

Insight into modulating osteoarthritis progression: lncRNAs and TGF- β /Smad signalling pathway

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a class of non-coding RNA molecules with a length of more than 200 nucleotides that play key roles in the regulation of gene expression and cell physiology. Studies have shown that lncRNAs can participate in the regulation of the TGF- β /Smad signalling pathway by sponging miRNAs or directly activating Smad protein phosphorylation. The TGF- β /Smad signalling pathway has become a key signalling pathway in osteoarthritis (OA), a traditional degenerative joint disease characterised by an imbalance between cartilage degradation and repair. This review systematically discusses the molecular mechanisms by which lncRNAs regulate OA cartilage repair through the TGF- β /Smad signalling pathway, as well as the regulatory roles of these lncRNAs in inflammatory response, extracellular matrix (ECM) homeostasis, and chondrocyte apoptosis. In addition, the article also summarised the clinical transformation strategies based on lncRNA, including nanoparticle delivery systems (such as exosomes and hydrogels), gene editing technologies (such as CRISPR-Cas9), and precision treatment guided by dynamic biomarkers. Although lncRNA therapy still faces challenges in terms of targeted delivery efficiency and specificity, its potential in early diagnosis and regenerative therapy of OA provides a theoretical basis for the development of novel intervention methods. In the future, combining cutting-edge technologies such as artificial intelligence, single-cell sequencing, and 3D organoids, the application of lncRNA regulatory networks is expected to open up new avenues for OA treatment.

Introduction

Osteoarthritis (OA) is a kind of joint degenerative disease characterised by

articular cartilage degeneration, subchondral bone remodelling, synovitis and osteophytes (1). The incidence of OA in the elderly population is increasing annually, especially in people with metabolic disorders, such as diabetic patients. OA usually affects weight-bearing joints such as the knee, hip and spine, causing pain, stiffness and a reduced range of motion (2, 3). Pathologically, OA disrupts the balance between cartilage catabolism and anabolism, and inflammation plays a central role in disease progression (4, 5). Synovial fibroblasts (SFs) are key participants in the pathological process of osteoarthritis, and their mechanisms of inflammation activation, aging, metabolic abnormalities, and intercellular interactions collectively promote joint cartilage degeneration, synovitis, and joint function loss (6, 7).

The TGF- β /Smad signalling pathway plays an important role in maintaining cartilage homeostasis in OA. As a core cell molecule involved in cartilage repair and fibrosis, TGF- β regulates the function of chondrocytes by activating Smad proteins. In OA, TGF- β signalling disorders lead to abnormal chondrocyte differentiation, extracellular matrix (ECM) degradation and cartilage degeneration (8-12). Activated TGF- β can recruit and phosphorylate Smad2 and Smad3, and phosphorylated Smad2 and Smad3 are transported to the nucleus to regulate the transcription of target genes, such as genes involved in inflammation progression and matrix remodelling (13, 14). The TGF- β /Smad signalling pathway plays a biphasic role in the process of OA; in the early stage of this disease, it can promote the expression of genes related to cartilage repair. However, in the late stage of the disease, once the pathway is overactivated, it leads to increased expression of genes related to ECM degradation

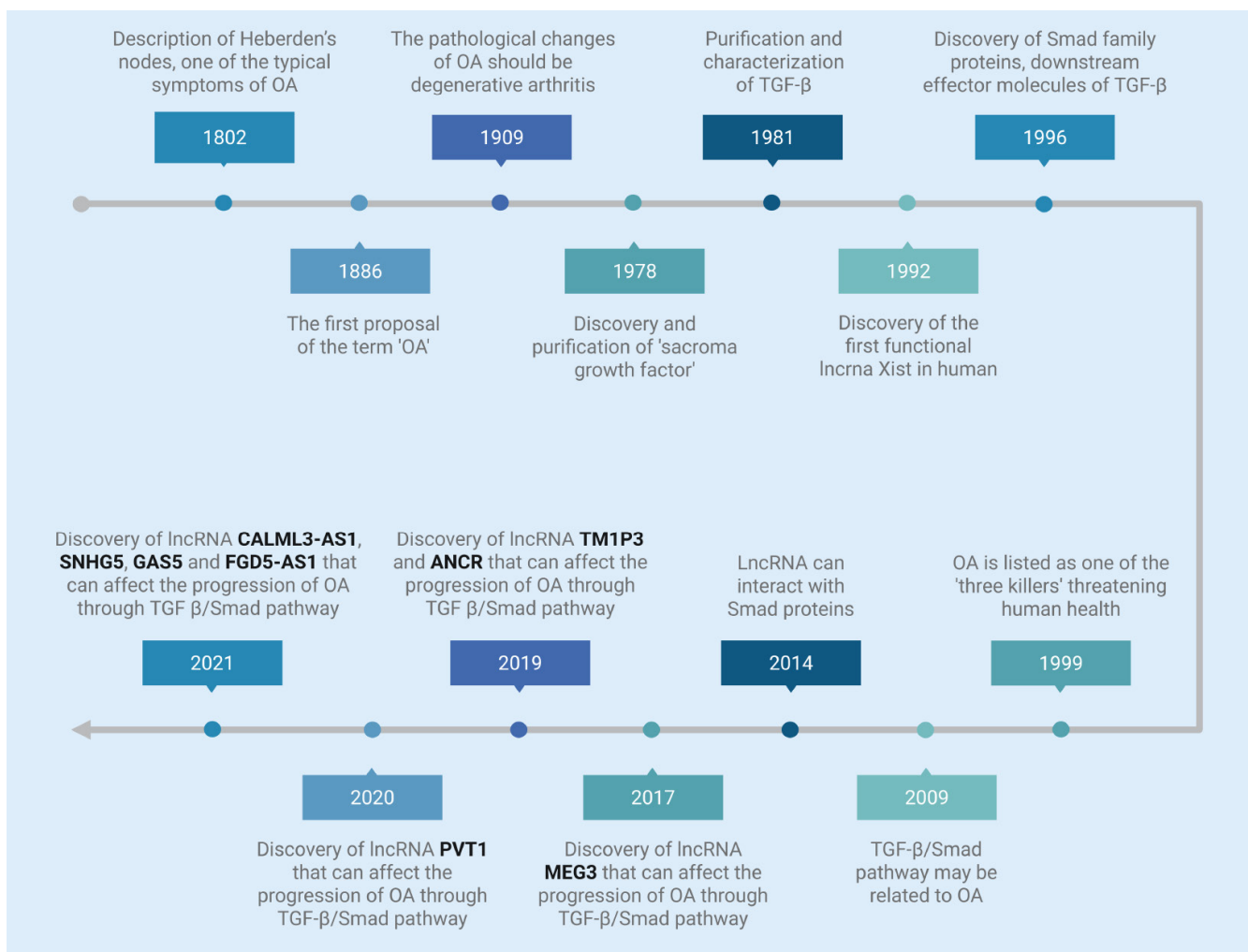


Fig. 1. The exploration history of lncRNAs affecting the progression of OA. The picture shows the exploration history. From the first discovery and proposal of osteoarthritis to the discovery that lncRNAs can affect the progression of osteoarthritis by regulating the TGF- β /Smad signalling pathway.

and accelerates fibrosis in cartilage tissue (15). A therapeutic strategy involving targeted intervention targeting the TGF- β /Smad pathway is expected to alleviate cartilage injury and prevent deterioration of the disease.

Long non-coding RNAs (lncRNAs) have emerged as critical regulators of the TGF- β /Smad signalling pathway in OA (16). As a non-coding RNA with a length of more than 200 nucleotides, lncRNAs are not involved in protein coding. Its function is reflected in the regulation of gene expression, which involves transcription, post-transcriptional modification and epigenetic regulation (17-19). In OA, lncRNAs such as PVT1, MALAT1, and HOTAIR can regulate the progression of inflammation and ECM degradation (16, 20). Specifically, the lncRNA PVT1 promotes the degradation of cartilage in

diabetic OA by inhibiting the expression of miR-146a pro-inflammatory cytokines and activating the Smad4 protein (21). In contrast, lncRNAs such as MEG3 and GAS5 can inhibit TGF- β , thereby inhibiting the inflammatory response and preventing cartilage degeneration. In view of the significant ability of lncRNAs to regulate TGF- β and other important signalling pathways, the potential of lncRNAs as therapeutic targets for OA should not be underestimated. Figure 1 shows the exploration history of lncRNAs affecting the progression of OA by regulating the TGF- β /Smad signalling pathway.

The competitive endogenous RNA (ceRNA) hypothesis was proposed by Salmena *et al.* in 2011: pseudogenes, lncRNAs and circular RNAs (circRNAs) can act as sponges of microRNAs (miRNAs) and play a role in in-

hibiting miRNA activity (22-24). This regulatory network, which combines mRNAs and non-coding RNAs (ncRNAs) through the bridging effect of miRNAs, is called the ceRNA regulatory network (CERNET) (25). Most of the lncRNAs mentioned in this review can act as miRNA sponges to affect the expression level of target mRNAs, thus indirectly affecting the activity of the TGF- β pathway. As the core component of CERNET, miRNA is an endogenous small single-stranded RNA (20-25 nucleotides). MiRNAs inhibit their target genes by complementary pairing with the 3' untranslated region of the target mRNA and reduce the expression of the target protein by decomposing the mRNA or inhibiting its translation (26, 27). Thus, CERNET is involved in a series of physiological and pathological processes, such as regulating angio-

Table I. Role of lncRNAs in OA by regulating TGF- β /Smad pathway.

lncRNA	Expression in OA	Interacting miRNAs	Target gene/pathway	Molecular mechanism	Effect on TGF- β /Smad pathway	Effect on cartilage repair	References
PVT1	Upregulated	miR-146a	TGF- β /Smad4 axis	Release inhibition of Smad4 by sponging miR-146a, thus promoting Smad4 expression	Activation	Inflammatory response↓	(21)
		miR-26b	CTGF/TGF β 1/Smad3 axis	Release inhibition of CTGF by sponging miR-26b, thus activating the TGF β 1/Smad3 axis	Activation	Type II collagen expression↓	(32)
TM1P3	Upregulated	miR-22	ALK1/Smad1/5 axis	Release inhibition of ALK1 by sponging miR-22, thus activating Smad1/5 phosphorylation	Activation	Inflammatory response↑ ECM degradation↑	(34)
MEG3	Downregulated	miR-93	TGFBR2/Smad2/3 axis	Release inhibition of TGFBR2 by sponging miR-93, thus activating Smad2/3 phosphorylation	Activation	Chondrocyte proliferation↑ Chondrocyte apoptosis↓	(35)
		miR-16	Smad7	Release inhibition of Smad7 by sponging miR-16, thus promoting Smad7 expression	Inhibition	Chondrocyte proliferation↓ Chondrocyte apoptosis↑	(36)
GAS5	Downregulated	miR-146a	Smad4	Release inhibition of Smad4 by sponging miR-146a, thus promoting Smad4 expression	Activation	Chondrocyte apoptosis↓	(39)
SNHG5	Downregulated	miR-181a-5p	TGFBR3/Smad axis	Release inhibition of TGFBR3 by sponging miR-181a-5p, thus activating the TGFBR3/Smad axis	Activation	ECM degradation↓	(44)
FGD5-AS1	Downregulated	miR-302d-3p	TGFBR2/Smad axis	Release inhibition of TGFBR2 by sponging miR-302d-3p, thus activating the TGFBR2/Smad axis	Activation	Chondrocyte apoptosis↓ ECM degradation↓	(48)
ANCR	Downregulated	–	TGF β 1/Smad axis	Downregulate the expression of TGF β 1, thus inhibiting TGF β 1/Smad axis	Inhibition	Inflammatory response↓ Chondrocyte proliferation↑ ECM degradation↓	(51)
CALML3-AS1	Downregulated	miR-146a	Smad4	Release inhibition of Smad4 by sponging miR-146a, thus promoting Smad4 expression	Activation	Chondrocyte apoptosis↓	(42)

The table provides a detailed comparison of different lncRNAs from various perspectives, including expression in OA, interacting miRNAs, target gene/pathway, molecular mechanism, effect on TGF- β /Smad pathway, effect on cartilage repair and references. – : no results available

genesis and cell proliferation, invasion and metastasis, and plays an important role in the occurrence and development of many diseases.

lncRNAs driving TGF- β /Smad signalling in OA

An increasing amount of evidence suggests that lncRNAs are key regulators of the TGF- β /Smad signalling pathway in OA, exerting a wide range of effects on cartilage homeostasis, inflammatory response, and chondrocyte fate. lncRNAs do not act as isolated molecular switches, but rather participate in a complex regulatory network that integrates transcription, post transcription, and epigenetic control layers. Among these mechanisms, the ceRNA paradigm has become the main mode for lncRNAs to regulate TGF- β /Smad signalling. Table I summarises some

key findings on the dysregulation of lncRNA expression and the potential biological roles of lncRNAs in OA. Figure 2 provides a more intuitive demonstration of the mechanism of action of these lncRNAs. These findings may provide potential targets for therapeutic interventions in OA.

In OA cartilage, abnormal expression of lncRNAs leads to dysregulation of TGF- β /Smad signalling and severe pathological consequences. Several lncRNAs are continuously upregulated in diseased cartilage and synovial tissues, typically amplifying inflammatory signals and ECM degradation. Plasmacytoma variant translocation 1 (PVT1) in plasma cell tumours is a typical example of this type (28-30). The upregulation of PVT1 expression in OA chondrocytes enhances TGF- β /Smad signalling through multiple ceR-

NA mediated axes. PVT1 alleviates the inhibition of Smad4 by sponging miR-146a, which is a core mediator regulating TGF- β signalling. MiR-146a is a miRNA which can inhibit inflammation and fibrosis. The activation of Smad dependent transcription promotes inflammatory response and cartilage matrix breakdown (21, 31). Meanwhile, PVT1 interacts with miR-26b to release connective tissue growth factor (CTGF), thereby activating the CTGF/TGF- β 1/Smad3 axis. This signalling cascade can disrupt the homeostasis of collagen, especially the synthesis of type II collagen, and lead to ECM imbalance in OA, especially in situations of high blood sugar or metabolic stress (32). Another upregulated lncRNA TM1P3 further illustrates how lncRNA dysregulation biases TGF- β signalling towards catabolic outcomes. TM1P3

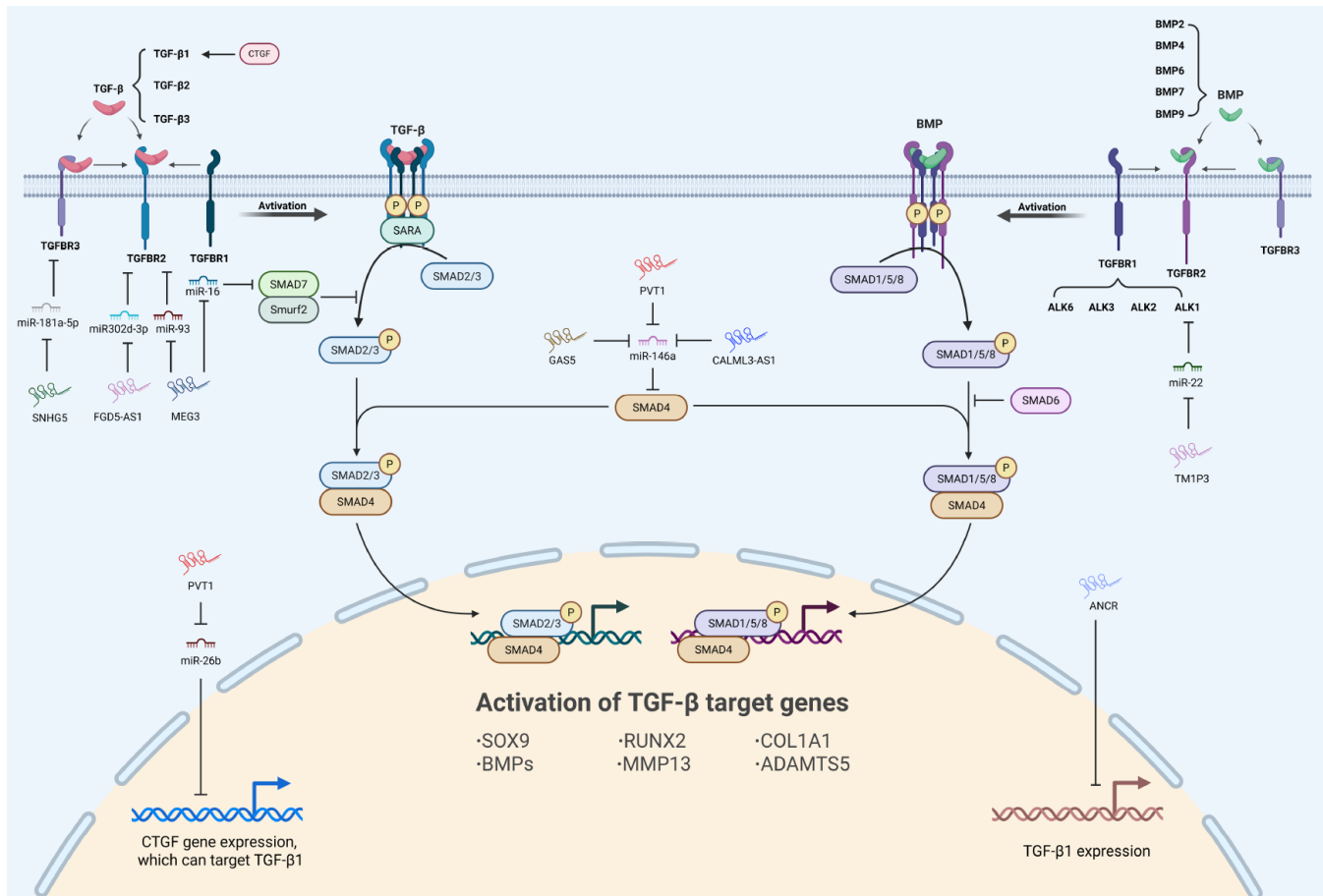


Fig. 2. A diagram of the mechanism by which lncRNAs regulate the TGF- β /Smad signalling pathway is shown. This figure illustrates the mechanism of action of the TGF- β /Smad signalling pathway and how different lncRNAs are involved in regulating this signalling pathway.

acts as a molecular sponge for miR-22, leading to increased expression of activin receptor-like kinase 1 (ALK1), a key TGF- β receptor associated with Smad1/5 signalling. Unlike the typical Smad2/3 pathway, ALK1 mediated activation of Smad1/5 is closely associated with cartilage degeneration. Enhanced Smad1/5 phosphorylation drives the expression of matrix degrading enzymes such as matrix metalloproteinase 13 (MMP13), thereby accelerating ECM degradation and exacerbating OA progression. These findings emphasise that lncRNAs can not only regulate the intensity of TGF- β signalling, but also redirect signals to different Smad branches, resulting in different biological consequences (33, 34).

In contrast to these pro-degenerative lncRNAs, a large number of lncRNAs are downregulated in OA, seemingly exerting a protective effect by maintaining the balance of TGF- β /Smad activity. Maternally expressed gene 3 (MEG3)

is one of the most extensively studied lncRNAs in this category. The expression of MEG3 is reduced in OA cartilage and synovial tissue, and its down-regulation is related to the severity of the disease. Mechanistically, MEG3 acts as a ceRNA for miR-93, thereby maintaining the expression of TGF- β receptor 2 (TGFBR2). TGFBR2 stably enhances Smad2/3 phosphorylation, promotes chondrocyte proliferation, inhibits apoptosis, and supports ECM synthesis (35). In addition, MEG3 also regulates the miR-16/Smad7 pathway. The absence of MEG3 leads to an increase in miR-16 activity, changes in Smad7 expression, interruption of TGF- β signalling negative feedback loop, and further progression of OA (36).

Growth arrest-specific transcript 5 (GAS5) represents another protective lncRNA with reduced expression in OA cartilage. GAS5 mainly regulates chondrocyte survival and inflammatory response through the miR-146a/Smad4

axis. By adsorbing miR-146a, GAS5 increased the availability of Smad4 and enhanced typical TGF- β /Smad signalling (37-39). This mechanism effectively alleviates chondrocyte apoptosis induced by inflammatory stimuli, highlighting the molecular protective role of GAS5 in preventing excessive inflammatory damage in OA. CALML3 antisense RNA 1 (CALML3-AS1) also has similar protective functions, targeting miR-146a and enhancing Smad4 mediated signalling, thereby promoting chondrocyte survival and resistance to apoptotic stress (40-42).

Other lncRNAs, such as small nucleolar RNA host gene 5 (SNHG5) and FGD5 antisense RNA 1 (FGD5-AS1), further expand the lncRNA mediated TGF- β /Smad signalling regulatory library. The expression of SNHG5 in OA cartilage is significantly reduced, and its up-regulation can alleviate ECM degradation by upregulating TGFBR3 through sponging miR-181a-5p. The enhanced

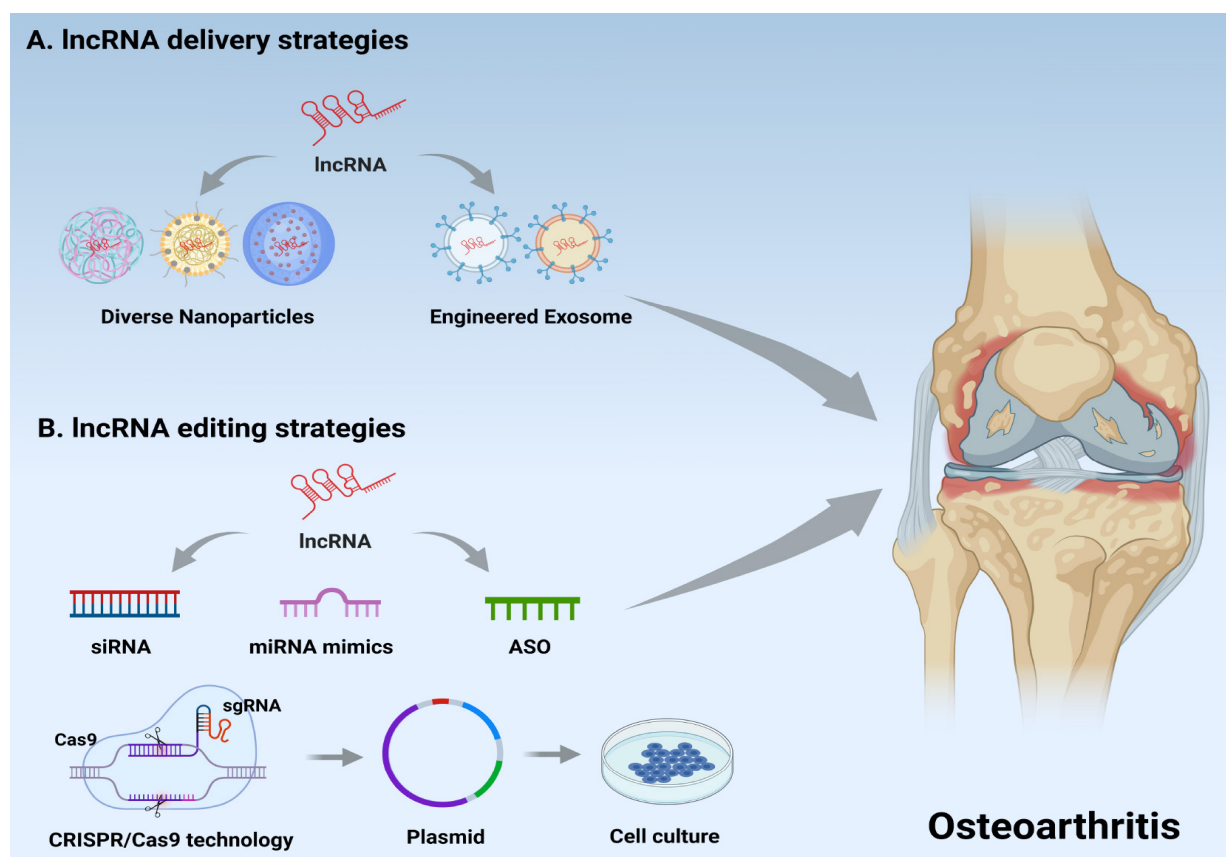


Fig. 3. The delivery and editing strategies of lncRNAs.

A: lncRNA delivery strategies. **B:** lncRNA editing strategies. These strategies can be combined for the treatment of osteoarthritis.

expression of TGFBR3 enhances Smad signalling and inhibits the expression of catabolic enzymes including MMP13 and (a disintegrin and metalloproteinase with thrombospondin motifs 5) ADAMTS5 (43-45). Similarly, FGD5-AS1 exerts cartilage protection through the miR-302d-3p/TGFBR2 axis, promotes Smad activation, inhibits cell apoptosis, and maintains ECM integrity (46-48). These findings collectively indicate that lncRNAs are key regulatory factors in maintaining the repair ability of TGF- β /Smad signalling in cartilage.

Importantly, lncRNAs also participate in upstream control of TGF- β ligand availability, adding another layer of regulatory complexity. Anti-differentiation non-coding RNA (ANCR) is an example of this mechanism. ANCR is down-regulated in OA, and its absence leads to increased expression of TGF- β 1, enhanced activation of Smad, and subsequent degradation of ECM. By maintaining appropriate levels of TGF- β 1, ANCR helps maintain physiological signal thresholds, promote chondrocyte

proliferation and cartilage repair, without triggering fibrosis or degenerative reactions (49-51). This observation emphasises the biphasic nature of TGF- β /Smad signalling in OA and highlights that insufficient and excessive pathway activation are both harmful.

Overall, these studies suggest that lncRNAs act as key regulators of the TGF- β /Smad signalling network in OA. Through the interaction of ceRNA and direct regulation of signalling components, lncRNAs determine the balance between protection and pathological outcomes in cartilage tissue. Understanding this regulatory pattern provides a mechanistic framework for explaining the heterogeneous role of TGF- β signalling in OA, and identifies lncRNAs as promising molecular targets for stage specificity and precise therapeutic strategies.

Therapeutic potential of lncRNAs

Nanoparticle delivery systems

Nanoparticle drug delivery systems have become a new star in the field of

targeted therapy, showing broad application prospects in regenerative medicine, especially in exosomes and hydrogels (52-54). In the treatment of OA, exosomes are favoured because of their excellent biocompatibility, low immunogenicity and ability to cross biological barriers. These systems can accurately deliver bioactive molecules, including lncRNAs, to specific targets and achieve controlled release. A variety of cell types, such as mesenchymal stem cells (MSCs), can produce exosomes, which are nanovesicles. They naturally have the ability to transport proteins, lipids, RNA and other bioactive substances (55, 56). Thermosensitive hydrogels can support cell adhesion, differentiation and tissue repair. The ingenious combination of exosomes or hydrogels with lncRNAs can significantly improve the delivery efficiency of therapeutic drugs to damaged tissues, thus effectively promoting the process of cartilage repair and regeneration (57).

Recent studies have highlighted the potential of exosomes and hydrogels for

application in the field of cartilage regeneration (58, 59). They can be used as efficient vectors for lncRNAs. Exosomes derived from MSCs can bind lncRNAs such as H19, which can regulate key signalling pathways such as the TGF- β /Smad pathway, thereby promoting the proliferation of chondrocytes, inhibiting their apoptosis and reducing matrix degradation. H19, an exosome derived from umbilical cord mesenchymal stem cells, can upregulate the expression of SOX9, which is a key transcription factor in cartilage formation, thereby promoting cartilage repair (56, 60). When sodium alginate/methacrylate gelatin (GelMA) hydrogels are combined with these exosome-loaded systems, they can further promote cartilage regeneration. Hydrogels provide a scaffold to support the local retention and controlled release of lncRNAs, thus promoting angiogenesis and cartilage repair in an OA model. *In vivo* experiments have confirmed that this combination can improve cartilage formation, inhibit inflammation, and enhance tissue repair ability in a longer time. This strategy provides a potential scheme for cartilage regeneration in OA (61, 62). Nanoparticle drug delivery systems provide new targeted treatments for OA and other diseases and thus have great potential for application, but their clinical application still faces many challenges (63). Improving the efficiency of drug delivery is one of the keys. The ability of nanoparticles such as exosomes and hydrogels to accurately deliver therapeutic molecules such as lncRNAs to specific cells or tissues is crucial. There are differences in the uptake of nanoparticles between different cell types in joint diseases. Fibroblasts, such as synoviocytes (FLSs), and chondrocytes are very different, and the heterogeneity of cell uptake increases the complexity of the delivery process (61, 64). Targeting specificity is another obstacle. Therefore, nanoparticles need to be able to deliver drugs to the target accurately to avoid off-target effects. Inflammation and tissue degradation in OA change cell behaviour. Surface modifications such as connecting targeted ligands can enhance the affinity and selectivity of nanoparticles for spe-

cific cells (62, 65). lncRNAs are easily degraded by ribonucleases, and their stability limits the efficiency of nanoparticle delivery systems. Surface modification and encapsulation technology can protect therapeutic agents from enzymatic hydrolysis and improve the stability of lncRNAs (56, 60). Despite these challenges, we believe that these difficulties will be solved in the near future, bringing new hope for improving the clinical treatment of joint diseases.

Gene editing technology

Gene editing technologies, particularly CRISPR-based systems, have revolutionised molecular biology by enabling precise modifications of DNA in living organisms (66, 67). The CRISPR-Cas9 system, which is derived from bacterial immune defenses, has gained widespread use in various biological fields due to its simplicity and efficiency (68). In particular, CRISPR activation (CRISPRa), which utilises catalytically dead Cas9 (dCas9) fused to transcription activators, enables the activation of specific genes without altering the underlying genetic code. This technology can guide the targeting of specific DNA sequences by synthetic guide RNAs (gRNAs), providing a powerful tool for gene regulation and therapeutic interventions, particularly in tissue regeneration and disease models (69, 70). Gene editing strategies such as CRISPRa have also been employed to regulate lncRNAs, which play crucial roles in cellular differentiation, proliferation, and disease pathogenesis. In the context of bone and cartilage repair, CRISPRa has been used to activate specific lncRNAs, such as H19 and DANCER, which regulate chondrogenesis and osteogenesis. For instance, CRISPR-mediated activation of the lncRNA H19 in MSCs has been shown to enhance chondrogenic differentiation, promote cartilage formation and improve bone healing in preclinical models of calvarial bone defects (71, 72). This strategy demonstrates the potential of CRISPR-mediated lncRNA activation for treating degenerative diseases such as OA by promoting tissue repair and regeneration. CRISPR/Cas9 gene editing technology has shown potential for facilitating the

clinical application of targeted gene intervention. However, its off-target effects, safety concerns, and ethical issues have created great challenges for its practical application. A mismatch between the guide RNA and target DNA often induces unexpected modifications in the genome, *i.e.* off-target effects, which may lead to serious harm, such as genotoxicity and unpredictable treatment results, while the complex regulatory effect of lncRNAs increases the risk of harm (73, 74). In addition, during the CRISPR process, the DNA repair mechanism may introduce additional mutations, which increase the risk of cancer or other unknown damage (75, 76). In terms of ethics, germline editing in human embryos may cause irreversible changes to the human gene pool, and its genetic risk poses a severe challenge to the existing ethical review system (77, 78). The development of enhanced Cas9 variants and improvement of predictive models for off-target effects are crucial for improving the accuracy of the CRISPR tool (75, 78, 79). The correct use of gene editing technology requires a stronger regulatory framework and wider public discussion, which can balance scientific progress with social and ethical considerations (80).

In summary, nanoparticle-based delivery systems and gene editing techniques provide two complementary pathways for translating lncRNA research into therapeutic strategies for osteoarthritis. Nanoparticle platforms, such as exosomes and hydrogels, mainly enhance the stability, targeting efficiency and local retention of lncRNA or lncRNA related molecules, thus promoting the effective regulation of cartilage repair and inflammatory response. In contrast, gene editing methods, especially CRISPR-based systems, can precisely regulate the expression of endogenous lncRNAs and provide potential for long-term correction of dysregulated signalling pathways, including TGF- β /Smad. Although both strategies face challenges related to delivery specificity, safety, and off target effects, their continuous optimisation and potential integration lay an important foundation for precise treatment of OA based on lncRNA.

Future prospects

lncRNAs have emerged as key regulators in the pathogenesis of OA, influencing processes such as inflammation, cartilage degradation, and chondrocyte apoptosis (81-83). As our understanding of lncRNA biology deepens, the integration of cutting-edge technologies holds enormous potential to enhance the therapeutic application of lncRNAs in OA treatment. Future progress will likely depend on multidisciplinary advances that allow precise, efficient, and personalised manipulation of lncRNA function.

Smart nanoparticles

Smart nanoparticles, particularly exosomes and hydrogels, are at the forefront of drug delivery systems due to their enhanced biocompatibility, ability to cross biological barriers, and potential for controlled release (84-88). These nanoparticle-based systems are crucial for the targeted delivery of lncRNAs to cartilage cells, ensuring effective therapy while minimising off-target effects (89, 90). Recent studies demonstrate the advantages of using mesenchymal stem cell (MSC)-derived exosomes to deliver lncRNAs, such as H19, which regulate key pathways like TGF- β /Smad, promoting cartilage regeneration (91). Furthermore, the use of thermosensitive hydrogels as carriers for lncRNA-loaded exosomes significantly enhances the therapeutic efficacy by supporting local tissue repair in OA models (92).

Future research should aim to refine these nanoparticle systems by incorporating surface modifications that target specific receptors on chondrocytes and synovial cells. For instance, using ligands that specifically bind to cartilage cells can enhance the precision of nanoparticle delivery, thereby improving the efficiency of lncRNA therapy. This approach could revolutionise the way lncRNAs are utilised for cartilage repair and regeneration in OA treatment.

3D Organoids

3D organoid models, which mimic the complex architecture and cellular interactions of human tissues, are becoming indispensable tools in biomedical

research (93, 94). These models can be used to simulate OA pathology and evaluate the effects of lncRNAs in a more physiologically relevant environment than traditional 2D cultures (95-97). Additionally, combining 3D organoid models with advanced gene editing technologies, such as CRISPR/Cas9, allows for precise manipulation of lncRNAs within a controlled *in vitro* setting (98-101). This approach will enable researchers to identify lncRNAs that play pivotal roles in OA and test the therapeutic efficacy of targeted lncRNA interventions in a more realistic, human-like system.

Personalised medicine in OA treatment could benefit immensely from the integration of 3D organoids with single-cell RNA sequencing (scRNA-seq) (102-104). By dissecting the cellular composition and gene expression profiles of patient-specific OA organoids, researchers can pinpoint which lncRNAs are most relevant to each individual's disease phenotype (105, 106). This personalised approach holds the potential for developing tailored lncRNA therapies, improving the overall therapeutic outcomes for OA patients.

Artificial intelligence

Artificial intelligence (AI) has made substantial progress in drug discovery and personalised medicine (107-109). In the context of lncRNA therapy for OA, AI algorithms can assist in predicting lncRNA-target interactions and identifying optimal therapeutic candidates. Machine learning models trained on large datasets of OA gene expression profiles could identify key regulatory lncRNAs involved in disease progression, facilitating the design of more effective lncRNA-based interventions (110, 111).

AI can also aid in optimising the delivery of lncRNA therapies. By analysing large-scale patient data, AI tools can predict the best delivery systems (*e.g.* nanoparticles, exosomes) for specific individuals based on factors like disease stage, genetic makeup, and tissue characteristics (112). This will enhance the precision and efficacy of lncRNA therapies, leading to more effective treatments with fewer side effects (113).

Gene editing technologies

Gene editing technologies, particularly CRISPR-based systems, offer a revolutionary approach to modulating lncRNA expression *in vivo* (114, 115). CRISPRa systems, which use catalytically dCas9 fused with transcriptional activators, can be used to precisely upregulate lncRNAs in OA tissues, thereby promoting cartilage repair and regeneration (106). For example, CRISPR-mediated activation of the lncRNA H19 in MSCs has been shown to enhance chondrogenic differentiation and improve cartilage healing in animal models (71). This approach could be further refined to target specific lncRNAs that regulate the TGF- β /Smad signalling pathway, optimising cartilage regeneration and minimising inflammation. However, the use of gene editing technologies for lncRNA regulation must overcome challenges related to off-target effects and delivery efficiency (116). Future studies will need to refine the precision of CRISPR-based systems and develop more efficient delivery vectors, such as nanoparticles or viral vectors, to achieve targeted modulation of lncRNAs in OA tissues.

Single-cell sequencing

Single-cell RNA sequencing (scRNA-seq) provides an unparalleled level of resolution in studying the heterogeneity of cell populations within tissues (117, 118). In OA, this technique can be used to profile gene expression at the single-cell level, identifying the specific lncRNAs involved in the pathological processes of cartilage degradation, inflammation, and fibrosis (119-122). Moreover, scRNA-seq can be combined with advanced bioinformatics tools to identify novel lncRNAs that regulate key OA-related signalling pathways, including TGF- β /Smad.

By identifying and characterising the role of lncRNAs in OA at the single-cell level, researchers will gain new insights into disease mechanisms, which will facilitate the development of more targeted and effective lncRNA-based therapies (123, 124). This approach could also help identify biomarkers for early diagnosis and prognosis, enabling timely intervention before irreversible cartilage damage occurs.

Overall, the future development of lncRNA-based treatment for OA is expected to rely on the integration of advanced technologies that enable precise regulation, realistic disease modelling, and personalised interventions. The intelligent nanoparticle system provides an increasingly complex platform for targeted and controlled delivery of lncRNA, while 3D organoid models provide a physiologically relevant environment for studying lncRNA function and therapeutic efficacy. AI further accelerates this process by facilitating the identification of key regulatory lncRNAs, predicting molecular interactions, and optimising treatment strategies based on large-scale data. Meanwhile, gene editing technology can directly and continuously regulate the expression of lncRNA, and single-cell sequencing reveals the cell type specific regulatory network behind OA heterogeneity. These emerging methods collectively form a convergent framework that will enhance understanding of mechanisms, improve translation accuracy, and ultimately drive lncRNA guided therapy towards personalised and effective treatment of OA.

Conclusion

OA is a degenerative joint disease characterised by progressive cartilage degeneration, subchondral bone remodelling, and synovial inflammation. The emerging evidence emphasises the crucial role of lncRNAs in regulating the TGF- β /Smad signalling pathway, which is a key regulator of cartilage homeostasis and repair. The dysregulation of lncRNAs such as PVT1, MEG3, GAS5, SNHG5, and FGD5-AS1 is associated with the pathogenesis of osteoarthritis by affecting chondrocyte proliferation, apoptosis, inflammation, and ECM metabolism. These lncRNAs mainly function through the miRNA sponge mechanism, fine-tuning the activity of TGF- β /Smad signalling to promote cartilage repair or exacerbate degeneration.

Treatment strategies for lncRNAs, including nanoparticle-based delivery systems (exosomes, hydrogels), CRISPR-Cas9 gene editing and RNA interference (siRNA/ASO), have great

prospects for OA treatment. However, before clinical translation, challenges such as delivery efficiency, tissue specificity, and off target effects must be addressed. Future research should focus on intelligent nanoparticles, 3D organoid models, AI guided lncRNA targeting, and single-cell sequencing to optimise precision therapy.

In summary, lncRNAs represent a novel class of biomarkers and therapeutic targets for OA. A deep understanding of its regulatory mechanism, combined with advanced biotechnology methods, may pave the way for effective and personalised OA treatment, restoring cartilage integrity and preventing disease progression.

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