DOI: 10.20514/2226-6704-2024-14-2-85-95
УДК 616.13.002.2
EDN: CEXECW

Р.Н. Мустафин*[1], Э.А. Галиева[2]

[1]ФГБОУ ВО «Башкирский государственный медицинский университет», Уфа, Россия.
[2]ФГБОУ ВО «Уфимский университет науки и технологий», Уфа, Россия

РОЛЬ МИКРОРНК И РЕТРОЭЛЕМЕНТОВ В ПАТОГЕНЕЗЕ АТЕРОСКЛЕРОЗА

R.N. Mustafin*[1], E.A. Galieva[2]

[1]Bashkir State Medical University, Ufa, Russia
[2]Ufa University of Science and Technology, Ufa, Russia

Role of MicroRNAs and Retroelements in the Pathogenesis of Atherosclerosis

Резюме

Атеросклероз является ведущей причиной сердечно-сосудистых заболеваний среди взрослого населения. Характерно значительное увеличение распространенности атеросклероза с возрастом, что свидетельствует о возможном влиянии на развитие болезни механизмов старения, в том числе изменений эпигенетических факторов, обусловленных регуляторным влиянием транспозонов. Триггерами атеросклероза являются также вирусные инфекции, которые способствуют активации ретроэлементов и стимуляции интерферонового ответа продуктами их экспрессии с развитием хронического воспаления, с нарушением регуляции генов иммунной системы, микроРНК и длинных некодирующих РНК. Перспективным направлением лечения атеросклероза является эпигенетическое воздействие на экспрессию специфических генов, вовлеченных в патогенез атеросклероза с помощью малых интерферирующих РНК. В данном отношении прошли клинические испытания препараты инклисиран и олпасиран, показавшие свою эффективность. Поэтому актуален поиск новых молекулярных мишеней в данном направлении, в качестве которых могут служить транспозоны, являющиеся источниками некодирующих РНК. Изменение активности ретроэлементов при старении оказывает глобальное регуляторное влияние на функционирование всего генома, способствуя развитию возраст-ассоциированной патологии. Анализ научной литературы позволил идентифицировать 29 произошедших от ретроэлементов микроРНК, изменения экспрессии которых определены как при старении, так и при атеросклерозе, что подтверждает предположение о роли активированных при старении ретроэлементов в развитии атеросклероза. Выявленные микроРНК предполагается использовать для таргетного воздействия с целью продления жизни и лечения атеросклероза.

Ключевые слова: *атеросклероз, микроРНК, ретроэлементы, таргетная терапия.*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 25.01.2024 г.
Принята к публикации 06.03.2024 г.

Для цитирования: Мустафин Р.Н., Галиева Э.А. РОЛЬ МИКРОРНК И РЕТРОЭЛЕМЕНТОВ В ПАТОГЕНЕЗЕ АТЕРОСКЛЕРОЗА. Архивъ внутренней медицины. 2024; 14(2): 85-95. DOI: 10.20514/2226-6704-2024-14-2-85-95. EDN: CEXECW

Abstract

Atherosclerosis is the leading cause of cardiovascular disease among adults. The incidence of atherosclerosis increases significantly with age, which indicates the possible influence of aging mechanisms on the development of the disease, including changes in epigenetic factors caused by pathological activation of transposable elements. Triggers of atherosclerosis are also viral infections, which promote the expression of retroelements that stimulate the interferon response with the development of chronic inflammation. Activated retroelements also alter the regulation of immune system genes and epigenetic factors, including the pathological production of microRNAs and long non-coding RNAs. A promising direction for

*Контакты: Рустам Наилевич Мустафин, e-mail: ruji79@mail.ru
*Contacts: Rustam N. Mustafin, e-mail: ruji79@mail.ru
ORCID ID: http://orcid.org/0000-0002-4091-382X

atherosclerosis treatment is the epigenetic impact on the expression of specific genes involved in the pathogenesis of atherosclerosis using small interfering RNAs. In this regard, the drugs inclisiran and olpasiran have undergone clinical trials and have shown their effectiveness. Therefore, it is important to search for new molecular targets in this direction, which can serve as transposons, which are sources of non-coding RNAs. Changes in the activity of retroelements during aging have a global regulatory effect on the functioning of the entire genome, contributing to the development of age-associated pathology. An analysis of the scientific literature made it possible to identify 29 microRNAs derived from retroelements, changes in the expression of which have been identified both during aging and atherosclerosis. These microRNAs can be used as tools for prolonging life and treating cardiovascular pathology. The results obtained also indicate that retroelements pathologically activated during aging cause the development of atherosclerosis.

Key words: *atherosclerosis, microRNAs, retroelements, targeted therapy.*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 25.01.2024
Accepted for publication on 06.03.2024

For citation: Mustafin R.N., Galieva E.A. Role of MicroRNAs and Retroelements in the Pathogenesis of Atherosclerosis. The Russian Archives of Internal Medicine. 2024; 14(2): 85-95. DOI: 10.20514/2226-6704-2024-14-2-85-95. EDN: CEXECW

AS — atherosclerosis, AS PLEA — atherosclerosis of peripheral lower extremity artery, VSMC — vascular smooth muscle cell, RE — retroelements, EC — endothelial cells

Introduction

Atherosclerosis (AS) is the leading cause of cardiovascular diseases globally. AS is characterised by a long-lasting latent period and frequently involves more than one vascular bed. The key clinical manifestations of the disease are AS with involvement of coronary, carotid arteries, peripheral lower extremity arteries (AS PLEA), etc., ischemic heart disease and cerebral ischemia. Fat deposits on arterial walls gradually develop into sebaceous cysts and distinctive plaques, the quick rupture of which causes local thrombosis and partial or complete occlusion of the involved artery [1]. The global incidence of AS PLEA (from the iliac segment to feet) has risen by 45 % over the period from 2000 to 2015 and reached 5.6 % of the adult population globally (7.4 % — in high-income nations and 5.1 % — in low- and medium-income nations) [2]. IHD-caused mortality in Eastern Europe, including Russia, was 434 per 100,000 for men and 235 per 100,000 for women; while the rate of deaths from ischemic stroke was 138 per 100,000 of population in Russia. In addition to environmental factors, such as smoking, unhealthy diet with dyslipidemia and obesity [1], ageing and genetics have an important role to play in aetiopathogenesis of AS [3]. AS development is facilitated by kidney diseases due to faster calcification both of vessel intima (resulting in calcium deposition in atheromatous plaque) and of the middle layer (with an increase in the vessel rigidity) [1]. Major contributors (as compared to IHD) to the development of AS PLEA are smoking and type 2 diabetes mellitus. However, two thirds of patients with AS PLEA also have IHD and cerebral ischemia, evidencing the systemic nature of vessel involvement. A simple and reliable test to diagnose AS PLEA is the ankle-brachial index, which is calculated by dividing ankle systolic arterial pressure by shoulder systolic pressure [3].

According to results of meta-analyses, peripheral atherosclerosis is associated with allelic variants of *SYTL3* (rs2171209), *TCF7L2* (rs290481), *CYP2B6* [3]. Ischemic heart disease is associated with polymorphisms of 57 various genes [4]. Cerebral ischemia is associated with allelic variants of *VCAM1, LAMC2, GP1BA, PROC, KLKB1, F11,* which are planned to be used in the management of the disease [5]. However, it is impossible to explain the role of these numerous genes in the development of AS and to use them as targets for the target therapy. A study of epigenetic mechanisms of AS, which are reversible and can be efficiently corrected with the help of non-coding RNA (ncRNA), would be more promising. The epigenetic factors include DNA methylation, histone modification and RNA interference using ncRNA. During the ontogeny, the epigenetic factors are regulated by transposons, which include retroelements (RE) and DNA transposons [6]. A comparative study conducted in 2022 to study the epigenetic factors in samples obtained from patients with AS and healthy controls showed 47 activated (hypomethylated) and 90 inactive (hypermethylated) genes in AS, as well as 10 key AS genes (*TCF7L2, CACNA1C, NRP1, GABBR2, FANCC, DCK, CCDC88C, TCF12, ABLIM1, PBX1*), differentially expressed under the influence of microRNA and abnormal methylation [7]. AS development is facilitated by age-associated vascular wall inflammation [8], whereas ageing is associated with abnormal activation of HERV (human endogenous retroviruses) RE [9] and LINE-1 (long interspersed nuclear elements-1) [10], the products of transcription and translation of which stimulate interferon hyperproduction, causing chronic inflammatory processes in the body [9, 11]. The role of transposons in the initiation and development of AS is a result not only of interferon-mediated inflammation, but also of the participation in the immune system functioning.

An evidence of this can be formation of RAG1 and RAG2 recombination from transposons necessary for V(D)J [12], use of ERV as HLA-G gene enhancers [13] and interferon-inducible genes (thus forming transcriptional networks for interferon response [14]). Meta-analyses demonstrated the role of RE dysregulation in an autoimmune pathology [15], which is associated with the development of AS [16].

AS presents with persistent inflammation as a result of polarisation of AS-associated macrophages from anti-inflammatory (M2-like) to pro-inflammatory (M1-like) macrophages under the influence of epigenetic drug resistance factors. Since macrophages are important for the organisation of the entire process of AS development — from initiation to plaque rupture — they are called AS-associated macrophages. Since AS presents with persistent inflammation, modern therapies, including statins, ACE inhibitors, beta blockers and aspirin, have no effect on disease progression, because they do not specifically affect macrophages and their polarisation [17]. HERV-K102 are expressed by activated monocytes and move to vacuoles connected to their surfaces, making the cells look foamy. HERV-K102 are released only during macrophage lysis. HERV-K102 protect human cells against viral infections and malignancies [18]. Since clinical trials demonstrate that HIV, HSV-1 and HSV-2, hepatitis C (HCV) and B, cytomegalovirus (CMV), T-cell leukaemia and papilloma (HPV), flu (similar to those described in the systemic review [19]) contribute to the development of AS, HERV-K102 hyperproduction to protect the cells [18] can cause impaired gene expression in macrophages, leading to a pathology and involvement in AS pathogenesis [20]. REs are activated by stress factors [21].

Transposons regulate gene expression during human ontogeny [22], acting as drivers of epigenetic regulation [6], because they are sources of ncRNA, such as microRNA [23] and long ncRNA [24, 25]. Therefore, changes in expression of specific mcRNA in AS can represent RE dysregulation in these processes (Fig. 1). At the same time, ncRNA is not only involved in post-transcription regulation of gene expression, but also is a key driver of DNA and histone modification [6] due to the mechanism of RNA-directed DNA-methylation (RdDM). This phenomenon, which was first observed in plants, has been found in humans as well [26]. Over the last decades, new methods to impact the inflammation in AS have been developed, such as blocking the recruitment of inflammatory cells (using antagonists of chemokine receptors and adhesion molecules), neutralisation of pro-inflammatory factors (monoclonal antibodies to chemokines and cytokines), plaques stabilisation (matrix metalloproteinase inhibitors). However, almost all of them failed to demonstrate efficacy during preclinical and early clinical trials. For example, canakinumab, a monoclonal antibody to IL-1β, reduces

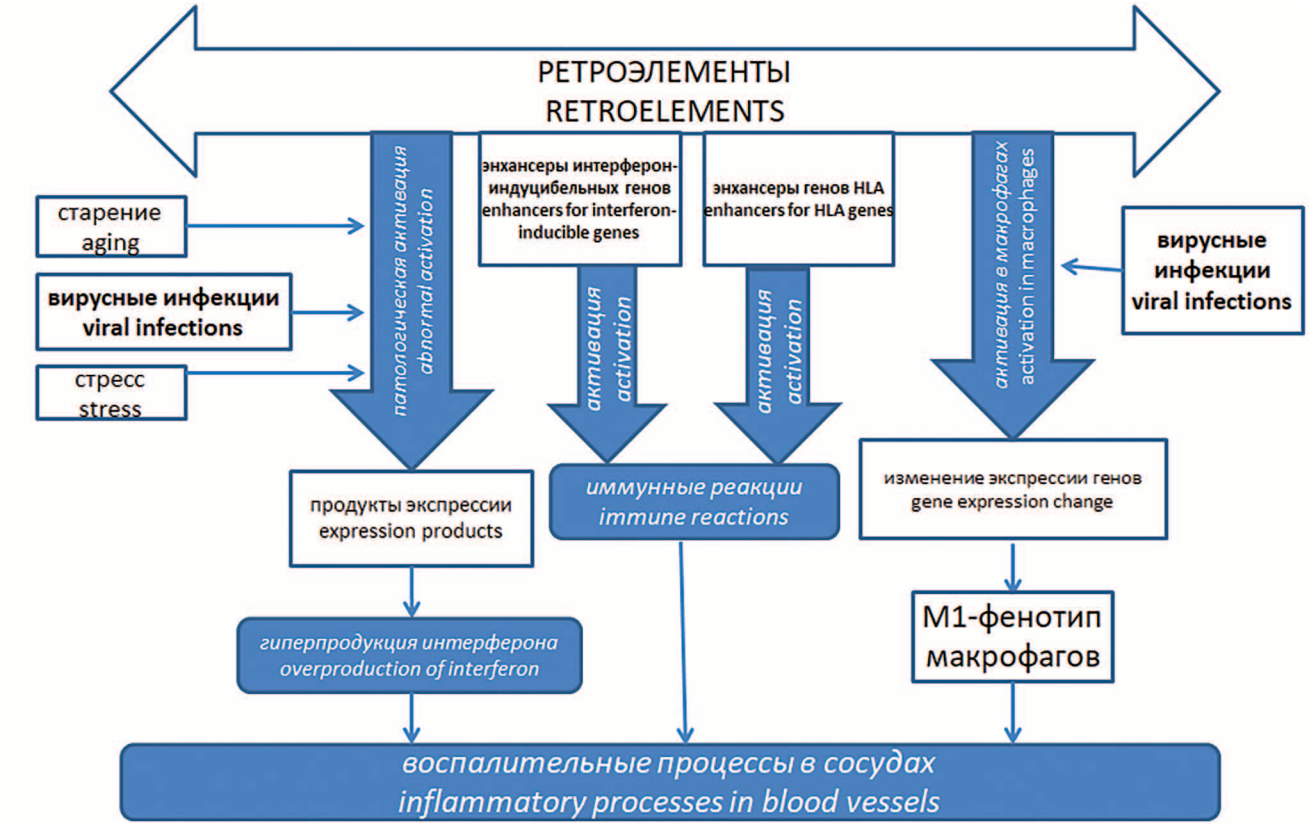

Figure 1. *Scheme of retroelements involvement in atherosclerosis development.*

C-reactive protein levels and the incidence of recurrent cardiovascular events without any impact on LDL cholesterol levels. Therefore, one promising area can be targeted change of macrophage polarisation as a result of targeting the epigenetic factors with microRNA [17]. The most optimal scheme is the use of microRNA, both for changing the macrophage polarisation and targeting abnormally active transposons.

Role of MicroRNA Derived from Retroelements in the Development of Atherosclerosis

RE involvement in aetiopathogenesis of atherosclerosis is related not only to the impact on gene expression, but also to immune system activation, however with mediation of direct formation of long ncRNA from LINE [27] and HERV transcripts [28], which have an important role to play in the development of AS [29]. Besides, microRNAs derived from retroelements [23] and involved in AS pathogenesis interact with their evolutionary sources (RE) in the genome structure and with molecules of their transcripts, leading to formation of abnormal gene networks, identification and description of which can become the basis of the efficient target therapy in AS. A potential therapeutic target can be miR-1246 originating from LTR-ERVL and partially complementary to its sequence [23]. This microRNA facilitates proliferation, invasion and differentiation of vascular smooth muscle cells (VSMC) [30]. Abnormal proliferation of VSMC causes AS plaques. VSMC can move to less differentiated forms, where VSMC markers are present, including macrophage-like cells, which facilitates progression of AS and inflammation [31].

Ageing-associated [32] miR-1248, which evolved from SINE/Alu [23], inhibits thrombomodulin expression by endothelial progenitor cells, thus evidencing its possible involvement in AS pathogenesis [33]. MiR-1257, which evolved from ERVL [23], is involved in protein assembly pathways in the major histocompatibility system (MHC) and regulates various target genes, mostly *CALR*, as well as *POMC, TLR4, IL10, ATF6*, facilitating AS progression [34]. Exosomes obtained from M2 macrophages of patients with myocardial infarction demonstrated high levels of miR-1271 [35], which evolved from LINE2 [23]. An examination of coronary artery samples of patients with AS showed a significant increase in expression of miR-1273 [36], the family of which evolved from LINE, SINE, ERVL [23].

Patients with ischemic stroke had higher levels of miR-1290 (which evolved from SINE/MIR [23]) in peripheral blood samples vs. healthy controls [37]. MiR-147, which evolved from LINE1 [23], has atherogenic effects and induces ICAM-1 (intracellular adhesion molecule 1) expression by endothelial cells (EC) [38]. During the evolution, LINE2 was a source of miR-151 [23], which inhibits EC apoptosis and plays a vital role in AS development. miR-151 targets IL-17A, BAX protein, c-caspases 3 and 9 [39]. Expression of miR-192 (which evolved from LINE2 [23]) is significantly higher in serum of patients with AS. This microRNA facilitates proliferation and migration of VSMC [40]. Serum of patients with AS demonstrates significantly reduced levels of miR-211 [41], which evolved from LINE2 [23].

Plasma samples obtained from patients with unstable angina demonstrate significantly higher levels of miR-28, which facilitates expression of ABCA1 (ATP-binding cassette subfamily, a regulator of homeostasis of cholesterol and phospholipids), which correlated with activation of LXRα translation in macrophages [42]. MiR-28 evolved from LINE2 [23] and is known for specific expression in patients with unstable angina. In this regard, miR-28 is a morphological substrate, since it is involved in pathophysiological causes of myocardial infarction. MiR-28 is located in intron 6 of *LPP* (lipoma preferable partner) and regulates migration, adhesion, proliferation, apoptosis of cells, including VSMC, in atherosclerosis [42]. High expression of miR-31 (which evolved from LINE2 [23]) facilitate AS progression as a result of effect on NOX4 (NADP oxidase-4, a non-phagocytal cell ferment which catalyses reconstruction of molecular oxygen to various active forms) [42]. Patients with chronic IHD have specifically higher expression of miR-320b, which regulates cholesterol outflow from macrophages. Administration of miR-320b to experimental animals caused atherosclerosis plaques to grow; the number of damaged macrophages increased; and pro-inflammatory cytokine levels increased due to higher phosphorylation of NF-κB [43]. During the evolution, the source of miR-320b is LINE2 [23]. Targeting miR-320b during AS therapy [43] can be a promising area, since it is the basis for resolving the issue with regulation of macrophage polarisation in a majority of current studies [17].

MiR-325, which evolved from LINE2, facilitates AS development due to inhibition of expression of *KDM1A* (which encodes lysine demethylase 1A, a component of HDAC), reducing SREBF1 (a transcription factor binding to promoter gene of low-density lipoprotein receptor) levels and inhibiting activation of PPARγ-LXR-ABCA1 pathway [44]. Plasma levels of miR-335, which evolved from SINE/MIR [23], were high in patients with AS [45]. Peripheral mononuclear cells demonstrated high levels of miR-342 [46], which evolved from SINE/tRNA-RTE [23] and positively correlated with serum concentrations of IL-6 and TNF-α [46]. Serum levels of miR-374 (which evolved from LINE2 [23] and stimulates proliferation and migration of VSMC) in patients with AS were high [47]. Reduced outflow of free cholesterol from macrophages and increased inflow of oxidised low-density lipoproteins is an important factor of AS development. MiR-378, which evolved from SINE/MIR and LINE2 [23], is involved in metabolic pathways regulating

these processes [48]. MiR-384 [49], which evolved from LINE-Dong-R4, also contributes to the development of AS due to effects on macrophages (interfering with their autophagy) [23].

Low expression of miR-421 (which originates from LINE2 [23]) in serum, plaques and VSMC in patients with IHD results in higher levels of CXCL2 (a secretory protein, which is involved in immunoregulatory and inflammatory processes) [50]. MiR-4487 (which evolved from LINE1 [23]) stimulates VSMC migration and survival and inhibits their apoptosis by targeting RASA1 (RAS suppressor, which controls cell proliferation and differentiation) [51]. Expression of miR-493 in large vessels of patients with AS is reduced as compared to controls [52]. This microRNA evolved from LINE2 [52]. MiR-495 (originating from ERVL [52]) is involved in AS pathogenesis by binding to circular RNA hsa_circ_0126672 [53]. MiR-520d (originating from SINE/Alu [23]) inhibits expression of *PCSK9* (proprotein convertase subtilisin/kexin, type 9, mutations in which cause familial hypercholesterolemia), which causes degradation of low-density lipoprotein receptors [54]. Fat tissue around coronary arteries of patients with IHD has reduced miR-548 expression. MicroRNAs in this family evolved from various REs (LINE1, LINE2, LTR-ERVL, LTR-Gypsy, LTR-ERV1, SINE/MIR) and DNA-TE (TcMar, hAT Charlie) [23]. MiR-548 regulates expression of HMGB1 (nonhistone protein binding chromatin and involved in control of DNA transcription, replication and reparation) [55]. Expression of miR-552 (which evolved from LINE1 [23]) in cerebral vessels of patients with AS increases under the influence of PDGF-BB (platelet-derived growth factor-BB) in VSMC, thus stimulating their proliferation, invasion and migration [56].

Circular RNA circ_0086296 induces AS via feedback pathway of IFIT1/STAT1, acting as a sponge for miR-576 (which evolved from LINE1 [23]). The latter inhibits expression of *IFIT1* (interferon induced protein with tetratricopeptide repeats) and prevent AS development [57]. Circular RNA has_circ_0008896 stimulates VSMC proliferation and migration by interacting with miR-633 (which evolved from SINE/MIR [23] and regulates CDC20B (cell division cycle 20B)) [58]. Expression of miR-641 (which evolved from SINE/MIR [23]) is reduced in VSMC, induced by oxidised low-density lipoproteins. This microDNA interacts with a long ncRNA MIAT, which regulates proliferation, migration and invasion of VSMC [59]. MiR-708, which evolved from LINE2 [23], is expressed in large numbers in epithelial cells of neointima in damaged vessels where the blood flow is normal. This micro RNA has anti-inflammatory effects; it inhibits expression of kinase linked to IL-1 receptor, IL-6 receptor, conserved helix-loop-helix ubiquitous kinase, inhibitor of subunit-γ of nuclear factor κB kinase [60]. Therefore, we have described 29 microRNAs which originate from RE and are involved in AS development in various ways (see Fig. 2).

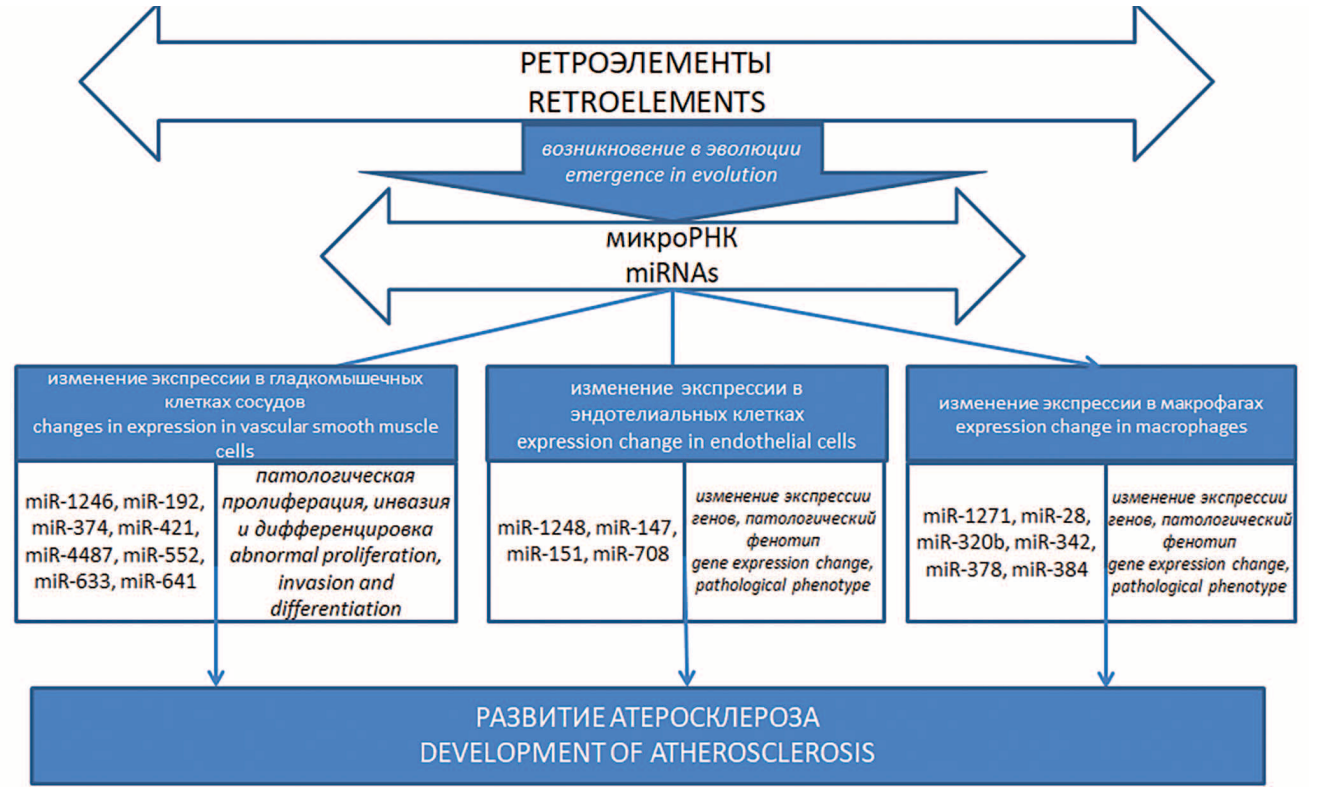

Figure 2. *Scheme of influence of microRNAs derived from retroelements in atherosclerosis development.*

Association with Ageing of MicroRNAs Originating from Retroelements, Which Are Involved in Atherosclerosis Pathogenesis

Since, during the development, REs are a source of the mentioned microRNAs, which are associated with AS, it can be assumed that one of the causes of changes in expression of these microRNAs is abnormal RE activation due to body ageing [9, 10] and resulting in chronic inflammatory processes [9, 11]. This is due to the presence of complementary RE sequences and derivative microRNAs and involvement in common epigenetic regulatory networks. In order to prove this hypothesis, scientific literature was analysed and the association between changes in the 29 microRNAs and ageing was identified. An analysis of common transcriptomic changes in microRNA with human fibroblast ageing vs. early passage cells, conducted in 2009 (Maes et al., 2009), demonstrated an association with ageing of miR-147 and miR-633 [61]. In 2010, similar works (Marasa et al., 2010) identified an increased expression of miR-1246, miR-1257, miR-1271, miR-1273, miR-548, miR-576, miR-641 [62]. In 2011, similar studies (Dhahbi et al., 2011) managed to identify changes in expression of miR-1246, miR-1290, miR-548 [63]. Serum of elderly patients (over 64 years of age) had lower miR-1248 and miR-151 concentrations as compared to a younger population [32].

A comparative analysis of extracellular vesicles showed significantly higher expression of miR-192 in old experimental animals (mice) vs. young animals. This microRNA turned out to be associated with immune processes and regulation of cytokine signalling [64]. Changes in microRNA levels in serum samples corresponded to reduced miR-211 and increased miR-374 levels in a group of people with short life expectancy vs. long-livers. MiR-211 targets mRNA of *CREB5* (encodes cAMP response element 5-binding protein), *DDIT4* (encodes DNA-damage-induced transcript 4), *IGF2R* (encodes insulin-like growth factor 2 receptor). MiR-374 targets mRNA of *ATM* (encodes serine threonine kinase ATM), *BCL2* (encodes BCL2 apoptosis regulator), *CDKN1A* (encodes cycline-dependent kinase 1A inhibitor), *CISH* (encodes cytokine-induced SH2-containing protein), *EP300* (encodes E1A-binding protein p300), *HMGB2* (encodes high mobility group box 2), *PARP1* (encodes poly(ADP-ribose) polymerase), *TP73* (encodes tumour protein p73) [65]. As far as circulating microRNAs are concerned, miR-28 [66] levels are reduced in physiologic ageing. The role of increased miR-31 expression in skin ageing has been identified, which has direct effect on mRNA of the circadian rhythm gene *Clock,* activating MAPK/ERK cascade and depleting stem cells of skin hair follicles [67]. Higher expression of miR-320b in ageing is associated with higher TNF-α levels [68]. Reduced production of miR-325 contributes to chondrocyte ageing due to activation of p53/p21 pathway [69]. MiR-335 induces EC ageing and inhibits mRNA of *sKlotho* (a protein gene product, acts as a humoral factor reducing peroxide-caused apoptosis and cellular ageing in EC) [70].

Peripheral blood mononuclears demonstrate reduced expression of miR-342 with ageing. This microRNA interacts with the coding sequence of mRNA of *SIRT6,* which facilitates ageing [71]. Computer-generated simulation aimed at decoding the impact of microRNA on skeletal muscles ageing demonstrated that miR-378 maintains stable myogenesis due to inhibition of *Msc* expression during late stages of differentiation. MiR-378 is located in the intron of *PGC-1β,* which regulates energy metabolism. MiR-378 also targets mRNA of *IGF-1* [72]. With ageing, expression of miR-384 is significantly higher in mesenchymal stem cells of the brain, which causes inhibition of osteogenetic differentiation, thus contributing to ageing. MiR-384 inhibits mRNA of *Gli2* (encodes the protein of zinc finger family GLI2) [73]. In ageing, expression of miR-421 in the anterior lens capsule is significantly reduced, which facilitates cataract development. MiR-421 is an apoptosis inhibitor and induces cell proliferation [74]. A study of skin samples taken from people of various ages demonstrated that increased expression of miR-4487, which interacts with circular RNAs, has a role to play in skin ageing [75]. The role of reduced miR-493 expression in myocardium ageing has been established [76].

Higher miR-495 expression contributes to cell apoptosis and ageing of mesenchymal stem cells by impacting *BM1* (encodes proto-oncogene BMI1) [77]. It has been established that miR-520d reduces expression of the long ncRNA GPRC5D-AS1, which inhibits cell apoptosis and activates factors of muscle regulation Mef2c, Myf5, MyoD, Myo G. MiR-520d facilitates skeletal muscles ageing [78]. One sign of skin ageing is impaired calcium gradient. Higher calcium concentrations in the basal layer inhibit cell proliferation, while reduced concentrations in the granular layer change the keratinised layer composition. Keratinocytes respond to calcium-induced blocking of mitosis with higher expression of specific microRNAs, including miR-552 [79]. With ageing, expression of miR-708 in joint tissue and serum drops [80]. Table 1 presents data on the changes in expression of the 29 microRNAs originating from RE, in ageing and atherosclerosis. The results allow assuming that, with ageing, RE activation leads to immunopathological processes and disorders in epigenetic networks for gene regulation, resulting in modified expression of specific microRNAs (which evolved from REs and have complimentary sequences), which contribute to AS development.

According to a systematic review of scientific literature conducted in 2023, both experimental and clinical trials are ongoing which seek to explore the direct impact on epigenetic factors of atherosclerosis. The role of

Table 1. *Association of retroelement-derived miRNAs with atherosclerosis and aging*

№	MiRNA	Retroelement-source	Changes in miRNAs expression in atherosclerosis (increase — ↑, decrease — ↓) [author]	Changes in miRNAs expression during aging (increase — ↑, decrease — ↓) [author]
1.	miR-1246	ERVL	↑ [30]	↑ [62, 63]
2.	miR-1248	SINE/Alu	↑ [33]	↓ [32]
3.	miR-1257	ERVL	↑ [34]	↓ [62]
4.	miR-1271	LINE2	↑ [35]	↑ [62]
5.	miR-1273	LINE, SINE, ERVL	↑ [36]	↑ [62]
6.	miR-1290	SINE/MIR	↑ [37]	↑ [63]
7.	miR-147	LINE1	↑ [38]	↓ [61]
8.	miR-151	LINE2	↓ [39]	↓ [32]
9.	miR-192	LINE2	↑ [40]	↑ [64]
10.	miR-211	LINE2	↓ [41]	↓ [65]
11.	miR-28	LINE2	↑ [42]	↓ [66]
12.	miR-320b	LINE2	↑ [43]	↑ [68]
13.	miR-325	LINE2	↑ [44]	↓ [69]
14.	miR-335	SINE/MIR	↑ [45]	↑ [70]
15.	miR-342	SINE/tRNA-RTE	↓ [46]	↓ [71]
16.	miR-374	LINE2	↑ [47]	↑ [65]
17.	miR-378	SINE/MIR, LINE2	↑ [48]	↓ [72]
18.	miR-384	LINE-Dong-R4	↑ [49]	↑ [73]
19.	miR-421	LINE2	↓ [50]	↓ [74]
20.	miR-4487	LINE1	↑ [51]	↑ [75]
21.	miR-493	LINE2	↓ [52]	↓ [76]
22.	miR-495	ERVL	↓ [53]	↑ [77]
23.	miR-520d	SINE/Alu	↓ [54]	↑ [78]
24.	miR-548	LINE, ERV, SINE	↓ [55]	↓ [62, 63]
25.	miR-552	LINE1	↑ [56]	↑ [79]
26.	miR-576	LINE1	↓ [57]	↓ [62]
27.	miR-633	SINE/MIR	↓ [58]	↑ [61]
28.	miR-641	SINE/MIR	↓ [59]	↑ [62]
29.	miR-708	LINE2	↓ [60]	↓ [80]

medicinal products in the mechanisms of the disease is being studied as well. For example, clinical trials demonstrated that aspirin absorption results in reduced methylation of *ABCB1* (encodes a member of ATP-binding cassette subfamily) in patients with stenotic intracraneal arteries. The role of plant mixes used in China, as well as of curcumin, resveratrol and geniposide on DNA methylation in AS was established. The efficacy of DNA methyltransferases (DNA-MT) inhibitors [81] (which are actively used in the treatment of malignancies [82]) for the treatment of AS was demonstrated. In mice experiments, an analogue of cytosine (5-azacytidine) inhibited AS development. Antisense oligonucleotides, e.g. MG98, can be successfully used as DNA-MT inhibitors for the treatment of AS. Epigenetic therapy can target histone modification enzymes; histone methyltransferase inhibitors (iHMT) and histone acetyltransferase inhibitors (iHAT) can be used. Currently, iHMTs are an unemployed resource, the most potent of them being GSK126, a highly-selective component to methyltransferase EZH2, which can inhibit expression of pro-inflammatory genes. Anacardic acid and garcinol are natural iHATs. MG149, a synthetic analogue of anacardic acid, inhibits NF-κB pathway, which contributes to AS development. A promising class of products is histone deacetylase inhibitors (iHDA), because they have already been approved by the FDA for the treatment of haematologic cancers and can re-activate silent genes by targeted impact on target gene

promoters. In mice experiments, the most promising iHDA was Vorinostat (approved for T-cell lymphoma) [81]. In addition to the described impact of plant mixes and known medicinal products on epigenetic changes in AS, an experiment on 36 male C57BL/6J mice with zero ApoE aged 10 weeks demonstrated an effect from exercises on microRNA expression: reduced miR-155 levels and increased miR-126, miR-146a levels. Mice were placed in a chamber with a run track 10 minutes before the running started. The pace was 13 m/min for 60 minutes daily from 06.00 pm to 07.00 pm, with a zero percent slope. These mice demonstrated higher expression of miR-126 and miR-146a, which facilitated reduction in inflammatory vascular damage by inhibition of TRAF and TLR4 signalling, vs. controls (statins and no treatment) [83].

The problem of epigenetic therapy is its low bioavailability and side effects, because target molecules are expressed in tissues all over the body. Therefore, nanomaterials are used to ensure targeted exposure of atherosclerotic foci in vessels. For this purpose, specific liposomes, micelles and nanoparticles of high-density lipoproteins are used [81]. The use of biologically mineralised, framed nanoparticles with a neutrophil membrane coating, containing anti-miR-155, has been described, which ensured inhibition of miR-155 expression in the endothelial wall of vessels, thus preserving translation of *BCL6* [84]. Currently, new drugs from the group of a modified double-stranded short interfering RNA have been registered and are used, e.g. Inclisiran, which inhibits translation of proprotein convertase subtilisin/kexin, type 9 (*PCSK9*), in liver and ensures stable reduction in LDL cholesterol. Phase 3 randomised, placebo-controlled clinical trials in 3,660 subjects demonstrated that, when Inclisiran is prescribed twice a year with or without the maximum tolerated statin dose, this drug is efficient, safe and well-tolerated in lowering LDL cholesterol levels in adult patients with heterozygous familial hypercholesterolemia and AS [85]. Another short interfering RNA, Olpasiran, inhibits expression of *LPA* at the mRNA level. Since plasma concentrations of apolipoprotein (a component of LDL), encoded by *LPA,* positively correlate with the risk of AS, Olpasiran is used in the therapy of AS. Olpasiran enters the liver via N-acetylgalactosamine fragment, which binds to apolipoprotein receptor on the liver surface. In hepatic cells, this short interfering RNA binds to mRNA of *LPA* with the help of an RNA-induced silencing complex (RISC) due to nucleotide sequence complementariness. A multicenter randomised, placebo-controlled trial OCEAN(a)-DOSE in patients with atherosclerosis and high apolipoprotein levels after Olpasiran therapy for 48 weeks (SC injections of the drug once every 12 weeks) demonstrated efficacy and safety vs. placebo [86]. The search for new drugs, where the main component is non-coding RNA, is ongoing. New potential RNA-targeting agents for reliable reduction of apolipoprotein levels are drugs encoded like SLN360 and LY3819469 (Lepodisiran), which are also short interfering RNAs targeting post-transcriptional inhibition of mRNA of *LPA* [87]. The microDNAs, described in this article and originating from RE, can also be the basis for inhibition of transposons, activated in atherosclerosis, which is one of the methods to overcome side effects caused by non-specific exposure to epigenetic therapy in AS.

Conclusion

Analysis of scientific literature allowed to conclude that the key role in AS initiation and development is played by ageing-mediated excessive activation of REs, which causes interferon stimulation and immunopathological processes. Viral infections and stress are also of importance; they activate RE to protect cells, which can be a cause of early onset and progression of AS. Since statins and aspirin used in the therapy of AS do not affect specifically macrophages and their polarisation and do not impact disease progression, new ways to affect AS should be searched for. There were attempts to use monoclonal antibodies to chemokines and cytokines, antagonists of chemokine receptors and adhesion molecules, matrix metalloproteinase inhibitors in the therapy of AS. However, these methods did not demonstrate any significant effect. The most promising area is epigenetic exposure of the genes involved in AS pathogenesis, *PCSK9* (Inclisiran) and *LPA* (Olpasiran), to short interfering RNAs, which demonstrated significant effect in clinical trials. Therefore, targets for epigenetic exposure in AS should be searched for; these can be REs. Their ageing-mediated excessive activation results in interferon stimulation and immunopathological processes. Since REs are a source of long ncRNAs and microRNAs, their impaired expression in AS reflects RE dysregulation. Thus, a promising therapy for this disease can be target therapy with specific microRNAs, directed against pathologically activated REs involved in AS pathogenesis. The 29 RE-originating microRNAs described in this study, which are associated both with ageing and AS, can be used as tools for epigenetic target therapy. These microRNAs are involved not only in immune reactions, but they also impact expression of various genes in VSMC, EC and macrophages, thus demonstrating complex mechanisms of AS development with involvement of various signalling pathways in specific cell types.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Мустафин Р.Н. (ORCID ID: http://orcid.org/0000-0002-4091-382X): разработка дизайна и написание рукописи, редактирование статьи, поиск литературных источников, утверждение финального варианта рукописи

Галиева Э.А.: (ORCID ID: http://orcid.org/0009-0009-4657-2665): разработка концепции, поиск литературных источников, редактирование статьи, утверждение окончательного варианта статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication
Mustafin R.N. (ORCID ID: http://orcid.org/0000-0002-4091-382X): development of the design and writing of the manuscript, editing the article, search for literary sources, approval of the final version of the manuscript.
Galieva E.A. (ORCID ID: http://orcid.org/0009-0009-4657-2665): development of the concept, search for literary sources, editing the article, approval of the final version of the manuscript.

Список литературы / References:

1. Herrington W., Lacey B., Sherliker P. et al. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. Circ. Res. 2016; 118: 535-46. doi: 10.1161/CIRCRESAHA.115.307611.
2. Aday A.W., Matsushita K. Epidemiology of Peripheral Artery Disease and Polyvascular Disease. Circ Res. 2021; 128(12):1818-1832. doi: 10.1161/CIRCRESAHA.121.318535.
3. Wassel C.L., Lamina C., Nambi V. et al. Genetic determinants of the ankle-brachial index: a meta-analysis of a cardiovascular candidate gene 50K SNP panel in the candidate gene association resource (CARe) consortium. Atherosclerosis. 2012; 222: 138-47. doi: 10.1016/j.atherosclerosis.2012.01.039.
4. Nikpay M., Goel A., Won H.H. et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet. 2015; 47: 1121-1130. doi: 10.1038/ng.3396.
5. Mishra A., Malik R., Hachiya T. et al. Stroke genetics informs drug discovery and risk prediction across ancestries. Nature. 2022; 611: 115-123. doi: 10.1038/s41586-022-05165-3.
6. Мустафин Р.Н., Хуснутдинова Э.К. Некодирующие части генома как основа эпигенетической наследственности. Вавиловский журнал генетики и селекции. 2017; 21: 742-749. doi: 10.18699/VJ17.30-o.
   Mustafin R.N., Khusnutdinova E.K. Non-coding parts of genomes as the basis of epigenetic heredity. Vavilov Journal of Genetics and Breeding. 2017; 21(6): 742-749. [in Russian].
7. Cui Y., Wang L., Huang Y. et al. Identification of Key Genes in Atherosclerosis by Combined DNA Methylation and miRNA Expression Analyses. Anatol J Cardiol. 2022; 26(11): 818-826. doi: 10.5152/AnatolJCardiol.2022.1723.
8. de Yebenes V.G., Briones A.M., Martos-Folgado I. et al. Aging-Associated miR-217 Aggravates Atherosclerosis and Promotes Cardiovascular Dysfunction. Arterioscler. Thromb. Vasc. Biol. 2020; 40: 2408-2424. doi: 10.1161/ATVBAHA.120.314333.
9. Autio A., Nevalainen T., Mishra B.H. et al. Effect of aging on the transcriptomic changes associated with the expression of the HERV-K (HML-2) provirus at 1q22. Immun. Ageing. 2020; 17: 11. doi: 10.1186/s12979-020-00182-0.
10. Cardelli M. The epigenetic alterations of endogenous retroelements in aging. Mech. Ageing Dev. 2018; 174: 30-46. doi: 10.1016/j.mad.2018.02.002.
11. De Cecco M., Ito T., Petrashen A.P. et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature. 2019; 566: 73-78. doi: 10.1038/s41586-018-0784-9.
12. Huang S., Tao X., Yuan S. et al. Discovery of an Active RAG Transposon Illuminates the Origins of V(D)J Recombination. Cell. 2016; 166: 102–14. doi: 10.1016/j.cell.2016.05.032.
13. Ferreira L.M. R., Meissner T.B., Mikkelsen T.S. et al. A distant trophoblast-specific enhancer controls HLA-G expression at the maternal-fetal interface. Proc Natl Acad Sci U S A. National Academy of Sciences. 2016; 113: 5364–5369. doi: 10.1073/pnas.1602886113
14. Chuong E.B., Elde N.C., Feschotte C. Regulatory evolution of innate immunity through co-option of endogenous retroviruses. Science. 2016; 351: 1083–1087.
15. de la Hera B., Varade J., Garcia-Montojo M. et al. Role of the human endogenous retrovirus HERV-K18 in autoimmune disease susceptibility: study in the Spanish population and meta-analysis. PLoS One. 2013; 8: e62090. doi: 10.1371/journal.pone.0062090.
16. Martinez-Ceballos M.A., Rey J.C. S., Alzate-Granados J.P. et al. Coronary calcium in autoimmune diseases: A systematic literature review and meta-analysis. Atherosclerosis. 2021; 335: 68-76. doi: 10.1016/j.atherosclerosis.2021.09.017.
17. Yang H., Sun Y., Li Q. et al. Diverse Epigenetic Regulations of Macrophages in Atherosclerosis. Front. Cardiovasc. Med. 2022; 9: 868788. doi: 10.3389/fcvm.2022.868788.
18. Laderoute M. The paradigm of immunosenescence in atherosclerosis-cardiovascular disease (ASCVD). Discov. Med. 2020; 29(156): 41-51.
19. Мустафин Р.Н. Перспективы применения статинов в противовирусной терапии. Клиническая микробиология и антимикробная химиотерапия. 2023; 25(1): 56-67. doi: 10.36488/cmac.2023.1.56-67.
20. Chai J.T., Ruparelia N., Goel A. et al. Differential Gene Expression in Macrophages From Human Atherosclerotic Plaques Shows Convergence on Pathways Implicated by Genome-Wide Association Study Risk Variants. Arterioscler. Thromb. Vasc. Biol. 2018; 38: 2718-2730. doi: 10.1161/ATVBAHA.118.311209.
21. Мустафин Р.Н., Хуснутдинова Э.К. Стресс-индуцированная активация транспозонов в экологическом морфогенезе. Вавиловский журнал генетики и селекции. 2019; 23: 380-389. doi: 10.18699/VJ19.506.
   Mustafin R.N., Khusnutdinova E.K. The role of transposable elements in the ecological morphogenesis under influence of stress. Vavilov Journal of Genetics and Breeding. 2019; 23(4): 380-389. [in Russian].
22. Мустафин Р.Н., Хуснутдинова Э.К. Роль транспозонов в эпигенетической регуляции онтогенеза. Онтогенез. 2018; 49: 69-90. doi: 10.7868/S0475145018020015.
   Mustafin R.N., Khusnutdinova E.K. The Role of Transposons in Epigenetic Regulation of Ontogenesis. Russian Journal of Developmental Biology. 2018; 49: 69-90. [in Russian].
23. Wei G., Qin S., Li W. et al. MDTE DB: a database for microRNAs derived from Transposable element. IEEE/ACM Trans. Comput. Biol. Bioinform. 2016; 13: 1155–1160. doi: 10.1109/TCBB.2015.2511767.
24. Johnson R., Guigo R. The RIDL hypothesis: transposable elements as functional domains of long noncoding RNAs. RNA. 2014; 20: 959–976. doi: 10.1261/rna.044560.114.
25. Kapusta A., Kronenberg Z., Lynch V.J. et al. Transposable elements are major contributors to the origin, diversification, and regulation of vertebrate long noncoding RNAs. PLoS Genet. 2013; 9: e1003470. doi: 10.1371/journal.pgen.1003470.
26. Chalertpet K., Pin-On P., Aporntewan C. et al. Argonaute 4 as an Effector Protein in RNA-Directed DNA Methylation in Human Cells. Front. Genet. 2019; 10: 645. doi: 10.3389/fgene.2019.00645.
27. Honson D.D., Macfarlan T.S. A lncRNA-like Role for LINE1s in Development. Dev. Cell. 2018; 46: 132–134. doi: 10.1016/j.devcel.2018.06.022.

28. Lu X., Sachs F., Ramsay L. et al. The retrovirus HERVH is a long noncoding RNA required for human embryonic stem cell identity. Nat. Struct. Mol. Biol. 2014; 21: 423–425. doi: 10.1038/nsmb.2799.
29. Xiong Y., Alnoud M.A. H., Ali H. et al. Beyond the Silence: A Comprehensive Exploration of Long Non-Coding RNAs as Genetic Whispers and their Essential Regulatory Functions in Cardiovascular Disorders. Curr. Probl. Cardiol. 2024; 15: 102390. doi: 10.1016/j.cpcardiol.2024.102390.
30. Pan D., Liu G., Li B. et al. MicroRNA-1246 regulates proliferation, invasion, and differentiation in human vascular smooth muscle cells by targeting cystic fibrosis transmembrane conductance regulator (CFTR). Pflugers. Arch. 2021; 473: 231-240. doi: 10.1007/s00424-020-02498-8
31. Bennett M.R., Sinha S., Owens G.K. Vascular Smooth Muscle Cells in Atherosclerosis. Circ. Res. 2016; 118: 692-702. doi: 10.1161/CIRCRESAHA.115.306361.
32. Noren Hooten N., Fitzpatrick M., Wood W.H. et al. Age-related changes in microRNA levels in serum. Aging (Albany NY). 2013; 5: 725–740.
33. Lin F.Y., Tsai Y.T., Huang C.Y. et al. GroEL of Porphyromonas gingivalis-induced microRNAs accelerate tumor neovascularization by downregulating thrombomodulin expression in endothelial progenitor cells. Mol. Oral. Microbiol. 2023. doi: 10.1111/omi.12415.
34. Xu X., Li H. Integrated microRNA-gene analysis of coronary artery disease based on miRNA and gene expression profiles. Mol. Med. Rep. 2016; 13:3063–3073.
35. Long R., Gao L., Li Y. et al. M2 macrophage-derived exosomes carry miR-1271-5p to alleviate cardiac injury in acute myocardial infarction through down-regulating SOX6. Mol. Immunol. 2021; 136: 26–35. doi: 10.1016/j.molimm.2021.05.006.
36. Wang R., Dong L.D., Meng X.B. et al. Unique MicroRNA signatures associated with early coronary atherosclerotic plaques. Biochem. Biophys. Res. Commun. 2015; 464: 574-579. doi: 10.1016/j.bbrc.2015.07.010.
37. Tan K.S., Armugam A., Sepramaniam S., et al. Expression profile of microRNAs in young stroke patients. PLoS ONE. 2009; 4: e7689.
38. Xu D., Liu T., He L. et al. LncRNA MEG3 inhibits HMEC-1 cells growth, migration and tube formation via sponging miR-147. Biol. Chem. 2020; 401: 601-615. doi: 10.1515/hsz-2019-0230.
39. Chen F., Ye X., Jiang H. et al. MicroRNA-151 Attenuates Apoptosis of Endothelial Cells Induced by Oxidized Low-density Lipoprotein by Targeting Interleukin-17A (IL-17A). J. Cardiovasc. Transl. Res. 2021; 14: 400-408. doi: 10.1007/s12265-020-10065-w.
40. Zhao L., Wang B., Sun L. et al. Association of miR-192-5p with Atherosclerosis and its Effect on Proliferation and Migration of Vascular Smooth Muscle Cells. Mol. Biotechnol. 2021; 63: 1244-1251. doi: 10.1007/s12033-021-00376-x.
41. Zhang Y., Wang H., Xia Y. The expression of miR-211-5p in atherosclerosis and its influence on diagnosis and prognosis. BMC Cardiovasc. Disord. 2021; 21: 371. doi: 10.1186/s12872-021-02187-z.
42. Liu J., Liu Y., Sun Y.N. et al. miR-28-5p Involved in LXR-ABCA1 Pathway is Increased in the Plasma of Unstable Angina Patients. Heart. Lung. Circ. 2015; 24: 724-730. doi: 10.1016/j.hlc.2014.12.160.
43. Lu X., Yang B., Yang H. et al. MicroRNA-320b Modulates Cholesterol Efflux and Atherosclerosis. J. Atheroscler. Thromb. 2022; 29: 200-220. doi: 10.5551/jat.57125.
44. Pu Y., Zhao Q., Men X. et al. MicroRNA-325 facilitates atherosclerosis progression by mediating the SREBF1/LXR axis via KDM1A. Life Sci. 2021; 277: 119464. doi: 10.1016/j.lfs.2021.119464.
45. Hildebrandt A., Kirchner B., Meidert A.S. et al. Detection of Atherosclerosis by Small RNA-Sequencing Analysis of Extracellular Vesicle Enriched Serum Samples. Front. Cell. Dev. Biol. 2021; 9: 729061. doi: 10.3389/fcell.2021.729061.
46. Ahmadi R., Heidarian E., Fadaei R. et al. miR-342-5p Expression Levels in Coronary Artery Disease Patients and its Association with Inflammatory Cytokines. Clin. Lab. 2018; 64: 603-609. doi: 10.7754/Clin.Lab.2017.171208.
47. Wang W., Ma F., Zhang H. MicroRNA-374 is a potential diagnostic biomarker for atherosclerosis and regulates the proliferation and migration of vascular smooth muscle cells. Cardiovasc. Diagn. Ther. 2020; 10: 687-694. doi: 10.21037/cdt-20-444.
48. Shao D., Lian Z., Di Y. et al. Dietary compounds have potential in controlling atherosclerosis by modulating macrophage cholesterol metabolism and inflammation via miRNA. NPJ Sci. Food. 2018; 2: 13. doi: 10.1038/s41538-018-0022-8.
49. Wang B., Zhong Y., Huang D. et al. Macrophage autophagy regulated by miR-384-5p-mediated control of Beclin-1 plays a role in the development of atherosclerosis. Am.J. Transl. Res. 2016; 8: 606-614.
50. Yang J., Liu H., Cao Q. et al. Characteristics of CXCL2 expression in coronary atherosclerosis and negative regulation by microRNA-421. J. Int. Med. Res. 2020; 48: 300060519896150. doi: 10.1177/0300060519896150.
51. Liang X., Hu M., Yuan W. et al. MicroRNA-4487 regulates vascular smooth muscle cell proliferation, migration and apoptosis by targeting RAS p21 protein activator 1. Pathol. Res. Pract. 2022; 234: 153903. doi: 10.1016/j.prp.2022.153903.
52. Niu M., Li H., Li X. et al. Circulating Exosomal miRNAs as Novel Biomarkers Perform Superior Diagnostic Efficiency Compared With Plasma miRNAs for Large-Artery Atherosclerosis Stroke. Front Pharmacol. 2021; 12: 791644. doi: 10.3389/fphar.2021.791644.
53. Rafiq M., Dandare A., Javed A. et al. Competing Endogenous RNA Regulatory Networks of hsa_circ_0126672 in Pathophysiology of Coronary Heart Disease. Genes (Basel). 2023; 14: 550. doi: 10.3390/genes14030550.
54. Salerno A.G., van Solingen C., Scotti E. et al. LDL Receptor Pathway Regulation by miR-224 and miR-520d. Front. Cardiovasc. Med. 2020; 7: 81.
55. Konwerski M., Gromadka A., Arendarczyk A. et al. Atherosclerosis Pathways are Activated in Pericoronary Adipose Tissue of Patients with Coronary Artery Disease. J. Inflamm. Res. 2021; 14: 5419-5431. doi: 10.2147/JIR.S326769.
56. Fang M., Zhou Q., Tu W. et al. ATF4 promotes brain vascular smooth muscle cells proliferation, invasion and migration by targeting miR-552-SKI axis. PLoS One. 2022; 17: e0270880. doi: 10.1371/journal.pone.0270880.
57. Zhang M., Zhu Y., Zhu J. et al. circ_0086296 induced atherosclerotic lesions via the IFIT1/STAT1 feedback loop by sponging miR-576-3p. Cell. Mol. Biol. Lett. 2022; 27: 80. doi: 10.1186/s11658-022-00372-2.
58. Hou X., Dai H., Zheng Y. Circular RNA hsa_circ_0008896 accelerates atherosclerosis by promoting the proliferation, migration and invasion of vascular smooth muscle cells via hsa-miR-633/CDC20B (cell division cycle 20B) axis. Bioengineered. 2022; 13: 5987-5998. doi: 10.1080/21655979.2022.2039467.
59. Ma G., Bi S., Zhang P. Long non-coding RNA MIAT regulates ox-LDL-induced cell proliferation, migration and invasion by miR-641/STIM1 axis in human vascular smooth muscle cells. BMC Cardiovasc. Disord. 2021; 21: 248. doi: 10.1186/s12872-021-02048-9.
60. Chen L.J., Chuang L., Huang Y.H. et al. MicroRNA mediation of endothelial inflammatory response to smooth muscle cells and

its inhibition by atheroprotective shear stress. Circ. Res. 2015; 116: 1157-69. doi: 10.1161/CIRCRESAHA.116.305987.
61. Maes O.C., Sarojini H., Wang E. Stepwise up-regulation of microRNA expression levels from replicating to reversible and irreversible growth arrest states in WI-38 human fibroblasts. J. Cell. Physiol. 2009; 221: 109–119. doi: 10.1002/jcp.21834.
62. Marasa B.S., Srikantan S., Martindale J.L. et al. MicroRNA profiling in human diploid fibroblasts uncovers miR-519 role in replicative senescence. Aging (Albany NY). 2010; 2: 333–343. doi: 10.18632/aging.100159.
63. Dhahbi J.M., Atamna H., Boffelli D. et al. Deep sequencing reveals novel microRNAs and regulation of microRNA expression during cell senescence. PLoS One. 2011; 6: e20509. doi: 10.1371/journal.pone.0020509.
64. Tsukamoto H., Kouwaki T., Oshiumi H. Aging-Associated Extracellular Vesicles Contain Immune Regulatory microRNAs Alleviating Hyperinflammatory State and Immune Dysfunction in the Elderly. iScience. 2020; 23: 101520. doi: 10.1016/j.isci.2020.101520.
65. Smith-Vikos T., Liu Z., Parsons C. A serum miRNA profile of human longevity: findings from the Baltimore Longitudinal Study of Aging (BLSA). Aging (Albany NY). 2016; 8: 2971-2987. doi: 10.18632/aging.101106.
66. Morsiani C., Bacalini M.G., Collura S. et al. Blood circulating miR-28-5p and let-7d-5p associate with premature ageing in Down syndrome. Mech. Ageing Dev. 2022; 206: 111691. doi: 10.1016/j.mad.2022.111691.
67. Yu Y., Zhang X., Liu F. et al. A stress-induced miR-31-CLOCK-ERK pathway is a key driver and therapeutic target for skin aging. Nat. Aging. 2021; 1: 795-809. doi: 10.1038/s43587-021-00094-8.
68. Dalmasso B., Hatse S., Brouwers B. et al. Age-related microRNAs in older breast cancer patients: biomarker potential and evolution during adjuvant chemotherapy. BMC Cancer. 2018; 18: 1014. doi: 10.1186/s12885-018-4920-6.
69. Zhao J., Li C., Qin T. et al. Mechanical overloading-induced miR-325-3p reduction promoted chondrocyte senescence and exacerbated facet joint degeneration. Arthritis Res. Ther. 2023; 25: 54. doi: 10.1186/s13075-023-03037-3.
70. Liu Y., Lai P., Deng J. et al. Micro-RNA335-5p targeted inhibition of sKlotho and promoted oxidative stress-mediated aging of endothelial cells. Biomark. Med. 2019; 13: 457-466. doi: 10.2217/bmm-2018-0430.
71. Owczarz M., Polosak J., Domaszewska-Szostek A. et al. Age-related epigenetic drift deregulates SIRT6 expression and affects its downstream genes in human peripheral blood mononuclear cells. Epigenetics. 2020; 15: 1336-1347. doi: 10.1080/15592294.2020.1780081.
72. Proctor C.J., Goljanek-Whysall K. Using computer simulation models to investigate the most promising microRNAs to improve muscle regeneration during ageing. Sci. Rep. 2017; 7: 12314. doi: 10.1038/s41598-017-12538-6.
73. Li X., Wu J., Zhang K. et al. miR-384-5p Targets Gli2 and Negatively Regulates Age-Related Osteogenic Differentiation of Rat Bone Marrow Mesenchymal Stem Cells. Stem. Cells Dev. 2019; 28: 791-798. doi: 10.1089/scd.2019.0044.
74. Li G., Song H., Chen L. et al. TUG1 promotes lens epithelial cell apoptosis by regulating miR-421/caspase-3 axis in age-related cataract. Exp. Cell. Res. 2017; 356: 20-27. doi: 10.1016/j.yexcr.2017.04.002.
75. Wang L., Si X., Chen S. et al. A comprehensive evaluation of skin aging-related circular RNA expression profiles. J. Clin. Lab. Anal. 2021; 35(4): e23714. doi: 10.1002/jcla.23714.
76. Chen J., Zou Q., Lv D. et al. Comprehensive transcriptional landscape of porcine cardiac and skeletal muscles reveals differences of aging. Oncotarget. 2018; 9: 1524-1541.
77. Li X., Song Y., Liu D. et al. MiR-495 Promotes Senescence of Mesenchymal Stem Cells by Targeting Bmi-1. Cell. Physiol. Biochem. 2017; 42: 780-796. doi: 10.1159/000478069.
78. Yu M., He X., Liu T. et al. lncRNA GPRC5D-AS1 as a ceRNA inhibits skeletal muscle aging by regulating miR-520d-5p. Aging (Albany NY). 2023; 15: 13980-13997. doi: 10.18632/aging.205279.
79. Breunig S., Wallner V., Kobler K. et al. The life in a gradient: calcium, the lncRNA SPRR2C and mir542/mir196a meet in the epidermis to regulate the aging process. Aging (Albany NY). 2021; 13: 19127–19144. doi: 10.18632/aging.203385.
80. Castanheira C.I. G.D., Anderson J.R., Fang Y. et al. Mouse microRNA signatures in joint ageing and post-traumatic osteoarthritis. Osteoarthr. Cartil Open. 2021; 3: 100186. doi: 10.1016/j.ocarto.2021.100186.
81. Zhang L., Xia C., Yang Y. et al. DNA methylation and histone post-translational modifications in atherosclerosis and a novel perspective for epigenetic therapy. Cell. Commun. Signal. 2023; 21(1): 344. doi: 10.1186/s12964-023-01298-8.
82. Мустафин Р.Н. Метод вирусной мимикрии в онкологии и перспективы его развития. Архивъ внутренней медицины. 2023; 13(3): 165-174. doi: 10.20514/2226-6704-2023-13-3-165-174. Mustafin R.N. The method of viral mimicry in oncology and prospects for its improvement. The Russian Archives of Internal Medicine. 2023;13(3):165-174. [in Russian].
83. Wu X.D., Zeng K., Liu W.L. et al. Effect of aerobic exercise on miRNA-TLR4 signaling in atherosclerosis. Int. J. Sports Med. 2014; 35(4): 344-350. doi: 10.1055/s-0033-1349075.
84. Liu Y., He M., Yuan Y. et al. Neutrophil-Membrane-Coated Biomineralized Metal-Organic Framework Nanoparticles for Atherosclerosis Treatment by Targeting Gene Silencing. ACS Nano. 2023; 17(8): 7721-7732. doi: 10.1021/acsnano.3c00288.
85. Wright R.S., Ray K.K., Raal F.J. et al. Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis. J.Am. Coll. Cardiol. 2021; 77(9): 1182-1193. doi: 10.1016/j.jacc.2020.12.058.
86. O'Donoghue M.L., G López J.A., Knusel B. et al. Study design and rationale for the Olpasiran trials of Cardiovascular Events And lipoproteiN(a) reduction-DOSE finding study (OCEAN(a)-DOSE). Am. Heart J. 2022; 251: 61-69. doi: 10.1016/j.ahj.2022.05.004.
87. Milosavljevic M.N., Stefanovic S.M., Pejcic A.V. Potential Novel RNA-Targeting Agents for Effective Lipoprotein(a) Lowering: A Systematic Assessment of the Evidence From Completed and Ongoing Developmental Clinical Trials. J. Cardiovasc. Pharmacol. 2023; 82(1): 1-12. doi: 10.1097/FJC.0000000000001429.