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SYSTEMATIC REVIEW

The function of lncRNAs in the pathogenesis of osteoarthritis

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Osteoarthritis (OA), one of the most common motor system disorders, is a degenerative disease involving progressive joint destruction caused by a variety of factors. At present, OA has become the fourth most common cause of disability in the world. However, the pathogenesis of OA is complex and has not yet been clarified. Long non-coding RNA (lncRNA) refers to a group of RNAs more than 200 nucleotides in length with limited protein-coding potential, which have a wide range of biological functions including regulating transcriptional patterns and protein activity, as well as binding to form endogenous small interference RNAs (siRNAs) and natural microRNA (miRNA) molecular sponges. In recent years, a large number of lncRNAs have been found to be differentially expressed in a variety of pathological processes of OA, including extracellular matrix (ECM) degradation, synovial inflammation, chondrocyte apoptosis, and angiogenesis. Obviously, lncRNAs play important roles in regulating gene expression, maintaining the phenotype of cartilage and synovial cells, and the stability of the intra-articular environment. This article reviews the results of the latest research into the role of lncRNAs in a variety of pathological processes of OA, in order to provide a new direction for the study of OA pathogenesis and a new target for prevention and treatment.

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Article focus

- A large number of differentially expressed long non-coding RNAs (lncRNAs) are involved in various pathological changes of osteoarthritis (OA), including extracellular matrix (ECM) degradation, synovial inflammation, chondrocyte apoptosis, and angiogenesis.
- The detailed mechanism of how lncRNA acts in the development of OA remains to be elucidated.

Key messages

- High-throughput sequencing technology has been used to screen and identify key lncRNAs associated with OA.
- LncRNA can regulate the key factors and signalling pathways in the pathogenesis of OA in various ways. Competitive endogenous RNA (ceRNA) is particularly prominent in recent research.

Strengths and limitations

- This systematic review summarizes the role and molecular mechanisms of lncRNAs related to OA in recent years, with a view to providing new directions for the study of the pathogenesis of OA.
- Interference or overexpression of specific lncRNAs can slow the occurrence and development of OA, but may cause adverse effects in other aspects of the body.

Introduction

Osteoarthritis (OA) is a degenerative joint disease caused by the degradation of cartilage matrix, the death of chondrocytes, and the formation of osteophytes.[1] The main manifestation is progressive joint destruction, leading to joint pain, deformity, dysfunction, joint apraxia, and sometimes even disability. In 1999, the World Health Organization listed OA, cardiovascular disease, and cancer as the three major killers threatening human health.[2] At present, OA is the fourth-largest cause of disability in the world. A variety of treatments are available to alleviate the symptoms of patients with OA. These include corticosteroids and non-steroidal anti-inflammatory drugs.[3–5] Experimental stem cell therapy has

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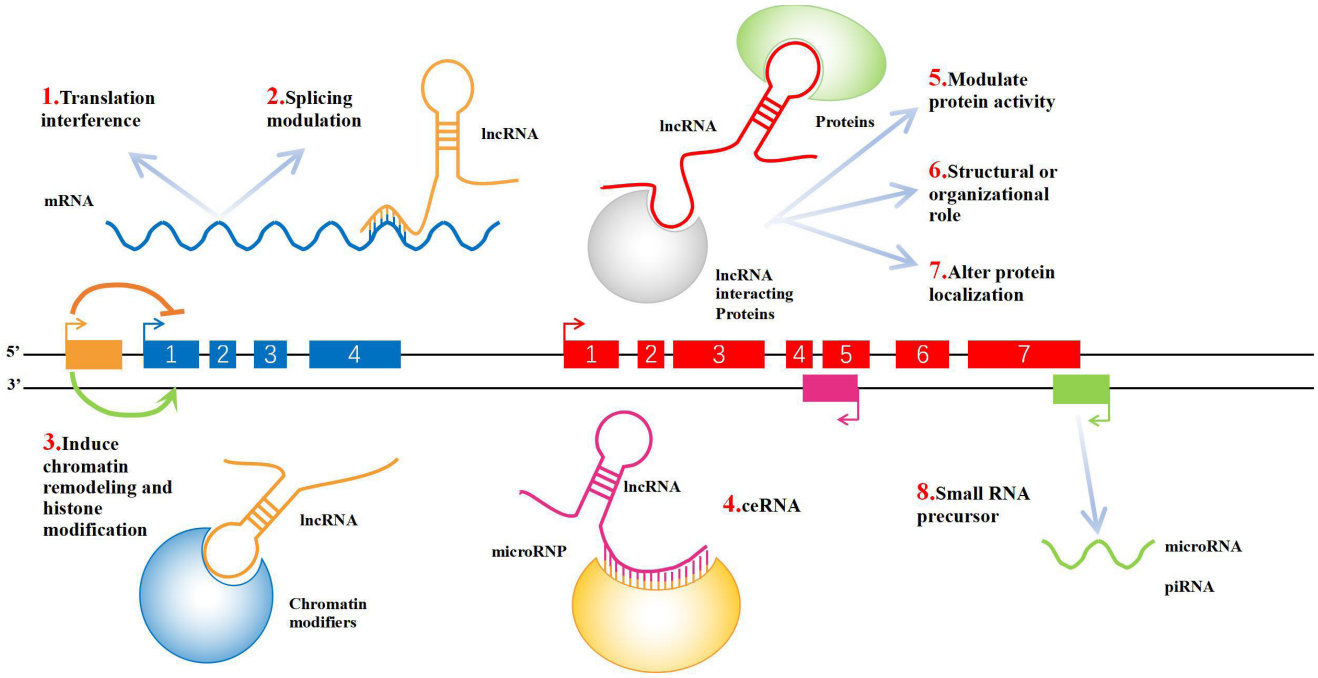

Fig. 1

Schematic diagram of long non-coding RNA (lncRNA) function. 1) LncRNA can be transcribed with the upstream promoter region of a protein-coding gene to interfere with the expression of downstream genes. 2) LncRNA can form complementary double strands with the transcript of a protein-coding gene, interfering with the splicing of messenger RNA (mRNA) and forming different forms of splicing. 3) LncRNA can mediate chromatin remodelling and histone modification, affecting the expression of downstream genes. 4) LncRNA has microRNA (miRNA) action sites, which can be competitively combined with miRNA. RNAs that act this way are known as miRNA sponges (competitive endogenous RNAs (ceRNAs)). 5) In combination with specific proteins, lncRNA transcripts can regulate the activity of corresponding proteins. 6) As a structural component, it forms a nucleic acid–protein complex with protein. 7) LncRNA can bind to a specific protein, changing its cellular location. 8) LncRNA can form the precursor molecule of small RNAs (such as miRNA, PIWI-interacting RNA (piRNA)).

been applied to treat specific forms of OA and biological agents are used to block inflammatory mediators such as cytokines, but there is still no specific cure for OA.

It is estimated that only 2% of the RNA in the human genome encodes proteins, while the vast majority (approximately 98%) is non-coding RNA.[6] According to its size, non-coding RNA can be divided into two categories: non-coding small RNA molecules, such as microRNA (miRNA), small interfering RNA (siRNA), PIWI-interacting RNA (piRNA), and small nucleolar RNA (snoRNA); and long non-coding RNA (lncRNA).[7] LncRNA is a type of non-coding RNA with a length greater than 200 nt, which lacks an obvious open reading frame and does not have the function of translating into protein.[8] According to the relative position of the lncRNA and the coding gene on the chromosome, lncRNAs can be divided into five types: sense; antisense; bidirectional; intronic; and intergenic. They regulate gene expression by folding into a unique conformation and interacting with DNA, RNA, or protein (Figure 1). Gene regulation mainly occurs at three levels: pre-transcriptional; transcriptional; and post-transcriptional. Pre-transcriptional regulation includes lncRNA-mediated histone modification, DNA methylation, and chromosome remodelling,[9] while transcriptional regulation includes lncRNA regulation of insulator function, interference with gene transcription, and control of transcription factors.[10] Meanwhile, post-transcriptional regulation involves variable splicing of genes and subcellular localization of RNA,[11] as well as binding to specific proteins to regulate protein activity[12] as a structural component[13] or by changing protein localization.[14] As a precursor of small RNA, lncRNA can be processed into miRNA and piRNA by ribonucleases (RNases).[15] Salmena et al[16] found that lncRNA has a miRNA action site and can also compete with miRNA; that is, it acts as a competitive endogenous RNA (ceRNA).[17,18] A large number of studies have shown that lncRNA plays important roles in growth and development and in the occurrence of many diseases, and is related to embryonic development, apoptosis, cell differentiation and maturation, immune system diseases, tumorigenesis, invasion, and distant metastasis.[19–23] Some lncRNAs are defined as key regulatory factors in the pathogenesis and development of OA.[24–27] In this article we review the role of lncRNA in the occurrence and development of OA, hoping to provide a new target and direction for the treatment of OA.

Non-coding RNAs and osteoarthritis. In the past, there have been many in-depth studies on the mechanism of miRNA in OA. miRNA is widely involved in the regulation of chondrogenesis, cartilage differentiation, chondrocyte proliferation, chondrocyte hypertrophy, endochondral

Table I. Abnormally expressed long non-coding RNAs described in the text and their functions.

lncRNA gene name	Expression*	Related factor	Function†	Tissue/cell
TM1P3	up	miR-22/TGF-β/MMP13[39]	ECM degradation (+)	Human primary chondrocytes
CIR	up	miR-27b/MMP13[37]	ECM degradation (+)	Human primary chondrocytes
		miR-130a/BIM[36]	Chondrocyte apoptosis (+)	Human primary chondrocytes
HOTAIR	up	miR-17-5p/FUT2/Wnt/β-catenin[40]	ECM degradation (+); Chondrocyte apoptosis (+)	Human primary chondrocytes
		miR-130a-3p[41]	Chondrocyte apoptosis (+)	Human primary chondrocytes
		Wnt/β-catenin[42]	Synovial cells proliferation (+) Synovial cells apoptosis (-)	Rat synoviocytes
MEG3	down	miR-361-5p/FOXO1[43]	ECM degradation (-) Chondrocyte apoptosis (-)	Human primary chondrocytes
		miR-93/TGFBR2[44]	ECM degradation (-) Chondrocyte apoptosis (-)	Rat chondrocytes
		VEGF[25]	Vascular invasion (-)	Human primary chondrocytes
HOTTIP	up	miR-455-3p/CCL3[45]	ECM degradation (+)	Human primary chondrocytes
XIST	up	miR-1277-5p[46]	ECM degradation (+)	Human primary chondrocytes
		TIMP-3[47,48]	ECM degradation (+)	Human primary chondrocytes
		miR-211/CXCR4[49]	Chondrocyte apoptosis (+)	Primary chondrocytes
		miR-142-5p/SGTB[50]	Chondrocyte apoptosis (+)	SW1353 (human osteosarcoma cells)
PART1	up	miR-373-3p/SOX4[51]	ECM degradation (+)	Human primary chondrocytes
	down	miR-590-3p/ TGFBR2/SMAD3[52]	ECM degradation (-) Chondrocyte apoptosis (-)	Human primary chondrocytes
SNHG15	down	miR-7/KLF4	ECM degradation (-)	Human primary chondrocytes
LINC01534	up	miR140-5p[53]	ECM degradation (+)	Human primary chondrocytes
GAS5	up	miR-34a/Bcl-2[54]	Chondrocyte apoptosis (+)	Human primary chondrocytes
H19	down	miR-615[55]	ECM degradation (-)	Human primary chondrocytes
	up	miR-130a[72]	Chondrocyte apoptosis (+)	Human primary chondrocytes
	up	miR-106a-5p[56]	Chondrocyte apoptosis (+)	Human primary chondrocytes
	up	miR-140-5p[57]	Chondrocyte apoptosis (+)	Human primary chondrocytes
PVT1	up	miR-27b-3p/TRAF3[58]	Chondrocyte apoptosis (+)	Human primary chondrocytes
		miR-149[59]	Inflammatory response (+)	Human primary chondrocytes
DANCR	up	miR-216a-5p/JAK2/STAT3[60]	Cartilage regeneration (+) Chondrocyte apoptosis (-)	Human primary chondrocytes
		miR-577/SphK2[61]	Chondrocyte apoptosis (-)	Human primary chondrocytes
NEAT1	up	miR-193a-3p/SOX5[62]	Inflammatory response (+) Chondrocyte apoptosis (+)	Human primary chondrocytes
		miR-181c/OPN[63]	Synovial cells proliferation (+)	Human synoviocytes
CHRF	up	miR-146a/JAK1/STAT3[64]	Inflammatory response (+) Chondrocyte apoptosis (+)	ATDC5 cells (mouse embryonic tumour cells)
ATB	down	miR-223/MyD88/NF-κB[65]	Inflammatory response (-) Chondrocyte apoptosis (-)	ATDC5 cells (mouse embryonic tumour cells)
NKILA	down	miR-145/SP1/NFκB[66]	Cartilage regeneration (+) Chondrocyte apoptosis (-)	Human primary chondrocytes

Continued

Table I. Continued

lncRNA gene name	Expression*	Related factor	Function†	Tissue/cell
CAIF	down	miR-1246[67]	Chondrocyte apoptosis (-)	CHON-001 cells (fibroblast immortalized with hTERT)
DNM3OS	down	miR-126/IGF1[68]	Chondrocyte apoptosis (-)	CHON-001 cells (fibroblast immortalized with hTERT)
HOTAIRM1-1	down	miR-125b/BMPR2[69]	Chondrocyte apoptosis (-)	Human primary chondrocytes
GACAT3	up	IL-6/STAT3[70]	Synovial cells proliferation (+)	Human synoviocytes
ANRIL	up	miR-122-5p/DUSP4[71]	Synovial cells proliferation (+) Synovial cells apoptosis (-)	Human synoviocytes
LOC101928134	up	IFNA1/JAK/STAT[72]	Synovial cells proliferation (+)	Rat synoviocytes
LINC00917	up	SPHK1[73]	Vascular invasion (-)	Human chondrocytes
CTD-2246P4.1	up	SPHK1[73]	Vascular invasion (-)	Human chondrocytes

*Long non-coding RNA expression during osteoarthritis.
†(+) means promotion, (-) means inhibition.
ANRIL, antisense noncoding RNA in the INK4 locus; ATB, activated by TGF-β; Bcl-2, B-cell lymphoma 2; BIM, B-cell lymphoma 2 interacting mediator of cell death; BMPR2, bone morphogenetic protein type II receptor; CAIF, cardiac autophagy inhibitory factor; CCL3, C-C Motif Chemokine Ligand 3; CHRF, cardiac hypertrophy related factor; CIR, cartilage injury–related; CXCR4, C-X-C motif chemokine receptor 4; DANCR, differentiation antagonizing non-protein coding RNA; DNM3OS, dynamin 3 opposite strand; DUSP4, Dual Specificity Phosphatase 4; ECM, extracellular matrix; FOXO1, forkhead box protein 1; FUT2, fucosyltransferase 2; GACAT3, gastric cancer associated transcript 3; GAS5, growth arrest-special transcript 5; H19, H19 imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense intergenic RNA; HOTAIRM1-1, HOXA transcript antisense RNA myeloid-specific 1-1; HOTTIP, HOXA transcript at the distal tip; IFNA1, Interferon Alpha 1; IGF, insulin-like growth factor; IL-6, interleukin- 6; JAK, Janus Kinase; KLF4, Kruppel Like Factor 4; LINC00917, Long Intergenic Non-Protein Coding RNA 917; LINC01534, Long Intergenic Non-Protein Coding RNA 1534; lncRNA, long non-coding RNA; MEG3, maternally-expressed gene 3; miR, microRNA; MMP, matrix metalloproteinase; MyD88, myeloid differentiation factor 88; NEAT1, nuclear paraspeckle assembly transcript 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NKILA, NF-KappaB Interacting LncRNA; OPN, osteopontin; PART1, prostate androgen regulated transcript 1; PVT1, plasmacytoma variant translocation 1; SGTB, Small Glutamine Rich Tetratricopeptide Repeat Containing Beta; SMAD3, SMAD Family Member 3; SNHG15, small nucleolar RNA host gene 15; SOX, SRY-associated high mobility protein; SP1, Sp1 Transcription Factor; SPHK1, Sphingosine Kinase 1; SphK2, Sphingosine Kinase 2; STAT3, signal transducer and transcriptional activator-3; TGF-β, transforming growth factor beta; TGFBR2, transforming growth factor β receptor 2; TIMP-3, tissue inhibitors of metalloproteinases-3; TRAF3, TNF Receptor-Associated Factor 3; VEGF, vascular endothelial growth factor; Wnt/β-catenin, Wnt/β-catenin pathway; XIST, X inactive specific transcript.

osteogenesis, and proteolytic enzyme hydrolyze protein, chondrocyte apoptosis, and other biological processes.[28–30] Compared with miRNA, lncRNA has longer transcripts and lower homology among species, but has higher tissue specificity and more conserved promoter sequences, which may indicate that the function of lncRNA is more conservative.[31] With the development of bioinformatics and high-throughput sequencing, more and more studies have reported that lncRNA can affect biological processes such as cell proliferation, apoptosis, and differentiation, and affect the occurrence and prognosis of diseases.[32] Fu et al[33] identified 4,714 differentially expressed lncRNAs in knee cartilage of OA and non-OA patients using gene chip and bioinformatics techniques. Liu et al[24] identified 153 lncRNAs differentially expressed in OA patients using gene chip technology, and considered that lncRNA-cartilage injury-related (*CIR*) is the key to matrix degradation of chondrocytes. Zhang et al[34] also identified 2,042 differentially expressed lncRNAs in OA patients using gene chips. Thus, it can be seen that the incidence of OA is closely related to lncRNAs.[35] Previous studies have found that: the lncRNA *FOXD2-AS1* can regulate the expression of *CCND1* through *miR-206*, regulating the proliferation of chondrocytes and promoting the occurrence of OA;[36] the lncRNA-*CIR* promotes the degradation of cartilage extracellular matrix (ECM) by regulating *miR-27b*, which aggravates the progress of OA;[37] and the lncRNA-*PVT1* and *miR-448-3p* form a ceRNA, to promote the apoptosis of chondrocytes and aggravate the progress of OA.[38] At present, research into the molecular mechanism of lncRNA in OA focuses on the binding of lncRNA and miRNA to form molecular sponges (ceRNAs). Many studies have shown that lncRNA plays an important role in regulating the synthesis and metabolism of ECM, synovitis, neovascularization, autophagy, and apoptosis of chondrocytes and other factors related to the occurrence and development of OA (Table I, Figure 2).

LncRNAs regulate ECM degradation. The essence of OA is that under the action of mechanical and biological factors, the normal synthesis and degradation of articular chondrocytes, ECM, and subchondral bone are out of balance, and its pathophysiological process is due to the catabolism of articular cartilage being significantly greater than its synthetic metabolism.[74] Studies have shown that the occurrence of OA is mainly manifested in the changes of articular cartilage, which is largely composed of chondrocytes and ECM, in which type II collagen (Col II) and aggrecan composed of hyaluronic acid (HA) and chondroitin sulfate (CS) constitute the ECM. When joint OA occurs, the expression and content of various matrix metalloproteinases (MMPs) increase, which enhances the hydrolysis and metabolism of Col II, destroys the ECM, and leads to cartilage wear and degeneration. Because the degradation products of cartilage matrix molecules can promote further degradation of the ECM, a persistent vicious circle develops. Recent studies have found that the expression of the lncRNA-*TM1P3* is significantly increased in OA chondrocytes. Li et al[39] revealed that lncRNA-*TM1P3*

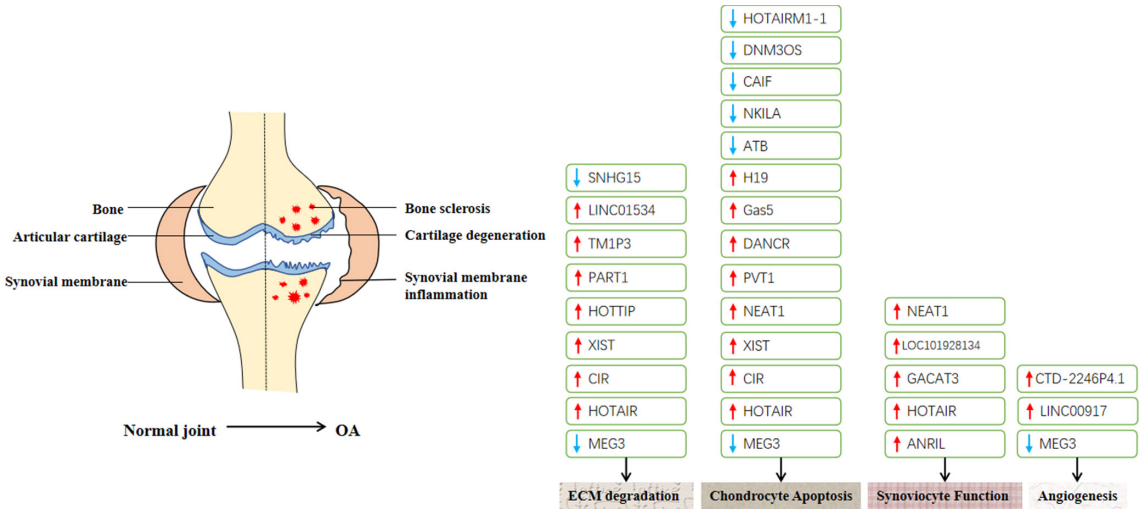

Fig. 2

Abnormally expressed long non-coding RNAs (lncRNAs) described in the text. It is known that extracellular matrix (ECM) degradation, chondrocyte apoptosis, synovitis, and angiogenesis play important roles in the occurrence and development of osteoarthritis (OA). The red arrow indicates upward adjustment, and the blue arrow indicates downward adjustment.

promotes the expression of activin receptor-like kinase 1 (*ALK1*) by acting as a *miR-22* ceRNA, further causing increased phosphorylation of SMAD, thereby upregulating the expression of MMP-13 and causing ECM degradation. ALK1 is a binding receptor for the transforming growth factor beta (TGF-β) signalling pathway. Activated ALK1 promotes the upregulation of phosphorylated SMAD and MMP13, suggesting that lncRNA-*TM1P3* promotes ECM degradation through the *miR-22/ALK1/MMP13* axis in OA. In another study by Li et al,[37] lncRNA-*CIR* was found to participate in the degradation of ECM in OA chondrocytes through the *miR-27b/MMP13* axis. In addition, inhibition of lncRNA-*CIR* expression in OA cartilage by small interference RNA (siRNA) can inhibit the expression of MMP-13 and a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5), thus promoting the anabolism of Col II, type I collagen, and aggrecan in OA cartilage.[24]

HOX transcript antisense intergenic RNA (lncRNA-*HOTAIR*) is a trans-acting lncRNA, proposed by Rinn et al[75] and reported to bind to polycomb repressive complex 2 (*PRC2*).[76] *HOTAIR* promotes cell proliferation by inhibiting *miR-148b-3p* in glioma cells and leads to tumour cell invasion and malignant tumour development.[77] Liu et al[78] reported that *HOTAIR* acts as the ceRNA of *miR-331-3p* to regulate the expression of human epidermal growth factor receptor-2 (*HER2*) in gastric cancer. Hu et al[40] found that the expression of *HOTAIR* and fucosyltransferase 2 (*FUT2*) was negatively correlated with *miR-17-5p* in OA cartilage. *HOTAIR* indirectly regulates *FUT2* in chondrocytes by acting as ceRNA of *miR-17-5p* to increase activity of the wnt/β-catenin pathway. The FUT family is a group of fucosyltransferases that catalyze the conversion of fucose to oligosaccharides, glycoproteins, or glycolipids on the substrate. Studies have reported that FUT1, FUT2, and FUT4 are abnormally upregulated in OA cartilage tissue, and FUT plays an important role in the activation of the wnt/β-catenin signalling pathway in various diseases.[79] Yang et al[80] found that FUT8 promotes epithelial-mesenchymal transformation of breast cancer stem cells by activating the wnt/β-catenin signalling pathway. Zhang et al[81] proved that FUT4 promotes embryo adhesion and implantation through the wnt/β-catenin signalling pathway. These results indicate that *HOTAIR* promotes degradation of the ECM through the *miR-17-5p/FUT2*/wnt/β-catenin axis.

LncRNA-maternally-expressed gene 3 (*MEG3*) has proven to be an important factor in tumour development.[82] In addition to its role in the development of a variety of cancers,[83] including lung cancer, breast cancer, and oesophageal cancer, studies have also found that *MEG3* is a potential therapeutic target for OA. Chen et al[44] found that *MEG3*, as a ceRNA of *miR-93*, can promote the expression of transforming growth factor β receptor 2 (*TGFBR2*), and then activate the TGF-β signalling pathway to reduce ECM degradation. In another study also aimed at *MEG3*, Wang et al[43] found that *MEG3* inhibits ECM degradation through the *miR-361-5p/FOXO1* axis. The expression of *MEG3* in human OA chondrocytes was downregulated, while overexpression of *MEG3* significantly downregulated the expression of *miR-93* and *miR-361-5p*, inhibiting the expression of MMP-13 and ADAMTS-5 which thus reduced degradation of the ECM.[43]

The lncRNA *HOTTIP* is a functional lncRNA transcribed from the 5' end of the *HOXA* gene.[84] With downregulation of the *HOXA13* gene, its expression increases significantly, and the level of integrin-α-1(*ITGα1*) decreases significantly after *HOXA-13* siRNA is introduced into human OA chondrocytes.[85] Overexpression of ITGα1 promotes cartilage formation, while mice lacking ITGα1 develop degenerated cartilage at a younger age and show an increase in (ITGα2) synthesis. *HOTTIP* may promote ECM degradation

in chondrocytes by inhibiting the *HOXA-13/ITGα1/MMP2* signalling pathway.[85] Mao et al[45] found that *HOTTIP* can also act as a molecular sponge of *miR-455-3p* to indirectly regulate the expression of the chemokine *CCL3*, leading to cartilage degradation.

The lncRNA X inactive specific transcript (*XIST*) has been extensively studied in many types of cancer, including colorectal cancer, pancreatic cancer, osteosarcoma, non-small cell lung cancer, and bladder cancer.[86,87] Wang et al[46] recently found that *XIST* promotes the degradation of ECM by acting as the ceRNA of *miR-1277-5p* in OA. *XIST* is upregulated in OA, while *miR-1277-5p* is downregulated. The detection of MMP-13 and ADAMTS5 showed that overexpression of *miR-1277-5p* could effectively reverse the degradation of ECM, and *XIST* could act as a molecular sponge of *miR-1277-5p* to competitively inhibit its function, resulting in increased expression of MMP-13 and ADAMTS5. In addition to the above-mentioned lncRNA, Zhu and Jiang[51] found increased expression of lncRNA *PART1* in cartilage of patients with OA and verified the interaction between the *PART1*, *miR-373-3p*, and SRY-associated high mobility protein 4 (*SOX4*) by double luciferase reporter assay and RNA immunoprecipitation (RIP). Sun et al[88] found that SOX4 led to the degradation of ECM. Takahata et al[89] believe that SOX4 induces cartilage degradation of OA by upregulating ADAMTS4 and ADAMTS5. In OA patients, the high expression of *PART1* upregulates the expression of *SOX4* through the ceRNA *miR-373-3p*, thus promoting the increased expression of MMP-13, ADAMTS4, and ADAMTS5, resulting in ECM degradation.[51] Interestingly, Lu et al[52] studied chondrocytes in OA patients and found that the expression of *PART1* in OA decreased. Silencing *PART1* in primary chondrocytes induced by interleukin (IL)-1β can reduce cell viability and induce apoptosis. It has been proven that *PART1*, as the ceRNA of *miR-590-3p*, regulates the TGFBR2/SMAD3 signalling pathway to inhibit the degradation and apoptosis of the ECM of OA chondrocytes. The results of these two studies on cartilage in patients with OA are thus diametrically opposed, and more experiments are needed to prove the role of *PART1* in OA.

LncRNAs regulate chondrocyte apoptosis. Apoptosis, also known as programmed cell death, is a programmed self-destruction process initiated by cysteinyl aspartate specific proteases (caspases) in disabled or damaged cells.[90] Disorders of apoptosis can lead to pathological conditions such as cancer, developmental abnormalities, and degenerative diseases.[91] In the process of apoptosis, cells exhibit distinct morphological characteristics such as cell contraction, plasma membrane blistering, chromatin condensation, DNA fragmentation, and apoptotic body formation.[92] Chondrocytes resist mechanical load by synthesizing ECM components and play a vital role in maintaining joint integrity and physiology.[93] It is well known that the decrease in the number of chondrocytes due to apoptosis is an important cause of cartilage degeneration in the development of OA.[94] In recent years, a large number of studies have found that there are a variety of abnormally expressed lncRNAs in chondrocytes during the pathogenesis of OA. Functional and mechanistic studies have shown that these lncRNAs regulate chondrocyte apoptosis at epigenetic, transcriptional, and post-transcriptional levels. LncRNA-growth arrest-special transcript 5 (*GAS5*) was originally identified from the subtracted complementary DNA (cDNA) library and its expression level was found to be increased with growth arrest in mammalian cells.[95] It is located at 1q25 and contains 11 introns and 12 exons. The exons are alternately spliced to produce two mature lncRNAs (*GAS5a* and *GAS5b*). The intron encodes a snoRNA of 10boxC/D. Because of the role of *GAS5* in cell growth inhibition and apoptosis, its abnormal expression has been found in many diseases.[96] Ji et al[54] found that the expression of *GAS5* was increased in OA chondrocytes, while silencing *GAS5* led to a decrease in the expression of tumour necrosis factor-α (TNF-α) and IL-6. Overexpression of *GAS5* inhibited the expression of *miR-34a* and promoted chondrocyte apoptosis.

H19 was the first lncRNA to be discovered.[97] It is located on chromosome 11p15.5 in the human genome, which is very close to the insulin-like growth factor 2 (*IGF2*) gene.[98] It is transcribed by RNA polymerase II into a non-coding RNA transcript of 2.3 kb and spliced to five exons. The *H19* sequence may contain a miRNA (*miR-675*), and can be used as the precursor of *miR-675* transfection to produce *miR-675*. Steck et al[55] found that *miR-675* regulates the expression of Col II, while proinflammatory cytokines IL-1β and TNF-α significantly downregulate the expression of *H19* and *miR-675*. Steck et al[55] believe that increasing the expression of *H19* can increase cartilage synthesis, reduce ECM degradation, and improve cartilage tissue regeneration. However, in several recent studies on *H19*, it was found that the expression of *H19* increased in chondrocytes treated with IL-1β and lipopolysaccharide (LPS). Zhang et al[99] found that *H19*, as the ceRNA of *miR-106a-5p*, could promote chondrocyte apoptosis, while Hu et al[56] found that *H19* could also promote chondrocyte apoptosis by acting as the ceRNA of *miR-130a*. Yang et al[57] found that *H19* can also be used as the ceRNA of *miR-140-5p* to promote chondrocyte apoptosis. LncRNAs can regulate the expression of multiple miRNAs through the ceRNA network, and these miRNAs can work together to promote or inhibit the progression of a disease. Two distinct results have been reported so far concerning the function and mechanism of *H19*. Further research is needed to explore the role of *H19* in the occurrence and development of OA.

Some studies have found that the lncRNA-plasmacytoma variant translocation 1 (*PVT1*) plays a key role in the occurrence and development of malignant tumours.[100] *PVT1* can act as a ceRNA, a variety of miRNA.[101,102] Lu et al[58] found that after stimulation of human chondrocytes with IL-1β, the expression of *PVT1* increased. Silencing *PVT1* enhanced the survival rate

and autophagy of cells treated with IL-1β, but inhibited apoptosis and inflammation. Silencing *PVT1* also antagonized the production of inflammatory factors including nitric oxide (NO) and cytokines such as prostaglandin E2 (PGE2), IL-6, IL-8, and TNF-α.[59] Overexpression of *miR-27b-3p* can reverse apoptosis and inflammation induced by *PVT1*, while TNF receptor-associated factor 3 (*TRAF3*) can weaken the inhibitory effect of *miR-27b-3p* on *PVT1*. Previous studies have suggested that *miR-27b-3p* and *TRAF3* can regulate the adenosine-monophosphate-activated protein kinase (AMPK) signalling pathway.[103] *PVT1* regulates chondrocyte apoptosis and inflammation through the *miR-27b-3p/TRAF3/*AMPK axis and participates in the occurrence of OA.

LncRNA differentiation-antagonizing non-protein-coding RNA (*DANCR*), formerly known as anti-differentiation non-coding RNA (*ANCR*), is located on human chromosome 4q12. It is reported to play an important role in a variety of cellular biological processes. Yuan et al[104] found that *DANCR* enhances the stemness features of hepatocellular carcinoma by reducing the expression of β-catenin (CTNNB1), promoting tumour formation and extrahepatic tumour colonization. In the cartilage of patients with OA, Zhang et al[60] found that the expression of *DANCR* was significantly increased, while silencing *DANCR* could significantly inhibit the expression of IL-6 and IL-8 in OA chondrocytes. *DANCR* also plays a role in promoting inflammation, cell proliferation, and anti-apoptosis as a ceRNA regulatory JAK2/signal transducer and transcriptional activator-3 (STAT3) signalling pathway of *miR-216a-5p*. Fan et al[61] also confirmed that DANCR can promote the proliferation of OA chondrocytes and reduce apoptosis through the *miR-577/SphK2* axis. In mouse ATDC5 cells, Yu et al[64] found that lncRNA cardiac hypertrophy related factor (*CHRF*) can also promote the apoptosis of OA chondrocytes through the JAK2/STAT3 signalling pathway.

LncRNA activated by TGF-β (*ATB*) is the first lncRNA that can be activated by TGF and has been found to be abnormal in breast cancer,[105] colon cancer,[106] and pancreatic cancer.[107] The imbalance of *ATB* can promote the growth, migration, and invasion of cancer cells in differentiated cancer.[108] Ying et al[65] found that the expression of *ATB* was downregulated in LPS-treated ATDC5 cells, while overexpression of *ATB* significantly reduced LPS-induced inflammatory damage in ATDC5 cells. Studies have further shown that lncRNA *ATB* inhibits the myeloid differentiation factor 88 (MyD88)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and p38MAPK signalling pathways by downregulating *miR-223* in cells, thereby reducing cell inflammation and apoptosis.[109] Other lncRNAs that can inhibit apoptosis in OA are NF-KappaB Interacting LncRNA (*NKILA*),[66] cardiac autophagy inhibitory factor (*CAIF*),[67] dynamin 3 opposite strand (*DNM3OS*),[68] and HOXA transcript antisense RNA myeloid-specific 1-1 (*HOTAIRM1-1*).[69] *NKILA* regulates cell proliferation and apoptosis through the *miR-145/SP1/NF-κB* axis. CAIF can downregulate *miR-1246* to inhibit the occurrence and development of OA. Overexpression of *DNM3OS* can upregulate the expression of insulin-like growth factor-1 (*IGF1*) to promote the proliferation of chondrocytes and inhibit apoptosis. *HOTAIRM1-1* can activate the janus kinase/mitogen-activated protein kinase/extracellular regulated protein kinases (JNK/MAPK/ERK) signalling pathway to inhibit apoptosis, and promote mesenchymal stem cells (MSC) activity and chondrogenic differentiation.

CIR is a lncRNA highly expressed in OA, discovered by Liu et al[24] using gene chip analysis. In addition, *CIR* can promote ECM degradation, promote chondrocyte apoptosis, and reduce chondrocyte autophagy. Lu et al[36] found that overexpression of *CIR* can inhibit the expression of *miR-130a* and promote the expression of B-cell lymphoma 2 (Bcl-2) interacting mediators of cell death (*BIM*) in chondrocytes stimulated by IL-1β or TNF-α, accompanied by increased levels of reactive oxygen species, release of inflammatory mediators, and apoptosis. Wang et al[110] found that silencing *CIR* increases expression of the autophagy-related proteins LC3BI/II and BECLIN-1 in cartilage of patients with OA. The above studies show that *CIR* is closely related to the occurrence and development of OA and can be used as a potential target for the treatment of OA. *HOTAIR*,[40] nuclear paraspeckle assembly transcript 1 (*NEAT1*),[62] *XIST*,[50] and *MEG3*[43,44] also regulate not only the metabolism of ECM but also the apoptosis of chondrocytes. Several studies have shown that *XIST* can promote apoptosis in OA chondrocytes. Li et al[49] found that *XIST* inhibits the proliferation of OA chondrocytes and promotes their apoptosis. In IL-1β-induced chondrocytes, *XIST*, as the ceRNA of *miR-211*, regulates the downstream MAPK signalling pathway by promoting the expression of *CXCR4*, which leads to reduced proliferation and increased apoptosis of chondrocytes. MAPK/ERK play an important role in inflammation and immune response.[47] Activation of the CXCR4/CXCL12 axis increases the expression of MAPK/ERK.[111] In addition, inhibition of the p38-MARK signalling pathway inhibits apoptosis of OA chondrocytes.[112] Also in IL-1β-induced primary chondrocytes, Sun et al[50] found that the increase of *XIST* was related to the decrease of Col2A1 and Bcl-2 and the increase of MMP13 and Bax. It is speculated that *XIST* may regulate the proliferation and apoptosis of chondrocytes through the *miR-142-5p*/small glutamine rich tetratricopeptide repeat containing beta (*SGTB*) axis.

LncRNAs regulate synoviocyte function. Synovitis is one of the most important pathological features of OA. Its histological features include synovial cell hypertrophy, proliferation, lining cell proliferation, and inflammatory cell infiltration. The stimulated synovial cells also secrete a large number of cytokines, chemokines, reactive oxygen species, lipids, lipid mediators, complement pathway components, and MMPs, which are all significantly increased in the synovial fluid of patients;[113] thus stimulating synovial tissue proliferation, causing cartilage tissue erosion,

and leading to cartilage matrix destruction, dissolution, and fibrosis. In contrast to chondrocytes, the increase in the number of synovial cells promotes the development of OA. Gastric cancer-associated transcript 3 (*GACAT3*) is a newly discovered lncRNA. Li et al[70] found that the expression of *GACAT3* was increased in osteoarthritis synovial cells (OAS), and the proliferation of OAS cells transfected with siRNA was significantly inhibited. In their experiment, the OAS cell cycle was blocked in G0/G1 phase, and the apoptosis rate increased. *GACAT3* affects the proliferation of OAS through the IL-6/STAT3 signalling pathway. In the synovium of the knee joint of OA rats, Yang et al[72] found that high expression of lncRNA *LOC101928134* regulates expression of the *IFNA1* gene and inhibits the JAK/STAT signalling pathway. Silencing *LOC101928134* inhibits the expression of IL-1β and TNF-α, which leads to the relief of knee synovitis, inflammatory injury, and knee cartilage injury in OA rats. In addition, silencing *LOC101928134* promotes the apoptosis of synovial cells and inhibits the apoptosis of chondrocytes in OA rats.

The antisense noncoding RNA in the INK4 locus (lncRNA *ANRIL*) is located in a full-length 3.8 kb sequence in the 9p21.3 region of the chromosome.[114] *ANRIL* is expressed in a variety of normal human tissues, with the highest expression in ovary and the lowest in muscle.[115] Genome-wide association studies (GWAS) have identified *ANRIL* as a risk site for a variety of cancers, including breast cancer, nasopharyngeal carcinoma, glioma, and others.[116] Li et al[71] found that the expression of *ANRIL* is increased in OAS cells, and *ANRIL* can act as a ceRNA of *miR-122-5p* to regulate the expression of dual specificity phosphatase 4 (*DUSP4*). Silencing *ANRIL* can block synovial cell proliferation and reduce apoptosis, while overexpression of *miR-122-5p* can have the same effect.

The lncRNA nuclear paraspeckle assembly transcript 1 (*NEAT1*) is transcribed from the transcriptional site of multiple endocrine neoplasia (MEN) type I located on human chromosome 11, and is involved in the occurrence and development of a variety of tumours including tumour cell proliferation, invasion, and metastasis.[117] *NEAT1* promotes the inflammation and apoptosis of chondrocytes in OA.[62] Wang et al[63] found that the expression of *NEAT1* and osteopontin (OPN) increased in OAS cells. OPN is reported to regulate the expression of a variety of inflammatory factors related to the pathogenesis of OA, including MMP13, IL-6, and IL-8. After *NEAT1* gene knockout, the expression of MMP13, IL-6, and IL-8 in synovial cells decreased, cell proliferation was inhibited, and the level of OPN protein decreased. *NEAT1*, which can inhibit synovial cell proliferation and promote synovial cell apoptosis, has a negative correlation with *miR-181c*. Other lncRNAs such as *HOTAIR*, *MEG3*, and prostate cancer gene expression marker 1 (*PCGEM1*) have also been reported to be involved in regulating the proliferation, apoptosis, and differentiation of synovial cells.[42,118] These lncRNAs are potential biomarkers and targets for the treatment of OA and synovitis.

LncRNAs regulate angiogenesis. Angiogenesis is very important for physiological processes such as tissue growth, development, regenerative circulation, and repair, but it also plays an important role in the pathological changes of some diseases. One study has suggested that OA is actually the activation of secondary ossification centres, resulting in repeated endochondral ossification.[119] Angiogenesis is an important link in the process of endochondral osteogenesis, which can lead to subchondral bone reconstruction, synovial hyperplasia, and osteophyte formation. There are no blood vessels in normal articular cartilage, but a large number of blood vessels can be found in OA cartilage. Other studies have pointed out that the invasion of blood vessels into cartilage destroys the barrier between articular bone and cartilage and aggravates the inflammatory reaction, which is an important factor leading to clinical symptoms and disease progression.[120] When normal articular cartilage was implanted into the chorioallantoic villi of chicken embryos, it retained its blood vessel-free character,[121] while cartilage derived from OA patients showed obvious vascular growth.[120] This indicates that normal cartilage has the ability to suppress angiogenesis, while this ability is significantly weakened in OA cartilage. Vascular endothelial growth factor (VEGF) is considered to be the key factor in angiogenesis. Inflammatory factors (IL-1β, TNF-α), hypoxia, and mechanical stress upregulate the expression of VEGF in OA joints through multiple signalling pathways.[122] The expression of VEGF in the surface, middle, and deep layers of OA cartilage has been shown to be upregulated, while angiogenesis mainly occurs in the deep cartilage.[120] The lncRNA-*MEG3* is a type of imprinted gene, which is located on chromosome 14q32.3. It is a human homologue of mouse maternally imprinted gene trap locus 2 (*Glt2*), which was first discovered by Miyoshi et al[123] in 2000. *MEG3* has been reported in previous studies to reduce ECM degradation in OA chondrocytes,[43,44] and the interaction between *MEG3* and SRY-associated high mobility protein-2 (*SOX2*) induces the expression of BMP4 to promote osteogenic differentiation of bone marrow mesenchymal stem cells.[124] In addition, other studies have pointed out that overexpression of *MEG3* leads to downregulation of the serine/threonine-specific protein kinase (known as protein kinase B (AKT)) signalling pathway in breast cancer, and the AKT signalling pathway plays a key role in the growth, invasion, and angiogenesis of breast cancer cells.[125] By comparing chondrocytes between patients with OA and normal controls, Su et al[25] found that the expression of *MEG3* in articular cartilage of OA was significantly downregulated and the expression of VEGF was significantly upregulated. Other studies have found that *MEG3* can stimulate the transcription of *p53*,[126] and *p53* negatively regulates the transcription of *VEGF* by binding to the transcription factor Sp1 site on the *VEGF* promoter.[127] Therefore, downregulation of *MEG3* in OA cartilage may promote the transcription of *VEGF* by reducing the activity of *p53*, which leads to angiogenesis

in OA cartilage. Sphingosine kinase 1 (SPHK1), a member of the sphingosine kinase (SPHK) family, has been shown to play a vital role in cell migration.[128] Some studies have shown that SPHK1 is involved in angiogenesis. In the absence of ECM, the overexpression of SPHK1 promotes the survival of endothelial cells and plays an important role in angiogenesis.[129] Minashima et al[130] found that the interaction between ankylosis protein/MYB binding protein 1a (ANK/MYBBP1a) and SPHK1 can affect catabolism in the process of cartilage degradation mediated by IL-1β. Studies have shown that SPHK1 can promote the development of OA. Chen et al[73] found that the lncRNAs *LINC00917* and *CTD-2246P4.1* regulate angiogenesis by affecting *SPHK1* and play an important role in the progression of OA.

In conclusion, the pathogenesis of OA is complex and has not been elucidated so far. Although many studies have partially revealed the regulatory mechanism of OA and explored the treatment of OA-related diseases, the results are still not satisfactory. As a new hot topic in the regulation of gene expression, lncRNA may play a key role in the pathogenesis of OA by regulating extrachondral matrix metabolism, chondrocyte apoptosis, synovial hyperplasia, and peripheral neovascularization. Through continuous research, it has been found that thousands of lncRNAs are differentially expressed in OA, and some of the maladjusted lncRNAs have potential as valuable diagnostic biomarkers and therapeutic targets. Once a new lncRNA is found, its function should be clarified and verified in vivo and in vitro. However, in the process of verifying the function of a lncRNA, because lncRNAs are not conserved among species there are often no homologous genes in animals. It is therefore not easy to find an in vivo model to test the function and mechanism of lncRNA in detail. Consequently, many animal models of lncRNA knockouts are constructed on the basis of gene disruption, targeted promoter deletions, and premature termination strategies.[131,132] The use of lncRNAs as an approach to treat cartilage-related disease is in its infancy. In the near future, lncRNA targeted therapy may become a new hope for the cure of OA. Through advanced technology, knockout or overexpression of key lncRNAs may become a feasible method for the treatment of cartilage-related diseases in future.[133] For example, since 2010 several new delivery strategies have been developed to reduce off-target effects, especially using nanoparticles which have the characteristics of improved stability, minimal size, biocompatibility, and self-assembly.[134] This also allows nanoparticles to improve the stability and targeting of lncRNA. However, silencing of *MEG3* aggravates LPS-stimulated human lung cell injury,[135] while silencing *NEAT1* can inhibit immunity[136] and silencing digeorge syndrome critical region gene 5 (*DGCR5*) can enhance the growth, migration, and invasion of cervical cancer.[136] If targeted knockout or overexpression of OA-related lncRNA is planned as a treatment for OA, it will first be necessary to pay attention to the side effects of the knockout or overexpression of the lncRNA. The specific mechanisms and functions of these OA-related lncRNAs need to be further studied and investigated, taking in vitro chondrocytes, OA animal models, and OA patients as the research objects. This is in order to further discover and verify the influence of lncRNA on the pathogenesis and pathological changes of OA, and lay the foundation for its diagnosis, prognosis, prevention, and treatment.

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