64]. Moreover, treatment with the autophagy inhibitor 3-MA significantly attenuates the positive effects of BANCR on autophagy and cell proliferation [65]. BANCR might exert pro-atherogenic effects by promoting VSMC autophagy and cell proliferation.

Guo et al. [66] found that apoE^{-/-} mice injected with lentiviral vector-siRNA-FA2H-2 exhibit defective autophagy, increased expression of mixed lineage kinase domain-like protein (MLKL), VCAM-1, MCP-1, and IL-6, and larger lesion areas in the aortic roots and aortic valves. *In vitro* studies have shown that the downregulation of FA2H-2 in VSMCs and ECs significantly increases the expression of MLKL, suppresses autophagic flux and amplifies the production of proinflammatory cytokines (IL-6, IL-8, IL-18, IL-1β, and TNF-α). Furthermore, pretreatment with 3-MA or ATG-7-shRNA reverses the effects induced by FA2H-2 knockdown, which demonstrates that FA2H-2 attenuates atherosclerotic plaque progression by enhancing autophagy in VSMCs and ECs to alleviate inflammation.

The lncRNA H19 reportedly exacerbates atherosclerosis and induces ischemic stroke [23]. The overexpression of H19 *in vivo* can increase VSMC inflammation [67]. Moreover, an inverse expression pattern of H19 and autophagy-related proteins (LC3-II/I ratio and Beclin-1) has been observed in both the thoracic aortae of apoE^{-/-} mice and human VSMCs. Further study showed that the H19-mediated suppression of the dual-specificity phosphatase 5 (DUSP-5)-ERK1/2 axis mitigates VSMC autophagy [68]. H19-induced atherogenesis is likely attributed to the repression of VSMC autophagy and the subsequent promotion of inflammation.

Macrophage

The overexpression of DYNLRB2-2 in THP-1 macrophages markedly increases the ABCA1-mediated efflux of cholesterol and reduces intracellular LDs. The upregulation of DYNLRB2-2 also augments the expression of p-AMPK, LC3-II and ATG-6/Beclin-1 and decreases the levels of phospho-m-TOR and SQSTM1/p62. Furthermore, the effects of DYNLRB2-2 on macrophage lipid accumulation are attenuated by pretreatment with the AMPK signaling pathway inhibitor compound C or the autophagy blocker 3-MA [69]. Another study by Hu et al. revealed that DYNLRB2-2 enhances ABCA1-mediated lipid efflux

and the anti-inflammatory response by amplifying the expression of G protein-coupled receptor 119 (GPR119) [70]. Further experiments are needed to verify whether DYNLRB2-2 protects against atherosclerosis through the enhancement of macrophage autophagy.

The TLR-4/NF-κB pathway has been well established as a facilitator of atherogenesis [71–73]. The available evidence shows that activation of the TLR-4/NF-κB pathway is positively correlated with the macrophage autophagy levels [74–77]. The lncRNA SNHG16 aggravates LPS-induced inflammation in mouse macrophages by upregulating TLR-4 expression [78]. The lncRNA HOTAIR promotes NF-κB activation and increases the expression of IL-6 and inducible nitric oxide synthase (iNOS) by accelerating IκBα degradation in RAW264.7 mouse macrophages [79]. The mechanism underlying the induction of inflammation by SNHG16 and HOTAIR might be related to overactivated autophagy. Additionally, MALAT1 overexpression inhibits the secretion of IFN-γ, TNF and IL-6 by increasing its interaction with the lncRNA NEAT1 in macrophages [62]. Another study performed by Zhao et al. [80] demonstrated that the MALAT1 levels in macrophages are upregulated by LPS, and MALAT1 reduces LPS-induced inflammation by acting as a negative feedback modulator of NF-κB. Because LPS is a potential inducer of excessive autophagy [59], MALAT1 might exert an anti-inflammatory effect in macrophages by repressing NF-κB-mediated autophagy.

LNCRNAS INVOLVED IN THE DEVELOPMENT OF ATHEROSCLEROSIS-RELATED DISEASES THROUGH AUTOPHAGY

LncRNA-induced autophagy is also involved in other factors that influence the progression of arteriosclerosis, such as hypertension and obesity [81, 82]. Placental tissues from preeclampsia patients diagnosed with hypertension exhibit significantly higher H19 levels [83]. As observed in a mechanistic study, H19 overexpression decreases the viability of trophoblasts, increases the LC3-II/I ratio and the Beclin-1 levels and suppresses SQSTM1/p62 expression. H19 might aggravate hypertension by inducing excessive autophagy and cell death [84]. In addition, in human adipocyte-derived stem cells, the lncRNA MEG3 levels are decreased during adipocyte differentiation [85]. MEG3 overexpression significantly decreases adipocyte differentiation by targeting miR-140-5p [85]. The enhancement of autophagy facilitates adipogenic differentiation and increases the size of adipose depots [86–88], and miR-140-5p induces autophagy in different

Table 2. lncRNAs that regulate autophagy in atherogenesis and the underlying mechanisms.

Cell type	lncRNAs	Pathways	Autophagy	Cell function	As	Refs.	
EC	GAS5	miR-26a↓	↓	Apoptosis↑	↑?	50-52	
	MALAT1	PI3K/AKT↓, miR-200c-3p↓/SIRT-1↑, miR-26b↓/ULK-2↑, miR-216-5p↓/Beclin-1↑	↑	Inflammation↓	↓?	53-58	
		TGFB2-OT1	miR-4459↓/LARP1↑	↑↑?	Inflammation↑	↑?	59
		FA2H-2	MLKL↓	↑	Inflammation↓	↓	66
	VSMC	MALAT1	miR-142-3p↓/ATG-7↑	↑	Synthetic phenotype↑	↑?	63
BANCR		JNK↑	↑?	Proliferation and migration↑	↑?	64, 65	
FA2H-2		MLKL↓	↑	Inflammation↓	↓	66	
H19		DUSP5-ERK1/2↓	↓	Inflammation↑	↑?	67, 68	
Macrophage		DYNLRB2-2	GPR119↑/ABCA1↑	↑	Foam cell formation↓, inflammation↓	↓?	69, 70
		SNHG16	TLR-4/NF-κB↑	↑↑?	Inflammation↑	↑?	78
	HOTAIR	NF-κB↑	↑↑?	Inflammation↑	↑?	79	
	MALAT1	NEAT1↓, NF-κB↓	↓↓?	Inflammation↓	↓?	62, 80	

Notes: ↑, stimulatory effects; ↑↑, excessive activation; ↓, inhibitory effects; ↓↓, restrain of excessive activation;?, needs to be confirmed.

Abbreviations: EC, endothelial cell; VSMC, vascular smooth muscle cell; As, atherosclerosis; SIRT-1, sirtuin 1; ULK-2, unc-51-like autophagy-activating kinase 2; LARP1, La ribonucleoprotein domain family member 1; MLKL, mixed lineage kinase domain-like protein; JNK, c-Jun N-terminal kinase; ATG-7, autophagy-related gene 7; DUSP-5, dual-specificity phosphatase 5; GPR119, G protein-coupled receptor 119; ABCA1, ATP-binding cassette transporter A1; TLR-4, Toll-like receptor 4; NF-κB, nuclear factor kappa-B.

cell types [89, 90], which implies that MEG3 might alleviate obesity by inhibiting autophagy.

LNCRNA-BASED THERAPEUTIC APPROACHES FOR CARDIOVASCULAR EVENTS

lncRNAs are appealing pharmacological targets due to their general cell type-specific functions, but many promising approaches for targeting lncRNAs remain in the preclinical phase [91]. Recombinant viral systems, such as adenoviruses and lentiviruses, are commonly used to deliver lncRNA transcripts into a target cell. The subcutaneous injection of the lncRNA CDKN2B-AS1-overexpressing lentiviral vector into apoE^{-/-} mice robustly mitigates atherosclerosis development by inhibiting ADAM10 [92]. The injection of adenovirus vectors containing lncRNA AZIN2-shRNA into the myocardium of rats significantly decreases the infarct size by sponging miR-214 and elevating PTEN expression [93]. Additionally, the intravenous injection of adenoviral-based siRNA against CHRF into an animal model antagonizes cardiac hypertrophy by targeting the miR-489/MyD-88 pathway [94]. Similarly,

the intraperitoneal injection of lncRNA Chast-targeted GapmeR into mice significantly ameliorates cardiac remodeling and hypertrophy through the suppression of Plekhl1 expression [95]. Thus, the development of more therapeutic strategies targeting lncRNAs is critical for the treatment of CVD.

CONCLUSIONS AND FUTURE DIRECTIONS

The entire process of atherogenesis is accompanied by autophagy impairment. Basal autophagy is beneficial in early atherosclerosis but severely dysfunctional in advanced atherosclerotic plaques. A beneficial level of autophagy in plaque cells, but not excessive autophagy, can protect cells against apoptosis, mitigate vascular inflammation and calcification, and alleviate lipid accumulation in atherosclerotic plaques. Additionally, autophagy can usually be overactivated in response to many stresses, including intracellular stresses (e.g., endoplasmic reticulum stress and reactive oxygen species) [96, 97], and extracellular stimuli (e.g., hypoxia, ox-LDL and LPS) [18, 23, 98]. In these cases, the cellular content is irreversibly depleted, which accelerates cell death and exacerbates the development

of atherosclerosis [11, 32, 99]. LncRNAs participate in atherogenesis by acting as determinants of the autophagy status in plaque cells (i.e., ECs, VSMCs and macrophages) (Table 2). As described above, TGFB2-OT1 might induce overactivated autophagy in ECs and subsequently promote inflammation. SNHG16 and HOTAIR might induce atherogenesis by enhancing macrophage-induced inflammation through the overactivation of autophagy. The improper regulation of autophagy cannot reverse atherosclerotic plaque formation but rather worsens the atherosclerosis outcomes [100]. Thus, identifying the trend and pattern of autophagic responses during atherogenesis is of great significance for predicting the sensitivity/resistance of cells to pathological changes.

The roles of other forms of autophagy in addition to macroautophagy, such as microautophagy, chaperone-mediated autophagy, mitophagy, aggrephagy, and xenophagy, in atherosclerosis have not been adequately addressed. By acting as critical determinants of autophagy, the lncRNA-miRNA and lncRNA-lncRNA axes exert profound influences on atherogenesis. Intriguingly, Liu et al. reported that the lncRNA NBR2 and AMPK kinase form a feed-forward loop under chronic energy stress conditions [101], which makes us wonder whether positive feedback loops between lncRNAs and autophagy components might promote the progression or remission of atherosclerosis. Unraveling these mechanisms will undoubtedly be helpful for the development of lncRNA-based drugs for atherosclerosis treatment.

AUTHOR CONTRIBUTIONS

Kun Ren, Kai Yin and Guo-Jun Zhao conceived and designed this review. Kun Ren and Xiao-Dan Xu drafted and wrote the manuscript. Xiao-Hai Yu, Meng-Qi Li, Meng-Wen Shi collected and organized the literature. Qi-Xian Liu, Ting Jiang, Xi-Long Zheng improved the English grammar of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest to disclose with respect to this manuscript.

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