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REVIEWS
AND THEORETICAL ARTICLES

Epigenetic Mechanisms of the Influence of Physical Activity on the Development of Atherosclerosis

R. N. Mustafin[a, *] and E. K. Khusnutdinova[b]

[a] *Bashkir State Medical University, Ufa, 450008 Russia*

[b] *Institute of Biochemistry and Genetics, Ufa Federal Research Centre, Russian Academy of Sciences, Ufa, 450054 Russia*

**e-mail: ruji79@mail.ru*

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Abstract—This work is an analytical review dedicated to the search for driver mechanisms of epigenetic changes in atherosclerosis pathogenesis. The disease affects the cardiovascular system in the adult population, mainly the elderly and senile. Atherosclerosis is accompanied by progressive deposition of cholesterol and lipoproteins in vessels intima with inflammation, narrowing of the lumen, and impaired blood supply to tissues and organs. These processes are characterized by changes in the expression of the *CACNA1C*, *GABBR2*, *TCF7L2*, *DCK*, *NRP1*, *PBX1*, *FANCC*, *CCDC88C*, *TCF12*, and *ABLIM1* genes. Prevention of atherosclerosis is physical activity, the mechanisms of which are not fully understood. Experimental models have shown that regular training not only has a protective effect on the development of atherosclerosis but also inhibits the progression of an already developed disease with a decrease in vascular stenosis and an increase in the concentration of collagen and elastin and matrix metalloproteinases in plaques. These results have been confirmed by clinical studies. The purpose of this review was to systematize the accumulated results on the causes of epigenetic changes, including those under the influence of regular training, causing changes in the expression of specific microRNAs in atherosclerosis. It was found that physical exercise in Apo–/– mice increases the expression of miR-126 and miR-146a (inhibiting the *TLR4* and *TRAF* genes), miR-20a (affecting *PTEN*), and miR-492 (suppressing *RETN* gene mRNA). Clinical studies have shown an increase in the levels of miR-146a, miR-126, miR-142-5p, and miR-424-5p and a decrease in the transcription of miR-15a-5p, miR-93-5p, and miR-451 under the influence of aerobic training. It has been suggested that the drivers of epigenetic changes in atherosclerosis are transposons pathologically activated during aging, the transcription of which can change under the influence of physical training, which is accompanied by impaired expression of long noncoding RNAs and microRNAs derived from transposons. Analysis of the published data allowed us to identify 36 such microRNAs, 25 of which showed identical changes in levels during aging and atherosclerosis.

Keywords: atherosclerosis, aerobic training, inflammation, microRNA, retroelements, aging, transposons, physical exercise

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INTRODUCTION

Atherosclerosis (AS) is the most common cardiovascular disease in the world, affecting the vessels of the heart, brain, and peripheral arteries [1]. The incidence of the disease increases significantly with age [2] owing to inflammation of the vascular walls during aging [3–5]. The development of AS is characterized by the deposition of cholesterol and lipoproteins in the walls of arteries with the formation of plaques, which gradually narrow the lumen of blood vessels and disrupt the blood supply to tissues and organs. The development of the disease is influenced by both environmental factors (poor diet, excess weight, smoking, alcohol intake, physical inactivity) and genetic predisposition [1]. According to the results of meta-analyses, AS is significantly associated with allelic variants of genes of interleukin *IL-10* (–1082G>A), beta chemokines *CCR5* (rs333), cyclooxygenase *COX2* (–765G>C), *FLAP* (–336G>A), lipoxygenase *5-LO* (–1078G>A), marenostrina *MEFV* (694M>V), and Toll-like receptors *TLR-4* (+896A>G) [6]. For specific AS sites, meta-analyses have shown an association of polymorphisms of specific genes in AS of peripheral arteries (*CYP2B6*, *SYTL3*, and *TCF7L2*) [7], in AS of cerebral arteries (*GP1BA*, *F11*, *LAMC2*, *VCAM1*, *PROC*, *KLKB1*) [8], and in AS of the coronary arteries (variants of 57 different polymorphisms located mainly in intergenic and intronic regions, as well as in genes *BCAS3*, *KSR2*, *NOA1*, *NOS3*, *SMAD3*, *SWAP70*) [9].

The development of AS is accompanied by changes in gene expression in the tissues of affected vessels, which is due to the influence of epigenetic factors,

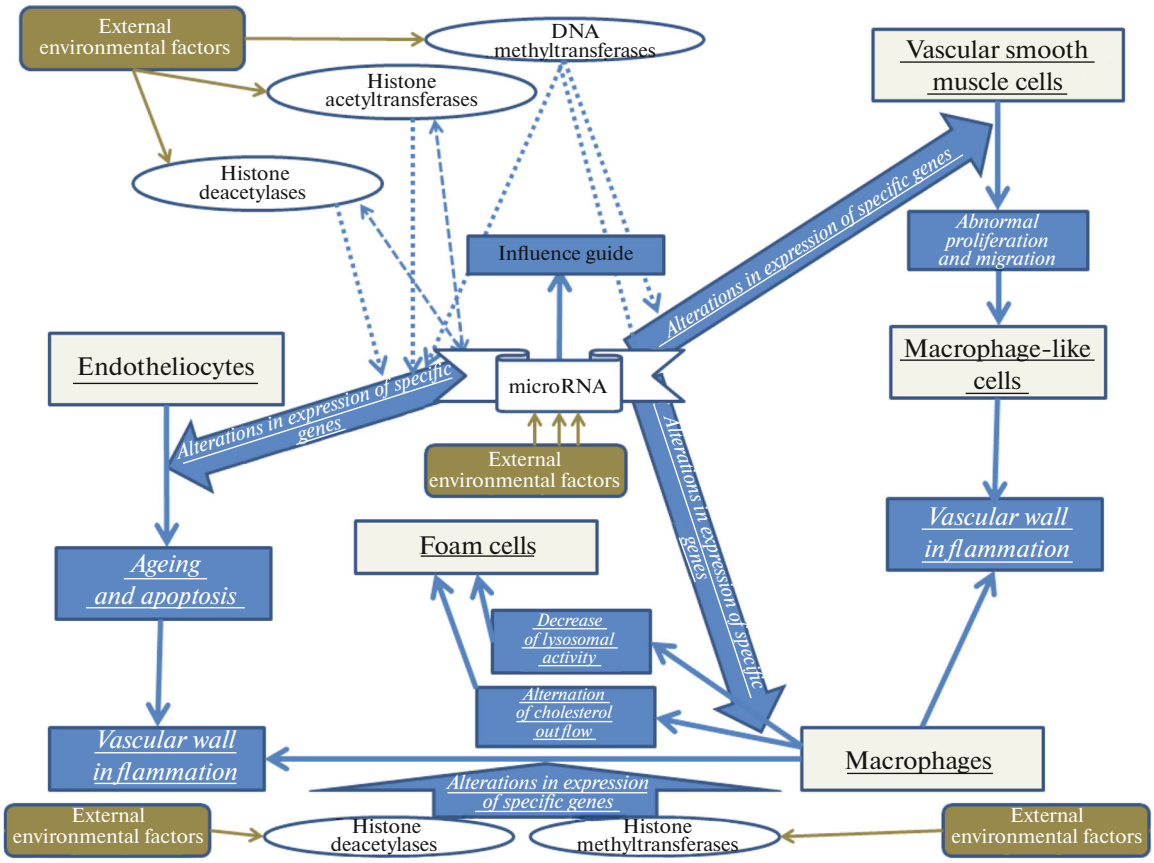

Fig. 1. Scheme of the role of microRNAs in the mechanisms of development of atherosclerosis.

which include DNA methylation, histone modifications, and RNA interference using microRNAs and long noncoding RNAs (ncRNAs) [10]. This is accompanied by a change in the cell phenotypes involved in the pathogenesis of AS, including endothelial cells (ECs) [4, 11, 12], vascular smooth muscle cells (VSMCs) [13, 14], and cells of the immune system [15], as well as disorders of lipid metabolism and inflammation [16] (Fig. 1). A comparative study conducted in 2022 on the role of epigenetic factors in the development of AS showed 47 activated (hypomethylated) and 90 inactivated (hypermethylated) genes in AS, as well as 10 key AS genes (*CACNA1C*, *GABBR2*, *TCF7L2*, *DCK*, *NRP1*, *PBX1*, *FANCC*, *CCDC88C*, *TCF12*, *ABLIM1*), differentially expressed under the influence of microRNAs and pathological methylation [17]. DNA methylation is carried out by the enzymes of DNA methyltransferases DNMT1, DNMT3a, and DNMT3b; demethylation is carried out by Tet-methylcytosine dioxygenases TET1, TET2, and TET3; and histone acetylation is carried out by acetyltransferases [10]. Disturbances in the expression of microRNAs have been described as pathogenetic factors in AS developing with aging [4, 5], since they change DNA methylation through the mechanisms of RNA-directed DNA methylation, affecting the transcription of specific genes. In these mechanisms, microRNAs are guides for changing epigenetic factors in specific loci of the genome [18], which results in the effects of DNA methyltransferases DNMT1/3a/3b and TET1/2/3, histone acetyltransferases HAT, and deacetylases HDAC on the expression of specific genes detected in AS [10].

Endothelial inflammation in AS is associated with increased levels of miR-126 and miR-221/222 and low levels of miR10a, miR-155, miR-181a, and 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 and miR-34 and a decrease in the production of miR-92a and miR-216a, which is accompanied by an increase in the concentrations of pro-inflammatory chemokines MCP1 (monocyte chemoattractant protein 1), CXCL12 (chemokine (C-X-C motif) ligand 12), VCAM (vascular cell adhesion protein), and ICAM (intercellular adhesion molecule) [4]. MiR-146a [11] and miR-200c (in response to reactive oxygen species) [12] are associated with EC aging in the pathogenesis of AS. Aging-associated miR-217 has been implicated in the development of AS and cardiovascular dysfunction by suppressing a network of endothelial nitric oxide synthase activa-

tors, including the VEGF (vascular endothelial growth factor) and apelin receptor pathways [5].

A systematic review of the scientific literature conducted in 2018 showed that microRNAs are able to control inflammation of the vascular wall by regulating its infiltration of activated leukocytes. These include miR-19a, miR-19b, and miR-21. The key microRNA in these AS mechanisms is miR-126, which inhibits VCAM-1 (vascular cell adhesion molecule 1) and pro-inflammatory TNF-α. In this regard, decreased miR-126 expression increases NF-κB activity, enhancing the interaction of leukocytes with ECs and promoting AS [15]. The function of macrophages in AS is influenced by miR-33, which regulates ABCA1 (ATP-binding cassette transporter A1)-dependent cholesterol efflux. Also, miR-33 inhibits genes *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 [19]. Changes in epigenetic regulation play an important role in the polarization of macrophages into M1-like (under the influence of histone deacetylases HDAC3, HDAC7, and HDAC9 and histone modifications H3K9me3 and H3K36me3), which contributes to inflammation of the vascular wall [20]. Inflammatory macrophages secrete vesicles containing specific microRNAs (such as miR-28, miR-146a, miR-185, miR-365, and miR-503), which are used for communication between cells of atherosclerotic vessels [15].

Abnormal proliferation and migration of VSMCs have been implicated in neointimal formation, contributing to restenosis [14] and plaque formation in AS. In this case, VSMCs can transition to less differentiated forms that lack markers of VSMCs, including macrophage-like cells, which contribute to the progression of AS and inflammation [13]. Characterized by their influence on VSMCs in the pathogenesis of AS are miR1 (targets are mRNA of genes *KLF4* and *PIM1*), miR-10a (affects mRNA of *HDAC4*), miR-126 (inhibits mRNA of genes *BCL2*, *IRS1*, and *FOXO3*), miR-22 (affects genes *MECP2*, *HDAC4*, and *EVI1*), miR-143 and miR-145 (affect genes *ACE*, *ELK1*, and *KLF4/5*), miR-21 (targets are mRNA of genes *DOCK* and *PDCD4*), miR-26a, miR-34a, miR-130a, and miR-221 [15]. Among the circulating microRNAs, the most specific to 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 [21].

It should be noted that the causes of disturbances of microRNA expression in AS may be the activation of mobile genetic elements (MGEs) with age [22], contributing to inflammatory processes in the human body during aging [3–5]. This is due to the emergence of many noncoding RNAs (ncRNAs), including microRNAs, from MGEs in evolution. Back in 2016, the MDTE DB database (miRNAs derived from transposable elements database) was published on the origin of 661 specific microRNAs from MGEs [23]. MGEs include retroelements (REs) HERVs (Human Endogenous Retroviruses) [24] and LINE-1s (Long Interspersed Nuclear Elements-1), the transposition of which occurs by the "copy and paste" mechanism, and DNA transposons, which move by "cut and paste" [25]. Owing to the presence of complementary sequences of microRNAs with MGEs, activation of the latter during aging and under the influence of environmental factors can affect the expression of microRNAs. In addition, the discovery of numerous polymorphisms located in intergenic regions and introns [9] associated with AS also indicates the influence of MGEs on the pathogenesis of the disease, since many MGEs are located in intergenic regions and introns. MicroRNA genes are also characterized by a similar distribution in the human genome [23].

THE EFFECT OF EXERCISE ON ATHEROSCLEROSIS AND AGING

In the development of AS, inflammation of the vascular walls associated with aging plays an important role [5], which can be influenced by environmental factors, including the performance of a sufficient amount of aerobic physical exercise, which changes the metabolism in the body [26]. At the same time, physical inactivity stimulates NADPH oxidases, promoting vascular dysfunction by increasing oxidative stress [27]. Regular exercise inhibits the expression of the pro-inflammatory molecule TNF-α [28]. Under the influence of aerobic exercise in elderly people, the concentrations of IL-18, IL-6, and CRP in the blood decrease [29], and in AS, the formation of foam cells from macrophages is prevented [30]. Thus, the molecular mechanisms of the influence of physical training on the development of AS have been described, but the most promising study is the study of the regulators of epigenetic factors that cause these changes. Such drivers may be MGEs, the pathological activation of which is a key mechanism of aging [22].

To confirm the effect of various factors on the development of atherosclerosis, specially modified lines of ApoE–/– mice are used in experiments, in the study of which a number of published works have reliably shown not only the protective effect of physical exercise on the development of AS but also the inhibition of the progression of the disease itself, which indicates about the rationality of recommendations for the introduction of regular physical education to patients even with developed AS. Thus, 6 weeks of running in ApoE–/– mice after a 16-week high-fat diet helped reduce plaque stenosis and increase the content of collagen and elastin in them [31]. Similar results were obtained in another study on ApoE–/– mice that developed severe AS: An 8-week run reduced plaque

stenosis and increased the concentration of elastin and collagen in plaques [32]. Suppression of inflammation and migration of immune system cells in the walls of blood vessels with a decrease in the number of leukocytes in AS plaques was also determined as a result of six weeks of voluntary running in ApoE–/– mice [33]. A decrease in lipid levels and reduction in plaque stenosis with an increase in elastin and collagen concentration and matrix metalloproteinases MMP2 (which destroy plaque matrix) were observed in ApoE–/– mice with early (age 12 weeks) and late (age 40 weeks) AS after 10 weeks of voluntary running [34].

The results obtained in animal experiments on the therapeutic effects of aerobic exercise on the development of AS were confirmed in clinical studies on patients. Prolonged (4 h) low-intensity exercise has been shown to increase triglyceride oxidation during exercise and decrease the rate of free fatty acids during recovery, the more so in trained individuals [35]. A study of older patients (58–70 years) with AS showed that 16 weeks of training using vibration feedback devices to stimulate physical activity reduced the production of interleukins IL-1β, IL-8, and IL-10 in peripheral mononuclear cells [26]. Since inflammation of the vascular walls associated with aging plays an important role in the pathogenesis of AS, the data obtained indicate a protective effect of regular physical exercise on the development of AS. A randomized study on elderly volunteers (mean age 69 years) with peripheral arterial atherosclerosis (AS) showed that high-intensity training for 12 months had a significantly more effective impact on the development of AS compared to low-intensity training [36]. A meta-analysis conducted in 2023 of 12 randomized controlled trials and seven cohort studies showed that physical exercises in patients with occlusive peripheral arterial AS have a therapeutic effect and reduce the risk of death after 12 months of regular exercise [37].

EFFECT OF PHYSICAL EXERCISE ON microRNA EXPRESSION AND SIGNALING PATHWAYS IN ATHEROSCLEROSIS

The effect of exercise on the development of AS may be due to changes in epigenetic factors. This is evidenced by the published results of experiments on male C57BL/6J mice with null ApoE at the age of 10 weeks. These animals demonstrated the effect of physical exercise on reducing the expression of miR-155 and increasing the expression of miR-126 and miR-146a. The mice were placed in a treadmill chamber for 10 min before running, after which the animals ran at a speed of 13 m per minute for one hour. Compared to control mice (with no exercise, with or without statin exposure), increased levels of miR-126 and miR-146a reduced inflammatory vascular damage through an inhibitory effect on expression of genes *TRAF* and *TLR4* [38]. In experiments on ApoE–/– and LDLR–/– rats in 2017, it was revealed that regular exercise in the form of swimming increases the expression of miR-20a by endothelial cells. MiR-20a suppresses transcription and translation of genes *PTEN* (encodes the protein phosphatase, a tumor suppressor that prevents rapid cell proliferation), *ANGII* (encodes angiotensin), *ET-1* (endothelin gene 1), and *TxA2* (thromboxane A2) [39]. Swimming also significantly reduced AS severity in Apo–/– mice by increasing levels of miR-492, which inhibits expression of the resistin gene (*RETN*) [40].

Clinical studies on patients with coronary artery AS revealed a decrease in the levels of miR-15a-5p, miR-93-5p, and miR-451a and an increase in miR-146a-5p in the blood under the influence of exercise. The conducted bioinformatic analysis showed the role of the miR-15a-5p and miR-93-5p genes in the mechanisms of biosynthesis and metabolism of fatty acids [41]. With regard to miR-146a, the results obtained coincide with data from experiments on mice [38]. Regular walking exercise in patients with peripheral arterial AS promoted the expression of miR-126, which plays a role in angiogenesis and adaptation through inhibition *PI3KR2*, owing to which the signaling pathway of the vascular endothelial growth factor VEGF is activated [42]. Moderate physical training in older patients (72 ± 7 years) with peripheral arterial AS contributed to an increase in the levels of miR-142-5p and miR-424-5p, which affect the VEGF and mTOR signaling pathways, preventing the development of AS [43]. Figure 2 shows a diagram of the effect of physical training (according to experimental and clinical studies) on the expression of specific microRNAs involved in the pathogenesis of AS.

Since even one microRNA affects many different genes, it is logical to assume that changes in the expression of these molecules affect specific mechanisms involved in the pathogenesis of AS. Indeed, in experiments on mice, aerobic training led to increased expression of SESN1. SESN proteins suppress inflammatory signaling pathways with decreased levels of proinflammatory factors [44]. Swimming exercise in C57BL/6J mice at 24 months of age increased the production of another representative of these proteins, SESN2, promoting increased sensitivity to insulin [45]. Exercise also affects AMP-activated protein kinase (AMPK) signaling. This helps restore lipid metabolism and normalize EC function through the interaction of AMPK with peroxisome proliferator-activated receptors [46]. In addition to mutations in the ApoE–/– gene to model AS, the development of AS is modeled in experimental animals by knocking out (inactivating) both alleles of the low-density lipoprotein receptor gene (LDLR–/–). Experiments on such mice showed that regular aerobic exercise for four weeks increased the production of hydrogen peroxide and nitric oxide, preventing endothelial dysfunction [47].

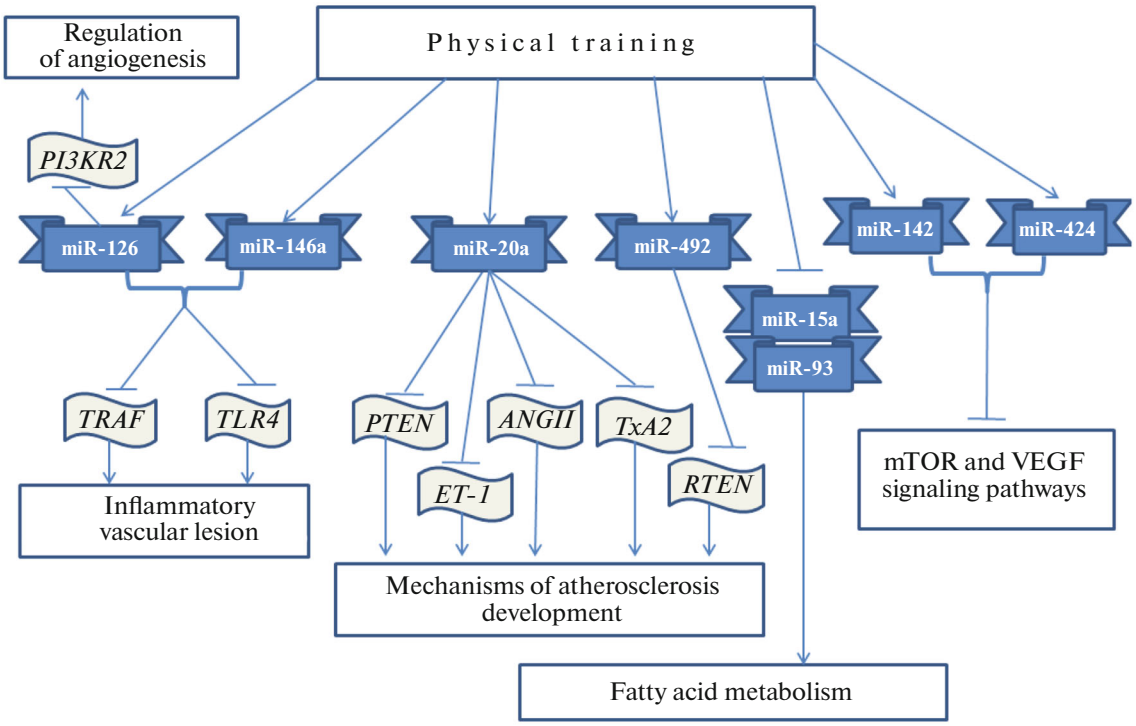

Fig. 2. Scheme of the effect of physical exercise on the expression of microRNAs involved in the pathogenesis of atherosclerosis.

THE ROLE OF TRANSPOSONS AND LONG NONCODING RNAs IN THE PATHOGENESIS OF ATHEROSCLEROSIS

The effect of physical training may be due to the effect on AS-activated transposons (MGEs), since MGE expression products during aging stimulate interferon overproduction and secondary chronic inflammatory processes in the body [24, 48]. Macrophages are characterized by the expression of HERV-K (HML-2), which correlates with immune activation of macrophages (polarization into M1 cells) and response to interferon-I [49]. During aging, dysfunctional LB foam macrophages (CD14+CD16+) produce HERV-K102 particles released to stimulate the trained innate immune system [50], which may be the cause of impaired gene expression in AS in these cells [51]. Macrophages also express the *ERVPb1* gene, which descended from *Env* endogenous RE HERV-P [52]. Indeed, a 2019 study of changes in epigenetic factors in peripheral blood leukocytes in humans under the influence of exercise showed increased methylation of Alu and LINE1, as well as *TNFα*, *NOS2*, and *EDN1* genes, which was accompanied by a decrease in blood pressure [53]. In skeletal muscles, physical exercise increases LINE1 methylation, which is normally reduced during physiological aging [54]. Experiments on transgenic mice fed a high-fat diet showed an increase in RE transcripts with their decrease under the influence of aerobic exercise [55].

The role of MGEs in the initiation and development of AS is due not only to interferon-mediated inflammation [24, 48] but also to participation 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 [56]. An imbalance in RE activation with age [22], which contributes to aging and inflammation of vascular walls [3–5], may be reflected in the dysregulation of DNA transposons and the V(D)J recombination genes derived from them, with subsequent changes in the functioning of the immune system [57], which affects the development of AS. Activation of RE during aging contributes to immune pathology also owing to the use of ERVs as enhancers of *HLA-G* genes [58] and interferon-inducible genes (forming transcriptional networks of the interferon response [59]). According to the results of meta-analyses, dysregulation of REs is important in the etiopathogenesis of autoimmune diseases [60], with which AS is reliably associated [61].

The role of MGEs in the development of AS is also mediated by the close relationship of their functioning with ncRNAs that evolved from MGEs, including not only microRNAs [23] but also long ncRNAs [62]. Because of this, MGEs serve as drivers of epigenetic regulation at both post-transcriptional and transcriptional levels [63] owing to the mechanism of RNA-directed DNA methylation [18]. In addition, MGEs are the most important sources of transcription factors [64] and binding sites for them [65], which indicates

the existence of an additional mechanism for the influence of transposons on epigenetic factors, since transcription factors influence various histone deacetylases [66]. The relationship between miR-148 and the DNA methyltransferases DNMT1, DNMT3a, and miR-140 with the histone deacetylase HDAC4 was also determined [67].

Long ncRNAs are epigenetic factors, and changes in their levels in the pathogenesis of AS may be a reflection of the expression patterns of MGEs, which are sources of ncRNAs in evolution [62]. This is due to the high sensitivity of REs to environmental influences [68] and hyperactivation of MGEs during aging [22]. The expression products of HERVs [69] and LINE-1s [70] themselves function as long ncRNAs. The role of RE interactions with long ncRNAs in the pathogenesis of AS has been described. *Alu* elements (related to nonautonomous RE) bind to the long ncRNA ANRIL, involved in the development of AC [71]. ANRIL interacts directly with sequences of *Alu* in the genome [72], which have a proatherogenic effect, located in the promoter regions of target genes [73], encoding proteins of the polycomb group PRC-1 and PRC-2. These proteins are recruited by ANRIL and are used to modify epigenetic factors to inhibit gene expression in cis-regulation of apoptosis, cell proliferation and adhesion, inflammation, and AS development [72].

Long ncRNAs VINAS [74] and H19 [75] influence the development of AS by regulating the MAPK and NF-κB signaling pathways involved in inflammation. VINAS knockdown reduces the expression of key inflammatory markers such as MCP-1, COX-2, TNF-α, and IL-1β in endothelial cells [74]. In the blood plasma and plaques of patients with AS, an increased level of long ncRNA AK136714 was determined, the inhibition of which in experiments suppresses the formation of AS and inflammation of EC and protects the endothelial barrier. AK136714 stimulates transcription of *Bim* and also directly binds to HuR, increasing the stability of mRNAs of genes *TNF-α*, *IL-1β*, and *IL-6* [76]. The long ncRNA RAPIA is expressed by macrophages during the progression of AS, stimulating their proliferation and suppressing apoptosis. Inhibition of RAPIA in vivo suppresses AS progression [77]. Expression of the macrophage-specific long ncRNA MAARS (Macrophage-Associated Atherosclerosis lncRNA Sequence) in the aortic intima increases 270-fold with AS progression and decreases by 60% with regression. In experiments on LDLR−/− mice (with both alleles of low-density lipoprotein receptors inactivated), MAARS knockdown reduced the formation of AS plaques by 52% by reducing inflammation and macrophage apoptosis and increasing efferocytosis in the vessel walls [74].

Modified transcripts of *Alu* elements in AS control the stability of the pro-inflammatory long ncRNA NEAT1, the expression of which is higher in patients with coronary artery AS and is enhanced under the influence of TNF-α. Suppression of NEAT1 leads to a weakening of the TNF-α-induced proinflammatory response of endothelial cells with the characteristic expression of the chemokines CXCL8 and CCL2 and immunoglobulins VCAM1 and ICAM1 [78]. During myocardial infarction with symptoms of an unstable atherosclerotic plaque, the level of long ncRNA MIAT, which acts as a sponge for miR-149-5p, promoting the expression of the antiphagocytic molecule CD47, is significantly increased in the serum of patients [79]. That is, the mechanism of influence of long ncRNAs on the development of AS may be associated with the regulation of microRNAs, which is probably due to the evolutionary origin of both long ncRNAs [62, 80] and microRNAs [23] from MGEs (the common origin contributes to the presence of complementary sequences). Therefore, it is logical to assume that the observed changes in ncRNA expression in AS are a consequence of pathological activation of MGEs during aging [22, 24, 25], which have not only a direct effect on the development of AS [3–5] but also an indirect one, owing to the interactions of the events of microRNAs and long ncRNAs that occurred from them (Fig. 3).

THE ROLE OF TRANSPOSON-DERIVED microRNAs IN THE DEVELOPMENT OF ATHEROSCLEROSIS AND AGING

Analysis of the scientific literature allowed us to identify changes in the expression of 35 microRNAs derived from transposons, the expression of which changes both with aging and with atherosclerosis. Thus, the level of miR-1246, which arises from LTR-ERVL and is partially complementary to its sequence [23], increases both in AS [81] and with aging (in human fibroblasts) [82, 83]. In atherosclerosis, miR-1246 promotes the proliferation, invasion, and differentiation of VSMCs [81]. Since miR-1248 (derived from SINE/Alu [23]) suppresses thrombomodulin expression in EC progenitors, a decrease in its level contributes to the development of AS [84]. Low concentrations of miR-1248 are also detected during aging [85]. In patients with myocardial infarction, exosomes obtained from macrophages contain high levels of miR-1271 [86], which is derived from LINE2 [23]. A study of samples of coronary arteries from patients with AS revealed a significant increase in the expression of miR-1273 [87], the family of which evolved from RE LINE, SINE, and ERVL [23]. With aging, the expression of miR-1271 and miR-1273 also increases [82, 83]. Increased levels of miR-1290, derived from SINE/MiR [23], are observed in aging [83] and in stroke-complicated AS in young patients [88].

LINE2-derived miR-151 [23] suppresses EC apoptosis in the development of AS. This microRNA affects the production of the proteins BAX, IL-17A, and c-caspase 3 and 9. In both AS [89] and aging, the

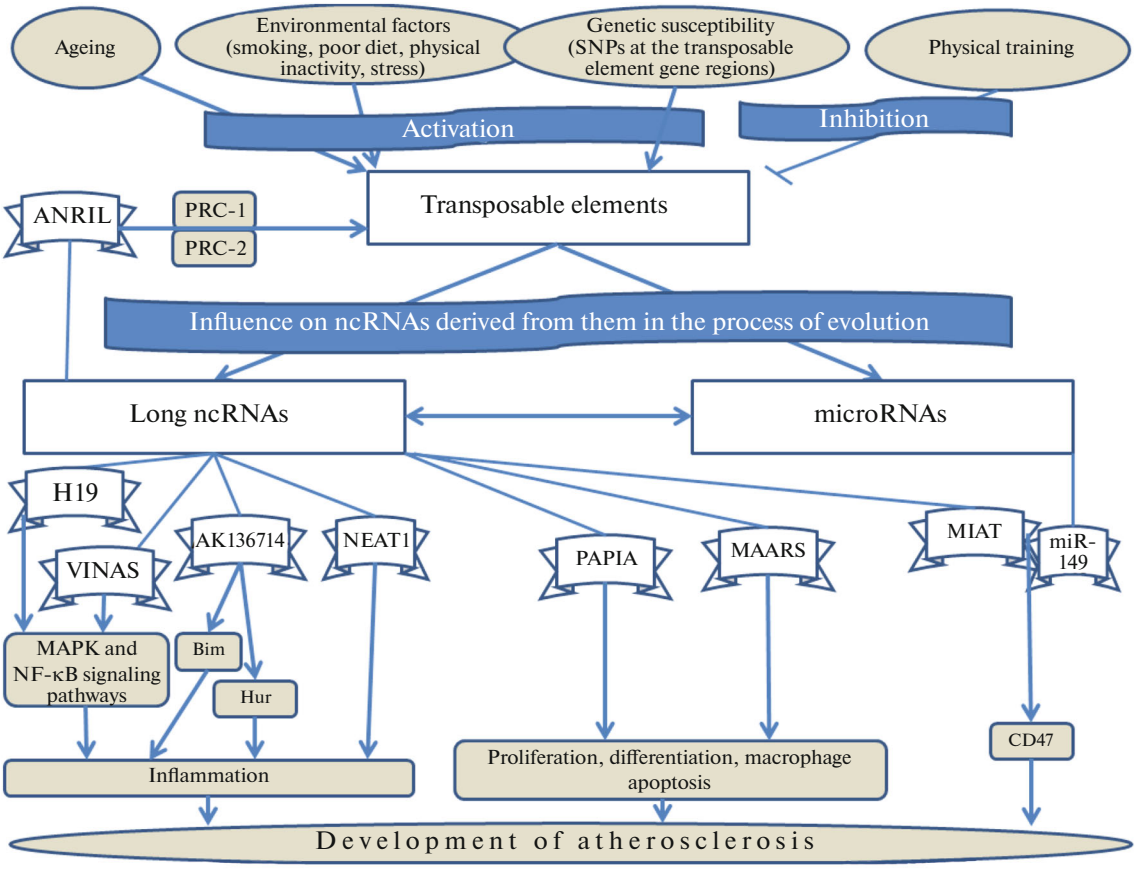

Fig. 3. Scheme of interaction of mobile genetic elements with noncoding RNAs (ncRNAs) in the pathogenesis of atherosclerosis.

level of miR-151 [85] decreases, which is reflected in the activation of inflammatory processes in both processes. The expression of miR-192 (derived from LINE2 [23]) is significantly higher in the serum of AS patients. MiR-192 promotes the proliferation and migration of VSMCs [90]. An increase in the expression of miR-192 is also observed with aging [91]. In the serum of AS patients, a significant decrease in the level of miR-211 [92], derived from LINE2, was detected [23]. Expression of miR-211 is significantly reduced in people with shorter life expectancy compared to centenarians [93]. MiR-224 evolved from the DNA transposon MER-135 [23], for which an inverse correlation with the AS of coronary arteries in humans was determined [94]. MiR-224 is associated with brain aging. Its target is the gene *CHOP*, which is involved in the regulation of mitochondrial proteins [95].

Increased expression of miR-31 (derived from LINE2 [23]) promotes AS progression by affecting NOX4 oxidase, which regulates the migration of VSMCs [96]. MiR-31 acts as a key driver of hair follicular stem cell aging by directly targeting mRNA of gene *Clock* (a core circadian clock gene whose dysregulation activates the MAPK/ERK cascade), causing HFSC depletion through transepidermal elimination. Conditional ablation of miR-31 provides effective protection against skin aging [97]. Patients with coronary artery AS have significantly increased expression of miR-320b, which regulates cholesterol efflux from macrophages. Administration of miR-320b to experimental animals increased the size of AS plaques, the content of damaged macrophages, and the levels of proinflammatory cytokines owing to increased phosphorylation of NF-κB [98]. The evolutionary source of miR-320b is LINE2 [23]. Increased levels of miR-320b are also associated with aging [99].

In the formation of oxidized foam cells in AS, the role of miR-326 (derived from the DNA transposon hAT-Tip100 [23]), involved in the network of interactions of circular RNAs with long ncRNAs, has been identified [100]. Increased expression of miR-326 is detected in skin fibroblasts during aging [101]. The concentration of SINE/MIR-derived miR-335 [23] is increased in the blood plasma of AS patients [102]. High concentrations of miR-335 promote EC senescence by inhibiting expression of gene *sKlotho* [103]. Transcription of miR-335 also increases in the hippocampus of the aging brain [104]. In macrophages, VSMCs and ECs, during atherogenesis, increased expression of miR-340, derived from the TcMar-Mariner DNA transposon, is detected [105]. Low life expectancy is associated with high levels of miR-340

[93]. In the serum of AS patients, a significant increase in the expression of miR-374 (derived from LINE2 [23]), which stimulates the proliferation and migration of VSMCs, was determined [106]. Rapid rates of aging are associated with high levels of miR-374 [93].

Reduced efflux of free cholesterol from macrophages and increased influx of oxidized low-density lipoproteins are important factors in the development of AS. The metabolic pathways regulating these processes involve miR-378 [107], derived from SINE/MIR and LINE2 [23], activated by the AP-1 complex, which is inhibited by coenzyme Q10 [108]. An increase in the expression of miR-378 was determined in elderly people during muscle regeneration. The targets of miR-378 are mRNAs of genes in the signaling pathways of insulin-like growth factor (*IGF-1*) [109]. MiR-384, derived from LINE-Dong-R4 [23], negatively regulates age-related osteogenic differentiation of bone marrow mesenchymal stem cells, indicating the role of this microRNA in aging [110]. MiR-384 accelerates the development of AS by inhibiting macrophage autophagy genes [111].

In patients with coronary artery AS, low levels of miR-421 (derived from LINE2 [23]) in serum, plaques and VSMCs are accompanied by increased expression of the chemokine CXCL2 [112]. Aging is also associated with a decrease in miR-421 transcription [113]. MiR-4487 (derived from LINE1 [23]) stimulates the migration and survival of VSMCs and inhibits their apoptosis by targeting RASA1 (a regulator of the RAS/MAPK signaling pathway) [114]. An increase in the expression of miR-4487 has been identified with skin aging [115]. In patients with AS of large vessels, a significant decrease in miR-493 expression was determined compared to controls [116]. This microRNA originated from LINE2 [23]. With aging, the expression of miR-493 in skeletal muscle decreases. The target of this microRNA is the fibrinogen beta subunit gene *FGB* [117]. In patients with AS of the coronary arteries, a decrease in the expression of miR-548 was determined in the adipose tissue around the affected vessels. Representatives of this microRNA family evolved from various REs (LINE1, LINE2, LTR-ERVL, LTR-Gypsy, LTR-ERV1, SINE/MIR) and DNA-TEs (TcMar, hAT Charlie) [23]. MiR-548 regulates expression of gene *HMGB1* (encodes a nonhistone protein that binds chromatin and is involved in the control of transcription, replication, and repair of DNA) [118]. During aging, a decrease in the level of miR-548 has also been determined [82, 83].

Increased expression of miR-552 (derived from LINE1 [23]) under the influence of PDGF-bb has been detected in VSMCs, leading to stimulation of their proliferation, invasion, and migration. The targets of miR-552 are mRNA of proto-oncogene *SKI* and transcription factor gene *ATF4* [119]. During aging in humans, an increase in miR-552 levels was determined to be 124 times greater compared to young people [120]. Circular RNA circ_0086296 induces AS through the IFIT1/STAT1 feedback loop, acting as a sponge for miR-576 (derived from LINE1 [23]), which inhibits expression of the gene of interferon-inducible tetratricopeptide repeat protein *IFIT1* and the gene of cytokine-regulated transcription factor *STAT1*, preventing the development of AS [121]. A decrease in the level of miR-576 was determined for aging of human fibroblasts [82, 83].

Derived from hAT-Blackjack DNA TE [23], miR-584 inhibits the endothelial nitric oxide synthase eNOS mRNA by binding to its 3'UTR, which is characteristic of inflammatory reactions and progression of plaque growth in AS. The eNOS protein is the main regulator of endothelial homeostasis [122]. Low levels of miR-584 are also associated with aging [82, 83]. LINE2 evolved from miR-708 [23], which is expressed at a high level in neointimal EC in damaged vessels during physiological blood flow, but is not expressed during stagnation. This microRNA has anti-inflammatory properties by suppressing the expression of IL-1 receptor-associated kinase, IL-6 receptor, conserved sprial-loop-helix ubiquitous kinase, and nuclear factor κB kinase subunit-γ inhibitor [123]. A decrease in miR-708 expression is also associated with aging [124]. Table 1 shows 25 microRNAs derived from transposons, the pattern of changes of which is identical for aging and AS. MicroRNAs miR-1248, -151, -211, -224, -421, -493, -548, -576, and -708 and their mimics can be used for pathogenetic therapy of AS and life extension. MicroRNA miR-1246, -1271, -1273, -1290, -192, -31, -320b, -326, -335, -340, -374, -378, -384, -4487, -552, and -584, for which increased expression has been determined, can serve as targets for targeted therapy of AS and for slowing down the aging process using antisense oligonucleotides [125].

A number of microRNAs are characterized by different patterns of expression during aging and AS, which indicates that in diseases the physiological course of development of the body is disrupted as a result of pathological activation of transposons, which is reflected in changes in the epigenetic regulation of tissues and organs. Therefore, such microRNAs are the most promising targets for targeted therapy of the disease. Thus, miR-1248, associated with aging (decrease in level) [85], exhibits increased expression in AS, suppressing the expression of thrombomodulin in endothelial progenitor cells, which indicates its possible participation in the pathogenesis of AS [84]. MiR-1248 evolved from SINE/Alu [23]. In patients with coronary artery AS, an increased level of miR-1257, derived from ERVL [23], which is involved in the assembly of proteins of the major histocompatibility complex MHC and regulates expression of genes *CALR*, *POMC*, *TLR4*, *IL10*, and *ATF6*, was detected [126]. During the aging of human fibroblasts, the expression of miR-1257 decreases [82]. The level of miR-1261, derived from the Tc-Mar DNA transposon

Table 1. Identical changes in the expression of transposon-derived microRNAs during atherosclerosis and aging

No.	MicroRNA	Source transposon	Changes in microRNA expression in atherosclerosis (increase ↑, decrease ↓) [author]	Changes in microRNA expression during aging (increase ↑, decrease ↓) [author]
1	miR-1246	LTR-ERVL	↑ [81]	↑ [82, 83]
2	miR-1248	SINE/Alu	↓ [84]	↓ [85]
3	miR-1271	LINE2	↑ [86]	↑ [82, 83]
4	miR-1273	LINE, SINE, ERVL	↑ [87]	↑ [82, 83]
5	miR-1290	SINE/MIR	↑ [88]	↑ [83]
6	miR-151	LINE2	↓ [89]	↓ [85]
7	miR-192	LINE2	↑ [90]	↑ [91]
8	miR-211	LINE2	↓ [92]	↓ [93]
9	miR-224	MER-135	↓ [94]	↓ [95]
10	miR-31	LINE2	↑ [96]	↑ [97]
11	miR-320b	LINE2	↑ [98]	↑ [99]
12	miR-326	hAT-Tip100	↑ [100]	↑ [101]
13	miR-335	SINE/MIR	↑ [102]	↑ [103, 104]
14	miR-340	TcMar-Mariner	↑ [105]	↑ [93]
15	miR-374	LINE2	↑ [106]	↑ [93]
16	miR-378	SINE/MIR, LINE2	↑ [107, 108]	↑ [109]
17	miR-384	LINE-Dong-R4	↑ [111]	↑ [110]
18	miR-421	LINE2	↓ [112]	↓ [113]
19	miR-4487	LINE1	↑ [114]	↑ [115]
20	miR-493	LINE2	↓ [116]	↓ [117]
21	miR-548	LINE, LTR, SINE, TcMar, hAT Charlie	↓ [118]	↓ [82, 83]
22	miR-552	LINE1	↑ [119]	↑ [120]
23	miR-576	LINE1	↓ [121]	↓ [82]
24	miR-584	hAT-Blackjack	↑ [122]	↑ [82, 83]
25	miR-708	LINE2	↓ [123]	↓ [124]

[23], is increased in complicated cerebral vascular AS [88] and decreased with aging [83].

The evolutionary source of miR-147 is LINE1 [23]. This microRNA has atherogenic properties, inducing the expression of the adhesion molecule gene *ICAM-1* [127]. However, low levels of miR-147 are associated with aging [128]. In the blood plasma of patients with unstable angina, a significant increase in the levels of miR-28 was determined, which enhances the expression of the ATP-binding transporter gene *ABCA1*, which correlates with the activation of mRNA translation of gene *LXR*α in macrophages [129]. This microRNA, derived from LINE2 [23], is considered a potential biomarker for unstable angina [129]. MiR-28 levels are significantly lower in older adults [130]. LINE2-derived miR-325 promotes AS development by suppressing histone demethylase expression of *KDM1A*, decreasing SREBF1 levels, and inhibiting the activation of the PPARγ-LXR-ABCA1 pathway [131]. At the same time, a decrease in miR-325 levels promotes chondrocyte aging through activation of the p53/p21 pathway [132]. During aging, a decrease in the expression of miR-342 (arising from SINE/tRNA-RTE [23]), targeting the mRNA of the histone deacetylase gene *SIRT6*, was determined in peripheral blood mononuclear cells [133]. High levels of miR-342 were detected in peripheral mononuclear cells, which positively correlated with serum concentrations of IL-6 and TNF-α, promoting the development of inflammation [134].

MiR-495 (source: ERVL [23]) is involved in the pathogenesis of AS by binding to the circular RNA hsa_circ_0126672 [135]. MiR-495 inhibits the formation of atherosclerotic plaques by reducing the expression of the Krüppel-like transcription factor KLF5 [136]. In experiments on human cell lines, miR-495 promoted the aging of mesenchymal stem cells by affecting mRNA of proto-oncogene *BMI1* [137].

Table 2. Multidirectional changes in the expression of transposon-derived microRNAs during atherosclerosis and aging

No.	MicroRNA	Source transposon	Changes in microRNA expression in atherosclerosis (increase ↑, decrease ↓) [author]	Changes in microRNA expression during aging (increase ↑, decrease ↓) [author]
1	miR-1248	SINE/Alu	↑ [84]	↓ [85]
2	miR-1257	ERVL	↑ [126]	↓ [82]
3	miR-1261	Tc-Mar	↑ [88]	↓ [83]
4	miR-147	LINE1	↑ [127]	↓ [128]
5	miR-28	LINE2	↑ [129]	↓ [130]
6	miR-325	LINE2	↑ [131]	↓ [132]
7	miR-342	SINE/tRNA-RTE	↑ [134]	↓ [133]
8	miR-495	ERVL	↓ [135, 136]	↑ [137]
9	miR-520d	SINE/Alu	↓ [138]	↑ [139]
10	miR-633	SINE/MIR	↓ [140]	↑ [128]
11	miR-641	SINE/MIR	↓ [141]	↑ [83]
12	miR-652	hAT-Tip100	↑ [142, 143]	↓ [124]

MiR-520d (derived from SINE/Alu [23]) inhibits the expression *PCSK9*, causing degradation of low-density lipoprotein receptors. Accordingly, miR-520d enhances the expression of these receptors and binding to atherogenic lipoproteins, suppressing the development of AS [138]. At the same time, miR-520d promotes skeletal muscle aging by influencing regulatory factors *MyoD*, *MyoG*, *Mef2c*, and *Myf5*. The long ncRNA GPRC5D-AS1, which inhibits miR-520d, has been proposed as a therapeutic target for the treatment of sarcopenia [139].

The level of miR-633 (derived from SINE/MIR [23]) is reduced in AS. This microRNA regulates CDC20B (mitotic anaphase-regulating protein) and is a target for the circular RNA hsa_circ_0008896, which affects VSMCs [140]. Increased expression of miR-633 is associated with aging [128]. The expression of miR-641 (derived from SINE/MIR [23]) is reduced in oxidized low-density lipoprotein-induced VSMCs. The long ncRNA MIAT interacts with this microRNA [141]. During the aging of human fibroblasts, the level of miR-641 decreases [83]. Aging is associated with a decrease in miR-652 expression [124]. The source of miR-652 in evolution is DNA-TE hAT-Tip100 [23]. Inhibition of this microRNA reduces AS progression and enhances endothelial repair by stimulating cyclin D2 expression [142]. In addition, inhibition of miR-652 normalizes lipid metabolism and reduces the secretion of proinflammatory cytokines by macrophages by restoring TP53 expression [143]. Table 2 shows 12 microRNAs derived from transposons, which are characterized by multidirectional changes in expression during aging and AS.

Analysis of the data obtained showed that transposon-derived microRNAs associated with aging influence the development of AS through disruption of functioning of genes in VSMCs (promoting pathological proliferation, differentiation, invasion, and apoptosis of cells) [14, 81, 84, 90, 106, 141], in endothelial cells [84, 89, 102, 115, 123], and in macrophages [98, 100, 107], as well as influencing immune processes (miR-1257 [126]; miR-28 [96]) and epigenetic factors through interaction with long ncRNAs [100, 101, 136, 141], histone modifiers [131, 133], and circular RNAs [135, 140].

CONCLUSIONS

Atherosclerosis is a multifactorial disease associated with allelic variants of many genes. According to meta-analyses, the greatest influence on the development of the disease is exerted by allelic variants of genes involved in the functioning of the immune system and polymorphisms located in intergenic and intronic regions, where MGEs and ncRNAs are located. Analysis of the scientific literature revealed the role of activated MGEs in the development of atherosclerosis, both directly through stimulation of the interferon response by transposon expression products and through interaction with noncoding RNAs that evolved from MGEs and contain complementary nucleotide sequences. In addition to genetic predisposition (substitution of nucleotides in areas where MGEs are located), transposon activation is influenced by aging (characterized by increased expression of MGEs) and environmental factors, including physical stress. This explains the effectiveness of regular training in the prevention and treatment of AS, which is reflected in changes in the expression of specific microRNAs. An analysis of the scientific literature showed identical changes in the expression of 25 trans-

poson-derived microRNAs during aging and AS, indicating that aging mechanisms caused by age-associated MGE activation underlie the disease. However, not all epigenetic mechanisms of aging are identical to the pathogenesis of AS, as evidenced by the data obtained on multidirectional changes in the expression of 12 microRNAs derived from transposons. The identified microRNAs are promising targets for the design of targeted therapy for AS.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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