EPIGENETIC MECHANISMS OF ATHEROSCLEROSIS ETIOPATHOGENESIS

R.N. Mustafin[*]

Bashkir State Medical University, 3 Lenin St., Ufa, 450008, Russia.

* Corresponding author: ruji79@mail.ru

Abstract. Epigenetic regulation of spatiotemporal gene expression in ontogenesis is determined by programmed species-specific activations of retroelements in successive cell divisions. Evolutionary selection of this genome control mechanism is aimed at achieving a mature state, after which unprogrammed activation of retroelements occurs, which expression products stimulate interferon response, aseptic inflammation and aging-associated diseases development, such as atherosclerosis. Interferon in atherosclerosis stimulates pro-inflammatory macrophage phenotype, which contributes to pathological immune response, foam cell formation and atherosclerosis progression. Activation of retroelements occurs under the influence of viral infections, which role in atherosclerosis development has been proven, which confirms my hypothesis. Dysfunctional foam macrophages produce HERV-K102, which stimulates innate immunity, HERV-K HML2 expression correlates with macrophage immune activation and interferon response. Data were obtained on association with atherosclerosis of microRNAs derived from retroelements, which are involved in the disease pathogenesis due to their influence on cholesterol metabolism (miR-498, -520d), immune processes (miR-1257, -28, -2909), activation of DNMT1 (miR-1264) and EZH2 (miR-630), gene expression in endothelial cells (10 specific miRNAs), vascular smooth muscle cells (14 specific miRNAs) and macrophages (miR-320b, -326, -378, -384), contributing to pathological phenotype of these cells. In atherosclerosis microRNAs derived from retroelements interact with circular RNAs (miR-495, -576, -579, -630, -633, -637, -942) and long non-coding RNAs (miR-326, -4731, -495, - 616, -641, -664a) the key sources of which are retroelements. Role of ANRIL, NEAT1, PAPIA, MAARS, VINAS, H19, AK136714, MIAT, and interaction of Alu elements with ANRIL and NEAT1, identified in atherosclerosis development. The data obtained can become the basis for targeted effect on retroelements activation in atherosclerosis using microRNAs.

Keywords: atherosclerosis, epigenetic factors, long noncoding RNAs, microRNA, retroelements.

List of Abbreviations

AS – atherosclerosis
ECs – endotheliocytes
IFN – interferon
lncRNAs – long noncoding RNAs
ncRNAs – noncoding RNAs
REs – retroelements
TF – transcription factor
VSMCs – vascular smooth muscle cells

Introduction

Aging-associated inflammation of vessel walls plays an important role in the development of atherosclerosis (AS) (Franceschi *et al.*, 2000; Menghini *et al.*, 2014; de Yebenes *et al.*, 2020). At the same time, during aging, pathological activation of HERV retroelements (REs) (Autio *et al.*, 2020) and LINE-1 (Cardelli, 2018) occurs in all people. Retroelement expression products stimulate interferon (IFN) overproduction, promoting chronic aseptic inflammation (De Cecco *et al.*, 2019; Autio *et al.*, 2020). REs belong to transposons, the movement of which occurs by reverse transcription of their RNA with insertion of the resulting cDNA into a new genomic locus (Cardelli, 2018). They occupy at least 45% of the human genome (Mustafin & Khusnutdinova, 2017).

The role of REs in the initiation and development of AS is due not only to IFN-mediated inflammation, but also to the participation of REs in the functioning of the immune system. This is evidenced by the emergence of RAG1 and RAG2, necessary for V(D)J recombination, from transposons (Huang *et al.*, 2016). In addition, ERVs are used as enhancers of HLA-G genes (Chuong *et al.*, 2018) and IFN-inducible genes (forming IFN response transcriptional networks (Chuong *et al.*, 2016)). Meta-analyses have shown the role of RE dysregulation in autoimmune pathology (de la Hera *et al.*, 2013), with which AS is reliably associated (Martinez-Ceballos *et al.*, 2021).

AS is characterized by persistent inflammation due to disproportionate polarization of AS-associated macrophages from anti-inflammatory (M2-like) to pro-inflammatory (M1-like) under the influence of epigenetic factors (Yang *et al.*, 2022). HERV-K102 is expressed by activated monocytes and is released into vacuoles associated with their surfaces, turning the cells into "foam cells." Release of HERV-K102 occurs only upon lysis of macrophages. At the same time, HERV-K102 protect human cells from viral infections and malignant neoplasms (Laderoute, 2020). Clinical studies have shown the role of viruses: (HIV (Freiberg *et al.*, 2013), herpes simplex HSV-1 and HSV-2 (Wu *et al.*, 2016), hepatitis C (Olubamwo *et al.*, 2016) and B (Rivero-Barciela *et al.*, 2021), cytomegalovirus (Jia *et al.*, 2017), influenza (Peretz *et al.*, 2019)), in the development of AS. Therefore, overproduction of HERV-K102 as a protective mechanism against infections (Badarinarayan & Sauter, 2021) may contribute to impaired gene expression in macrophages and the development of AS (Chai *et al.*, 2018).

REs serve as regulators of gene expression in human ontogenesis, being drivers of epigenetic regulation (Mustafin & Khusnutdinova, 2017), since they serve as sources of non-coding RNAs (ncRNAs), such as microRNAs (Wei *et al.*, 2016) and long ncRNAs (lncRNAs) (Johnson, Gugo, 2014). Moreover, HERVs (Lu *et al.*, 2014) and LINE-1s (Honson & Macfarlan, 2018) can serve as direct ncRNA genes, as they are transcribed into functional lncRNAs involved in the regulation of ontogenesis. Therefore, changes in the expression of specific ncRNAs and epigenetic factors in AS may reflect dysregulation of REs.

Epigenetic factors of atherosclerosis development

The main epigenetic factors include DNA methylation, histone modifications, and RNA interference with ncRNA. At the same time, ncRNAs are not only involved in the post-transcriptional regulation of gene expression, but are also key drivers of DNA and histone modifications (Mustafin & Khusnutdinova, 2017) due to the mechanism of RNA-directed DNA methylation (Chalertpet *et al.*, 2019). DNA methylation is carried out by DNA methyltransferase enzymes DNMT1, DNMT3a, DNMT3b, DNA demethylation is performed by Tet-methylcytosine dioxygenases TET1, TET2, TET3, acetylation of histones is carried out by acetyltransferases (HATs) (Xu *et al.*, 2018). Histone deacetylases (HDAC) are classified into Class I (HDAC core enzymes-1, -2, -3, -8), Class II (HDAC-4, -5, -6, -7, -9, -10), III (sirtuins 1-7), IV (HDAC-11). Various HDACs are influenced by both microRNAs (for example, miR-34a (Li *et al.*, 2018)) and transcription factors (TF), regulating their effect on gene expression (Lee *et al.*, 2019).

In evolution, TFs (Feschotte, 2008) and binding sites for them (Mustafin, 2019), as well as microRNAs (Wei *et al.*, 2016), arose from transposons, which indicates the mechanisms of their influence on epigenetic regulation. Changes in modifications of DNMT1/3a/3b, TET1/2/3, HAT and HDAC in the development of AS are described in a systematic review (Xu *et al.*, 2018). An important role is played by changes in epigenetic regulation in the polarization of macrophages into M1-like macrophages under the influence of HDAC3, HDAC7, HDAC9 and H3K9/36me3 modifications (Yang *et al.*, 2022a).

Changes in microRNA expression are described as pathogenetic factors of aging-developing AS (Menghini *et al.*, 2014; de Yebenes *et al.*, 2020). The role of microRNAs in the pathogenesis of AS is due to various mechanisms, including the regulation of lipid metabolism and inflammation (Arora *et al.*, 2014), and the aging of endotheliocytes (ECs) themselves. Inflammation in atherosclerosis is associated with elevated levels of miR-126, miR-221/222 and low levels of miR10a, miR-155, miR-181a, miR-221/222, which leads to apoptosis, cell cycle arrest, and the production of reactive oxygen species. With aging of the endothelium, there is an increase in the expression of miR-217, miR-34; a decrease in the production of miR-92a, miR-216a, which is accompanied by an increase in VCAM (vascular cell adhesion protein), ICAM (intercellular adhesion molecule), MCP1 (monocyte chemoattractant protein 1),

CXCL12 (chemokine (C-X-C motif) ligand 12) concentrations (Menghini *et al.*, 2014). In addition to miR-34a and miR-217, miR-146a (Deng *et al.*, 2017) and miR-200c (in response to reactive oxygen species) are associated with EC aging (Novak *et al.*, 2017). Aging-associated miR-217 has been implicated in the development of AS and cardiovascular dysfunction by suppressing a network of activators of endothelial nitric oxide synthetases, including VEGF and apelin receptor pathways (de Yebenes *et al.*, 2020). Inhibition of miR-34a, which promotes the development of AS, prevents cell apoptosis, contributing to their viability (Li *et al.*, 2018).

A systematic review of the scientific literature conducted in 2018 showed that miR-19a, miR-19b, and miR-21 control inflammation of the vascular wall by regulating its infiltration by leukocytes and their activation. The key in the mechanisms of AS is miR-126, which inhibits VCAM-1 and proinflammatory TNF-α. Reduced expression of miR-126 activates NF-κB with increased interactions of leukocytes with endothelial cells and the development of AS. The influence on vascular smooth muscle cells (VSMCs) in the pathogenesis of AS is characterized by miR-1 (targets are mRNA of the KLF4, PIM1 genes), miR10a (target is HDAC4 mRNA), miR-126 (targets are BCL2, IRS1, FOXO3 mRNA), miR-22 (inhibits the MECP2, HDAC4, EVI1 genes), miR-143 and miR-145 (affect the ACE, ELK1, KLF4/5 genes), miR-21 (DOCK, PDCD4 genes are targets), miR-26a, miR- 34a, miR-130a, miR-221. Abnormal proliferation and migration of VSMCs are involved in neointimal formation and contributes to AS and restenosis (Chen *et al.*, 2018).

Inflammatory macrophages secrete vesicles containing specific RNAs (miR-28, miR-146a, miR-185, miR-365, miR-503) that are used to communicate with cells of atherosclerotic vessels (Lu *et al.*, 2018). Among circulating microRNAs specific for AS are miR-17, miR-17-5p, miR-29b, miR-30, miR-92a, miR-126, miR-143, miR-145, miR-146a, miR-212, miR -218, miR-221, miR-222 and miR-361-5p, which have been proposed as biomarkers for disease diagnosis (Sharma *et al.*, 2022). MiR-33, which regulates ABCA1 (ATP-binding cassette transporter A1)-dependent cholesterol efflux, influences the function of macrophages in AS. miR-33 also inhibits TFEB and FOXO3, reducing lysosomal activity and phagocytosis of macrophages. Therefore, exposure to anti-miR-33 increases efferocytosis, lysosomal biogenesis, and degradation of apoptotic material in macrophages. In experiments with Ldlr-/- mice with AS, anti-miR-33 restored defective autophagy in macrophage foam cells in plaques, promoting clearance of apoptotic cells and reducing plaque necrosis (Ouimet *et al.*, 2017).

Relationship between long ncRNAs and retroelements in atherosclerosis

The observed changes in lncRNA levels in the pathogenesis of AS may be a reflection of the expression characteristics of RE, which serve as sources of ncRNAs (Wei *et al.*, 2016; Johnson, Gugo, 2014; Lu *et al.*, 2014; Honson & Macfarlan, 2018). In addition to the emergence of lncRNAs from retroelements (Johnson and Gugo, 2014) and their direct processing of mRNA from RE genes (Lu *et al.*, 2014; Honson & Macfarlan, 2018), the role of interactions of RE with lncRNAs in the pathogenesis of AS has been described. Alu elements (belonging to non-autonomous RE) bind to lncRNA ANRIL, involved in the development of AS (Hueso *et al.*, 2018). In turn, ANRIL interacts directly with Alu sequences in the genome (Chi *et al.*, 2017), which have a proatherogenic effect, as they are located in the promoter regions of target genes (Holdt *et al.*, 2013), such as those encoding proteins of the PRC-1 and PRC-2 groups. ANRIL recruits these proteins used for epigenetic modification of chromatin and inhibition of gene expression in cis-regulation of apoptosis, cell proliferation and adhesion, inflammation and AS development (Chi *et al.*, 2017). In atherosclerosis, lncRNA RAPIA is expressed by macrophages, stimulating their proliferation and suppressing apoptosis. Inhibition of RAPIA in vivo suppresses the progression of AS and has an antiatherogenic effect (Sun *et al.*, 2020). Expression of the macrophage-specific lncRNA MAARS in the aortic

intima increases 270-fold with AS progression and decreases by 60% with regression. In experiments on LDLR-/- mice, knockdown of MAARS reduced the formation of AS plaques by 52% due to a decrease in inflammation, macrophage apoptosis and an increase in efferocytosis in the vessel walls (Simion *et al.*, 2020).

LncRNAs VINAS (Simon *et al.*, 2020) and H19 (Pan, 2017) regulate MAPK and NF-κB signaling pathways involved in inflammation. Knockdown of VINAS reduces the expression of key inflammatory markers such as MCP-1, COX-2, TNF-α, IL-1β in endothelial cells (Simon *et al.*, 2020). In the blood plasma and plaques of patients with AS, an increased level of lncRNA AK136714 was detected, the inhibition of which suppresses AS and inflammation of endothelial cells. AK136714 enhances Bim transcription, directly binds to HuR, increasing the stability of TNF-α, IL-1β and IL-6 mRNA (Bai *et al.*, 2021). The expression of the myocardial infarction-associated lncRNA MIAT is significantly increased in the serum of AS patients with unstable plaques. MIAT acts as a sponge for miR-149-5p by stimulating the antiphagocytic molecule CD47 (Ye *et al.*, 2019).

Macrophages are characterized by the expression of autonomous REs, which can function as direct sources of lncRNAs (Lu *et al.*, 2014). HERV-K HML-2 expression correlates with macrophage immune activation (polarization in M1) and response to IFNI (Russ *et al.*, 2023). According to a new paradigm of immunosenescence, dysfunctional (LB-) foamy macrophages (CD14+CD16+) produce HERV-K102 particles released to stimulate the trained innate immune system (Laderoute, 2020). Macrophages are also characterized by the expression of the *ERVPb1* gene, which is derived from the *Env* gene of HERV-P (Matsuzawa *et al.*, 2021). The RNA molecule of Alu elements modified by adenosine-inosine editing controls the stability of the pro-inflammatory lncRNA NEAT1 in AS. NEAT1 expression, induced by TNF-α, is more than 2 times higher in blood monocytes of patients with coronary artery AS. Suppression of NEAT1 leads to attenuation of TNF-α-induced pro-inflammatory response of endothelial cells, as manifested by the expression of CXCL8, CCL2, VCAM1 and ICAM1 (Vlachogiannis *et al.*, 2021).

The relationship between microRNA and retroelements in atherosclerosis

REs are the evolutionary sources of many microRNAs. According to the MDTE DB database, in humans, 661 miRNAs originate from transposons, mainly from REs (Wei *et al.*, 2016). They can have both pro-atherogenic (increased concentration in patients with AS) and anti-atherogenic (low expression) effects, and participate in the pathogenesis of AS in various ways (Table 1). MicroRNA expression is determined both in patients with AS (for example, miR-1253, miR-1202 and many others) and in animal experiments (miR-31 (Liu *et al.*, 2015b), miR-320b (Lu *et al.*, 2022), miR-630 (Mia *et al.*, 2022)). In patients with AS, the levels of these molecules are determined in blood plasma exosomes (miR-1202 (Sorrentino *et al.*, 2020)) or macrophages (miR-1271 (Long *et al.*, 2021)), coronary artery samples (miR-1273 (Wang *et al.*, 2021) al., 2015)), in plasma (miR-1296, miR-493 (Niu *et al.*, 2021), miR-335 (Hildebrandt *et al.*, 2021)) and serum (miR-211 (Zhang *et al.*, 2021), miR-3646 (Fan *et al.*, 2020), miR-374 (Wang *et al.*, 2020a), miR-502 (Wang *et al.*, 2014), miR-582 (Hildebrandt *et al.*, 2021)), in vascular smooth muscle cells (miR-421 (Yang *et al.*, 2020)), in peripheral mononuclear cells (miR-2909 (Arora *et al.*, 2014), miR-342 (Ahmadi *et al.*, 2018)) and in adipose tissue around coronary arteries (miR-548 (Konwerski *et al.*, 2021)).

Pathological proliferation, apoptosis, invasion and differentiation of VSMCs contribute to plaque formation in AS. In this case, VSMCs can transform into less differentiated forms that lack VSMC markers, including macrophage-like cells, which contribute to the progression of AS and inflammation (Bennett *et al.*, 2016). This process is influenced by miR-1246 (Pan *et al.*, 2021), miR-1253 (Wang *et al.*, 2020b), miR-1278 (Ma *et al.*, 2023), miR-192 (Zhao *et al.*, 2021), miR-374 (Wang *et al.*, 2020a), miR-4459 (Lin *et al.*, 2022), miR-4487 (путем целевого воздействия на RASA1 (Liang *et al.*, 2022)), miR-4731 (взаимодействуя с FOXO3)

Table 1

Association of transposon-derived microRNAs with atherosclerosis

№	MicroRNA	Transposon-source	MicroRNA expression (increase - ↑, decrease - ↓)	Author
1.	miR-1202	LTR-ERV1	↑	(Sorrentino *et al.*, 2020)
2.	miR-1246	LTR-ERVL	↑	(Pan *et al.*, 2021)
3.	miR-1248	SINE/Alu	↑	(Lin *et al.*, 2023)
4.	miR-1253	LINE2 и SINE/MIR	↓	(Wang *et al.*, 2020)
5.	miR-1257	ERVL	↑	(Xu, Li, 2016)
6.	miR-1264	LINE2	↓	(Wen *et al.*, 2021)
7.	miR-1271	LINE2	↑	(Long *et al.*, 2021)
8.	miR-1273	LINE, SINE, ERVL	↑	(Wang *et al.*, 2015)
9.	miR-1278	SINE/MIR	↓	(Ma *et al.*, 2023)
10.	miR-1296	LINE2	↓	(Niu *et al.*, 2021)
11.	miR-151	LINE2	↓	(Chen *et al.*, 2021)
12.	miR-192	LINE2	↑	(Zhao *et al.*, 2021)
13.	miR-211	LINE2	↓	(Zhang *et al.*, 2021)
14.	miR-28	LINE2	↑	(Liu *et al.*, 2015a)
15.	miR-2909	LTR-ERVL	↑	(Arora *et al.*, 2014)
16.	miR-31	LINE2	↑	(Liu *et al.*, 2015b)
17.	miR-320b	LINE2	↑	(Lu *et al.*, 2022)
18.	miR-326	LINE2	↑	(Wang *et al.*, 2019).
19.	miR-335	SINE/MIR	↑	(Hildebrandt *et al.*, 2021)
20.	miR-342	SINE/tRNA-RTE	↑	(Ahmadi *et al.*, 2018)
21.	miR-3646	SINE/MIR	↑	(Fan *et al.*, 2020)
22.	miR-374	LINE2	↑	(Wang W. *et al.*, 2020)
23.	miR-378	SINE/MIR, LINE2	↑	(Shao *et al.*, 2018)
24.	miR-384	LINE-Dong-R4	↑	(Wang *et al.*, 2016)
25.	miR-421	LINE2	↓	(Yang *et al.*, 2020)
26.	miR-4286	ERVL	↓	(He *et al.*, 2020)
27.	miR-4459	SINE/Alu	↓	(Lin *et al.*, 2022)
28.	miR-4487	LINE1	↑	(Liang *et al.*, 2022)
29.	miR-4731	LINE-CR1	↑	(Ye *et al.*, 2020)
30.	miR-487	SINE/MIR	↑	(Wang *et al.*, 2021)
31.	miR-493	LINE2	↓	(Niu *et al.*, 2021)
32.	miR-495	ERVL	↓	(Rafiq *et al.*, 2023)
33.	miR-498	LINE1	↑	(Liu *et al.*, 2020)
34.	miR-502	LINE2	↑	(Wang *et al.*, 2014)
35.	miR-511	LINE1	↑	(Karagiannis *et al.*, 2013)
36.	miR-520d	SINE/Alu	↓	(Salerno *et al.*, 2020).
37.	miR-544	LINE1	↓	(Guo *et al.*, 2020)
38.	miR-548	LINE, HERV, SINE	↓	(Konwerski *et al.*, 2021)
39.	miR-552	LINE1	↑	(Feng *et al.*, 2022)
40.	miR-576	LINE1	↓	(Zhang *et al.*, 2022)
41.	miR-579	LINE1	↓	(Wang *et al.*, 2024)
42.	miR-582	LINE-CR1	↑	(Hildebrandt *et al.*, 2021)
43.	miR-612	SINE/MIR	↓	(Chen *et al.*, 2018)
44.	miR-616	LINE2	↑	(Chen *et al.*, 2020)
45.	miR-630	SINE/MIR	↓	(Miao *et al.*, 2022)
46.	miR-633	SINE/MIR	↓	(Hou *et al.*, 2022)
47.	miR-637	LINE1	↓	(Zhang *et al.*, 2023)
48.	miR-641	SINE/MIR	↓	(Ma *et al.*, 2021)
49.	miR-664a	LINE1	↓	(Li *et al.*, 2018)
50.	miR-708	LINE2	↓	(Chen *et al.*, 2015)
51.	miR-769	LINE/CR1	↑	(Hildebrandt *et al.*, 2021)
52.	miR-7975	LTR-ERV1	↑	(Karere *et al.*, 2023).
53.	miR-942	LINE2	↓	(Yang *et al.*, 2023)

(Ye *et al.*, 2020), miR-552 (ингибирует SKI и ATF4 (Fang *et al.*, 2022)), miR-579 (Wang *et al.*, 2024), miR-612 (Chen *et al.*, 2018), miR-630 (Miao *et al.*, 2022), miR-641 (Ma *et al.*, 2021). MiR-511 is a component of a multisubunit complex involved in the terminal stages of cholesterol synthesis with the regulation of a family of GPCR proteins that are involved in the transformation of VSMC phenotypes and the pathogenesis of AS (Karagiannis *et al.*, 2013).

A number of microRNAs derived from retroelements affect the expression of EC genes and their precursors, for example, miR-1248 suppresses the expression of thrombomodulin (Lin *et al.*, 2023), microRNA miR-151 (targeting IL-17A, c-caspases 3 and 9, BAX) inhibits EC apoptosis (Chen *et al.*, 2021). In AS, a low level of miR-4286 was detected, which inhibits TGF-β1 (promotes damage to the ECs (He *et al.*, 2020)). MiR-487 inhibits p53 and CBP, enhancing EC proliferation (Wang *et al.*, 2021). MiR-544 promotes the maturation and antioxidant properties of EC-like cells by regulating the YY1/TET2 signaling pathways (Guo *et al.*, 2020). MiR-637 suppresses TRAF6 expression, promoting EC proliferation and angiogenesis, inhibiting apoptosis and inflammation (Zhang *et al.*, 2023). MiR-708 is expressed in EC in AS and inhibits the expression of IL-1 receptor-associated kinase, IL-6 receptor, conserved helix-loop-helix ubiquitous kinase, nuclear factor κB kinase subunit-γ inhibitor (Chen *et al.*, 2015). High levels of miR-769, which targets GSK3B and TRAPPC2B (Hildebrandt *et al.*, 2021) and miR-7975, proposed as a potential biomarker of AS, were detected in the arteries of patients with AS (Karere *et al.*, 2023).

MicroRNAs derived from REs influence AS by regulating immune processes. Thus, miR-1257, involved in the MHC protein assembly pathways, inhibits CALR, POMC, TLR4, IL10, ATF6, promoting the progression of CAD (Xu, Li, 2016). MiR-28 increases ABCA1 expression, which correlates with LXRα translation activation in macrophages (Liu *et al.*, 2015a). MiR-2909 regulates genes involved in inflammation and immunity (Arora *et al.*, 2014).

RE-derived microRNAs also influence AS by modulating epigenetic factors. Thus, miR-1264 suppresses the expression of DNMT1 and phosphorylated STAT3 (Wen *et al.*, 2021). MiR-630 targets the methyltransferase EZH2, which modulates TIMP2 transcription in regulating VSMC migration and promoting AS (Miao *et al.*, 2022).

MicroRNAs are involved in the pathogenesis of AS through their effects on macrophages. Thus, miR-320b (Lu *et al.*, 2022) and miR-378 (Shao *et al.*, 2018) regulate cholesterol efflux from macrophages. Administration of miR-320b to animals increased the size of AS plaques, the content of damaged macrophages and cytokine levels due to increased phosphorylation of NF-κB (Lu *et al.*, 2022). MiR-326 is involved in the formation of oxidized foam cells in AS (Wang *et al.*, 2019). MiR-384 accelerates the development of AS by disrupting macrophage autophagy (Wang *et al.*, 2016).

A number of microRNAs derived from RE and involved in the pathogenesis of AS interact with lncRNAs in these processes. These include miR-326 (Wang *et al.*, 2019), miR-4731 (interacts with lncRNA SENCR (Ye *et al.*, 2020)). NORAD silencing increases miR-495 levels, inhibiting AS plaques by reducing KLF5 expression (Fu *et al.*, 2021). In the serum of patients with AS, the levels of PON1 and lncRNA, which acts as a competitive endogenous RNA for miR-616, are reduced (inhibits PON1 expression, promotes AS (Chen *et al.*, 2020)). LncRNA MIAT interacts with miR-641, affecting the proliferation and migration of VSMCs (Ma *et al.*, 2021). LncRNA Punisher regulates apoptosis and mitochondrial homeostasis of VSMCs by interacting with miR-664a (Yang *et al.*, 2022b).

MicroRNAs arising from REs are also involved in the pathogenesis of AS through interaction with circular RNAs: miR-495 binds to hsa_circ_0126672 (Rafiq *et al.*, 2023). Circ_0086296 induces AS through the IFIT1/STAT1 feedback loop, acting as a sponge for miR-576, which inhibits the expression of IFIT1-STAT1, preventing the development of AS (Zhang *et al.*, 2022a). Hsa_circ_0031891 targets miR-579 to enhance HMGB1 expression (Wang *et al.*, 2024). CircARHGAP12, which stimulates VSMC proliferation and migration, binds to miR-630 (Miao

et al., 2022). Hsa_circ_0008896 has a similar mechanism of action, affecting VSMCs through interaction with miR-633 and regulating CDC20B (Hou *et al.*, 2022). Circ_0003575 interacts with miR-637 and also activates the NF-κB pathway (Zhang *et al.*, 2023). MiR-942, targeting the GPR56 adhesin family gene (Caparosa *et al.*, 2019), interacts with circ_0090231 to inhibit VSMC proliferation and migration (Yang *et al.*, 2023).

RE-derived microRNAs are also involved in cholesterol metabolism in the pathogenesis of AS. Thus, miR-498 inhibits the SCD (stearoyl-CoA desaturase) gene, which reduces serum cholesterol levels (Liu *et al.*, 2020). MiR-520d inhibits the expression of PCSK9, which causes degradation of low-density lipoprotein receptors, suppressing the development of AS (Salerno *et al.*, 2020).

Conclusion

In the pathogenesis of AS, an important role is played by aging-induced hyperactivation of retroelements, which leads to IFN stimulation, various immunopathological processes and changes in the phenotype of VSMCs, ECs and macrophages due to the influence of microRNAs derived from REs on gene expression. Various viral infections are also important, under the influence of which REs is activated as a protective reaction of cells, which can lead to the early onset and rapid progression of AS. Since ERs are sources of lncRNAs and microRNAs, impaired expression of non-coding RNAs in AS reflects dysregulation of REs. This is evidenced by an analysis of the MDTE DB database, in which 53 microRNAs derived from REs were found, the expression of which changes in AS. In accordance with this, targeted therapy using specific microRNAs aimed at pathologically activated REs involved in the pathogenesis of AS may become a promising method for treating the disease.

The author declares no conflicts of interest.

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