# SYSTEMATIC REVIEW

## The function of lncRNAs in the pathogenesis of osteoarthritis

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...
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. 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). 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. 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, while transcriptional regulation includes lncRNA regulation of insulator function, interference with gene transcription, and control of transcription factors. Meanwhile, post-transcriptional regulation involves variable splicing of genes and subcellular localization of RNA, as well as binding to specific proteins to regulate protein activity as a structural component or by changing protein localization. As a precursor of small RNA, lncRNA can be processed into miRNA and piRNA by ribonucleases (RNases). Salmena et al found that lncRNA has a miRNA action site and can also compete with miRNA; that is, it acts as a competitive endogenous RNA (ceRNA).

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. Some lncRNAs are defined as key regulatory factors in the pathogenesis and development of OA. 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 1. Abnormally expressed long non-coding RNAs described in the text and their functions.

| IncRNA gene name | Expression | Related factor | Function† | Tissue/cell |
|------------------|------------|----------------|-----------|-------------|
| TM1P3            | up         | miR-22/TGF-β/MMP13 | ECM degradation (+) | Human primary chondrocytes |
|                  |            | miR-27b/MMP13    | ECM degradation (+) | Human primary chondrocytes |
|                  |            | miR-130a/BIM56   | Chondrocyte apoptosis (+) | Human primary chondrocytes |
| HOTAIR           | up         | miR-17-5p/FUT2/Wnt/β-catenin50 | ECM degradation (+); Chondrocyte apoptosis (+) | Human primary chondrocytes |
|                  |            | miR-130a-3p83    | Chondrocyte apoptosis (+) | Human primary chondrocytes |
|                  |            | Wnt/β-catenin82  | Synovial cells proliferation (+); Synovial cells apoptosis (-) | Rat synoviocytes |
| MEG3             | down       | miR-361-5p/FOXO141 | ECM degradation (-) | Human primary chondrocytes |
|                  |            | miR-93/TGFBR244  | ECM degradation (-) | Human primary chondrocytes |
|                  |            |                 | Chondrocyte apoptosis (-) | Rat chondrocytes |
|                  |            | VEGF23          | Vascular invasion (-) | Human primary chondrocytes |
| HOTTIP           | up         | miR-455-3p/CCL355 | ECM degradation (+) | Human primary chondrocytes |
| XIST             | up         | miR-1277-5p46   | ECM degradation (+) | Human primary chondrocytes |
|                  |            | TIMP-3354       | ECM degradation (+) | Human primary chondrocytes |
|                  |            | miR-211/CXCR449 | Chondrocyte apoptosis (+) | Primary chondrocytes |
|                  |            | miR-142-5p/SCGTB40 | Chondrocyte apoptosis (+) | SW1353 (human osteosarcoma cells) |
| PART1            | up         | miR-373-3p/5OX411 | ECM degradation (+) | Human primary chondrocytes |
|                  | down       | miR-590-3p/TGFBR2/Smad352 | ECM degradation (-); Chondrocyte apoptosis (-) | Human primary chondrocytes |
| SNHG15           | down       | miR-7/KLF4      | ECM degradation (-) | Human primary chondrocytes |
| LINC01534        | up         | miR140-5p13     | ECM degradation (+) | Human primary chondrocytes |
| GASS             | up         | miR-34a/Bcl-2134 | Chondrocyte apoptosis (+) | Human primary chondrocytes |
| H19              | down       | miR-61515      | ECM degradation (-) | Human primary chondrocytes |
|                  | up         | miR-130a2720    | Chondrocyte apoptosis (+) | Human primary chondrocytes |
|                  | up         | miR-106a-5p24    | Chondrocyte apoptosis (+) | Human primary chondrocytes |
|                  | up         | miR-140-5p27    | Chondrocyte apoptosis (+) | Human primary chondrocytes |
| PVT1             | up         | miR-27b-3p/TRAF358 | Chondrocyte apoptosis (+) | Human primary chondrocytes |
|                  |            | miR-14959       | Inflammatory response (+) | Human primary chondrocytes |
| DANCR            | up         | miR-216a-5p/JAK1/STAT350 | Cartilage regeneration (+); Chondrocyte apoptosis (-) | Human primary chondrocytes |
|                  |            | miR-577/SphK2261 | Chondrocyte apoptosis (-) | Human primary chondrocytes |
| NEAT1            | up         | miR-193a-3p/SOX552 | Inflammatory response (+); Chondrocyte apoptosis (+) | Human primary chondrocytes |
| CHRF             | up         | miR-181c/OPN363 | Synovial cells proliferation (+) | Human synoviocytes |
| ATB              | down       | miR-223/MyD88/NF-κB46 | Inflammatory response (-); Chondrocyte apoptosis (-) | ATDCS cells (mouse embryonic tumour cells) |
| NKILA            | down       | miR-145/SP1/NFκB46 | Cartilage regeneration (+); Chondrocyte apoptosis (-) | Human primary chondrocytes |

Continued
osteogenesis, and proteolytic enzyme hydrolyze protein, chondrocyte apoptosis, and other biological processes. Compared with miRNA, IncRNA 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 IncRNA is more conservative. With the development of bioinformatics and high-throughput sequencing, more and more studies have reported that IncRNA can affect biological processes such as cell proliferation, apoptosis, and differentiation, and affect the occurrence and prognosis of diseases. Fu et al identified 4,714 differentially expressed IncRNAs in knee cartilage of OA and non-OA patients using gene chip and bioinformatics techniques. Liu et al identified 153 IncRNAs differentially expressed in OA patients using gene technology, and considered that IncRNA-cartilage injury-related (CIR) is the key to matrix degradation of chondrocytes. 

| IncRNA gene name | Expression† | Related factor | Function‡ | Tissue/cell |
|------------------|-------------|----------------|-----------|-------------|
| CAIF down        | miR-1246    | Chondrocyte apoptosis (-) | CHON-001 cells (fibroblast immortalized with hTERT) |
| DNM3OS down      | miR-126/GF1  | Chondrocyte apoptosis (-) | CHON-001 cells (fibroblast immortalized with hTERT) |
| HOTAIRM1-1 down  | miR-125b/BMPR2 | Chondrocyte apoptosis (-) | Human primary chondrocytes |
| GACAT3 up        | IL-6/STAT3   | Synovial cells proliferation (+) | Human synoviocytes |
| ANRIL up         | miR-122-5p/DUSP4 | Synovial cells proliferation (+) | Human synoviocytes |
| LOC101928134 up  | IFNA1/JAK/STAT | Synovial cells proliferation (+) | Rat synoviocytes |
| LINC00917 up     | SPHK1      | Vascular invasion (-) | Human chondrocytes |
| CTD-2246P4.1 up  | SPHK1      | Vascular invasion (-) | Human chondrocytes |

*Long non-coding RNA expression during osteoarthritis.
†(+) means promotion, (-) means inhibition.
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 cartilage.24 In another study by Li et al.,37 lncRNA-miR-22/ALK1/MMP13 degradation through the miR-22/ALK1/MMP13 axis in OA. 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 inhibition of lncRNA-CIR 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.78

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.

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.84 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.85 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 may promote ECM degradation from the 5’ end of the HOXA gene.85 With downregulation of the HOXA13 gene, its expression increases significantly, and the level of integrin-α-1(ITGa1) decreases significantly after HOXA-13 siRNA is introduced into human OA chondrocytes.85 Overexpression of ITGa1 promotes cartilage formation, while mice lacking ITGa1 develop degenerated cartilage at a younger age and show an increase in (ITGa2) synthesis. HOTTIP may promote ECM degradation.
in chondrocytes by inhibiting the HOXA-13/ITGa1/MMP2 signalling pathway.\(^9\) 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.\(^{66,67}\) 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 ADAMTSS 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 ADAMTSS. 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\(^{46}\) believe that SOX4 induces chondrocyte apoptosis at epigenetic, transcriptional, and post-transcriptional levels. LncRNA-growth arrest-special transcript 5 (GASS) 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.\(^9\) It is located at 1q25 and contains 11 introns and 12 exons. The exons are alternately spliced to produce two mature lncRNAs (GASSa and GASSb). The intron encodes a snoRNA of 10boxC/D. Because of the role of GASS 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 GASS was increased in OA chondrocytes, while silencing GASS led to a decrease in the expression of tumour necrosis factor-α (TNF-α) and IL-6. Overexpression of GASS 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\(^{100}\) found that H19 could also promote chondrocyte apoptosis by acting as the ceRNA of miR-130a. Yang et al\(^{101}\) 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.69 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 al104 found that DANCR enhances the stemness features of hepaticcellular 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 al60 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 al61 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 al64 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 al65 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 IncRNA ATB inhibits the myeloid differentiation factor 88 (MyD88)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and p38 MAPK signalling pathways by downregulating miR-223 in cells, thereby reducing cell inflammation and apoptosis.109 Other IncRNAs that can inhibit apoptosis in OA are NF-KappaB Interacting LncRNA (NKILA).66 cardiac autophagy inhibitory factor (CAIF).67 Dynamic 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 kinase (JNK/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 al104 using gene chip analysis. In addition, CIR can promote ECM degradation, promote chondrocyte apoptosis, and reduce chondrocyte autophagy. Lu et al106 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 al110 found that silencing CIR increases expression of the autophagy-related proteins LC3B/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,109 nuclear paraspeckle assembly transcript 1 (NEAT1),62 XIST,64 and MEG343,44 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 al50 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.67 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 al10 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 IncRNA. Li et al.\(^{10}\) 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.\(^{12}\) found that high expression of IncRNA 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 (IncRNA ANRIL) is located in a full-length 3.8 kb sequence in the 9p21.3 region of the chromosome.\(^{11}\) ANRIL is expressed in a variety of normal human tissues, with the highest expression in ovary and the lowest in muscle.\(^{12}\) 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.\(^{13}\) Li et al.\(^{14}\) 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 IncRNA 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.\(^{15}\) NEAT1 promotes the inflammation and apoptosis of chondrocytes in OA.\(^{16}\) Wang et al.\(^{17}\) 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 IncRNAs 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.\(^{18}\) These IncRNAs 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 enchondral ossification.\(^{119}\) Angiogenesis is an important link in the process of enchondral 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.\(^{122}\) 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.\(^{123}\) 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.\(^{124}\) The IncRNA-MEG3 is a type of imprint-ed 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.\(^{125}\) in 2000. MEG3 has been reported in previous studies to reduce ECM degradation in OA chondrocytes,\(^{41,44}\) 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.\(^{126}\) 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.\(^{127}\) By comparing chondrocytes between patients with OA and normal controls, Su et al.\(^{128}\) 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,\(^{129}\) 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 al130 found that the interaction between ankylosis protein/MB binding protein 1a (ANK/MBBP1a) 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 al131 found that the IncRNAs 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, IncRNA may play a key role in the pathogenesis of OA by regulating extrachondal matrix metabolism, chondrocyte apoptosis, synovial hyperplasia, and peripheral neovascularization. Through continuous research, it has been found that thousands of IncRNAs are differentially expressed in OA, and some of the maladjusted IncRNAs have potential as valuable diagnostic biomarkers and therapeutic targets. Once a new IncRNA is found, its function should be clarified in vivo and in vitro. However, in the process of verifying the function of a IncRNA, because IncRNAs 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 IncRNA in detail. Consequently, many animal models of IncRNA knockouts are constructed on the basis of gene disruption, targeted promoter deletions, and premature termination strategies.131,132 The use of IncRNAs as an approach to treat cartilage-related disease is in its infancy. In the near future, IncRNA targeted therapy may become a new hope for the cure of OA. Through advanced technology, knockout or overexpression of key IncRNAs 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 IncRNA. However, silencing of MEG3 aggravates LPS-stimulated human lung cell injury,135 while silencing NEAT1 can inhibit immunity136 and silencing dgeorge syndrome critical region gene 5 (DGC5R5) can enhance the growth, migration, and invasion of cervical cancer.136 If targeted knockout or overexpression of OA-related IncRNA 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 IncRNA. The specific mechanisms and functions of these OA-related IncRNAs need to be further studied and investigated, taking in vitro chondrocyte, OA animal models, and OA patients as the research objects. This is in order to further discover and verify the influence of IncRNA on the pathogenesis and pathological changes of OA, and lay the foundation for its diagnosis, prognosis, prevention, and treatment.

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Author information:

- C. P. He, MM, Surgeon
- X. C. Jiang, MM, Surgeon
- C. Chen, MD, Chief Surgeon, Associate Dean
- W. D. Cao, MM, Surgeon
- Q. Wu, MM, Surgeon
- Department of Orthopedics, The Second Affiliated Hospital, Hunan Normal University, Hunan, China.
- H. B. Zhang, MM, Surgeon, Department of Orthopedics, The Xiangya Hospital of Central South University Changsha, Hunan, China.
- C. Ma, MM, Attending Surgeon, Department of Orthopedics, The First Affiliated Hospital (People’s Hospital of Xiangxi Autonomous Prefecture), Jishou University, Jishou, China.

Author contributions:

- C. P. He: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- X. C. Jiang: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- C. Chen: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- H. B. Zhang: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- W. D. Cao: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- Q. Wu: Collected, assembled, analyzed, and interpreted the data, Critically revised the article for important intellectual content.
- C. Ma: Created the illustrations, Checked and modified the references.

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- The authors declare that they have no conflict of interest.

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