Regulatory roles of noncoding RNAs in intervertebral disc degeneration as potential therapeutic targets (Review)

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Abstract. Intervertebral disc degeneration (IDD) is the leading cause of lower back pain, which is one of the primary factors that lead to disability and pose a serious economic burden. The key pathological processes involved are extracellular matrix degradation, autophagy, apoptosis, and inflammation of nucleus pulposus cells. Non-coding RNAs (ncRNAs), including microRNAs, long ncRNAs and circular RNAs, are key regulators of the aforementioned processes. ncRNAs are differentially expressed in tissues of the intervertebral disc between healthy individuals and patients and participate in the pathological progression of IDD via a complex pattern of gene regulation. However, the regulatory mechanisms of ncRNAs in IDD remain unclear. The present review summarizes the latest insights into the regulatory role of ncRNAs in IDD and sheds light on potentially novel therapeutic strategies for IDD that may be implemented in the future.

Contents

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1. Introduction

Intervertebral disc degeneration (IDD) is one of the primary causes of lower back pain, which poses serious social and economic burdens (1). The global prevalence of IDD is >60%, which leads to high costs for society (2). The pathogenesis of IDD is complex and involves genetic, aging and environmental (3) and inflammatory factors (4). The gross anatomy of the ID primarily comprises interdependent tissue compartments: The nucleus pulposus (NP) is surrounded by a fibrocartilaginous annulus fibrosus (5). The NP serves an essential role in maintaining homeostasis of the ID and the key cellular change during the development of IDD concerns centrally located NP cells that undergo phenotypical transition, compromising the structural integrity of discs (5). Although numerous researchers have performed experimental studies on the potential mechanism of IDD in recent years (6,7), the underlying precise pathological mechanisms of IDD remain unclear. Therefore, a further investigation of the molecular regulatory mechanisms underlying the homeostasis of the ID may contribute to identifying novel potential therapeutic targets for IDD.

A series of genetic and biological regulators are associated with IDD pathogenesis and non-coding RNAs (ncRNAs) are the critical factors (8,9). ncRNAs, primarily consisting of microRNAs (miRNAs or miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs), are critical regulators in various cellular processes, such as cell proliferation, autophagy and apoptosis. miRNAs, a class of ncRNAs ~22 nucleotides in length, can recognize the 3'-untranslated regions of target mRNAs via complementary base pairing and suppress gene expression at the post-transcriptional level (10). lncRNA is a type of ncRNA with a length >200 nucleotides that binds to proteins or mRNAs using its nucleotide sequence or folded secondary structure and regulates gene expression through multiple mechanisms at the transcriptional and post-transcriptional levels (11). circRNA, primarily formed through reverse splicing, is a type of endogenous covalently closed RNA molecule that serves as a miRNA sponge to regulate the miRNA-associated cell processes (12). It has been previously documented that the level of aberrant ncRNAs is involved in various aspects of IDD, including NP cell proliferation (13),

autophagy (14), apoptosis (15), extracellular matrix (ECM) regeneration (16) and inflammatory response (17). Therefore, dysregulation of ncRNAs in NP cells may be a crucial pathological mechanism underlying the initiation and development of IDD. Lan *et al* (18) reported 76 pairs of differentially expressed circRNAs in IDD using microarray datasets. Liu *et al* (19) documented that 636 circRNAs are differentially expressed in IDD compared with normal controls. lncRNA human leukocyte antigen complex group 18 (HCG18) is upregulated in patients with IDD and luciferase reporter assays have indicated that HCG18 may act as an endogenous sponge to decrease expression of miR-146a-5p in NP cells, thus upregulating the target gene of miR-146a-5p, decreasing the proliferation of NP cells and finally resulting in cell apoptosis (20). Zhu *et al* (21) reported that circVMA21, serving as a sponge for miR-200c, downregulates expression of X-linked inhibitor of apoptosis (XIAP). Thus, decreased expression of XIAP in inflammatory cytokine-treated NP cells is directly associated with excessive cell apoptosis. Furthermore, intradiscal injection of circVMA21 may alleviate IDD in a rat model (21). Accumulating evidence has shown the key regulatory role of ncRNAs in IDD (22,23). In addition, it has been reported that ncRNAs, targeted to IDs using viruses and other vectors, can reverse the pathological process of IDD and rescue ID function at the genetic level (22). These findings indicate the therapeutic potential of ncRNAs in IDD.

The present review aimed to summarize the latest studies on ncRNAs involved in IDD pathology and clarify the key roles of ncRNAs in the IDD process though regulating ECM degradation, autophagy, apoptosis and inflammation, which could provide a novel biotherapeutic strategy for clinical treatment of IDD (Fig. 1).

2. ncRNAs in ECM degradation

The primary features of IDD are the decrease in NP cell number and ECM (23). The structural components of ECM primarily comprise type-II collagen and aggrecan, which play a critical role in the mechanical functionality of the ID (24). However, reduced synthesis or increased degradation of ECM, induced by dysregulation of NP cell metabolism, leads to a reduced water-binding capacity of the tissue and structural collapse (24). NP cells maintain homeostasis and compositional integrity of the ID by regulating the metabolism of the ECM (25). Dysregulation of gene expression in NP cells induces enhanced release of ECM-degrading enzymes and decreased production of ECM structural molecules during the development of IDD (25). ncRNAs, as regulators of epigenetic modification, are involved in metabolic dysregulation in NP cells (26) (Table I).

Zhou *et al* (27) reported that expression of miR-31-5p is downregulated in IDD. Moreover, miR-31-5p facilitates NP cell proliferation, inhibits apoptosis, promotes ECM formation and downregulates expression of matrix-degrading enzymes in NP cells (27). Mechanistically, miR-31-5p regulates the pathway of stromal cell-derived factor-1/chemokine receptor 7 in IDD and upregulation of miR-31-5p can suppress the development of IDD *in vitro* (27). Xie *et al* (28) documented that miR-31-5p can inhibit apoptosis in endplate chondrocytes via regulating activating transcription factor 6 (ATF6) and that mesenchymal stem cell-derived exosomes containing miR-31-5p suppress apoptosis and calcification in endplate chondrocytes. miR-31-5p serves an important role in promoting tumorigenesis and metastasis in several types of cancer, such as colon adenocarcinoma and lung adenocarcinoma (29). miR-654-5p has been reported to be involved in various biological activities, such as cancer progression, liver regeneration and cardioprotection (30,31). Wang *et al* (32) showed that the expression of miR-654-5p is dysregulated in degenerated NP tissues obtained from patients with IDD. Further assays indicated that miR-654-5p promotes ECM degradation by upregulating expression levels of matrix metalloproteinase (MMP)-3, MMP-9 and MMP-13, while downregulating collagen I, collagen II, SRY-box transcription factor 9 (SOX9) and aggrecan via autophagy suppression by binding to autophagy-related (ATG)7 to activate the PI3K/AKT/mTOR pathway (32). Du *et al* (33) explored the role of miR-16 in the inflammatory response in NP cells stimulated by lipopolysaccharide (LPS); miR-16 upregulated the expression of ECM genes (aggrecan and collagen II) in NP cells, while it downregulated genes associated with ECM-degrading enzymes [MMP3, MMP13, A disintegrin and metallopeptidase (ADAM) with thrombospondin type 1 motif (ADAMTS)4 and ADAMTS5]. Mechanistically, they found that miR-16 suppressed nuclear factor-kappa β (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways by targeting their upstream TGF-β-activated kinase 1 and MAP3K7-binding protein 3 gene, which serves a protective role in LPS-induced IDD (33). Several studies have shown that miR-129-5p is involved in the process of IDD (34,35). He *et al* (34) analyzed microarray datasets from the Gene Expression Omnibus database and found that miR-129-5p was dysregulated in IDD specimens, indicating that it may participate in the development of IDD and thus may serve as a potential therapeutic target for IDD. Li *et al* (35) reported that miR-129-5p serves a protective role in IDD via inhibiting apoptosis and promoting the proliferation of NP cells. Yang and Sun (36) found that miR-129-5p is downregulated in patients with IDD and is involved in the development of IDD via inhibition of NP cell apoptosis through targeting bone morphogenetic protein 2. miR-129-5p is reported to be downregulated in the NP obtained from patients with IDD (37). Furthermore, enhancer of zeste homolog 2 (EZH2) suppresses miR-129-5p, a target of MAPK1, via H3K27me3 modification, thereby facilitating development of IDD (37). Cui and Zhang (38) found that miR-129-5p is downregulated in NP tissues obtained from patients with IDD and delivery of miR-129-5p to NP cells via extracellular vesicles causes NP cell apoptosis. Moreover, they revealed that miR-129-5p plays a protective role in IDD by inhibiting the p38/MAPK pathway via targeting leucine-rich α2-glycoprotein1, thus providing a novel therapeutic target for IDD (38).

Tan *et al* (39) detected the expression of lncRNA growth arrest specific 5 (GAS5) in normal and degenerative NP cells and found that lncRNA GAS5 was significantly upregulated in degenerative NP cells. In addition, they found that the silencing of GAS5 promoted the viability of NP cells and improved ECM formation. Mechanistically, lncRNA GAS5, which is located in the cytoplasm, sponges miR-26a-5p to improve the expression of phosphatase and tensin homolog (PTEN) and suppress the PI3K/Akt signaling pathway, thus

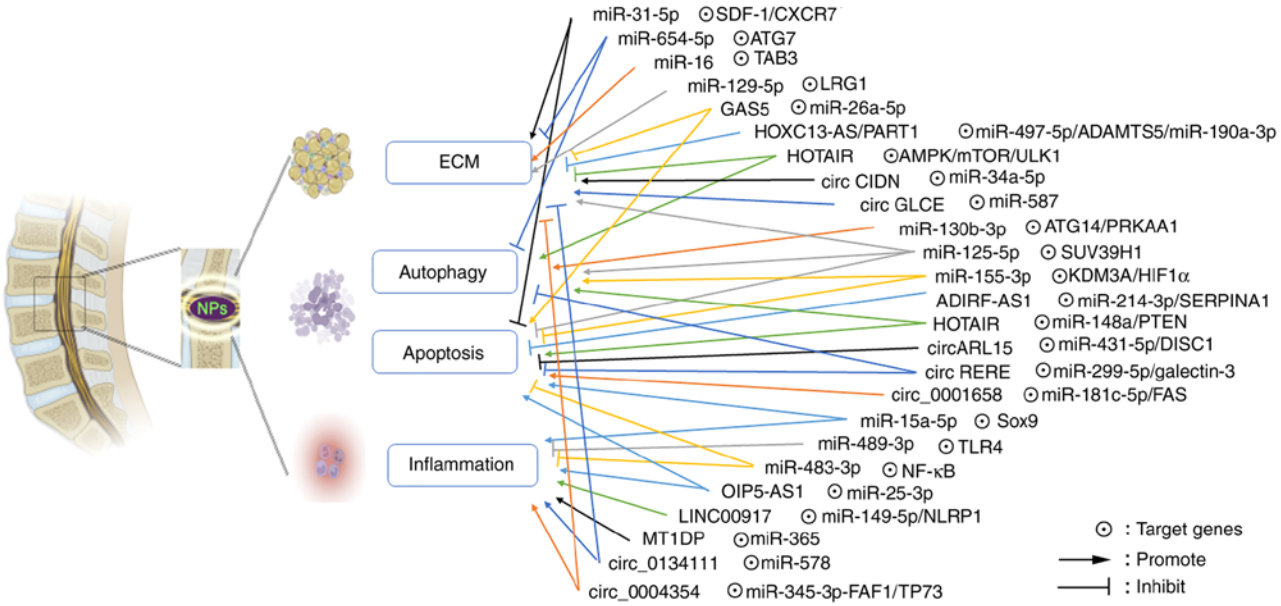

Figure 1. Regulatory role and the target genes of ncRNAs in the pathology of IDD. The ncRNAs have been investigated for their role in IDD via affecting ECM degradation, autophagy, apoptosis and inflammation. ncRNAs may simultaneously promote or inhibit one or multiple biological processes to participate in the progress of IDD, such as miR-125-5p, HOTAIR, circ_0004354 and others. IDD, intervertebral disc degeneration; ncRNA, non-coding RNA; ECM, extracellular matrix; HOTAIR, HOX transcript antisense intergenic RNA; NP, nucleus pulposus. Each color represents one ncRNA.

inhibiting ECM formation (39). Jing and Liu (40) found that lncRNA HOXC13-antisense (AS) is upregulated in IDD specimens and the aberrant expression of HOXC13-AS increases expression levels of MMP-3 and ADAMTS4 while suppressing the expression of aggrecan and collagen II in NP cells. In addition, the same study found that upregulated HOXC13-AS also promoted expression of inflammatory cytokines in NP cells. Mechanistically, HOXC13-AS promotes inflammatory cytokine production and ECM degradation via regulation of the miR-497-5p/ADAMTS5 pathway, which indicates that HOXC13-AS may be a potential therapeutic target for IDD (40). Prior studies have shown that lncRNA HOX transcript AS intergenic RNA (HOTAIR) is involved in several cellular processes, such as apoptosis, autophagy, proliferation and tumorigenesis (41-43). Zhan *et al* (44) reported that expression of HOTAIR in NP cells is associated with IDD grade and HOTAIR upregulation induces autophagy to improve ECM degradation via the AMP-activated protein kinase/mTOR/Unc-51 like autophagy activating kinase 1 pathway *in vitro*. A further *in vivo* study indicated that the suppression of HOTAIR alleviates IDD in rats, suggesting that the inhibition of HOTAIR has the potential to become a therapeutic target for IDD (44). In addition, Zhan *et al* (45) also demonstrated that HOTAIR promotes ECM degradation through the Wnt/β-catenin signaling pathway. lncRNA prostate androgen-regulated transcript 1 (PART1) is involved in various types of cancer as an oncogene by regulating different signaling pathways (46,47). Zhao *et al* (48) found that lncRNA PART1 is upregulated in the NP tissue obtained from patients with IDD using genome-wide RNA sequencing. Recently, Zhang *et al* (49) showed that expression of PART1 was upregulated in LPS-treated NP cells while knockdown of PART1 ameliorated cell apoptosis and promoted ECM degradation in NP cells stimulated with LPS. Furthermore, the same study showed that PART1 participated in progression of IDD by targeting miR-190a-3p to regulate cell viability and ECM degradation, indicating that PART1 may serve as a potential target for IDD treatment (49).

Xiang *et al* (50) examined the circRNA expression profile from compression-treated NP cells using circRNA microarray assays and found that circRNA-CIDN was downregulated and upregulated expression of circRNA-CIDN suppressed NP cell apoptosis and ECM degradation. circRNA-CIDN binds to miR-34a-5p and serves as a sponge to regulate silent mating type information regulation 2 homolog 1, which suggested the use of circRNA-CIDN may be a potential treatment strategy for IDD (50). Chen *et al* (51) performed microarray assays of IDD samples and found that circGLCE was downregulated. The same study confirmed that circGLCE exists in the cytoplasm of NP cells and knockdown of circGLCE induced apoptosis and improved expression of matrix-degrading enzymes in NP cells (51). Mechanistically, circGLCE alleviates IDD by suppressing the apoptosis of NP cells and ECM degradation via binding to miR-587 as a sponge to regulate signal transducing adaptor family member 1 expression, which demonstrates that circGLCE may serve as a potential therapeutic target for IDD (51).

3. ncRNAs in autophagy and apoptosis

Autophagy, a highly conserved biological phenomenon, is the primary intracellular degradation process by which cytoplasmic organelles, macromolecules and proteins are transported and degraded in lysosomes, so it plays a critical role in maintaining cellular homeostasis of NP in response to stressful stimulation (52). Dysregulation of autophagy may lead to human diseases such as obesity, atherosclerosis, metabolic disorder and osteoporosis (53). The latest research indicates that autophagy may serve a role in the pathophysiology of IDD (54). Emerging evidence has shown that ncRNAs

Table I. Roles of ncRNAs in ECM degradation.

A, miR

First author/s, year	ncRNA	Target	Function	(Refs.)
Zhou *et al*, 2021	miR-31-5p	Stromal cell-derived factor-1/ chemokine receptor 7	Promote proliferation and ECM formation; inhibit apoptosis	(27)
Wang *et al*, 2021	miR-654-5p	Autophagy-related 7	Inhibit autophagy; promote ECM degradation	(32)
Du *et al*, 2021	miR-16	TGF-β-activated kinase 1 and MAP3K7-binding protein 3 gene	Promote ECM formation	(33)
Cui and Zhang, 2021	miR-129-5p	Leucine-rich α2-glycoprotein1	Inhibit ECM degradation	(38)

B, Long ncRNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Tan *et al*, 2021	GAS5	miR-26a-5p	Inhibit ECM formation	(39)
Jing and Liu, 2021	HOXC13-AS	miR-497-5p/disintegrin and metallopeptidase with thrombospondin type 1 motif 5	Promote ECM degradation	(40)
Zhan *et al*, 2020	HOTAIR	AMP-activated protein kinase/ mTOR/ Unc-51 like autophagy activating kinase 1	Promote autophagy and ECM degradation	(44)
Zhang *et al*, 2021	PART1	miR-190a-3p	Promote ECM degradation	(49)

C, circRNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Xiang *et al*, 2020	circCIDN	miR-34a-5p	Inhibit ECM degradation	(50)
Chen *et al*, 2020	circGLCE	miR-587	Inhibit ECM degradation	(51)

ncRNA, non-coding RNA; ECM, extracellular matrix; circ, circular; miR, microRNA.

are essential for cellular functions of the NP, including autophagy (54).

Normal apoptosis, which is autonomous programmed cell death regulated by genes, can preserve the stability of the intracellular environment (55). The apoptosis of NP cells is a key pathological feature of IDD and high rates of apoptosis are associated with degenerative processes involving IDs, which reduce the number of cells in NP tissue, damage ID structure and function and induce a disturbance of tissue homeostasis (55). Degenerated IDs exhibit higher rates of apoptosis, but the underlying mechanisms remain unclear (55). Importantly, evidence indicates that ncRNAs are involved in abnormal apoptosis of NP cells during IDD (56). It is reported that numerous ncRNAs can simultaneously affect the process of apoptosis and autophagy during development of IDD (57,58). Several studies have indicated that autophagy alleviates IDD to protect NP cells from apoptosis and the imbalance between autophagy and apoptosis is involved in IDD progress (6,59) (Table II).

miR-130b is involved in various pathophysiological processes, such as regulation of cell proliferation and metastasis in cancer as an oncogene (60,61), affecting macrophage polarization (62) and modulation of epithelial-mesenchymal crosstalk in pulmonary fibrosis (63). Recently, Wu *et al* (57) discovered that miR-130b-3p is dysregulated in degenerative NP obtained from humans and rats and that miR-130b-3p significantly influences IDD progression both *in vivo* and *in vitro*. In addition, they found that inhibiting miR-130b-3p protects NP cells from oxidative stress-stimulated dysfunction and miR-130b-3p inhibition promotes autophagy of NP cells. Mechanistically, they illustrated that miR-130b-3p regulated autophagy-related 14 (ATG14) and protein kinase AMP-activated catalytic subunit α 1 (PRKAA1) directly and inhibited expression of ATG14 or PRKAA1 while the application of the autophagy inhibitor (3-Methyladenine) suppressed autophagic flux and attenuated the protective effects of miR-130b-3p inhibition in tertbutyl hydro-peroxide (TBHP)-stimulated NP cells. Notably, IDD was improved in a rat model by the injection of AAV-miR-130b-3p, which inhibits miR-130b-3p (57). These findings showed that by focusing on ATG14 and PRKAA1, miR-130b-3p inhibition may increase

Table II. Roles of ncRNAs in autophagy and apoptosis.

A, miR

First author/s, year	ncRNA	Target	Function	(Refs.)
Wu *et al*, 2022	miR-130b-3p	Autophagy-related 14/protein kinase AMP-activated catalytic subunit α 1	Promote autophagy	(57)
Chen and Jiang, 2022	miR-125-5p	Suppressor of variegation 3-9 homolog 1	Promote autophagy; inhibit apoptosis and ECM degradation	(66)
Zhou *et al*, 2021	miR-155-3p	Lysine demethylase 3A/Hypoxia-inducible factor 1-α	Promote autophagy; inhibit apoptosis	(71)
Yan *et al*, 2022	miR-328-5p	WW domain containing E3 ubiquitin protein ligase 2	Promote apoptosis; inhibit proliferation	(73)

B, Long ncRNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Yu *et al*, 2022	Growth arrest specific 5	miR-17-3p/ Ang-2	Promote apoptosis; promote ECM degradation	(58)
Zhong *et al*, 2022	ADIRF-AS1	miR-214-3p/ SERPINA1	Inhibit apoptosis and senescence	(79)
Zhang *et al*, 2022	HOTAIR	miR-148a/PTEN	Promote apoptosis and autophagy	(84)

C, circRNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Wang *et al*, 2021	circARL15	miR-431-5p circRERE/DISC1	Inhibit apoptosis; promote proliferation	(85)
Wang *et al*, 2021	circRERE	miR-299-5p/galectin-3	Inhibit apoptosis and autophagy	(86)
Meng and Xu 2021	circ_0001658	miR-181c-5p/FAS	Promote apoptosis; inhibit proliferation	(89)

ncRNA, non-coding RNA; ECM, extracellular matrix; miR, microRNA; circ, circular.

autophagic flow and decrease IDD, which suggested that miR-130b-3p may serve as a useful treatment approach for IDD.

Exosomes are protein and nucleic acid-containing membrane vesicles with a diameter of 40-100 nm that are released from cells via exocytosis following fusion with the plasma membrane (64). A recent report indicated that exosomes serve a key role in NP apoptosis and autophagy (65). Recently, Chen and Jiang (66) found that cartilage endplate stem cell-derived exosomes induce NP cell autophagy but suppress apoptosis and ECM degradation. Furthermore, they discovered that expression of miR-125-5p is significantly upregulated in exosomes and miR-125-5p regulates suppressor of variegation 3-9 homolog 1 (SUV39H1) to improve autophagy and inhibit apoptosis and as ECM degradation in NP cells. They found that miR-125-5p derived from cartilage endplate stem cell-derived exosomes improves microtubule associated protein 1 light chain 3 (LC3)B expression in NP tissue of IDD rats, which suggested that miR-125-5p may serve as a therapeutic target for IDD. In addition, miR-125-5p could influence the inflammatory response and be involved in the apoptosis of intestinal epithelial cells via the Janus kinase 1/STAT3 and NF-κB pathways in ulcerative colitis (67). miR-125a-5p was also reported to downregulate TNF receptor superfamily member 1B gene (TNFRSF1B) expression and improve osteoclast differentiation, which indicated that miR-125a-5p is involved in osteoclast differentiation (68).

Studies have shown that miR-155-3p, derived from miR-155, is associated with IDD. Wang *et al* (69) documented that Fas-induced apoptosis is promoted when miR-155 is suppressed and inhibited when miR-155 is upregulated in human NP cells. Zhang *et al* (70) reported that upregulation of miR-155 decreases IDD, while its suppression worsens IDD. Recently, Zhou *et al* (71) revealed that miR-155-3p is downregulated in NP tissues and cells of IDD. In addition, upregulation of the expression of miR-155-3p or suppression of lysine demethylase 3A (KDM3A) contribute to autophagy and inhibit apoptosis of NP cells. Mechanistically, miR-155-3p suppresses expression of KDM3A and Hypoxia-inducible factor 1-α in NP cells from IDD samples, which may be a potential

approach for the treatment of IDD. According to a recent study, miR-328-5p is abnormally expressed in numerous types of cancer (colorectal cancer and lung cancer) and is associated with apoptosis of cancer cells (72). Yan *et al* (73) found that the expression of miR-328-5p is upregulated significantly, while the expression of its target gene WW domain containing E3 ubiquitin protein ligase 2 (WWP2) is downregulated in IDD tissues compared with normal tissues. miR-328-5p upregulation is positively, whereas WWP2 downregulation is inversely, linked with the degeneration grade of IDD. In addition, they identified that miR-328-5p suppresses proliferation and causes apoptosis of NP cells via regulation of the expression of Bcl-2, Bax and caspase-3. Mechanistically, miR-328-5p may affect NP cell apoptosis by targeting WWP2 and consequently be involved in the development of IDD, which may provide a novel potential target for IDD therapy.

lncRNAs are involved in the processes of apoptosis and autophagy of NP cells in IDD (74). Growth arrest-specific transcript 5 (GAS5), which has been documented to serve as a tumor suppressor in various types of cancer, is related to the process of osteoarthritis as a pathogenic lncRNA (75). A previous study revealed the ability of GAS5 to promote apoptosis of NP cells via targeting miR-26-5p and suppression of GAS5 expression is a potential therapeutic target for the treatment of IDD (39). In addition, GAS5 has also been shown to target other miRNAs, such as miR-18a-5p and miR-17-5p (39,76). Recently, Yu *et al* (58) found that lncRNA GAS5 is upregulated in the NP tissue obtained from patients with IDD and it could target miR-17-3p and affect Ang-2 expression. Furthermore, they reported that downregulation of GAS5 suppresses levels of activated caspase-3, activated caspase-7, activated caspase-9, MMP13 and ADAMTS4, whereas GAS5 upregulates collagen II expression. Importantly, they discovered that GAS5 suppression inhibits apoptosis and ECM degradation in NP cells while promoting proliferation via upregulating miR-17-3p. In addition, GAS5 inhibition or miR-17-3p upregulation relieves the degree of IDD in mouse models, which demonstrates that inhibition of GAS5 suppresses NP cell apoptosis and improves ECM remodeling, ultimately alleviating IDD via miR-17-3p-dependent inhibition of Ang-2. These results indicated that GAS5 could serve as a novel therapeutic target for IDD treatment.

lncRNA adipogenesis regulatory factor-antisense RNA 1 (ADIRF-AS1), located at 10q23.2, is broadly expressed in numerous types of cell, such as endothelial and epithelial cells. Previously, it has been reported that expression of ADIRF-AS1 is downregulated in more than 100 cancer cell lines (77). Xu *et al* (78) reported that ADIRF-AS1 is upregulated in osteosarcoma (OS) and the overall survival of patients with OS and high ADIRF-AS1 expression levels is shorter than that of those with low ADIRF-AS1 expression levels. Furthermore, ADIRF-AS1 suppression inhibits migration and invasiveness of OS cells and promotes apoptosis. Mechanistically, ADIRF-AS1 could target miR-761 and upregulate insulin receptor substrate 1. Recently, Zhong *et al* (79) showed that ADIRF-AS1 expression is inhibited in high-grade degenerated NP tissues and is positively correlated with expression of serpin family A member 1 (SERPINA1). In addition, ADIRF-AS1 upregulation decreases degenerative changes in NP cells. miR-214-3p directly binds to SERPINA1 and ADIRF-AS1 and negatively regulates ADIRF-AS1 expression. Furthermore, upregulation of ADIRF-AS1 relieves IDD via targeting miR-214-3p to promote the expression of SERPINA1, which suggested that ADIRF-AS1 may be used as a potential target for IDD treatment.

HOTAIR has been reported to be involved in the development of numerous types of cancer, such as breast and lung cancer as well as hepatocellular carcinoma (80-82). Wang *et al* (83) reported that HOTAIR is involved in autophagy. Recently, HOTAIR was documented to participate in progression of IDD by regulating NP cell apoptosis, senescence and autophagy (44). Zhan *et al* (44) found that expression of HOTAIR is positively correlated with IDD grade and its upregulation improves autophagy. Further *in vivo* experiments demonstrated that downregulation of HOTAIR ameliorates IDD in rat model of IDD, which indicated that suppression of HOTAIR expression may serve as a treatment for IDD. Zhang *et al* (84) reported that HOTAIR is significantly upregulated in degenerative NP cells and its downregulation suppresses degenerative NP cell apoptosis and autophagy. In addition, they showed that HOTAIR increases expression of PTEN via sponging miR-148a. *In vivo* assay confirmed that HOTAIR suppression inhibits autophagy and apoptosis in ID tissues, which ameliorates pathological injury in the IDD model.

Studies have reported that circRNAs, acting as competing endogenous RNAs, are associated with pathogenesis of IDD by affecting NP cell apoptosis and autophagy. Recently, Wang *et al* (85) analyzed the dataset GSE67567 from the Gene Expression Omnibus database and found that the expression of circARL15 was significantly downregulated in IDD tissues. They also found that circARL15 expression was negatively associated with miR-431-5p and positively correlated with DISC1 scaffold protein (DISC1). In addition, they showed that circARL15 suppresses NP cell apoptosis but contributes to NP cell proliferation via regulating the miR-431-5p/DISC1 signaling axis, which suggested that circARL15 may serve as a biomarker and provide a promising therapeutic target for patients with IDD.

Wang *et al* (86) recently discovered that miR-299-5p is downregulated in IDD tissues and H_2O_2-induced NP cells, while the overexpression of miR-299-5p improves cell viability and suppresses apoptosis and autophagy under H_2O_2 stimulation. Moreover, circRERE expression is significantly upregulated in IDD tissues and H_2O_2-stimulated NP cells Inhibition of circRERE reverses the effects of miR-299-5p upregulation on cell viability, apoptosis and autophagy in NP cells. Mechanistically, circRERE assists in H_2O_2-stimulated apoptosis and autophagy of NP cells via the miR-299-5p/galectin-3 pathway, which may provide a potential target for clinical therapy of IDD in the future (86). Liu *et al* (87) found that circRERE is downregulated in osteoarthritis cartilage and chondrocytes because of its increased N6-methyladenosine (m6A) modification. circRERE downregulation promotes the apoptosis of chondrocytes and upregulation of circRERE improves osteoarthritis via targeting the miR-195-5p/IRF2BPL/β-catenin signaling pathway (87). These reports indicated that circRERE serves a critical role in bone-associated disease.

Wang *et al* (88) reported that circ_0001658 is significantly upregulated in osteosarcoma tissue and increases proliferation,

Table III. Role of ncRNAs in inflammation.

A, miR

First author/s, year	ncRNA	Target	Function	(Refs.)
Zhang *et al*, 2021	miR-15a-5p	Sox9	Promote inflammation and apoptosis	(94)
Dong and Dong, 2021	miR-489-3p	Toll-like receptor 4	Inhibit inflammation	(95)
Ji *et al*, 2021	miR-483-3p	NF-κB	Inhibit inflammation and apoptosis	(96)

B, Long ncRNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Che *et al*, 2021	OIP5-AS1	miR-25-3p	Promote apoptosis and inflammation; inhibit proliferation	(97)
Li *et al*, 2022	LINC00917	miR-149-5p/NLR Family Pyrin domain Containing 1	Promote inflammation, inhibit proliferation	(102)
Liao *et al*, 2021	MT1DP	miR-365	Promote inflammation	(103)

C, Circular RNA

First author/s, year	ncRNA	Target	Function	(Refs.)
Yan *et al*, 2022	circ_0134111	miR-578	Promote inflammation and ECM degradation	(106)
Li *et al*, 2022	circ_0004354	miR-345-3p-FAF1/tumor protein P73	Promote inflammation and ECM degradation	(107)

ncRNA, non-coding RNA; ECM, extracellular matrix; miR, microRNA.

migration and invasion of osteosarcoma cells and suppresses apoptosis by targeting the miR-382-5p/YB-1 signaling pathway. Meng and Xu (89) found that circ_0001658 expression is significantly increased in the NP tissue obtained from patients with IDD and hsa-miR-181c-5p is downregulated. In addition, they revealed that circ_0001658 upregulation suppressed proliferation of NP cells and increased apoptosis. Mechanistically, circ_0001658 served as a sponge for miR-181c-5p and regulated expression of Fas in NP cells, which indicated that circ_0001658 may be a novel target for the treatment of IDD in the future. Recently, circ_0001658 was found to be upregulated in gastric cancer tissue (90). In addition, the same study showed that the inhibition of circ_0001658 expression resulted in decreased autophagy and apoptosis of gastric cancer cells via miR-182 targeting, which suggested that circ_0001658 may serve as a potential target for gastric cancer treatment. The aforementioned results indicated that circ_0001658 may serve a key role in a variety of diseases.

4. ncRNAs in inflammation

Aggravation of inflammatory cytokine levels contributes to IDD. Various studies have demonstrated upregulation of the proinflammatory cytokines, such as Tumor necrosis factor (TNF)-α, IL-6, IL-1β and IL-1α, in IDD (91,92). These proinflammatory cytokines stimulate ECM degradation and reformation of the phenotype of NP cells, thus causing degeneration of the ID (93). Studies (Table III) have indicated that ncRNAs are associated with production of inflammatory cytokines in NP tissue.

Zhang *et al* (94) reported that miR-15a-5p is upregulated in ID tissues obtained from patients with IDD and mouse models and downregulating miR-15a-5p expression increases Sox9 to trigger phospho-p65 expression, inhibit NP cell apoptosis and inflammatory factor levels, facilitate proliferation of NP cells and arrest the NP cells at the S and G_2/M phase. Furthermore, they revealed that inhibition of miR-15a-5p promotes Sox9 expression to suppress the inflammatory response and apoptosis of NP cells in mice with IDD via the NF-κB signaling pathway, which indicated that targeting miR-15a-5p may be helpful for IDD therapy. Dong and Dong (95) found that miR-489-3p is significantly downregulated in LPS-stimulated human NP cells. In addition, miR-489-3p inhibits LPS-stimulated suppression of cell viability and increases apoptosis as well as levels of inflammatory cytokines. miR-489-3p plays an important role in inhibiting LPS-induced suppression of ECM deposition through downregulation of the expression of aggrecan and collagen type II in human NP cells. Mechanistically, miR-489-3p is involved in suppressing LPS-induced activation of the NF-κB pathway in human NP

cells, which indicates that miR-489-3p may serve as a potential treatment target for IDD. Arctigenin (ATG), an active ingredient of the Chinese herbal medicine *Arctium lappa*, serves a key role in anti-inflammatory and antioxidant effects. Recently, Ji *et al* (96) reported that ATG suppresses apoptosis and inflammation while improving miR-483-3p expression. Moreover, inhibition of miR-483-3p reverses these effects.

Previously, OIP5 antisense RNA 1 (OIP5-AS1) was reported to induce apoptosis of oxidized low-density lipoprotein (ox-LDL)-stimulated vascular endothelial cells by regulating glycogen synthase kinase 3 β (GSK-3β) via recruiting EZH2 (97), while inhibition of OIP5-AS1 improves cell viability and suppresses apoptosis in ox-LDL-stimulated human endothelial cells (98). Moreover, it was demonstrated that lncRNA OIP5-AS1 serves an important role in suppressing osteoblast differentiation of valve interstitial cells via the miR-137/twist-related protein 11 signaling pathway (99). Further study indicated that lncRNA OIP5-AS1 is associated with occurrence and development of osteoarthritis and downregulation of lncRNA OIP5-AS1 worsens osteoarthritis by regulating the miR-29b-3p/progranulin axis (100). Recently, Che *et al* (97) found that OIP5-AS1 is upregulated in IDD tissues and silencing of OIP5-AS1 promotes cell proliferation but inhibits apoptosis and ECM degradation. In addition, OIP5-AS1 suppression inhibits the inflammatory response in LPS-induced NP cells. Mechanistically, OIP5-AS1 regulates proliferation, apoptosis, inflammation and ECM degradation via targeting miR-25-3p, which suggested that the OIP5-AS1/miR-25-3p axis may be a potential target for IDD treatment. Previously, it was reported that 135 lncRNAs are increased and 170 lncRNAs are decreased in IDD samples, among which LINC00917 is the most upregulated lncRNA and is hypothesized to regulate IDD progression (101). Recently, Li *et al* (102) found that LINC00917 is significantly increased in TBHP-stimulated NP cells and inhibition of LINC00917 improves proliferation and suppresses the inflammatory response and pyroptosis of NP cells. Furthermore, they revealed that LINC00917 silencing restores NP cellular function and inhibits IDD progression by regulating the miR-149-5p/NLR family pyrin domain containing 1 signaling pathway. Liao *et al* (103) reported that metallothionein 1D pseudogene (MT1DP) and miR-365 are significantly upregulated in human IDD NP tissue and NP cells, while the expression of nuclear factor erythroid 2-related factor 2 (NRF-2) is significantly downregulated. They found that upregulation of MT1DP and miR-365 and restriction of NRF-2 inhibit NP cell viability and cause apoptosis and inflammation. Furthermore, MT1DP and miR-365 induce inflammation in NP cells by damaging the mitochondrial membrane and mitochondrial function.

circRNAs have been suggested as treatment targets for several types of disease, such as cancer and metabolic and cardiovascular diseases (104). Liu and Zhang (105) reported that expression of circ_0134111 is increased in IL-1β-activated chondrocytes and knockdown of circ_0134111 reverses IL-1β-induced cell decreases by suppressing apoptosis. In addition, they reported that circ_0134111 causes osteoarthritis progression via targeting miR-224-5p and regulating C-C motif chemokine ligand 1. Recently, Yan *et al* (106) found that circ_0134111 expression is significantly upregulated in IDD tissue and the elevation of circ_0134111 is greater in severe IDD cases. In addition, they discovered that IL-1β and TNF-α significantly increase circ_0134111 expression in NP cells. Furthermore, circ_0134111 overexpression increases proliferation, inflammatory cytokine production and ECM degradation in NP cells. circ_0134111 promotes progression of IDD by improving NP cell inflammation and ECM degradation partly by regulating miR-578, which suggested that circ_0134111 may serve as a potential target for IDD treatment. Li *et al* (107) found that circ_0004354 competes with circ_0040039 to stimulate the progression of IDD by regulating miR-345-3p-FAF1/tumour protein P73 pathway-mediated apoptosis, inflammatory response and ECM degradation of NP cells. These results provide insight into the circ_0004354-mediated post-transcriptional regulation of IDD, thus contributing to the development of a promising treatment target for IDD in future.

5. Conclusion

Over the past few years, emerging studies have indicated that a series of ncRNAs are involved in the progression of IDD, particularly NP cell phenotypical regulation, which provides insight into the pathogenesis of IDD (8,9). Certain dysregulated ncRNAs may be useful diagnostic biomarkers and therapeutic targets in the future with continued research (108). The present review discussed progression of IDD, the role of miRNAs and lncRNAs and control of downstream target genes to regulate ECM degradation, inflammation, autophagy and apoptosis of NP cells. The present section discusses the key regulatory role of ncRNAs in the intervention and treatment of IDD from a macro perspective, as well as limitations of research in clinical practice and potential future research directions.

ncRNAs have potential for investigation as medications or biomarkers for the treatment of IDD according to the findings of prior studies (108,109). However, to the best of our knowledge, no clinical trials have been performed on ncRNAs in IDD and all discussed studies have only used cell/animal experiments. Nonetheless, the theoretical approach needs to translate into a real course of action. Based on animal models, it is possible to slow down or stop the progression of IDD by boosting, lowering or eliminating the expression of one or more particular miRNAs, lncRNAs and circRNAs *in vivo* (21,44). To date, most studies have primarily focused on disease samples, cells and small animals, which are dissimilar from the biomechanics of humans (106,107). Therefore, there is an urgent need for an improved animal model of the human spine. Additionally, the regulatory mechanism of humans is complex. Thus, delivering therapeutic ncRNAs to nearby degenerating IDs via a carrier appears to be a workable treatment plan for IDD in the future (108).

Numerous obstacles still need to be overcome, such as the fact that an ncRNA binding to its target gene is not entirely complementary (44,84), indicating that one ncRNA may control several targets or that one target can be controlled by multiple ncRNAs. The first challenge to be addressed in clinical application of ncRNAs will be improvement of the specificity of ncRNAs toward the targets. Therefore, highly selective ncRNAs that serve a role in numerous IDD-associated processes may provide opportunities to prevent IDD. Thus, ncRNAs, such as miRNAs, lncRNAs and circRNAs, as targets for the therapy of IDD may become a unique research

area with the development of nanoparticle technology which could delivery ncRNAs and a thorough understanding of the etiology of IDD. Several delivery methods have been created to minimize off-target effects, particularly concerning nanoparticles, which stand out due to their stability, small size, biocompatibility and self-assembly properties (110,111). Thus, the potential of nanoparticles as efficient ncRNA delivery systems is appealing and merits further research.

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Authors' contributions

CG and YC wrote the manuscript. YW and YH edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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