ISSN 1022-7954, Russian Journal of Genetics, 2025, Vol. 61, No. 1, pp. 19–30. © Pleiades Publishing, Inc., 2025.

REVIEW
AND THEORETICAL ARTICLES

Relationship of MicroRNAs to Transposons in Osteoarthritis Development

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*

Received May 12, 2024; revised June 14, 2024; accepted June 18, 2024

Abstract—The 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 encoding transposable elements and noncoding 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 owing to pathological activation of transposable elements complementary to the sequences of noncoding RNAs derived from them in evolution.

Keywords: immune system, microRNA, transposable elements, retroelements, osteoarthritis

DOI: 10.1134/S1022795424701357

INTRODUCTION

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

TEs make up at least 45% of the human genome and are genetic elements that move within the genome and are divided into RE (class I) and DNA transposons (class II). REs include elements containing long terminal repeats (LTRs) and elements that do not contain them (including autonomous LINEs and nonautonomous SINEs and SVAs) [12]. The probable role of TEs in the development of OA is evidenced by the location of disease-associated SNPs mainly in intronic and intergenic regions [2, 3], where the majority of TEs are located, as well as the microRNA genes that evolved from them [13–15]. In addition, experiments on mice have shown that synovial inflammation in joints affected by OA is accompanied by a decrease in the concentration of histone deacetylase SIRT6. As a result, polarization of M1 macrophages is induced with the release of proinflammatory cytokines [16]. Depletion of SIRT6 is observed during aging and is considered one of the epigenetic drivers of this process in connection with a decrease in TE

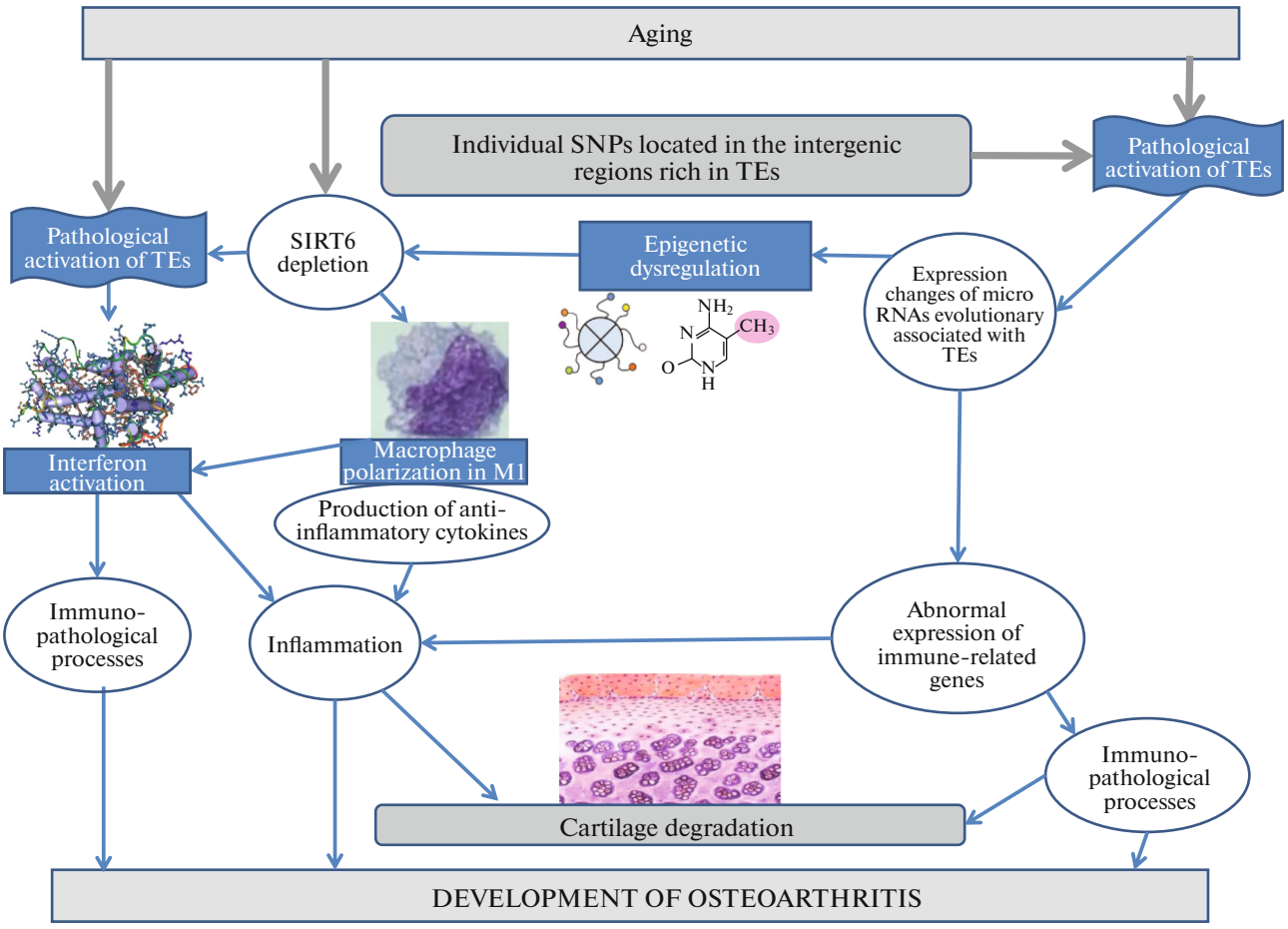

Fig. 1. Schematic diagram of possible pathways by which transposable elements (TEs) activated during aging influence epigenetic mechanisms in development of osteoarthritis.

silencing [17], the expression products of which stimulate the interferon response [8]. The latter, in turn, activates M1 macrophages, causing them to produce interleukins IL-1β, IL-6, and IL-12, tumor necrosis factor-α (TNF-α), reactive oxygen species, and inducible nitric oxide synthetase (iNOS) [18]. In the blood plasma and synovial fluid of OA patients, a significant increase in the concentration of CXCL10 (C-X-C motif chemokine ligand 10)—an interferon gamma-induced protein 10 (IP-10)—was also determined compared to healthy controls [19]. The listed facts indicate the probable role of pathological expression of TEs during aging as a driver process for the development of OA. Since TEs are regulators of epigenetic factors [20], the features of their changes in OA should be considered.

A GWAS conducted in 2021 using DNA samples from 826690 patients with various types of OA made it possible to determine an independent association of 100 different SNPs [2]. GWAS of individual OA types have also identified many different SNPs associated with the disease. For example, 42 SNPs were associated with hip OA according to a GWAS conducted in 2023 [3]. It is very difficult to explain the influence of such a number of genetic variants even with the help of modern bioinformatic technologies. At the same time, the results of meta-analyses show a reliable association of OA with allelic variants of only a few genes of the immune system: *IL17A* [21], *IL1RN* [22], *IL6* [23], and a component of connective tissue *COL11A1* [24]. These associations cannot explain the complex heterogeneous nature of OA. However, the location of most disease-associated SNPs in introns and noncoding regions of the genome [2, 3] supports the hypothesis of a role for TEs in the etiopathogenesis of OA, since TEs are located mainly in introns and intergenic regions [13–15]. Figure 1 presents a schematic of the likely pathways by which TEs influence the development of aging-associated OA.

The results of the study of disturbances of gene expression in the tissues of OA-affected joints are of interest, since this reflects 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

Table 1. Genes up-regulated in immune responses in osteoarthritis

Gene name	Name of the protein—product of gene expression	Protein function [author]
C5AR1	Anaphylotoxin receptor C5a expressed by immune cells	Chemical attractant and inflammatory mediator [25]
CTLA4	Immunoglobulin receptor cell	Stimulates the immune response [26]
EDNRB	Endothelin receptor type B, G-protein-coupled	Activates the 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 responses [28]
IL1B	Interleukin-1-beta	Proinflammatory cytokine produced by immune cells [25]
IL1R1	Interleukin 1 receptor	Transmission of proinflammatory signals [27]
IL4R	Interleukin 4 receptor	Immune signaling [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 pro-inflammatory signaling [30]
RHOB	Small vesicular GTPase RhoB	Activates proinflammatory IL-1β, LPS, TNFα [30]
SOX13	SRY-related HMG-box transcription factor	Autoimmune antigen modulating the inflammatory response [30]
TNFSF11	Member of the tumor necrosis factor family	Stimulates activation of B and T lymphocytes and their infiltration of joint tissues [27]

under the influence of activated TEs that cause an immune response. According to the results of a number of studies, in OA, under the influence of microRNA, the expression of genes of various proinflammatory proteins increases (Table 1) [25–30], targeted inhibition of which through regulation of epigenetic factors is promising in the treatment of OA [31]. In addition, according to the results of analysis of gene expression in tissues of joints affected by OA, the expression of genes *KLF2*, *KLF4* [32], and *KLF9* [33] involved in immune responses decreases during the disease, whose protein products, Kruppel-like transcription factors, inhibit inflammation, *JUN*, encoding a transcription factor that stimulates apoptosis of immune cells. In OA, low expression of MYC, which suppresses proliferation of cells, stimulates their apoptosis, and inhibits IL-1β, TNF-α, IL-6, and MMP-13, was also determined. In patients with OA, a decrease in expression of the following genes was found in joint tissues: *NFKBIA*, NFKB inhibitor that prevents the formation of NFKB/REL complexes associated with inflammation [34]; *TFNAIP3*, encoding the tumor necrosis factor-induced zinc finger protein, which edits ubiquitin and is involved in immune and inflammatory responses [35]; *MCL1*, a regulator of apoptosis necessary for the survival of fibroblasts, macrophages, and lymphocytes [36]; *CEACAM-1*, an immune regulator of T lymphocytes that suppresses inflammation; *TNFRSF18*, encoding protein GITRL, glucocorticoid-induced TNF receptor ligand, which regulates inflammation and has an anti-inflammatory effect [26]. The cause of the disruption of the expression of these genes may be epigenetic dysregulation caused by the influence of microRNAs owing to pathological activation of TE.

MUTUAL REGULATION OF TRANSPOSONS AND microRNAs

Pathological activation of TEs during aging, which is reflected in the development of OA, may be due to various mechanisms of TEs action on epigenetic regulation (Fig. 2). These mechanisms are due to the presence of complementary sequences between TEs and microRNAs owing to the emergence of microRNAs from TEs in evolution or the direct formation of microRNAs from TE transcripts [15]. Back in 2016, G. Wei et al. created a database on the origin of microRNAs from specific TEs, called MDTE DB (miRNAs derived from transposable elements database), which included 661 human microRNAs [15]. Activated TEs can influence their derived miRNAs by binding to TE transcription products, which act as "sponges" for miRNAs by complementary binding to nucleotide sequences owing to their evolutionary relationship. This blocks the effect of RNA interference on the mRNA of the target genes of these microRNAs [37]. This principle of regulation is determined not

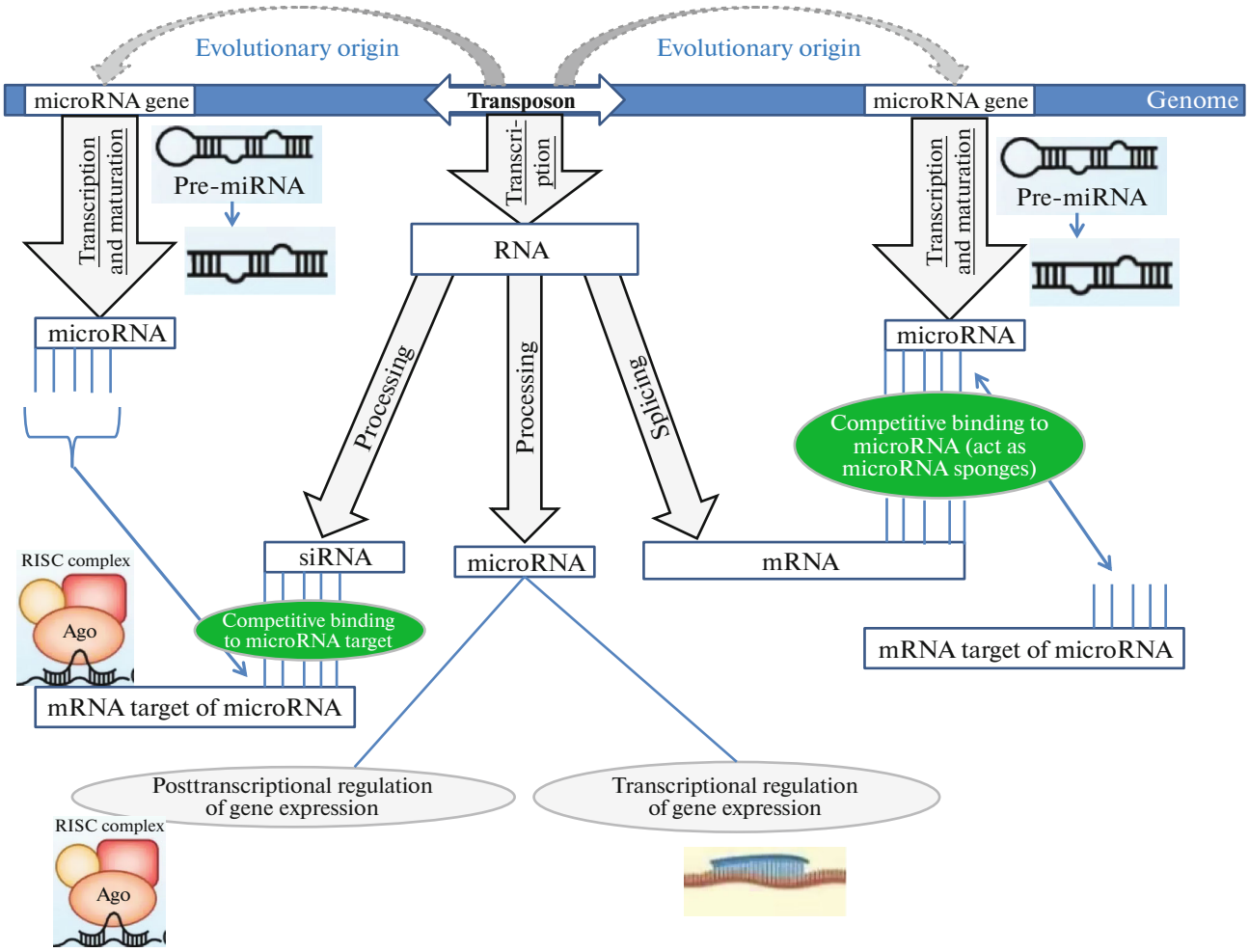

Fig. 2. Mechanisms of influence of transposons on epigenetic regulation of microRNAs with the participation of small interfering RNAs (siRNAs).

only in animals but also in plants. For example, a transcript of an LTR-containing retroelement *MIKKI* (translated from Korean as "bait"), expressed in rice roots, is a mimic for miR-171, which destabilizes the mRNA of root transcription factors like SCARECROW. Processed transcripts *MIKKI* act as traps for miR-171, triggering their degradation and ensuring the accumulation of root-specific mRNA transcription factors [38]. LTR-containing RE [39] and LINE1 transcripts function as long noncoding RNA molecules, interacting with specific chromatin regions and regulating gene expression (including those controlled by microRNAs) [40].

Some miRNAs are formed directly from TE genes, which are the basis for pre-miRNA hairpin structures. As a result, various microRNAs are formed, forming a regulatory network for controlling gene expression, which changes during ontogenesis in human tissues and organs. To analyze such processes, a web application Brain miRTExplorer was created [41]. Therefore, pathological activation of TEs leads to the formation of various microRNAs from their transcripts, which affect the regulatory networks of other microRNAs in the body. TEs exert a regulatory effect on microRNAs through the formation of small interfering RNAs (siRNA) from TE transcripts. In this case, siRNAs are competitive molecules for binding to mRNA targets for microRNAs, leveling their impact on gene expression. This effect is associated with host cell defense systems against activated TEs in their genomes, triggering the degradation of TE transcripts by ribonucleases to miRNAs. The latter exert post-transcriptional inhibition of mRNA of genes that do not contain TE fragments in their composition owing to partial complementarity of nucleotide sequences [42].

One of the ways in which microRNAs interact with TEs in regulating gene activity is also the suppression of their expression when microRNAs bind to specific DNA structures formed owing to TEs embedded in these regions. In the human genome, the Z-form of DNA is produced by endogenous retroviruses, which provide functional genes with alternative promoters

[43]. Thus, the Z-form of DNA located in the promoter region of the prostaglandin reductase gene (*PTGR1*) is formed by the MER4 retroelement. miR-6867-5p (containing complementary 5'-GUGUGUG-3' repeats) binds to the 5'-CACACACA-3' sequences of this region, suppressing expression of gene *PTGR1* by inhibiting the formation of the Z-form (which involves activation of expression) [12]. In addition, the phenomenon of RNA-directed DNA methylation (RdDM) has been described in humans, by which microRNAs [41] and siRNAs [42] formed from TE transcripts can influence the expression of microRNAs that evolved from them owing to the presence of complementary sequences in the genome structure [44]. At the same time, TEs themselves are targets for epigenetic regulation by both microRNAs derived from them [15] and those that have no evolutionary relationship with them owing to partial complementarity of sequences. For example, microRNA let-7 inhibits the expression of various LINE1s by binding to the transcription product ORF2p of their genes, suppressing translation on ribosomes [45].

EFFECT OF TRANSPOSON-DERIVED microRNAs ASSOCIATED WITH AGING ON THE DEVELOPMENT OF OSTEOARTHRITIS

The above-described mechanisms of action of activated TEs on the regulatory effects of their derived miRNAs suggest that TEs dysregulation during aging affects such miRNAs involved in OA pathogenesis. According to the scientific literature, 23 TE-derived miRNAs from the MDTE DB [15] are involved in the mechanisms of aging and OA (Table 2). Indeed, in patients with OA, increased expression of miR-1246, derived from LTR-ERVL, was detected in macrophages of synovial fluid of affected joints [15]. This microRNA inhibits expression of *GSK3*β (glycogen synthase kinase-3 beta), and *Axin2* (Axis inhibition protein 2, a protein that inhibits axis 2 in humans and promotes activation of Wnt/β-catenin pathways and resulting inflammation) genes [46]. Increased miR-1246 levels have also been found in aging human fibroblasts [47]. In OA joints, increased expression of miR-1271 [48], derived from LINE2 [15], induces chondrocyte apoptosis via inhibition of mitogen-activated protein kinase MAPK [49]. Increased expression of miR-1290 [50], which inhibits the gene *CCNG2*, encoding cyclin, which regulates the cell cycle [51], has been identified in exosomes from patients with OA. High levels of miR-1271 and miR-1290 have also been detected in aging human fibroblasts [47].

A comprehensive analysis of the regulatory network of OA development conducted in 2021 showed a decrease in the expression of miR-151a [5], which is derived from LINE2 [15]. The level of this microRNA in the blood serum is significantly higher in elderly people compared to young people [52]. The direct target of miR-151a is the mRNA of the gene *AGMAT*, encoding agmatinase, a key enzyme in the metabolism of agmantine, which acts as a neurotransmitter. Accordingly, suppression of agmatinase expression under the influence of miR-151a may cause disturbances in the innervation of tissues and organs during aging, including joints in OA [53]. miR-192, derived from LINE2 [15], is upregulated in OA and has a damaging effect on chondrocytes by inhibiting expression of gene *GDF11*, encoding a secreted ligand of the superfamily of transforming growth factors beta, which recruits SMAD transcription factors necessary for cell growth and proliferation [54]. With aging, miR-192 levels also increase in kidney tissue [55]. Low expression of miR-211, which is derived from LINE2 [15], is associated with short life span, suggesting its protective effect against aging [56]. In OA, miR-211 levels are also reduced. MiR-211 promotes chondrocyte differentiation by suppressing expression of *EFEMP2*, (EGF containing fibulin extracellular matrix protein 2) gene, which encodes fibulin-4, which prevents the production of proinflammatory cytokines and cartilage-destroying proteinases [57].

MiR-224, derived from the MER-135 DNA transposon [15], inhibits the expression of the proinflammatory chemokine CCL1, also preventing cartilage degradation [58]. Nanoparticles with miR-224 have been developed as a promising treatment for OA [59]. MiR-224 is associated with aging of the brain. Its target is the *CHOP* (C/EBP homologous protein) gene, which is involved in the regulation of mitochondrial proteins [60]. Reduced levels of miR-28 have been detected in the blood serum of OA patients [61]. During physiological aging, miR-28 expression is also reduced [62]. The target of miR-28 is the mRNA of the *IL-34* (interleukin-34) gene. Accordingly, low miR-28 levels in aging and OA promote inflammation owing to increased IL-34 production [63].

In severe OA, increased expression of miR-31 has been identified, the targets of which are mRNAs of the following genes: *PAPOLG*, encoding polyadenylate polymerase; *SP1*, specificity protein 1, encoding a zinc finger transcription factor; *SRC*, encoding the nonreceptor tyrosine kinase proto-oncogene; *ZC3H12C*, encoding endoribonuclease. The product of the gene *SP1* is a transcription factor that plays an important role in the differentiation of bones and chondrocytes and the regulation of cell growth [64]. Elevated levels of miR-31 have been identified in aging human endothelial cells [65]. LINE2-derived miR-320b [15] is associated with rapid progression of OA and has been proposed as a prognostic biomarker for the disease [66]. This microRNA is involved in gene networks involving apoptosis regulatory genes. 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*, the tumor

Table 2. Patterns of expression of transposon-derived microRNAs in aging and OA

MicroRNA (source transposon)	Mechanism of microRNA action in osteoarthritis	Changes in expression with aging (increase (↑); decrease (↓)) [author]	Changes in expression in osteoarthritis (increase (↑); decrease (↓)) [author]
miR-1246 (LTR-ERVL)	Suppresses the expression of GSK3β and Axin2, promoting the activation of Wnt/β-catenin pathways 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 by disrupting polyamine metabolism [49]	↓ [52]	↓ [5]
miR-192 (LINE2)	Damages chondrocytes in response to lipopolysaccharides, causing inflammation [54]	↑ [55]	↑ [54]
miR-211 (LINE2)	Suppresses the expression of fibulin-4 and proinflammatory cytokines [57]	↓ [56]	↓ [57]
miR-224 (MER-135)	Inhibits expression of proinflammatory chemokine CCL1 [58]	↓ [60]	↓ [58]
miR-28 (LINE2)	Inhibits IL-34 expression [63]	↓ [62]	↓ [61]
miR-31 (LINE2)	Suppresses mRNA of genes *PAPOLG*, *SP1*, *SRC*, *ZC3H12C* [64]	↑ [65]	↑ [64]
miR-320b (LINE2)	Participates in gene networks regulating apoptosis involving *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 expression of genes *MMP13*, *VCAM1* [71]; inhibits enchondral ossification of cartilage [72]	↑ [73]	↑ [71, 72]
miR-340 (DNA-TE/TcMar)	Affects mRNA of genes *YTHDF3, IGF2BP3*; inhibits ERK signaling by suppressing *FMOD* [74]	↓ [75]	↓ [74]
miR-374 (LINE2)	Prevents lipopolysaccharide-induced cartilage destruction by inhibiting Wnt5b [77]	↓ [76]	↓ [77]
miR-378a (SINE/MIR)	Inhibits mRNA of genes *Sox6* and *Atg2a* [78]	↑ [79]	↑ [78]
miR-384 (LINE-Dong-R4)	Suppresses SOX9 expression and NF-kB signaling, preventing cartilage cell proliferation [80]	↑ [81]	↑ [80]
miR-421 (LINE2)	Inhibits IL-1β-induced apoptosis and inflammation [82]	↓ [83]	↓ [82]
miR-450b (LINE1)	Regulates expression of gene *SKAP2* 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 the Wnt5a pathway [97]	↑ [96]	↓ [95]
miR-708 (LINE2)	Binds to mRNA of the gene *SATB2*, inhibiting cartilage regeneration [88]	↑ [89]	↑ [88]
miR-885 (SINE/MIR)	Suppresses expression of genes *IGF1R*, *CTNNB1*, *OXR1* [90]	↑ [91]	↑ [90]

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 expression of gene *SIRT1*, sirtuin-1, and NAD-dependent deacetylase and stimulation of *VEGF*, vascular endothelial growth factor, with activation of inflammation and angiogenesis [68]. The level of miR-326 is significantly elevated in rheumatoid arthritis patients with positive rheumatoid factor [69]. Expression of miR-326 is increased in skin fibroblasts during aging [70].

In OA, elevated levels of miR-335 have been identified [71], which suppresses enchondral ossification of articular cartilage [72] by inhibiting the following 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 involved in the regulation of leukocyte adhesion [71]. High levels of miR-335 have been detected in aging in general, as well as in aging cultures of human astrocytes and the hippocampus of mouse brains compared to young cells and the hippocampus of young mice, and they lead to impaired memory consolidation in the hippocampus of the brain owing to the inhibition of mRNA of the gene *PSD95*, which encodes the postsynaptic density protein [73]. In OA, decreased expression of the TcMar DNA transposon-derived miR-340 [15] activates *YTHDF3* (encodes an RNA-binding protein), *IGF2BP3* (gene of mRNA-binding protein of insulin-like growth factor), and *FMOD* (the interstitial proteoglycan fibromodulin gene) genes and ERK signaling, extracellular signal-regulated kinase, which promotes cell proliferation, motility, and survival [74]. With aging, the level of miR-340 in serum is decreased [75].

The level of miR-374, derived from LINE2 [15], is reduced in aging [76] and in cartilage tissue of OA-affected joints [77]. MiR-374 prevents lipopolysaccharide-induced cartilage destruction by inhibiting *Wnt5b.* The name of the gene is formed from the words Wingless and Int-1. Gene *Wnt5b* encodes proteins of the WNT family of signaling proteins that transmit signals to the cell through cell surface receptors, stimulating cell proliferation and differentiation, including physiological regeneration of chondrocytes. Accordingly, inhibition of *Wnt5b* leads to degradation of cartilage [77]. In patients with OA, miR-378 is expressed at high levels in the synovium of affected joints, especially in the late stage of the disease. MiR-378 targets mRNAs of *Sox6* (sex determining region Y-box 6, encoding the regulator of chondrogenesis), and *Atg2a,* (autophagy related 2A, encoding an autophagy-related protein) genes [78]. In mouse models, intra-articular injections of anti-miR-378 lentivirus slowed OA progression by promoting regeneration and suppressing pathological hypertrophy [78]. Increased levels of miR-378 have also been shown in aging of the thymus [79]. MiR-384, which evolved from LINE-DONG-R4 [15], inhibits expression of *SOX9* (SRY-box transcription factor 9) gene, and NF-kB signaling, nuclear factor kappa B, preventing the proliferation of cartilage cells. The SOX9 protein regulates transcription of the anti-Müllerian hormone gene during chondrocyte differentiation. NF-kB is a transcriptional regulator that stimulates the expression of genes involved in immune responses, including the regulation of inflammation [80]. MiR-384 negatively regulates age-related osteogenic differentiation of bone marrow mesenchymal stem cells, promoting aging [81].

Expression of LINE2-derived miR-421 [15] is reduced in chondrocytes from OA-affected joints. This microRNA prevents IL-1β-induced apoptosis and inflammation [82]. Aging is also associated with decreased miR-421 levels [83]. In fibroblast-like cells in OA, expression of miR-450b, which targets the mRNA of the *SKAP2* gene, is reduced, which encodes Src kinase-associated phosphoprotein 2, which plays a role in kinase signaling pathways in macrophages [84]. Since activation of macrophages in OA [16] promotes progression of disease through their production of interleukins IL-1β, IL-6, IL-12, and TNF-α, reactive oxygen species, and iNOS [18], disruption of kinase signaling pathways in these cells is important in the pathogenesis of OA [84]. In experiments, a decrease in miR-450b was detected during aging of mouse fibroblasts. Fibroblasts are essential cellular components of joints, and their aging contributes to degenerative processes and progression of OA [85]. In patients with OA, elevated levels of miR-495 were detected in the cartilage tissue of affected joints [86]. MiR-495 inhibits mRNA of the *AKT1* (RAC-alpha serine/threonine-protein kinase) gene, encoding 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 originated from ERV-L/MaLR [15]. MiR-495 arrests the cell cycle in the S phase and promotes cell apoptosis, inducing senescence in human mesenchymal stem cells [87].

In osteoarthritis, increased miR-708 levels cause inhibition of *SATB2* gene, special AT-rich sequence-binding protein 2, the protein product of which promotes cartilage regeneration in OA. Therefore, the decrease in expression of *SATB2* under the influence of miR-708 causes a disruption of regeneration and, as a result, cartilage degradation [88]. Increased expression of miR-708 is also associated with aging [89]. The evolutionary source of the miR-708 gene is LINE2 [15]. Overexpression of miR-885, derived from SINE/MIR [15], is associated with OA [90] and aging. The target of miR-885 is the mRNA of the *IGF1R* gene, insulin-like growth factor 1 receptor, involved in cellular internalization of IGF-1 and activation of signaling cascades PI3K/Akt/GSK-3β, phosphoinositide 3-kinases/AKT serine/threonine kinase/glycogen

synthase kinase-3 beta. MiR-885 also targets mRNA of *CTNNB1* (catenin beta-1, a regulator of canonical Wnt signaling), *MAN1C1* (mannosidase alpha class 1C member 1, the protein product of which is involved in N-glycosylation of proteins), and *OXR1* (oxidation resistance 1, encoding a protein that regulates oxidative stress sensitivity) genes [91].

For some TE-derived miRNAs, opposite changes in expression of identical miRNAs were detected during aging and OA, indicating that not all aging mechanisms overlap with the etiopathogenesis of OA, but change in TEs influences the disruption of expression of miRNAs containing identical sequences. Thus, miR-487b [15], which is derived from SINE/MIR and is a direct target of the long ncRNA MAR1 (muscle anabolic regulator 1), exerts targeted inhibition of the mRNA of the gene *Wnt5a*, which leads to suppression of myogenesis regulatory pathways, promoting muscle tissue aging [92]. Activation of Wnt5a pathways in OA promotes progression of disease in connection with low expression of miR-487b [93], which promotes chondrogenic differentiation of mesenchymal stem cells [94]. Similar changes have been identified in the expression of LINE1-derived [15] miR-576, the level of which is reduced in chondrocytes in OA compared to the norm [95]. In older people, an association between increased expression of miR-576 and geriatric frailty syndrome (progressive deterioration of physical health) has been identified [96]. Wnt5a is also a target of miR-576 [97]. Thus, the analysis of scientific literature allowed us to identify 23 microRNAs derived from TEs and involved in the pathogenesis of OA (Table 2).

CONCLUSIONS

A hypothesis is proposed according to which pathological activation of TEs during aging contributes to the development of OA in the presence of individual SNP characteristics in the intergenic and intronic regions where TE genes are located. This may explain the significant prevalence of OA, which increases with age, as well as the influence of environmental factors on the development of the disease, since TEs are highly sensitive genomic sensors to stress effects. During aging, inflammatory and degenerative processes occur in the body, caused by the activation of the interferon response to products of TEs expression. Similar mechanisms have been described in the pathogenesis of OA. Furthermore, TE-derived miRNAs, which are characterized by cross-regulation with their evolutionary sources through nucleotide sequence complementarity, have been implicated in the development of OA. A total of 23 such microRNAs were identified, whose involvement in the pathogenesis of OA is due to the inhibition of the expression of genes involved in immune, inflammatory, and degenerative processes. In the future, it will be possible to use such microRNAs for targeted therapy of OA.

FUNDING

This work was supported by ongoing institutional funding. No additional grants to carry out or direct this particular research were obtained.

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.

REFERENCES

1. GBD 2021 Osteoarthritis Collaborators, Global, regional, and national burden of osteoarthritis, 1990—2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021, *Lancet Rheumatol.*, 2023, vol. 5, pp. e508—e522. https://doi.org/10.1016/S2665-9913(23)00163-7
2. Boer, C.G., Hatzikotoulas, K., Southam, L., et al., Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations, *Cell*, 2021, vol. 184, pp. 4784—4818. https://doi.org/10.1016/j.cell.2021.07.038
3. Faber, B.G., Frysz, M., Boer, C.G., et al., The identification of distinct protective and susceptibility mechanisms for hip osteoarthritis: findings from a genome-wide association study meta-analysis of minimum joint space width and Mendelian randomisation cluster analyses, *eBioMedicine*, 2023, vol. 95. https://doi.org/10.1016/j.ebiom.2023.104759
4. Chen, X., Wu, Q., Cao, X., et al., Menthone inhibits type-I interferon signaling by promoting Tyk2 ubiquitination to relieve local inflammation of rheumatoid arthritis, *Int. Immunopharmacol.*, 2022, vol. 112. https://doi.org/10.1016/j.intimp.2022.109228
5. Jiang, Y., Shen, Y., Ding, L., et al., Identification of transcription factors and construction of a novel miRNA regulatory network in primary osteoarthritis by integrated analysis, *BMC Musculoskeleton Disord.*, 2021, vol. 22, p. 1008. https://doi.org/10.1186/s12891-021-04894-2
6. Allen, K.D., Thoma, L.M., and Golightly, Y.M., Epidemiology of osteoarthritis, *Osteoarthritis Cartilage*, 2022, vol. 30, pp. 184—195. https://doi.org/10.1016/j.joca.2021.04.020
7. Vos, T., Flaxman, A.D., Naghavi, M., et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990—2010: a systematic analysis for the Global Burden of Disease Study 2010, *Lancet*, 2012, vol. 380. pp. 2163—2196. https://doi.org/10.1016/S0140-6736(12)61729-2
8. De Cecco, M., Ito, T., Petrashen, A.P., et al., L1 drives IFN in senescent cells and promotes age-associated inflammation, *Nature*, 2019, vol. 566, pp. 73—78.

9. Gorbunova, V., Seluanov, A., Mita, P., et al., The role of retrotransposable elements in ageing and age-associated diseases, *Nature*, 2021, vol. 596, pp. 43—53. https://doi.org/10.1038/s41586-021-03542-y

10. Bendiksen, S., Martinez-Zubiavrra, I., Tümmler, C., et al., Human endogenous retrovirus W activity in cartilage of osteoarthritis patients, *Biomed. Res. Int.*, 2014, vol. 2014. https://doi.org/10.1155/2014/698609

11. Teerawattanapong, N., Udomsinprasert, W., Ngarmukos, S., et al., Blood leukocyte LINE-1 hypomethylation and oxidative stress in knee osteoarthritis, *Heliyon*, 2019, vol. 5. https://doi.org/10.1016/j.heliyon.2019.e01774

12. Lee, D.H., Bae, W.H., Ha, H., et al., The human PTGR1 gene expression is controlled by TE-derived Z-DNA forming sequence cooperating with miR-6867-5p, *Sci. Rep.*, 2024, vol. 14, p. 4723. https://doi.org/10.1038/s41598-024-55332-x

13. Conley, A.B. and Jordan, I.K., Cell type-specific termination of transcription by transposable element sequences, *Mob. DNA*, 2012, vol. 3, p. 15. https://doi.org/10.1186/1759-8753-3-15

14. Daniel, C., Behm, M., and Öhman, M., The role of Alu elements in the cis-regulation of RNA processing, *Cell. Mol. Life Sci.*, 2015, vol. 72, pp. 4063—4076. https://doi.org/10.1007/s00018-015-1990-3

15. Wei, G., Qin, S., Li, W., et al., MDTE DB: a database for microRNAs derived from transposable element, *IEEE/ACM Trans. Comput. Biol. Bioinf.*, 2016, vol. 13, pp. 1155—1160. https://doi.org/10.1109/TCBB.2015.2511767

16. Chen, J., Chen, S., Cai, D., et al., The role of Sirt6 in osteoarthritis and its effect on macrophage polarization, *Bioengineered*, 2022, vol. 13, pp. 9677—9689. https://doi.org/10.1080/21655979.2022.2059610

17. van Meter, M., Kashyap, M., Rezazadeh, S., et al., SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age, *Nat. Commun.*, 2014, vol. 5, p. 5011. https://doi.org/10.1038/ncomms6011

18. Zhou, F., Mei, J., Han, X., et al., Kinsenoside attenuates osteoarthritis by repolarizing macrophages through inactivating NF- κ B/MAPK signaling and protecting chondrocytes, *Acta. Pharm. Sin. B*, 2019, vol. 9, pp. 973—985. https://doi.org/10.1016/j.apsb.2019.01.015

19. Saetan, N., Honsawek, S., Tanavalee, S., et al., Association of plasma and synovial fluid interferon-γ inducible protein-10 with radiographic severity in knee osteoarthritis, *Clin. Biochem.*, 2011, vol. 44, pp. 1218—1222. https://doi.org/10.1016/j.clinbiochem.2011.07.010

20. Mustafin, R.N. and Khusnutdinova, E.K., Non-coding parts of genomes as the basis of epigenetic heredity, *Vavilovskii Zh. Genet. Sel.*, 2017, vol. 21, no. 6, pp. 742—749.

21. Lu, F., Liu, P., Zhang, Q., et al., Association between the polymorphism of IL-17A and IL-17F gene with knee osteoarthritis risk: a meta-analysis based on case—control studies, *J. Orthop. Surg. Res.*, 2019, vol. 14, p. 445. https://doi.org/10.1186/s13018-019-1495-0

22. Budhiparama, N.C., Lumban-Gaol, I., and Sudoyo, H., Interleukin-1 genetic polymorphisms in knee osteoarthritis: what do we know? A meta-analysis and systematic review, *J. Orthop. Surg.* (Hong Kong), 2022, vol. 30. https://doi.org/10.1177/23094990221076652

23. Deng, X., Ye, K., Tang, J., and Huang, Y., Association of rs1800795 and rs1800796 polymorphisms in interleukin-6 gene and osteoarthritis risk: evidence from a meta-analysis, *Nucleosides Nucleotides Nucleic Acids*, 2023, vol. 42, pp. 328—342. https://doi.org/10.1080/15257770.2022.2147541

24. Rodriguez-Fontenla, C., Calaza, M., Evangelou, E., et al., Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies, *Arthritis Rheumatol.*, 2014, vol. 66, pp. 940—949. https://doi.org/10.1002/art.38300

25. Liu, Y., Lu, T., Liu, Z., et al., Six macrophage-associated genes in synovium constitute a novel diagnostic signature for osteoarthritis, *Front. Immunol.*, 2022, vol. 13. https://doi.org/10.3389/fimmu.2022.936606

26. Yang, L., Chen, Z., Guo, H., et al., Extensive cytokine analysis in synovial fluid of osteoarthritis patients, *Cytokine*, 2021, vol. 143. https://doi.org/10.1016/j.cyto.2021.155546

27. Pan, L., Yang, F., Cao, X., et al., Identification of five hub immune genes and characterization of two immune subtypes of osteoarthritis, *Front. Endocrinol.* (Lausanne), 2023, vol. 14. https://doi.org/10.3389/fendo.2023.1144258

28. Xu, J., Chen, K., Yu, Y., et al., Identification of immune-related risk genes in osteoarthritis based on bioinformatics analysis and machine learning, *J. Pers. Med.*, 2023, vol. 13, p. 367. https://doi.org/10.3390/jpm13020367

29. Cheng, P., Gong, S., Guo, C., et al., Exploration of effective biomarkers and infiltrating immune cells in osteoarthritis based on bioinformatics analysis, *Artif. Cells Nanomed. Biotechnol.*, 2023, vol. 51, pp. 242—254. https://doi.org/10.1080/21691401.2023.2185627

30. Li, J., Wang, G., Xv, X., et al., Identification of immune-associated genes in diagnosing osteoarthritis with metabolic syndrome by integrated bioinformatics analysis and machine learning, *Front. Immunol.*, 2023, vol. 14. https://doi.org/10.3389/fimmu.2023.1134412

31. Grandi, F.C. and Bhutani, N., Epigenetic therapies for osteoarthritis, *Trends Pharmacol. Sci.*, 2020, vol. 41, pp. 557—569. https://doi.org/10.1016/j.tips.2020.05.008

32. Knights, A.J., Redding, S.J., and Maerz, T., Inflammation in osteoarthritis: the latest progress and ongoing challenges, *Curr. Opin. Rheumatol.*, 2023, vol. 35, pp. 128—134.

33. Zhang, J., Zhang, S., Zhou, Y., et al., KLF9 and EPYC acting as feature genes for osteoarthritis and their association with immune infiltration, *J. Orthop. Surg. Res.*, 2022, vol. 17, p. 365. https://doi.org/10.1186/s13018-022-03247-6

34. Zhang, Q., Sun, C., Liu, X., et al., Mechanism of immune infiltration in synovial tissue of osteoarthritis: a gene expression-based study, *J. Orthop. Surg. Res.*, 2023, vol. 18, p. 58. https://doi.org/10.1186/s13018-023-03541-x
35. Xia, D., Wang, J., Yang, S., et al., Identification of key genes and their correlation with immune infiltration in osteoarthritis using integrative bioinformatics approaches and machine-learning strategies, *Medicine* (Baltimore), 2023, vol. 102. https://doi.org/10.1097/MD.0000000000035355
36. Xu, L., Wang, Z., and Wang, G., Screening of biomarkers associated with osteoarthritis aging genes and immune correlation studies, *Int. J. Gen. Med.*, 2024, vol. 17, pp. 205—224. https://doi.org/10.2147/IJGM.S447035
37. Cornec, A. and Poirier, E.Z., Interplay between RNA interference and transposable elements in mammals, *Front. Immunol.*, 2023, vol. 14. https://doi.org/10.3389/fimmu.2023.1212086
38. Cho, J. and Paszkowski, J., Regulation of rice root development by a retrotransposon acting as a microRNA sponge, *eLife*, 2017, vol. 6. https://doi.org/10.7554/eLife.30038
39. 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, vol. 21, pp. 423—425. https://doi.org/10.1038/nsmb.2799
40. Honson, D.D. and Macfarlan, T.S., A lncRNA-like role for LINE1s in development, *Dev. Cell*, 2018, vol. 46, pp. 132—134. https://doi.org/10.1016/j.devcel.2018.06.022
41. Playfoot, C.J., Sheppard, S., Planet, E., and Trono, D., Transposable elements contribute to the spatiotemporal microRNA landscape in human brain development, *RNA*, 2022, vol. 28, pp. 1157—1171. https://doi.org/10.1261/rna.079100.122
42. McCue, A.D., Nuthikattu, S., and Slotkin, R.K., Genome-wide identification of genes regulated in trans by transposable element small interfering RNAs, *RNA Biol.*, 2013, vol. 10, pp. 1379—1395. https://doi.org/10.4161/rna.25555
43. Lee, D.H., Bae, W.H., Ha, H., et al., Z-DNA-containing long terminal repeats of human endogenous retrovirus families provide alternative promoters for human functional genes, *Mol. Cells*, 2022, vol. 45, pp. 522—530. https://doi.org/10.14348/molcells.2022.0060
44. Chalertpet, K., Pin-On, P., Aporntewan, C., et al., Argonaute 4 as a effector protein in RNA-directed DNA methylation in human cells, *Front. Genet.*, 2019, vol. 10, p. 645. https://doi.org/10.3389/fgene.2019.00645
45. Tristán-Ramos, P., Rubio-Roldan, A., Peris, G., et al., The tumor suppressor microRNA let-7 inhibits human LINE-1 retrotransposition, *Nat. Commun.*, 2020, vol. 11, p. 5712. https://doi.org/10.1038/s41467-020-19430-4
46. Peng, S., Yan, Y., Li, R., et al., Extracellular vesicles from M1-polarized macrophages promote inflammation in the temporomandibular joint via miR-1246 activation of the Wnt/β-catenin pathway, *Ann. N. Y. Acad. Sci.*, 2021, vol. 1503, pp. 48—59. https://doi.org/10.1111/nyas.14590
47. 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, vol. 6. https://doi.org/10.1371/journal.pone.0020509
48. Lu, M.Y., Yang, Y.H., Wu, X., et al., Effect of needle-knife on chondrocyte apoptosis of knee joint in rabbits with knee osteoarthritis based on CircSERPINE2-miR-1271-5P-ERG axis, *Zhongguo Zhen Jiu*, 2023, vol. 43, pp. 447—453. https://doi.org/10.13703/j.0255-2930.20220411-k0001
49. Xie, W.P., Ma, T., Liang, Y.C., et al., Cangxi Tongbi capsules promote chondrocyte autophagy by regulating circRNA_0008365/miR-1271/p38 MAPK pathway to inhibit development of knee osteoarthritis, *Zhongguo Zhong Yao Za Zhi*, 2023, vol. 48, pp. 4843—4851. https://doi.org/10.19540/j.cnki.cjcmm.20230510.708
50. Ju, C., Liu, R., Zhang, Y., et al., Exosomes may be the potential new direction of research in osteoarthritis management, *Biomed. Res. Int.*, 2019, vol. 3. https://doi.org/10.1155/2019/7695768
51. Qin, W.J., Wang, W.P., Wang, X.B., et al., MiR-1290 targets CCNG2 to promote the metastasis of oral squamous cell carcinoma, *Eur. Rev. Med. Pharmacol. Sci.*, 2019, vol. 23, pp. 10332—10342. https://doi.org/10.26355/eurrev_201912_19671
52. Noren Hooten, N., Fitzpatrick, M., Wood, W.H. III, et al., Age-related changes in microRNA levels in serum, *Aging* (Albany NY), 2013, vol. 5, pp. 725—740. https://doi.org/10.18632/aging.100603
53. Xie, Y., Zhang, Y., Liu, X., et al., miR-151-5p promotes the proliferation and metastasis of colorectal carcinoma cells by targeting AGMAT, *Oncol. Rep.*, 2023, vol. 49, p. 50. https://doi.org/10.3892/or.2023.8487
54. Wang, Y., Yu, C., and Zhang, H., Lipopolysaccharides-mediated injury to chondrogenic ATDC5 cells can be relieved by Sinomenine via downregulating microRNA-192, *Phytother. Res.*, 2019, vol. 33, pp. 1827—1836. https://doi.org/10.1002/ptr.6372
55. Sataranatarajan, K., Feliers, D., Mariappan, M.M., et al., Molecular events in matrix protein metabolism in the aging kidney, *Aging Cell*, 2012, vol. 11, pp. 1065—1073. https://doi.org/10.1111/acel.12008
56. Smith-Vikos, T., Liu, Z., and Parsons, C., A serum miRNA profile of human longevity: findings from the Baltimore Longitudinal Study of Aging (BLSA), *Aging* (Albany NY), 2016, vol. 8, pp. 2971—2987. https://doi.org/10.18632/aging.101106
57. Liu, H. and Luo, J., miR-211-5p contributes to chondrocyte differentiation by suppressing Fibulin-4 expression to play a role in osteoarthritis, *J. Biochem.*, 2019, vol. 166, pp. 495—502. https://doi.org/10.1093/jb/mvz065
58. Liu, Y. and Zhang, Y., Hsa_circ_0134111 promotes osteoarthritis progression by regulating miR-224-5p/CCL1 interaction, *Aging* (Albany NY), 2021, vol. 13, pp. 20383—20394. https://doi.org/10.18632/aging.203420
59. Chen, H., Chen, F., Hu, F., et al., MicroRNA-224-5p nanoparticles balance homeostasis via inhibiting cartilage degeneration and synovial inflammation for synergistic alleviation of osteoarthritis, *Acta Biomater.*, 2023, vol. 167, pp. 401—415. https://doi.org/10.1016/j.actbio.2023.06.010

60. Francisco, S., Martinho, V., Ferreira, M., et al., The role of microRNAs in proteostasis decline and protein aggregation during brain and skeletal muscle aging, *Int. J. Mol. Sci.*, 2022, vol. 23, p. 3232. https://doi.org/10.3390/ijms23063232

61. Beyer, C., Zampetaki, A., Lin, N.Y., et al., Signature of circulating microRNAs in osteoarthritis, *Ann. Rheum. Dis.*, 2015, vol. 74, p. e18. https://doi.org/10.1136/annrheumdis-2013-204698

62. 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, vol. 206. https://doi.org/10.1016/j.mad.2022.111691

63. Zhou, S.L., Hu, Z.Q., Zhou, Z.J., et al., miR-28-5p-IL-34-macrophage feedback loop modulates hepatocellular carcinoma metastasis, *Hepatology*, 2016, vol. 63, pp. 1560—1575. https://doi.org/10.1002/hep.28445

64. Costa, V., De Fine, M., Carina, V., et al., How miR-31-5p and miR-33a-5p regulates SP1/CX43 expression in osteoarthritis disease: preliminary insights, *Int. J. Mol. Sci.*, 2021, vol. 22, p. 2471. https://doi.org/10.3390/ijms22052471

65. Dellago, H., Preschitz-Kammerhofer, B., Terlecki-Zaniewicz, L., et al., High levels of oncomiR-21 contribute to the senescence-induced growth arrest in normal human cells and its knock-down increases the replicative lifespan, *Aging Cell*, 2013, vol. 12, pp. 446—458. https://doi.org/10.1111/acel.12069

66. Ali, S.A., Espin-Garcia, O., Wong, A.K., et al., Circulating microRNAs differentiate fast-progressing from slow-progressing and non-progressing knee osteoarthritis in the Osteoarthritis Initiative cohort, *Ther. Adv. Musculoskeletal Dis.*, 2022, vol. 14. https://doi.org/10.1177/1759720X221082917

67. 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, vol. 18, p. 1014. https://doi.org/10.1186/s12885-018-4920-6

68. Lin, Z., Ma, Y., Zhu, X., et al., Potential predictive and therapeutic applications of small extracellular vesicles-derived circPARD3B in osteoarthritis, *Front. Pharmacol.*, 2022, vol. 13. https://doi.org/10.3389/fphar.2022.968776

69. Paradowska-Gorycka, A., Wajda, A., Rzeszotarska, E., et al., miR-10 and its negative correlation with serum IL-35 concentration and positive correlation with STAT5a expression in patients with rheumatoid arthritis, *Int. J. Mol. Sci.*, 2022, vol. 23, p. 7925. https://doi.org/10.3390/ijms23147925

70. Yang, X., Tan, J., Shen, J., et al., Endothelial cell-derived extracellular vesicles target TLR4 via miRNA-326-3p to regulate skin fibroblasts senescence, *J. Immunol.*, 2022, vol. 2022, p. 3371982. https://doi.org/10.1155/2022/3371982

71. Wilson, T.G., Baghel, M., Kaur, N., et al., Characterization of miR-335-5p and miR-335-3p in human osteoarthritic tissues, *Arthritis Res. Ther.*, 2023, vol. 25, p. 105. https://doi.org/10.1186/s13075-023-03088-6

72. Xia, S., Zhao, J., Zhang, D., et al., MiR-335-5p inhibits endochondral ossification by directly targeting SP1 in TMJ OA, *Oral Dis.*, 2023, vol. 20. https://doi.org/10.1111/odi.14736

73. Raihan, O., Brishti, A., Molla, M.R., et al., The age-dependent elevation of miR-335-3p leads to reduced cholesterol and impaired memory in brain, *Neuroscience*, 2018, vol. 390, pp. 160—173. https://doi.org/10.1016/j.neuroscience.2018.08.003

74. Duan, Y., Yu, C., Yan, M., et al., m6A regulator-mediated RNA methylation modification patterns regulate the immune microenvironment in osteoarthritis, *Front. Genet.*, 2022, vol. 13. https://doi.org/10.3389/fgene.2022.921256

75. Zhang, H., Yang, H., Zhang, C., et al., Investigation of microRNA expression in human serum during the aging process, *J. Gerontol., Ser. A*, 2015, vol. 70, pp. 102—109. https://doi.org/10.1093/gerona/glu145

76. ElSharawy, A., Keller, A., Flachsbart, F., et al., Genome-wide miRNA signatures of human longevity, *Aging Cell*, 2012, vol. 11, pp. 607—616. https://doi.org/10.1111/j.1474-9726.2012.00824.x

77. Shi, F.L. and Ren, L.X., Up-regulated miR-374a-3p relieves lipopolysaccharides induced injury in CHON-001 cells via regulating Wingless-type MMTV integration site family member 5B, *Mol. Cell. Probes*, 2020, vol. 51. https://doi.org/10.1016/j.mcp.2020.101541

78. Feng, L., Yang, Z., Li, Y., et al., MicroRNA-378 contributes to osteoarthritis by regulating chondrocyte autophagy and bone marrow mesenchymal stem cell chondrogenesis, *Mol. Ther. Nucleic Acids*, 2022, vol. 28, pp. 328—341. https://doi.org/10.1016/j.omtn.2022.03.016

79. Guo, D., Ye, Y., Qi, J., et al., Age and sex differences in microRNAs expression during the process of thymus aging, *Acta Biochim. Biophys. Sin.* (Shanghai), 2017, vol. 49, pp. 409—419. https://doi.org/10.1093/abbs/gmx029

80. Zhang, W., Cheng, P., Hu, W., et al., Inhibition of microRNA-384-5p alleviates osteoarthritis through its effects on inhibiting apoptosis of cartilage cells via the NF-κB signaling pathway by targeting SOX9, *Cancer Gene Ther.*, 2018, vol. 25, pp. 326—338. https://doi.org/10.1038/s41417-018-0029-y

81. 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, vol. 28, pp. 791—798. https://doi.org/10.1089/scd.2019.0044

82. Zhang, H., Xiang, X., Zhou, B., et al., Circular RNA SLTM as a miR-421-competing endogenous RNA to mediate HMGB2 expression stimulates apoptosis and inflammation in arthritic chondrocytes, *J. Biochem. Mol. Toxicol.*, 2023, vol. 37. https://doi.org/10.1002/jbt.23306

83. 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, vol. 356, pp. 20—27. https://doi.org/10.1016/j.yexcr.2017.04.002

84. Chen, Y.J., Chang, W.A., Wu, L.Y., et al., Identification of novel genes in osteoarthritic fibroblast-like synoviocytes using next-generation sequencing and bioinformatics approaches, *Int. J. Med. Sci.*, 2019, vol. 16, pp. 1057—1071. https://doi.org/10.7150/ijms.35611
85. Nidadavolu, L.S., Niedernhofer, L.J., and Khan, S.A., Identification of microRNAs dysregulated in cellular senescence driven by endogenous genotoxic stress, *Aging* (Albany NY), 2013, vol. 5, pp. 460—473. https://doi.org/10.18632/aging.100571
86. Zhao X., Wang T., Cai B., et al., MicroRNA-495 enhances chondrocyte apoptosis, senescence and promotes the progression of osteoarthritis by targeting AKT1, *Am. J. Transl. Res.,* 2019, vol. 11, pp. 2232—2244.
87. Li, X., Song, Y., Liu, D., et al., MiR-495 promotes senescence of mesenchymal stem cells by targeting Bmi-1, *Cell Physiol. Biochem.*, 2017, vol. 42, pp. 780—796. https://doi.org/10.1159/000478069
88. Wang, Y., Su, Q., Tang, H., et al., Microfracture technique combined with mesenchymal stem cells inducer represses miR-708-5p to target special at-rich sequence-binding protein 2 to drive cartilage repair and regeneration in rabbit knee osteoarthritis, *Growth Factors*, 2023, vol. 41, pp. 115—129. https://doi.org/10.1080/08977194.2023.2227269
89. Lee, B.P., Buric, I., George-Pandeth, A., et al., MicroRNAs miR-203-3p, miR-664-3p and miR-708-5p are associated with median strain lifespan in mice, *Sci. Rep.*, 2017, vol. 7. https://doi.org/10.1038/srep44620
90. Kwak, Y.H., Kwak, D.K., Moon, H.S., et al., Significant changes in serum microRNAs after high tibial osteotomy in medial compartmental knee osteoarthritis: potential prognostic biomarkers, *Diagnostics* (Basel), 2021, vol. 11, p. 258. https://doi.org/10.3390/diagnostics11020258
91. Behbahanipour, M., Peymani, M., Salari, M., et al., Expression profiling of blood microRNAs 885, 361, and 17 in the patients with the Parkinson's disease: integrating interaction data to uncover the possible triggering age-related mechanisms, *Sci. Rep.*, 2019, vol. 9, p. 13759. https://doi.org/10.1038/s41598-019-50256-3
92. Zhang, Z.K., Li, J., Guan, D., et al., A newly identified lncRNA MaR1 acts as a miR-487b sponge to promote skeletal muscle differentiation and regeneration, *J. Cachexia Sarcopenia Muscle*, 2018, vol. 9, pp. 613—626. https://doi.org/10.1002/jcsm.12281
93. Chang, L., Yao, H., Yao, Z., et al., Comprehensive analysis of key genes, signaling pathways and miRNAs in human knee osteoarthritis: based on bioinformatics, *Front. Pharmacol.*, 2021, vol. 12. https://doi.org/10.3389/fphar.2021.730587
94. Alizadeh, A.H., Lively, S., Lepage, S., et al., MicroRNAs as prognostic markers for chondrogenic differentiation potential of equine mesenchymal stromal cells, *Stem Cells Dev.*, 2023, vol. 32, pp. 693—702. https://doi.org/10.1089/scd.2022.0295
95. Díaz-Prado, S., Cicione, C., Muiños-López, E., et al., Characterization of microRNA expression profiles in normal and osteoarthritic human chondrocytes, *BMC Musculoskeletal Disord.*, 2012, vol. 13, p. 144. https://doi.org/10.1186/1471-2474-13-144
96. Ipson, B.R., Fletcher, M.B., Espinoza, S.E., and Fisher, A.L., Identifying exosome-derived microRNAs as candidate biomarkers of frailty, *J. Frailty Aging*, 2018, vol. 7, pp. 100—103. https://doi.org/10.14283/jfa.2017.45
97. Luo, J., Liu, L., Shen, J., et al., MiR-576-5p promotes epithelial to mesenchymal transition in colorectal cancer by targeting the Wnt5a mediated Wnt/β catenin signaling pathway, *Mol. Med. Rep.*, 2021, vol. 23, p. 94. https://doi.org/10.3892/mmr.2020.11733