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REVIEW AND THEORETICAL ARTICLES

RELATIONSHIP OF microRNAs AND TRANSPOSONS IN OSTEOARTHRITIS DEVELOPMENT

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Abstract. Conducted GWAS identified the association of osteoarthritis with more than 100 different SNPs, most of which are located in intronic and intergenic regions where genes of transposons and non-coding RNAs derived from them are located. A number of studies have also determined the activation of retroelements in joint tissues and in peripheral blood of patients with osteoarthritis. An assumption has been made that activated transposons, which cause aging and associated inflammation, influence the etiopathogenesis of osteoarthritis. To confirm this hypothesis, a search was conducted for data on changes in the expression of specific microRNAs derived from transposons during aging and osteoarthritis. As a result, 23 such microRNAs were found, the participation of which in the development of the disease is associated with an impact on genes and signaling pathways regulating cell proliferation and apoptosis, inflammatory and metabolic processes, and mechanisms of cartilage degradation. Changes in expression of these microRNAs indicate that the epigenetic mechanisms of aging are involved in osteoarthritis etiopathogenesis due to pathological activation of transposons complementary to the sequences of non-coding RNAs derived from them in evolution.

Keywords: *immune system, microRNA, mobile genetic elements, retroelements, transposons, osteoarthritis*

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INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis [1] and represents a heterogeneous multifactorial disease characterized by association with more than 100 different single nucleotide polymorphisms (SNPs), most of which are located in gene introns and intergenic regions [2, 3]. The disease is characterized by the development of inflammation in the synovial membrane of the joint with cartilage degradation [4]. In addition to genetic factors, age, female gender, family history, smoking, occupational exposure to excessive loads, and obesity influence the risk of OA [5]. The global prevalence of OA in the world, according to statistical data for 2020, is 7.6% of the total population, increasing to 14.8% for people over 30 years old. A pronounced association of OA with aging has been noted [1]. Thus, the frequency of OA in people over 50 years old is already 29.3% [6], and over 70 years old — 40% [7]. Since aging is characterized by the development of autoimmune aseptic inflammation and overproduction of interferon in response to the progressive hyperactivation of mobile genetic elements (MGEs) [8, 9], it can be assumed that these mechanisms also influence the etiopathogenesis of OA. Indeed, transcripts of endogenous retroviruses HERV-E2 and HERV-WE1 are detected in tissues of joints affected by OA [10], and a significant decrease in methylation of LINE1 retroelements (REs) compared to healthy controls has been revealed in blood leukocytes of OA patients, indicating their activation [11].

MGEs occupy at least 45% of the human genome and are genetic elements that move within the genome and are divided into REs (class I) and DNA transposons (class II). REs include elements containing long terminal repeats (LTR) and those without them (including autonomous LINE and non-autonomous SINE and SVA) [12]. The probable role of MGEs in OA development is evidenced by the location of disease-associated SNPs mainly in intronic and intergenic regions [2, 3], where most MGEs

are found, as well as microRNA genes that evolved from them [13–15]. Additionally, experiments in mice showed that during synovial inflammation in joints affected by OA, a decrease in histone deacetylase SIRT6 concentration is detected. This results in induced polarization of M1 macrophages with the release of proinflammatory cytokines [16]. SIRT6 depletion is observed during aging and is considered one of the epigenetic drivers of this process due to decreased silencing of MGEs [17], whose expression products stimulate interferon response [8]. The latter, in turn, activates M1 macrophages, causing them to produce interleukins IL-1β, IL-6, IL-12, tumor necrosis factor-α (TNF-α), reactive oxygen species, and inducible nitric oxide synthase (iNOS) [18]. In blood plasma and synovial fluid of OA patients, a significant increase in CXCL10 (C-X-C motif chemokine ligand 10) concentration – interferon gamma-induced protein 10 – (IP-10) – has also been determined compared to healthy controls [19]. These facts indicate the probable role of pathological MGE expression during aging as a driving process for OA development. Since MGEs are regulators of epigenetic factors [20], the peculiarities of their changes in OA should be considered.

The GWAS conducted in 2021 using DNA samples from 826,690 patients with various types of OA identified an independent association of 100 different SNPs [2]. GWASs of specific OA types have also identified numerous different SNPs associated with the disease. For example, according to the GWAS conducted in 2023, 42 SNPs are associated with hip OA [3]. Explaining the impact of such a number of genetic variants, even with the help of modern bioinformatic technologies, is very challenging. At the same time, the results of meta-analyses show a significant association of OA with allelic variants of only a few immune system genes: *IL17A* [21], *IL1RN* [22], *IL6* [23] and connective tissue component *COL11A1* [24]. These associations cannot explain the complex heterogeneous nature of OA. However, the location of most disease-associated SNPs in introns and non-coding parts of the genome [2, 3] supports the assumption about the role of MGEs in the etiopathogenesis of OA, since MGEs are mainly found in introns and intergenic regions [13–15]. Fig. 1 presents a diagram of probable pathways through which MGEs influence the development of age-associated OA.

The results of studying gene expression disorders in tissues of OA-affected joints are of interest, as they reflect the influence of changes in epigenetic factors. The cause of such changes may be the effects of microRNAs that regulate the expression of genes encoding factors involved in inflammation, the stimulation of which is also characteristic of aging under the influence of activated MGEs that trigger an immune response. According to several studies, in OA, under the influence of microRNAs, the expression of genes of various pro-inflammatory proteins increases (see Table 1) [25–30], the targeted inhibition of which through regulation of epigenetic factors is promising in OA treatment [31]. Furthermore, according to the results of gene expression analysis in tissues of OA-affected joints, the disease reduces the expression of genes involved in immune reactions *KLF2, KLF4* [32], *KLF9* [33], whose protein products, Kruppel-like transcription factors, inhibit inflammation, *JUN,* encoding a transcription factor that stimulates immunocyte apoptosis. OA is also characterized by low expression of MYC, which suppresses cell proliferation, stimulates their apoptosis, and inhibits IL-1β, TNF-α, IL-6, MMP-13. In patients with OA, a decrease in the expression of *NFKBIA,* an inhibitor of NFKB that prevents the formation of NFKB/REL complexes associated with inflammation [34], *TFNAIP3,* encoding the tumor necrosis factor-induced zinc finger protein that edits ubiquitin and participates in immune and inflammatory reactions [35], *MCL1,* an apoptosis regulator necessary for the survival of fibroblasts, macrophages, and lymphocytes [36], *CEACAM-1,* an immune regulator of T-lymphocytes that suppresses inflammation, *TNFRSF18,* encoding the GITRL protein, a glucocorticoid-induced TNF receptor ligand that regulates inflammation and has an anti-inflammatory effect [26]. The cause of the disruption in the expression of these genes may be epigenetic dysregulation due to the influence of microRNAs resulting from pathological activation of MGEs.

Mutural regulation of transposons and microRNAs

Pathological activation of MGEs during aging, which affects OA development, can be caused by various mechanisms of transposon impact on epigenetic regulation (see Fig. 2). These mechanisms are due to the presence of complementary sequences between MGEs and microRNAs due to the evolution of microRNAs from MGEs or direct formation of microRNAs from MGE transcripts [15]. Back in 2016, Wei et al. created a database on the origin of microRNAs from specific MGEs, called MDTE DB (miRNAs derived from transposable elements database), which included 661 human microRNAs [15]. Activated MGEs can influence microRNAs derived from them by binding to MGE transcription products that act as "sponges" for microRNAs through complementary binding with nucleotide sequences due to their evolutionary relationship. This blocks the effect of RNA interference on mRNA of target genes of these microRNAs [37].

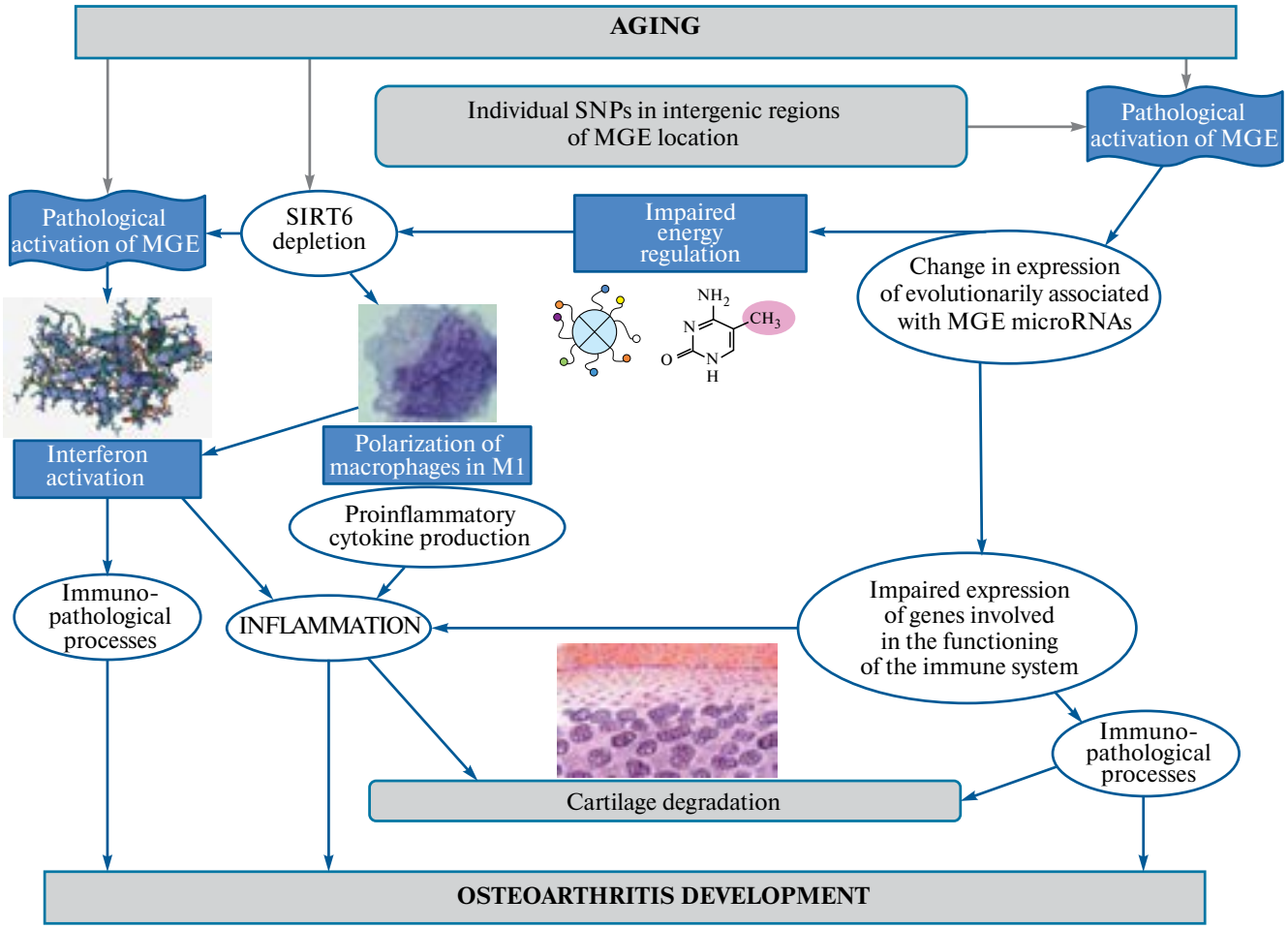

Fig. 1. Diagram of probable pathways of influence of mobile genetic elements (MGEs) activated during aging on epigenetic mechanisms of osteoarthritis development

This principle of regulation has been identified not only in animals but also in plants. For example, the transcript of the LTR-containing retroelement *MIKKI* (translated from Korean as "bait"), expressed in rice roots, is an imitator for miR-171, which destabilizes mRNA of root transcription factors similar to SCARECROW. Processed transcripts of *MIKKI* act as traps for miR-171, triggering their degradation and ensuring the accumulation of root-specific mRNA transcription factors [38]. Transcripts of LTR-containing REs [39] and LINE1 function as long non-coding RNA molecules, interacting with specific chromatin regions and regulating gene expression (including those controlled by microRNAs) [40].

Some microRNAs are formed directly from MGE genes, which serve as the basis for hairpin structures of pre-microRNAs. This results in various microRNAs that form a regulatory network controlling gene expression, which changes during ontogenesis in human tissues and organs. To analyze such processes, the web application Brain miRTExplorer was created [41]. Therefore, pathological activation of MGEs leads to the formation of various microRNAs from their transcripts, affecting the regulatory networks of other microRNAs in the body. MGEs exert regulatory effects on microRNAs through the formation of small interfering RNAs (siRNAs) from MGE transcripts. These siRNAs are competitive molecules for binding to mRNA targets for microRNAs, neutralizing their impact on gene expression. This effect is associated with the defense systems of host cells against activated MGEs in their genomes, triggering the degradation of MGE transcripts by ribonucleases into siRNAs. The latter cause post-transcriptional inhibition of mRNAs of genes that do not contain MGE fragments in their composition due to partial complementarity of nucleotide sequences [42].

One of the ways microRNAs interact with MGEs in regulating gene activity is also by suppressing their expression when microRNAs bind to specific

Table 1. Increased expression of genes involved in immune responses in osteoarthritis

Gene name	Name of protein – gene expression product	Protein function [author]
C5AR1	anaphylatoxin C5a receptor, expressed by immune cells	chemical attractant and inflammatory mediator [25]
CTLA4	cellular immunoglobulin receptor	stimulates immune response [26]
EDNRB	endothelin type B receptor, G-protein coupled	activates phosphatidylinositol-calcium system [27]
FSH	follicle-stimulating hormone	stimulates inflammation in the joint [26]
HLA-DMB	major histocompatibility complex class II proteins, DM beta	participate in immune reactions [28]
IL1B	interleukin-1-beta	pro-inflammatory cytokine produced by immune cells [25]
IL1R1	interleukin 1 receptor	transmission of pro-inflammatory signals [27]
IL4R	Interleukin 4 receptor	transmission of immune signals [29]
IL6R	Interleukin 6 receptor	transmission of anti-inflammatory signals [29]
IL10	interleukin 10	anti-inflammatory cytokine produced by immune cells [25]
IRAK3	interleukin-1 receptor-associated kinase	promotes transmission of pro-inflammatory signals [30]
RHOB	small vesicular GTPase RhoB	activates pro-inflammatory IL-1β, LPS, TNFα [30]
SOX13	transcription factor SRY-related HMG-box	autoimmune antigen that modulates inflammatory response [30]
TNFSF11	tumor necrosis factor family member	stimulates activation of B and T lymphocytes and their infiltration into joint tissues [27]

DNA structures formed due to MGEs integrated into these regions. In the human genome, Z-form DNA is formed by endogenous retroviruses, which provide functional genes with alternative promoters [43]. For instance, the Z-form DNA located in the promoter region of the prostaglandin reductase gene (*PTGR1*) is formed by the MER4 retroelement. The miR-6867-5p (containing complementary repeats 5'-GUGUGUG-3') binds to the 5'-CACACACA-3' sequences in this region, suppressing the expression of the *PTGR1* gene by inhibiting the formation of Z-form (which is assumed to activate expression) [12]. Additionally, humans exhibit the phenomenon of RNA-directed DNA methylation (RdDM), through which microRNAs [41] and miRNAs [42] formed from MGE transcripts can affect the expression of microRNAs that evolved from them due to the presence of complementary sequences in the genome structure [44]. At the same time, MGEs themselves are targets for epigenetic regulation both by microRNAs that evolved from them [15] and those without evolutionary relationship due to partial sequence complementarity. For example, the microRNA let-7 inhibits the expression of various LINE1 elements by binding to the ORF2p transcription product of their genes, suppressing translation on ribosomes [45].

Influence of transposon-derived microRNAs associated with aging mechanisms on the development of osteoarthritis

The above-described mechanisms of activated MGEs impact on the regulatory effects of microRNAs

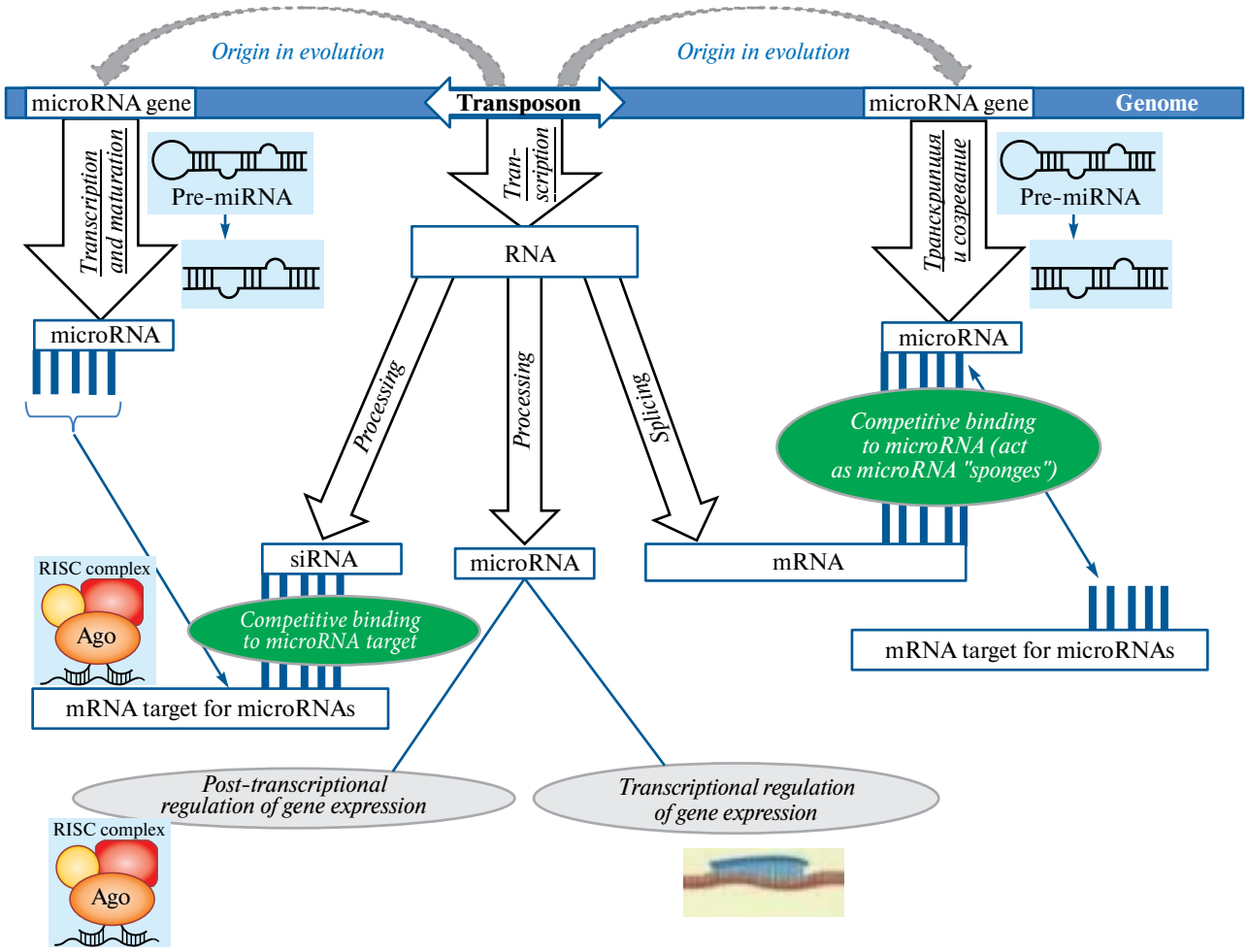

Fig. 2. Mechanisms of transposon influence on epigenetic regulation of microRNAs involving small interfering RNAs (siRNAs)

derived from them suggest that MGE dysregulation during aging affects such microRNAs involved in OA pathogenesis. According to scientific literature data, 23 MGE-derived microRNAs from the MDTE DB database [15] are involved in aging mechanisms and OA (see Table 2). Indeed, patients with OA have increased expression of miR-1246, derived from LTR-ERVL [15], in synovial fluid macrophages of affected joints. This microRNA suppresses the expression of genes *GSK3β*, glycogen synthase kinase-3 beta and *Axin2,* Axis inhibition protein 2, in humans, promoting activation of Wnt/β-catenin pathways and the resulting inflammation [46]. Increased levels of miR-1246 have also been detected during aging of human fibroblasts [47]. In OA joints, increased expression of miR-1271 [48], derived from LINE2 [15], causes chondrocyte apoptosis by inhibiting mitogen-activated protein kinase (MAPK) [49]. In exosomes of OA patients, increased expression of miR-1290 [50] has been identified, which inhibits the *CCNG2* gene encoding cyclin that regulates the cell cycle [51]. High levels of miR-1271 and miR-1290 have also been determined during aging of human fibroblasts [47].

A comprehensive analysis of the regulatory network of OA development conducted in 2021 showed a decrease in miR-151a expression [5], which originated from LINE2 [15]. The level of this microRNA in blood serum is significantly higher in elderly people compared to young people [52]. The direct target of miR-151a is the mRNA of the *AGMAT* gene, which encodes agmatinase – a key enzyme in the metabolism of agmatine, which acts as a neurotransmitter. Accordingly, suppression of agmatinase expression under the influence of miR-151a can cause innervation disorders of tissues and organs during aging, including joints in OA [53]. The level of miR-192, which originated from LINE2 [15], increases in OA and has a damaging effect on chondrocytes by inhibiting the expression of the *GDF11* gene, which

Table 2. Expression characteristics of microRNAs derived from transposons during aging and OA

microRNA (transposon-source)	Mechanism of microRNA action in osteoarthritis	Expression change during aging (increase — ↑; decrease — ↓) [author]	Expression change in osteoarthritis (increase — ↑; decrease — ↓) [author]
miR-1246 (LTR-ERVL)	suppresses GSK3β and Axin2 expression, promoting Wnt/β-catenin pathway activation and inflammation [46]	↑ [47]	↑ [46]
miR-1271 (LINE2)	inhibits MAPK [49]	↑ [47]	↑ [48, 49]
miR-1290 (SINE/MIR)	suppresses CCNG2 [51]	↑ [47]	↑ [50]
miR-151a (LINE2)	inhibits agmatinase expression, disrupting polyamine metabolism [49]	↓ [52]	↓ [5]
miR-192 (LINE2)	damages chondrocytes in response to lipopolysaccharides, causing inflammation [54]	↑ [55]	↑ [54]
miR-211 (LINE2)	suppresses expression of Fibulin-4 and pro-inflammatory cytokines [57].	↓ [56]	↓ [57]
miR-224 (MER-135)	inhibits the expression of pro-inflammatory chemokine CCL1 [58]	↓ [60]	↓ [58]
miR-28 (LINE2)	inhibits the expression of IL-34 [63].	↓ [62]	↓ [61]
miR-31 (LINE2)	suppresses mRNA of *PAPOLG, SP1, SRC, ZC3H12C* genes [64]	↑ [65]	↑ [64]
miR-320b (LINE2)	participates in gene networks regulating apoptosis with the involvement of *YWHAZ, YWHAQ, YWHAH, YWAHE, YWHAB, YWHAG, SFN* [66]	↑ [67]	↑ [66]
miR-326 (hAT-Tip100)	inhibits SIRT1 with activation of inflammation and angiogenesis [68]	↑ [70]	↑ [68]
miR-335 (SINE/MIR)	inhibits the expression of MMP13, VCAM1 genes [71], suppresses enchondral ossification of cartilage [72]	↑ [73]	↑ [71, 72]
miR-340 (DNA-TE/TcMar)	affects mRNA of *YTHDF3, IGF2BP3* genes, inhibits ERK signaling by suppressing *FMOD* [74]	↓ [75]	↓ [74]
miR-374 (LINE2)	prevents lipopolysaccharide-induced cartilage destruction by inhibiting Wnt5b [77]	↓ [76]	↓ [77]

Ending

microRNA (transposon-source)	Mechanism of microRNA action in osteoarthritis	Expression change during aging (increase — ↑; decrease — ↓) [author]	Expression change in osteoarthritis (increase — ↑; decrease — ↓) [author]
miR-378a (SINE/MIR)	inhibits mRNA of *Sox6* and *Atg2a* genes [78]	↑ [79]	↑ [78]
miR-384 (LINE-Dong-R4)	suppresses S_{OX9} expression and NF-kB signaling, preventing cartilage cell proliferation [80]	↑ [81]	↑ [80]
miR-421 (LINE2)	prevents IL-1β-induced apoptosis and inflammation [82]	↓ [83]	↓ [82]
miR-450b (LINE1)	regulates the expression of the *SKAP2* gene in macrophages [84]	↓ [85]	↓ [84]
miR-487b (SINE/MIR)	targeted inhibition of the Wnt5a pathway [92].	↑ [92]	↓ [93, 94]
miR-495 (ERV-L/MaLR)	inhibits mRNA of the gene *AKT1*, with suppression of p-S6, p-mTOR and chondrocyte proliferation [86].	↑ [87]	↑ [86]
miR-576 (LINE1)	targeted inhibition of Wnt5a pathway [97]	↑ [96]	↓ [95]
miR-708 (LINE2)	binds to mRNA of the *SATB2* gene, inhibiting cartilage regeneration [88]	↑ [89]	↑ [88]
miR-885 (SINE/MIR)	suppresses the expression of *IGF1R*, *CTNNB1, OXR1* genes [90]	↑ [91]	↑ [90]

encodes a secreted ligand of the transforming growth factor-beta superfamily, recruiting SMAD transcription factors necessary for cell growth and reproduction [54]. During aging, the level of miR-192 also increases in kidney tissues [55]. Low expression of miR-211, which originated from LINE2 [15], is associated with a short lifespan, indicating its protective effect against aging [56]. In OA, the level of miR-211 is also reduced. MiR-211 promotes chondrocyte differentiation by suppressing the expression of the *EFEMP2* gene, EGF containing fibulin extracellular matrix protein 2, which encodes fibulin-4, preventing the production of pro-inflammatory cytokines and cartilage-destroying proteinases [57].

MiR-224, which originated from the DNA transposon MER-135 [15], inhibits the expression of the pro-inflammatory chemokine CCL1, also preventing cartilage degradation [58]. Nanoparticles with miR-224 have been developed as a promising method for treating OA [59]. MiR-224 is associated with brain aging. Its target is the *CHOP* gene, C/EBP homologous protein, which is involved in the regulation of mitochondrial proteins [60]. A reduced level of miR-28 has been determined in the blood serum of OA patients [61]. During physiological aging, miR-28 expression is also decreased [62]. The target of miR-28 is the mRNA of the *IL-34* gene, interleukin-34. Accordingly, a low level of miR-28 during aging and OA promotes inflammation due to increased production of IL-34 [63].

In severe OA, increased expression of miR-31 was determined, which targets mRNAs of genes *PAPOLG*, encoding poly(A) polymerase; *SP1* (specificity protein 1), encoding a zinc finger transcription factor; *SRC*, encoding a non-receptor tyrosine kinase proto-oncogene; *ZC3H12C*, encoding an endoribonuclease. The product of the *SP1*

gene is a transcription factor that plays an important role in bone and chondrocyte differentiation and cell growth regulation [64]. Elevated levels of miR-31 have been identified in aging human endothelial cells [65]. Derived from LINE2, miR-320b [15] is associated with rapid progression of OA and has been proposed as a prognostic biomarker of the disease [66]. This microRNA is involved in gene networks with genes that regulate apoptosis. These include genes of signal transduction pathways *YWHAZ*, 14-3-3 protein zeta/delta; *YWHAQ*, 14-3-3 protein theta; *YWHAH*, 14-3-3 protein eta; *YWAHE*, 14-3-3 protein epsilon; *YWHAB*, 14-3-3 protein beta/alpha; *YWHAG*, 14-3-3 protein gamma and *SFN*, tumor suppressor stratifin [66]. Increased expression of miR-320b is associated with aging of human fibroblasts [67]. Originating from the DNA transposon hAT-Tip100, miR-326 [15] promotes OA development by inhibiting the expression of the *SIRT1*, sirtuin-1, NAD-dependent deacetylase gene and stimulating *VEGF*, vascular endothelial growth factor with activation of inflammation and angiogenesis [68]. The level of miR-326 is significantly elevated in patients with rheumatoid arthritis with positive rheumatoid factor [69]. Expression of miR-326 is increased in skin fibroblasts during aging [70].

In OA, an elevated level of miR-335 [71] has been identified, which suppresses endochondral ossification of articular cartilage [72] by inhibiting genes *MMP13*, matrix metallopeptidase 13, encoding matrix metallopeptidase involved in cartilage degradation; *VCAM1,* vascular cell adhesion molecule 1, encoding a protein of the immunoglobulin superfamily that participates in the regulation of leukocyte adhesion [71]. High levels of miR-335 have been determined in aging in general, as well as in aging human astrocyte cultures and mouse brain hippocampus compared to young cells and hippocampus of young mice, and leads to impaired memory consolidation in the brain hippocampus by inhibiting the mRNA of the *PSD95* gene, which encodes the postsynaptic density protein [73]. In OA, decreased expression of the TcMar DNA transposon-derived miR-340 [15] activates genes *YTHDF3* (encodes an RNA-binding protein), *IGF2BP3* (insulin-like growth factor mRNA-binding protein gene), *FMOD* (fibromodulin interstitial proteoglycan gene) and ERK signaling, extracellular signal-regulated kinase, which promotes cell proliferation, motility, and survival [74]. During aging, the level of miR-340 in blood serum decreases [75].

The level of miR-374, derived from LINE2 [15], is reduced during aging [76], as well as in the cartilage tissue of affected joints in OA [77]. MiR-374 prevents lipopolysaccharide-induced cartilage destruction by inhibiting *Wnt5b*. The gene name is derived from the words Wingless and Int-1. The gene *Wnt5b* encodes proteins of the WNT signaling protein family, which transmit signals into the cell through cell surface receptors, stimulating cell proliferation and differentiation, including physiological regeneration of chondrocytes. Consequently, inhibition of *Wnt5b* leads to cartilage degradation [77]. In patients with OA, miR-378 is expressed at high levels in the synovial membrane of affected joints, especially at late stages of the disease. The targets of miR-378 are mRNAs of the *Sox6* genes, sex determining region Y-box 6, which encodes a regulator of chondrogenesis, and *Atg2a,* autophagy related 2A, which encodes an autophagy-related protein [78]. In mouse models, intra-articular injections of anti-miR-378 lentivirus slowed the progression of OA, promoting regeneration and suppressing pathological hypertrophy [78]. An increase in miR-378 levels has also been detected during thymus aging [79]. MiR-384, which evolved from LINE-DONG-R4 [15], suppresses the expression of S_{OX9} (SRY-box transcription factor 9) genes and NF-kB signaling (nuclear factor kappa B), inhibiting the proliferation of cartilage cells. The S_{OX9} protein regulates the transcription of the anti-Müllerian hormone gene during chondrocyte differentiation. NF-kB is a transcription regulator that stimulates the expression of genes involved in immune responses, including inflammation regulation [80]. MiR-384 negatively regulates age-related osteogenic differentiation of bone marrow mesenchymal stem cells, contributing to aging [81].

Expression of LINE2-derived miR-421 [15] is decreased in chondrocytes of OA-affected joints. This microRNA inhibits IL-1β-induced apoptosis and inflammation [82]. Aging is also associated with decreased levels of miR-421 [83]. In fibroblast-like cells in OA, the expression of miR-450b is reduced, which targets the mRNA of the *SKAP2* gene, which encodes Src kinase-associated phosphoprotein 2 that plays a role in kinase signaling pathways in macrophages [84]. Since macrophage activation in OA [16] contributes to disease progression through production of interleukins IL-1β, IL-6, IL-12, TNF-α, reactive oxygen species, and iNOS [18], disruption of kinase signaling pathways in these cells is important in OA pathogenesis [84]. In experiments, decreased miR-450b was detected during aging of mouse fibroblasts. Fibroblasts are essential cellular components of joints, so their aging contributes to degenerative processes and OA progression [85]. In OA patients, elevated levels of miR-495 have been detected in the cartilage tissue of affected joints [86].

MiR-495 inhibits the mRNA of the *AKT1* gene, RAC-Alpha Serine/Threonine-Protein Kinase, which encodes a protein kinase regulating cell growth and proliferation with mediated suppression of *p-S6*, ribosomal protein S6, p-mTOR (phosphorylated mammalian target of rapamycin), and cell proliferation [86]. This microRNA is derived from ERV-L/MaLR [15]. MiR-495 blocks the cell cycle in S phase and promotes cell apoptosis, inducing aging of human mesenchymal stem cells [87].

In osteoarthritis, elevated levels of miR-708 cause inhibition of the *SATB2* (Special AT-Rich Sequence-Binding Protein 2) gene, whose protein product promotes cartilage regeneration in OA. Therefore, decreased expression of SATB2 under the influence of miR-708 causes impaired regeneration and, as a result, cartilage degradation [88]. Enhanced expression of miR-708 is also associated with aging [89]. The evolutionary source of the miR-708 gene is LINE2 [15]. Increased expression of miR-885, which originated from SINE/MIR [15], is associated with OA [90] and aging. The target of miR-885 is the mRNA of the *IGF1R (*Insulin-like growth factor 1 receptor), involved in cellular internalization of IGF-1 and activation of the PI3K/Akt/GSK-3β signaling cascades, Phosphoinositide 3-kinases/ AKT Serine/ Threonine Kinase/ Glycogen synthase kinase-3 beta. MiR-885 also targets the mRNAs of *CTNNB1* (Catenin beta-1) genes, a regulator of canonical Wnt signaling; *MAN1C1* (mannosidase alpha class 1C member 1), whose protein product participates in N-glycosylation of proteins; *OXR1* (oxidation resistance 1), which encodes a protein that regulates sensitivity to oxidative stress [91].

For some microRNAs derived from MGEs, opposite changes in the expression of identical microRNAs have been identified during aging and OA, indicating that not all aging mechanisms overlap with OA etiopathogenesis, but changes in MGEs affect the dysregulation of microRNAs containing identical sequences. For example, SINE/MIR-derived miR-487b [15], which is a direct target of the long ncRNA MAR1 (muscle anabolic regulator 1), exerts targeted inhibition of the *Wnt5a* gene mRNA, leading to suppression of myogenesis regulatory pathways, contributing to skeletal muscle aging [92]. Activation of Wnt5a pathways in OA contributes to disease progression due to low expression of miR-487b [93], which promotes chondrogenic differentiation of mesenchymal stem cells [94]. Similar changes were identified regarding the expression of LINE1-derived [15] miR-576, the level of which is decreased in chondrocytes in OA compared to normal [95]. In elderly people, an association of increased miR-576 expression with the geriatric frailty syndrome (progressive deterioration of physical health) has been determined [96]. The target of miR-576 is also Wnt5a [97]. Thus, analysis of scientific literature revealed 23 microRNAs derived from MGEs and involved in the pathogenesis of OA (Table 2).

CONCLUSION

A hypothesis is proposed according to which pathological activation of MGEs during aging contributes to the development of OA in the presence of individual SNP characteristics in intergenic and intronic regions where MGE genes are located. This can explain the significant prevalence of OA that increases with age, as well as the influence of environmental factors on disease development, since MGEs are highly sensitive genome sensors to stress impacts. During aging, inflammatory-degenerative processes occur in the body due to activation of the interferon response to MGE expression products – similar mechanisms are described in the pathogenesis of OA. In addition, microRNAs derived from MGEs, characterized by mutual regulation with their evolutionary sources due to complementarity of nucleotide sequences, have been found to be involved in the development of OA. Twenty-three such microRNAs were identified, whose participation in OA pathogenesis is due to inhibition of gene expression involved in immune, inflammatory, and degenerative processes. In the future, such microRNAs may be used for targeted OA therapy.

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STATEMENT OF COMPLIANCE WITH ETHICS REQUIREMENTS

This article does not contain any studies using animals and humans as objects.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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