Roles of long non-coding RNA in osteoarthritis (Review)

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Abstract. Osteoarthritis (OA) is a chronic bone and joint disease characterized by articular cartilage degeneration and joint inflammation and is the most common form of arthritis. The clinical manifestations of OA are chronic pain and joint activity disorder, which severely affect the patient quality of life. Long non-coding RNA (lncRNA) is a class of RNA molecules >200 nucleotides long that are expressed in animals, plants, yeast, prokaryotes and viruses. lncRNA molecules lack an open reading frame and are not translated into protein. The present review collated the results of recent studies on the role of lncRNA in the pathogenesis of OA to provide information for the prevention, diagnosis and treatment of OA.

Contents

1. Introduction

Osteoarthritis (OA) is a chronic bone and joint disease characterized by articular cartilage degeneration and joint inflammation (1). OA is the most common form of arthritis, and the main clinical manifestations of OA are chronic pain and joint activity disorder (1), which severely affect quality of life. OA is most common in middle-aged and elderly individuals (2-3). The pathogenesis of OA is complex, and its etiology remains unclear. At present, the occurrence of OA is considered to be associated with various risk factors including mechanical, genetic and physical factors (4-6). A number of these factors, such as age, sex, obesity and bone density, increase the risk of OA; age has been reported to be an independent risk factor (4-6). The treatment of OA aims to alleviate or control pain, delay or prevent disease progression, improve or reconstruct joint function, correct deformity and ensure quality of life. OA treatment is based on the combination of disease education, sports activity guidance, drug and, if necessary, surgical treatment. In addition, an individualized treatment plan may be developed considering the patient's age, sex, location, OA extent, symptoms and underlying diseases. However, the clinical results obtained by conventional treatment are poor, and the risk of side effects is high (7). Therefore, elucidating the pathological mechanism of OA may be helpful in finding novel specific biomarkers that can contribute to the development of effective treatments for controlling the symptoms of OA.

The human genome is estimated to contain ~2% protein-coding RNA, whereas the vast majority of the genome comprises non-protein-coding RNA (8,9). According to their sequence length, non-coding RNA molecules are divided into two categories: i) Small non-coding RNAs, including microRNA (miRNA), ribosomal, small nucleolar, piwi-interacting and small interfering RNA; and ii) long non-coding RNA (lncRNA) (10-13). The latter category includes circular RNA, a class of lncRNA abundantly expressed and highly conserved in mammals (14) that are mainly derived from transcripts of exon or intron splicing (15).

lncRNA is a class of RNA molecules >200 nucleotides long expressed including animals, plants, yeast, prokaryotes and viruses (16,17). lncRNAs lack an obvious open reading frame and do not serve the function of translation into protein (18). Numerous lncRNAs are named according to their host protein-coding gene. Based on the process through which they are generated from host protein-coding genes, lncRNAs are divided into five major classes: i) Long intergenic lncRNA, transcribed from intergenic regions; ii) intronic lncRNA, completely transcribed from introns; iii) sense lncRNA, transcribed from the sense strand of a protein-coding gene, including gene coding sequences of exons or introns; iv) antisense lncRNA, transcribed from the antisense strand of a protein-coding gene; and v) bidirectional lncRNA, transcribed in the opposite direction of

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Abbreviations: ECM, extracellular matrix; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; MB, methylene blue; miRNA, microRNA; OA, osteoarthritis; RBP, RNA-binding protein

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the protein-coding gene and its exons (16). In humans, the synthesis of lncRNA is similar to that of mRNA; following splicing, it is modified by the addition of a 5' cap and 3' polyadenylation, resulting in the lncRNA obtaining transcriptional activation functions (19).

Previous studies have reported that the epigenetic effects of histone modification, DNA methylation and non-coding RNA may promote the pathological development of OA (20). lncRNAs can be used as diagnostic and therapeutic biomarkers for evaluating OA progression and prognosis (21,22). The present review collated the findings of recent studies on the roles of lncRNA in the pathogenesis of OA to provide information for the prevention, diagnosis and treatment of OA.

2. Biological functions of lncRNA

lncRNAs function by regulating the epigenetic state of their proximal and distal protein-coding genes via cis- and trans-acting mechanisms (23,24). lncRNAs mediate gene expression at the transcriptional, RNA processing and translational levels mainly by binding to chromatin-modifying complexes and acting as scaffolding modifiers, or by binding to transcription factors as transcriptional co-regulators (23,24). lncRNAs control gene transcription in several manners: By regulating transcription factor combination and assembly (25); by forming three-chain complexes with regulatory sequences of protein-coding genes (26); and by binding to RNA polymerase II in order to interfere with the transcription process (27). In addition, lncRNAs control chromatin remodeling and histone modification, and also interact with miRNAs to participate in numerous biological processes, including embryonic development, cell growth, cell proliferation, cell cycle, gene transcription, splicing, translation, cell structure maintenance, chromatin remodeling, apoptosis, immune and heat shock responses (28-30). Deregulation of lncRNA expression may be involved in various types of cancer and inflammatory diseases (31,32).

Chondrocytes are the only cells in the articular cartilage; extracellular matrix (ECM) degradation, chondrocyte apoptosis and cytokine production are crucial for the pathological progression of OA (33,34). lncRNAs serve important roles in the development of bone and cartilage, and their abnormal expression in OA cartilage promotes the degradation of the cartilage ECM (33,34). By contrast, modulation of lncRNAs may lead to the inhibition of ECM degradation, reduction in chondrocyte apoptosis and an inflammatory response that may delay the pathological progression of OA (33,34).

3. Relationship between lncRNAs and osteoarthritis

Previous studies have reported that lncRNAs are involved in the development of numerous diseases, such as cancer, metabolic, cardiovascular, neurodegenerative and mental disorders (35,36). However, the role of lncRNAs in the pathogenesis of OA is not well understood. In the OA cartilage tissue, certain lncRNAs are expressed at high levels, whereas others are expressed at low levels. Previous studies have reported that compared with healthy cartilage tissue, the expression levels of six lncRNAs [homeobox transcript antisense RNA (HOTAIR), growth arrest-specific transcript 5 (GAS5), PMS1 homolog 2 mismatch repair system component pseudogene 2 (PMS2P2), RP11-445H22.4, H19 and CTD-2574D22.4] are upregulated in OA cartilage, and this upregulation may serve a role in the pathogenesis of OA by increasing the mRNA expression levels of MMP9, MMP13, bone morphogenic protein 2 and the disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) (36). Another study has demonstrated that compared with healthy cartilage tissue, expression levels of the lncRNA maternal expression gene 3 (MEG3) are downregulated in OA cartilage, whereas vascular endothelial growth factor (VEGF) expression levels are upregulated, with a significant correlation between the two (37). VEGF has been reported to promote hypertrophic cartilage remodeling, ossification and vascular invasion of the cartilage-subchondral bone junction, thus serving an important role in the progression of OA (38). Taken together, these studies suggest that various lncRNAs may modulate the pathological progression of OA.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). MALAT1 is expressed in numerous tissues and is involved in certain diseases and biological processes; the expression of MALAT1 is upregulated in various types of cancer, such as lung cancer (39). Upregulation of MALAT1 promotes cell proliferation and inhibits apoptosis, whereas its downregulation inhibits cell proliferation and promotes apoptosis (39). A previous study has reported that MALAT1 is involved in the pathological process of OA, where its levels are upregulated together with AKT3 compared with those in healthy cartillage, whereas the levels of miR-150-5p are downregulated (40). This suggests that the expression levels of miR-150-5p is negatively associated with those of MALAT1 and AKT3. In addition, overexpression of MALAT1 inhibits the expression of miR-150-5p and promotes that of AKT3 (40). Overexpression of MALAT1 also reduces the expression of MMP13 and ADAMTS-5 and promotes the expression of type II collagen and aggrecan in chondrocytes treated with IL-1β (40). Furthermore, overexpression of MALAT1 inhibits apoptosis and ECM degradation, whereas the overexpression of miR-150-5p has the opposite effect; lncRNA MALAT1 has been reported to participate in OA via the miR-150-5p/AKT3 axis (40). Pan *et al* (41) have demonstrated that MALAT1 attenuates lipopolysaccharide (LPS)-induced inflammatory injury in ATDC5 cells by upregulating the levels of miR-19b and inhibiting the Wnt/β-catenin and NF-κB pathways, and provides a potential target for the diagnosis and treatment of OA. Another study has reported that MALAT1 binds directly to miR-127-5p to inhibit its activity, increase the expression levels of osteopontin and promote chondrocyte proliferation via the PI3K/Akt pathway, which constitutes another target for the treatment of OA (42).

MEG3 lncRNA. A previous study has demonstrated a negative correlation between MEG3 lncRNA and VEGF levels in patients with OA (37). Li *et al* (43) have reported that Methylene blue (MB) attenuates OA-related pain by upregulating the expression levels of MEG3 lncRNA, and that MEG3 inhibits P2X purinoceptor 3 (P2X3) expression in a rabbit OA model and alleviates OA-related inflammation. Chen *et al* (44) have demonstrated that the levels of MEG3 are upregulated in OA compared with those in normal cartilage tissue, and that

transforming growth factor-β receptor type II (TGFBR2) is a direct target of miR-93 and is involved in the progression of OA; lncRNA MEG3 targets the miR-93/TGFBR2 axis, inhibits the degradation of cartilage ECM and delays the progression of OA (45). Another has reported that knockdown of MEG3 attenuates LPS-induced inflammatory damage in ATPS5 cells by modulating miR-203 expression (46). In addition, miR-203 stimulates Sirt1 expression, and Sirt1 mediates the PI3K/AKT and NF-κB pathways to attenuate LPS-induced inflammatory damage (46). Sirt1 is a key factor in the induction of OA, and the reduction of Sirt1 in chondrocytes may lead to chondrocyte hypertrophy and cartilage matrix loss (47). With the development of OA, the expression levels of Sirt1 are reduced, promoting the production of inflammatory factors (48). Additionally, Xu and Xu (49) have demonstrated that, in a rat OA model, silencing of MEG3 exerts antiproliferative and proapoptotic effects through the miR-16/SMAD7 axis, inhibits rat chondrocyte proliferation and promotes apoptosis.

HOTAIR. HOTAIR serves an important role in cancer progression, such as gastrointestinal stromal tumors, breast and pancreatic cancer (50). A previous study has demonstrated that HOTAIR is expressed in the human cartilage (36). In addition, the levels of α-1,2 fucosyltransferase 2 (FUT2) are upregulated in OA compared with those in healthy cartilage tissue (51). Hu *et al* (52) have reported that HOTAIR and FUT2 are upregulated in OA cartilage compared with healthy cartilage tissue, aggravating ECM degradation and chondrocyte apoptosis and promoting OA progression through the Wnt/β-catenin pathway. HOTAIR and ADAMTS-5 have also been reported to be upregulated in OA cartilage, aggravate ECM degradation and promote OA progression (53). Inhibition of HOTAIR expression may be a novel strategy for human OA therapy.

H19 lncRNA. H19 is a maternal-expressed lncRNA that regulates the inflammatory response (54). Hu *et al* (54) have reported that H19 lncRNA is highly expressed in OA chondrocytes and aggravates LPS-induced C28/I2 cell injury by inhibiting miR-130a. Another study has confirmed that H19 lncRNA induces chondrocyte damage by promoting the expression of miR-675 (55), suggesting that H19 lncRNA acts on miRNAs to promote the progress of OA.

X-inactive-specific transcript (XIST) lncRNA. The lncRNA XIST is involved in the pathogenesis of various types of cancer, such as bladder cancer (56). A previous study has reported that XIST is upregulated in OA cartilage compared with healthy cartilage tissue (22). XIST acts as a competitive endogenous RNA of miR-1277-5p in OA, promoting the expression of MMP-13 and ADAMTS5 and degrading the ECM; downregulation of XIST protects the ECM (57). Previous studies have reported that a specific receptor for chemokine stromal cell-derived factor-1 termed C-X-C chemokine receptor 4 (CXCR4) serves a key role in cartilage damage and repair (58-61). XIST has also been demonstrated to promote the proliferation and apoptosis of OA chondrocytes via the miR-211/CXCR4 axis (62). Therefore, inhibition of XIST expression may delay OA progression.

FOXD2-adjacent opposite strand RNA 1 (FOXD2-AS1) lncRNA. A previous study has demonstrated that FOXD2-AS1 promotes the degradation of ECM (63). Toll-like receptors (TLRs) are pattern recognition receptors that are involved in the inflammatory process (64,65), and TLR4 may serve a key role in the progression of OA (66). Wang *et al* (67) have reported that the levels of FOXD2-AS1 are upregulated in OA compared with those in healthy cartilage tissue, and overexpression of FOXD2-AS1 upregulates TLR4 expression levels via miR-27a-3p, inducing inflammation and ECM degradation, and promoting OA progression. Cyclin D1 (CCND1) is a regulator of OA progression, and CCND1 gene silencing has been demonstrated to promote IL-1β-induced apoptosis in rat chondrocytes (68). Cao *et al* (69) have reported that FOXD2-AS1 knockdown significantly inhibits the expression of CCND1 at the mRNA and protein levels. Therefore, high expression levels of FOXD2-AS1 may promote the expression of CCND1 by inhibiting the expression of miR-206, promoting the viability of chondrocytes in OA, and FOXD2-AS1 may represent a potential target for the treatment of OA.

GAS5. GAS5 exerts a tumor-suppressive effect, which promotes apoptosis and inhibits the proliferation of various types of cancer cells, such as hepatocellular carcinoma and breast cancer (70-72). GAS5 expression levels are downregulated in OA chondrocytes compared with those in healthy cartilage tissue, and overexpression of GAS5 may ameliorate LPS-induced inflammatory damage in ATPS5 chondrocytes by inhibiting the NF-κB and Notch signaling pathways. Kruppel-like factor 2 is the target of GAS5 (73). However, another study has demonstrated that GAS5 levels are upregulated in OA chondrocytes,compared with those in healthy cartilage tissue, and that it increases the expression of MMPs, stimulates apoptosis and inhibits autophagy (74). GAS5 participates in the pathogenesis of OA by negatively regulating miR-21 (74). Therefore, the specific mechanism of GAS5 in OA pathological processes require further study.

Cartilage injury-related (CIR) lncRNA. The lncRNA CIR is associated with ECM degradation and serves a key role in the pathogenesis of OA (21). Dysregulation of autophagy-related gene expression is involved in the pathogenesis of OA (75-77). Wang *et al* (78) have demonstrated that CIR is highly expressed in OA and increases MMP-3 expression levels by activating autophagy, reduces the levels of collagen type II α1 and promotes OA progression. Another study has confirmed that CIR is significantly upregulated in patients with OA compared with healthy subjects, and that overexpression of CIR increases the expression levels of MMP-13, whereas miR-27 inhibits the expression of MMP-13 (79). These changes can be detected in the target tissue or serum. CIR is involved in the degradation of ECM in OA chondrocytes via the CIR/miR-27/MMP-13 axis (79). Therefore, CIR may represent a novel target for the treatment of OA.

Differentiation antagonizing non-protein coding RNA (DANCR). A previous study has demonstrated that DANCR promotes human mesenchymal stem cell proliferation and chondrogenic differentiation by upregulating the expression of Smad3 and STAT3 (80). A recent study has reported that

DANCR promotes the proliferation of OA chondrocytes and inhibits apoptosis by regulating the miR-216a-5p/JAK2/STAT3 signaling pathway; DANCR may be a useful biomarker and a potential therapeutic target for OA (81). Zhang *et al* (80) have also demonstrated that DANCR activates cartilage formation in synovium-derived mesenchymal stem cells by upregulating Smad3 and STAT3. Sphingosine kinase (SPHK) is the major limiting enzyme for sphingoid-based phosphate synthesis in cells and has two isotypes, Sphk1 and SphK2. SPHK2 can promote apoptosis and inhibit cell proliferation (82,83). A previous study has demonstrated that DANCR may promote OA chondrocyte proliferation and reduce apoptosis through the miR-577/SPHK2 axis (84), suggesting that DANCR lncRNA may be a potential therapeutic target for OA.

Other lncRNAs. Myocardial infarction-associated transcript (MIAT), also termed retinal non-coding RNA 2 or Gomafu, is a functional lncRNA associated with the risk of myocardial infarction (85) that is involved in numerous diseases, such as neurological diseases (86), neovascularization disease (87) and cancer, such as neuroendocrine prostate cancer (88). MIAT has been reported to be involved in the inflammatory response in diseases such as myocardial infarction, schizophrenia, ischemic stroke, diabetes complications, age-related cataract and cancer (89). miR-132 is one of the miRNAs that regulate chondrogenic differentiation (90); a previous study has demonstrated that miR-132 is a downstream effector of MIAT, through which MIAT exerts its biological functions (91). A recent study has reported that silencing MIAT protects ATDC5 cells from LPS-induced damage, potentially by upregulating the expression levels of miR-132 and inhibiting the NF-κB and JNK pathways (92).

The plasmacytoma variant translocation 1 (PVT1) lncRNA is located at human 8q24.21 and is dysregulated in various diseases, such as OA (36). The levels of PVT1 are upregulated in patients with OA compared those in healthy subjects (36). A recent study has demonstrated that PVT1 lncRNA directly binds to miR-149 to inhibit its expression and activity. Overexpression of PVT1 lncRNA promotes OA progression by aggravating cartilage imbalance, leading to catabolism and an inflammatory response (93). Li *et al* (94) have reported that the expression levels of PVT1 lncRNA are upregulated in OA chondrocytes compared with those in healthy cartilage tissue, whereas its overexpression promotes normal chondrocyte apoptosis. Further experiments have revealed that PVT1 lncRNA regulates chondrocyte apoptosis by sponging miR-488-3p in OA.

lncRNA PTGS2 antisense NFKB1 complex-mediated expression regulator RNA (PACER) is associated with chondrocyte inflammation, which contributes to OA (38). A previous study has demonstrated that the levels of PACER are downregulated in OA compared with those in healthy cartilage tissue, whereas the levels of HOTAIR are upregulated, and PACER overexpression inhibits chondrocyte apoptosis by downregulating the levels of HOTAIR, thus delaying OA (95). Cancer susceptibility 2 (CASC2) lncRNA is a tumor suppressor that inhibits cell proliferation and promotes apoptosis (96,97). A previous study has reported that the expression levels of CASC2 lncRNA are upregulated in the plasma of patients with OA compared with those in healthy subjects; overexpression of CASC2 lncRNA leads to the upregulation of IL-17 expression levels in CHON-001 human chondrocytes, inhibition of cell proliferation and increased chondrocyte apoptosis (98). Chu *et al* (99) have reported that the highly upregulated in liver cancer (HULC) lncRNA protects ATDC5 cells from TNF-α-induced inflammatory damage by inhibiting miR-101 and blocking the NF-κB and MAPK signaling pathways. Therefore, HULC lncRNA may be used as a therapeutic agent for OA.

lncRNA activated by transforming growth factor-β (lncRNA-ATB) is a cancer-associated lncRNA (100,101). MyD88 is a key adaptor of the TLR4 signaling pathway and initiates the transduction of downstream inflammatory factors, such as TLRs (100). lncRNA-ATB downregulates the expression levels of miR-223 and inhibits the MyD88/NF-κB and p38 MAPK pathways to protect ATDC5 cells from LPS-induced inflammatory injury (101). The expression levels of the oncogene taurine upregulated gene 1 (TUG1) are associated with a poor prognosis in OA. Tang *et al* (102) have demonstrated that TUG1 lncRNA overexpression inhibits the expression of miR-195, collagen and aggrecan, increases the expression of levels of MMP13 and promotes ECM degradation in OA. Induced myeloid leukemia cell differentiation protein (MCL1) is an antiapoptotic member of the Bcl-2 family of proteins and is a key regulator of chondrocyte death (103). Li *et al* (104) have reported that PMS2L2 increases cell viability, reduces apoptosis and inhibits the release of pro-inflammatory factors in ATDC5 cells exposed to LPS; in addition, PMS2L2 acts through the PMS2L2/miR-203/MCL1 axis, which may provide a novel gene therapy strategy for OA. MB enhances the key biochemical pathways in the mitochondria and may hinder oxidant production (105); MB has been demonstrated to inhibit the degradation of chondrocytes in OA by targeting chondrocyte inflammation-associated lincRNA02 in order to regulate the expression levels of tissue inhibitor of metalloproteinase-1 and MMPs (106). TNF and hnRNPL-associated immunoregulatory lincRNA (THRIL) serves a key role in the regulation of TNF expression and inflammation through interaction with hnRNPL (107). Liu *et al* (108) have demonstrated that overexpression of THRIL downregulates the levels of miR-125b and activates the JAK1/STAT3 and NF-κB pathways to promote LPS-induced inflammatory injury in ATDC5 cells. A recent study has reported that the expression levels of the antisense strand of intron 1 of Fas gene (FAS-AS1) are increased in OA compared with those in healthy cartilage tissue; FAS-AS1 lncRNA is involved in the development of OA by inhibiting the proliferation of chondrocytes, promoting apoptosis and the degradation of ECM (63).

Recent studies have reported that 384 mRNAs and 17 lncRNAs are differentially expressed in the OA compared with healthy synovium (109). These differentially expressed lncRNAs may serve key roles in OA synovitis and provide a reference for OA diagnosis (109). Another study has suggested that exogenous prostate cancer gene expression marker 1 lncRNA may be a suitable indicator for distinguishing between early and advanced OA (110). Taken together, these studies suggest that the functional genetic variation of lncRNAs serves an important role in the pathogenesis of OA. The targets and functions of various lncRNAs involved in OA are summarized in Table I.

Table I. Biological functions of lncRNAs in osteoarthritis.

lncRNA	Target	Signaling pathway/axis	Function	(Refs.)
MALAT1	miR-150-5p miR-19b miR-127-5p	Akt Wnt/β-catenin, NF-κB PI3K/Akt	Increase in cell proliferation, inhibition of apoptosis, ECM degradation and inflammation	(40-42)
MEG3	P2X3 miR-93 miR-203 miR-16	P2X3 miR-93/TGFBR2 PI3K/AKT, NF-κB B miR-16/SMAD7	Increase in cell proliferation, inhibition of apoptosis, ECM degradation and inflammation, pain relief	(43-46,49)
HOTAIR	FUT2 ADAMTS	Wnt/β-catenin	Increase in apoptosis, ECM degradation	(52,53)
H19	miR-130a miR-675	PI3K/Akt	Aggravation of inflammatory response, induction of chondrocyte injury	(54,55)
XIST	miR-1277-5p miR-211	miR-1277-5p/ADAMTS5 miR-211/CXCR4	ECM degradation, increase in apoptosis	(57,62)
FOXD2-AS1	miR-27a-3p miR-206	miR-27a-3p/TLR4 miR-206/cyclin D1	ECM degradation, induction of inflammation	(67,69)
GAS5	KLF2 miR-21	NF-κB, Notch miR-21/MMPs	Reduction in inflammation, induction of apoptosis, inhibition of autophagy	(73,74)
CIR	LC3II, beclin-1 miR-27b	Autophagy signaling miR-27b/MMP13	Activation of autophagy, ECM degradation	(78,79)
DANCR	miR-216a-5p Myc miR-577	miR-216a-5p/JAK2/STAT3 Myc/SMAD3/STAT3 miR-577/SPHK2	Increase in cell proliferation, inhibition of apoptosis	(80,81,84)
MIAT	miR-132	NF-κB, JNK	Increase in inflammatory responses	(92)
PVT1	miR-149 miR-488-3p	PI3K/Akt	Increase in inflammatory responses, apoptosis and catabolism	(93,94)
HULC	miR-101	NF-κB, MAPK	Reduction in inflammation	(99)
ATB	miR-223	MyD88/NF-κB, p38MAPK	Reduction in inflammation	(101)
TUG1	miR-195	miR-195/MMP-13	ECM degradation	(102)
PMS2L2	miR-203	miR-203/MCL-1	Increase in cell viability, reduction in apoptosis and inflammation	(104)
THRIL	miR-125b	JAK1/STAT3, NF-κB	Increase in inflammatory responses	(108)
FAS-AS1	MMP1, MMP13	PI3K/Akt	Increase in cell proliferation and apoptosis, ECM degradation	(63)

lncRNA, long non-coding RNA; MALAT1, Metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternal expression gene 3; HOTAIR, homeobox transcript antisense RNA; XIST, X-inactive-specific transcript; FOXD2-AS1, FOXD2-adjacent opposite strand RNA 1; GAS5, growth arrest-specific transcript 5; CIR, cartilage injury-related; DANCR, differentiation antagonizing non-protein coding RNA; MIAT, myocardial infarction-associated transcript; PVT1, plasmacytoma variant translocation 1; HULC, highly upregulated in liver cancer; ATB, transforming growth factor-β; TUG1, taurine-upregulated gene 1; PMS2L2, PMS1 homolog 2 mismatch repair system component pseudogene 2; THRIL, TNF and hnRNPL-associated immunoregulatory long intergenic non-coding RNA; FAS-AS1, antisense strand of intron 1 of Fas gene; miR, microRNA; P2X3, P2X purinoceptor 3; FUT2, α-1,2 fucosyltransferase 2; KLF2, ADAMTS, disintegrin and metalloproteinase with thrombospondin motifs; Kruppel-like factor 2; TGFBR2, TGF-β receptor type II; CXCR4, C-X-C chemokine receptor 4; TLR4, Toll-like receptor 4; SPHK2, sphingosine kinase 2; MCL-1, induced myeloid leukemia cell differentiation protein; ECM, extracellular matrix.

4. Conclusions and perspectives

OA is one of the most common degenerative joint diseases, and pain that leads to restriction of physical activity is the main symptom. OA seriously affects quality of life and inflicts a heavy economic burden on families and society. Despite numerous studies on OA, its pathogenesis is still not fully understood, and it cannot be completely cured. The role of lncRNAs in the pathogenesis of OA has attracted increasing attention from scientists, as differentially expressed lncRNAs may provide new directions for the diagnosis and treatment of OA.

Various signaling pathways are involved in the pathological process of OA. Since lncRNAs serve a wide range of roles in biology, the majority of their targets are often essential cell signaling molecules. Identification of novel lncRNA-related pathway molecules may help to gain a deeper understanding of the role of lncRNAs in OA and provide a theoretical basis for targeted therapy.

The present review represents a resource that described the important roles of lncRNAs in the pathogenesis of OA and reveals the interaction of lncRNAs, miRNAs and OA. Overall, this interaction suggests a potential role of lncRNAs in cell signaling and OA pathogenesis. Although previous studies have demonstrated the therapeutic effects of lncRNAs in OA, further research is needed to focus on the potential for the widespread use of lncRNAs as biomarkers in the diagnosis of OA and to develop novel therapeutic targets for OA. For example, a certain lncRNA molecule administered as a capsule or other type of medicine orally or via local injection, the lncRNA target may promote the proliferation of chondrocytes, inhibit ECM degradation, reduce the inflammatory response and alleviate the progress of OA. The ultimate goal is to use these targets to develop new drugs, delay the progress of OA and improve the patient quality of life.

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JW and YZ drafted the manuscript and revised the manuscript. YS, JL, BY, TW, ZZ, XJ and YG contributed to manuscript conception. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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