The role of miRNA, IncRNA and circRNA in the development of intervertebral disc degeneration (Review)

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Abstract. Intervertebral disc degeneration (IVDD) is a degenerative musculoskeletal disorder with multiple causative factors, such as age, genetics, mechanics and life style. IVDD contributes to non-specific lower back pain (NLBP), which is a globally prevalent and debilitating musculoskeletal disorder. NLBP has a substantial impact on medical resources and creates an economic burden for the public. Dysregulated phenotypes of nucleus pulposus (NP) cells and endplate chondrocytes, such as proliferation, senescence and apoptosis, along with aberrant expression of extracellular matrix components, including type II collagen and aggrecan, are involved in the pathological process of IVDD. Evidence indicates that non-coding RNAs, mainly microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), play a vital role in the development of IVDD. In the present review, the potential molecular mechanisms of miRNAs, lncRNAs and circRNAs in the initiation and progression of IVDD were described based on the latest literature. Furthermore, ways to influence the functions of NP cells and endplate chondrocytes in IVDD were also summarized. The presented insights suggested that non-coding RNAs may function as potential targets for the treatment of IVDD.

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1. Introduction

Non-specific low back pain (NLBP) is a prevalent and debilitating musculoskeletal disorder that affects people globally (1). NLBP causes a substantial burden on medical resources and the economy (2-4). It is estimated that the medical costs of NLBP in the USA alone are ~$253 billion per year (5). Efforts have been made by clinicians and researchers to investigate the pathogenesis of NLBP and develop effective treatment strategies. Increasing evidence suggests that one of the major causes of NLBP is intervertebral disc degeneration (IVDD) (6), which can be caused by inflammatory factors (7), genetic factors (8), aging (9), intervertebral instability (10) and metabolic disorders (11). Currently, the underlying molecular mechanisms between these factors and IVDD have not yet been investigated. It is well known that the IVDD is composed of the inner nucleus pulposus (NP); a proteoglycan-rich gelatinous substance, the outer annulus fibrosus, as well as the upper and lower cartilage endplates (CEP) (12) (Fig. 1). NP cells play an important role in secreting extracellular matrix (ECM) components, such as type II collagen and aggrecan, in addition to retaining water (13). CEP, a crucial nutrition and metabolic exchange channel, maintains the balance between catabolism and anabolism within IVDD (14,15). Therefore, dysfunction of NP cells and CEP cells, including apoptosis, senescence and abnormal cell proliferation, may cause an imbalance between catabolism and anabolism, which is known to be involved in the pathology of IVDD (16,17).
Non-coding RNAs form a large segment of RNA molecules that are transcribed from DNA, but lack the potential to be translated into proteins or peptides (18). Non-coding RNAs include short hairpin RNA, small interfering RNA, antisense RNA, microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA) and extracellular RNAs (18-25). Increasing evidence suggests that miRNAs, lncRNAs and circRNAs have a vital regulatory function in the pathological process of several diseases, such as cancer (26-31), cardiac disease (32-35) and IVDD (36-41). The structures of miRNAs, lncRNAs and circRNAs are presented in Fig. 2 miRNAs, a class of small non-coding RNAs that are 19-25 nucleotides in length, suppress gene expression by directly binding to the 3'-untranslated regions (UTR), 5'-UTR and coding sequence regions of their target mRNAs, leading to translational repression and/or cleavage (42). This direct binding to 3'‑UTR is the primary method by which miRNAs regulate target genes (43-49). Conversely, lncRNAs are the largest non-coding RNAs (>200 nucleotides in length) without an open reading frame (50). lncRNAs exert physiological functions by modulating gene expression at multiple levels, including DNA methylation, recruitment of transcriptional factors, miRNA sponges and protein-protein interactions (50-55). Unlike the linear structures of miRNAs and lncRNAs, circRNAs are characterized by covalently closed single-stranded loop structures without free 3' and 5' ends (56-58). circRNAs are produced by a precursor mRNA back-splicing mechanism (59). Furthermore, they are widely expressed in eukaryotes with cell type- and tissue-specific patterns, acting as competing endogenous RNAs (ceRNAs) and transcriptional regulators (29,60,61). The present review article provides an overview of the role of miRNAs, lncRNAs and circRNAs in the pathological process of IVDD based on recent studies, in an attempt to clarify the diagnosis and treatment of IVDD.

2. miRNA in IVDD

Evidence indicates that abnormal proliferation of NP cells and formation of cell clusters are implicated in IVDD pathogenesis (45). Li et al (62) demonstrated that the expression of miR-184 was positively associated with Pfirrmann scores (63) and upregulated in degenerative NP samples compared with that in normal NP samples. Furthermore, luciferase assays from the same study indicated that growth arrest specific gene 1 (GAS1) is a target of miR-184, and degenerative NP tissues present low expression of GAS1 compared with normal NP samples (59). Functionally, overexpression of miR-184 can promote abnormal proliferation and cluster formation of NP cells by inducing AKT phosphorylation, which plays an important role in the development of IVDD (62). However, unequivocal evidence demonstrates that apoptosis exists in diverse biological processes, including IVDD (64). The expression levels of miR-138-5p and miR-494 in degenerated NP tissues compared with normal tissue controls, and their effects on apoptosis were investigated by Wang et al and Wang et al (43,65). The aim of their research was to identify the role of miRNAs in the pathogenesis of IVDD. A total of two signaling pathways (miR-138-5p/SIRT1/PTEN/PI3K/Akt and miR-494/JunD) were discovered through gain- and loss-of-function studies. The results demonstrated that miR-138-5p (43) and miR-494 (65) promote tumor necrosis factor-α (TNF-α)-induced apoptosis of NP cells in IVDD by targeting silent mating type information regulation 2 homolog-1 and the transcription factor jun-D via the PTEN/PI3K/AKT signaling pathway and cytochrome c apoptotic signaling, respectively.

Recent studies have reported an imbalance between anabolism and catabolism of ECM in the development of IVDD, predominantly due to excessive ECM degradation. Wang et al and Wang et al (37,66) investigated whether miR-210 and miR-21 facilitate the degradation of ECM components, such as type II collagen and aggrecan within NP tissues. The results indicated that the expression levels of miR-210 and miR-21 are significantly upregulated in degenerated NP specimens compared with healthy controls. Furthermore, miR-210 and miR-21 expression exhibited a positive association with the grade of IVDD disease, using miRNA microarray and reverse transcription-quantitative (RT-q)PCR validation assays. Knockdown and overexpression of miR-210/miR-21 were followed by observation of downstream target genes and ECM-related gene expression compared with the control group. The aforementioned gain- and loss-of-function studies demonstrated that miR-210 and miR-21 promote ECM degradation by suppressing autophagy, targeting both the autophagy-related protein 7 and the PTEN/AKT/mTOR signaling pathway in human NP cells. Conversely, several miRNAs are downregulated in degenerative NP tissues, indicating that miRNAs may exert a protective effect on normal NP tissues against degeneration (45). Studies have indicated that 51 miRNAs are differentially expressed in degenerated intervertebral discs compared with normal intervertebral discs (67). Of these, downregulation of miR-127-5p, miR-193a-3p, miR-133a and miR-98 induce loss of ECM components by targeting matrix metalloproteinase (MMP)-13, MMP-14, MMP-9 and interleukin-6, respectively (68-71). Other miRNAs that have not been studied further may be found to have no differential expression using (RT-q)PCR.

The dysregulation of cell proliferation, matrix hardness and ECM degradation of CEP are also involved in the progression...
of IVDD (72). Chen et al. (72) performed a RT-qPCR analysis, which verified that the expression of miR-34a is markedly elevated in the CEP samples obtained from patients with IVDD compared with samples of healthy donors. Functionally, apoptosis and proliferation of CEP cells are facilitated by upregulating miR-34a through targeting Bcl-2. Liu et al. and Xiao et al. (73,74) investigated the underlying molecular mechanisms of miR-20a and miR-455-5p in the pathogenesis of IVDD. The results demonstrated that matrix stiffness and ECM loss of CEP are positively associated with the degree of IVDD. Overexpression of miR-20a, which is upregulated in degenerative CEP tissues, accelerates the development of IVDD.
and facilitates calcification in CEP cells resulting in matrix stiffness by suppressing the expression of ankylosis protein homolog. Similarly, enforced expression of miR-455-5p, which is downregulated in degenerative CEP samples, promotes the progression of IVDD and increases ECM loss by targeting Runt-related transcription factor 2 (73). Based on these findings, it is speculated that miRNA may serve as a potential novel therapeutic target for IVDD (Fig. 3).

3. lncRNAs in IVDD

Evidence indicates that lncRNAs are involved in the pathological process of IVDD and play a key role in relevant signaling axes (75). Previous studies have demonstrated that the ectopic expression of homeobox transcript antisense intergenic RNA (HOTAIR), IncPolE, growth arrest specific 5, long intergenic non-protein coding RNA 969 and HLA complex group 18 (HCG18) contributes to initiation of IVDD by inducing apoptosis of NP cells through diverse signaling pathways (76-80). Of these lncRNAs, HOTAIR is downregulated in degenerative NP samples and inhibits TNF-α-induced apoptosis of NP cells by regulating Bcl-2 through sponging miR-34a (76). However, the other aforementioned lncRNAs are markedly upregulated in degenerative NP tissues and promote apoptosis of NP cells by targeting DNA polymerase Ε catalytic subunit A, miR-335-3p and miR-146a-5p, respectively (77-80). HCG18 increases the rate of apoptosis of NP cells and inhibits the proliferation of NP cells through the miR-146a-5p/TNF receptor-associated factor 6/NFκB axis (80). Tan et al, Wang et al and Wei et al (39,81,82) first demonstrated that ectopic expression of small nucleolar RNA host gene 1, RNA component of mitochondrial RNA processing endoribonuclease (RMRP) and IQ motif and ankyrin repeat containing (FAM83H-AS1), which are substantially upregulated in IVDD samples compared with control samples, promote the progression of IVDD by enhancing NP cell proliferation. Mechanistically, they suppress the expression of miR-326, miR-206 and Notch1 to promote NP cell proliferation. Furthermore, RMRP and FAM83H-AS1 also demonstrate the ability to modulate the expression of ECM components, including type II collagen and aggrecan (39,81,82). Ruan et al and Wang et al (83,84) confirmed that nuclear paraspeckle assembly transcript 1 (NEAT1) and long intergenic non-protein coding RNA (linc)-A disintegrin and MMP with thrombospondin motifs.
(ADAMTS)5 play crucial roles in the progression of IVDD by regulating the balance between synthesis and degradation of the ECM. However, the expression levels of NEAT1 and linc-ADAMTS5 are different in NP tissues isolated from patients with IVDD. In IVDD, NEAT1 and linc-ADAMTS5 are notably upregulated and downregulated, respectively. Functionally, NEAT1 promotes ECM degradation by upregulating MMP-13 and ADAMTS4 (genes encoding ECM-associated enzymes), and downregulating collagen II and aggrecan through the ERK/mitogen-activated protein kinase signaling pathway. Linc-ADAMTS5 interacts with Ras-responsive element-binding protein 1 to suppress the degradation of ECM and inhibit the expression of ADAMTS5 (83,84). Notably, it was identified that two different IncRNAs, taurine upregulated gene 1 (TUG1) and H19, which are both upregulated in degenerative NP tissues, modulate NP cell senescence, apoptosis and ECM synthesis through the Wnt/β-catenin signaling pathway (85,86). Functionally, TUG1 and H19, which are both upregulated in degenerative NP tissues, promote NP cell senescence, apoptosis and ECM degradation by targeting Wnt/β-catenin and miR-22, respectively (85,86). A recent study by Wang et al (87) focused on the role of autophagy in the pathogenesis of IVDD and demonstrated that the long intergenic non-protein coding RNA 641, which is markedly upregulated in NP samples obtained from patients with IVDD compared with controls, regulate the development of IVDD by inducing autophagic cell death through targeting miR-153-3p and autophagy-related gene 5. In addition, some treatments can be used to target IncRNAs in IVDD, such as silencing of IncRNAs, locked nucleic acid GapmeRs, small molecule inhibitors, antisense nucleotides and zinc-finger nucleases (88). IncRNAs may represent potential effective novel targets for the treatment of IVDD (Fig. 4).

### 4. circRNAs in IVDD

circRNAs are involved in the regulation of manifold diseases as a novel subtype of non-coding RNAs. Cheng et al (40) were the first to demonstrate that circVMA21 derived from vacuolar ATPase assembly factor gene is markedly decreased in the degenerative NP specimens compared with the normal NP tissues based on RT-qPCR analyses. Functionally, circVMA21 is able to protect against IVDD by suppressing inflammatory cytokine-induced NP cell apoptosis, downregulating the expression of catabolic enzymes (MMP-3, MMP-13, ADAMTS4 and ADAMTS5) and promoting synthesis of ECM. Mechanistically, circVMA21 is expected to function as ceRNAs to modulate the pathological process of IVDD through sponging miR-200c and targeting X-linked inhibitor-of-apoptosis protein. Recently, Wang et al (89) analyzed the expression profiling of human lumbar disc circRNAs based on an online database and reported that circSEMA4B is substantially downregulated in degenerative lumbar disc tissues. Functionally, circSEMA4B can inhibit the development of IVDD by enhancing NP cell proliferation and alleviating cell senescence and ECM degradation. Mechanistically, circSEMA4B is a potential therapeutic target for IVDD as it represses miR-431 via the Wnt/β-catenin signaling pathway (89). However, circRNA_104670 and circRNA_0058097 are upregulated in degenerative NP tissues and tension-induced degenerative endplate chondrocytes, and it has been reported that they promote the progression of IVDD by acting as ceRNAs (41,90). Furthermore, Song et al (41) confirmed via the dual-luciferase and EGFP/RFP reporter assays that circRNA_104670 directly binds to miR-17-3p, while MMP-2 is the direct target of miR-17-3p. Knockdown and overexpression of circRNA 104670 was followed by the

### Table I. Characteristics of miRNAs involved in the process of intervertebral disc degeneration.

| miRNA  | Specimen | Expression | Target   | Function              | Author, year       | (Refs.) |
|--------|-----------|------------|----------|-----------------------|--------------------|---------|
| miR-210 | NP        | Up         | ATG7     | ECM-degradation†      | Wang et al, 2017   | (37)    |
| miR-138-5p | NP      | Up         | SIRT1    | Apoptosis†             | Wang et al, 2016   | (43)    |
| miR-184 | NP        | Up         | GAS1     | Proliferation†         | Li et al, 2017     | (62)    |
| miR-494 | NP        | Up         | JunD     | Apoptosis†             | Wang et al, 2016   | (65)    |
| miR-21  | NP        | Up         | PTEN     | ECM-degradation†       | Wang et al, 2018   | (66)    |
| miR-193a-3p | NP    | Down       | MMP-14   | ECM-degradation†       | Wang et al, 2016   | (68)    |
| miR-133a | NP       | Down       | MMP-9    | ECM-degradation†       | Xu et al, 2016     | (69)    |
| miR-127-5p | NP      | Down       | MMP-13   | ECM-degradation†       | Hua et al, 2017    | (70)    |
| miR-98  | NP        | Down       | IL-6     | ECM-degradation†       | Ji et al, 2016     | (71)    |
| miR-34a | CEP       | Up         | Bcl-2    | Apoptosis†             | Chen et al, 2016   | (72)    |
| miR-20a | CEP       | Up         | ANKH     | Calcification†         | Liu et al, 2016    | (73)    |
| miR-455-5p | CEP     | Down       | RUNX2    | ECM-degradation†       | Xiao et al, 2018   | (74)    |

†, promotion; †, inhibition. miRNA/miR, microRNA; ATG7, autophagy-related protein 7; SIRT1, silent mating type information regulation 2 homolog-1; GAS1, growth arrest specific gene 1; JunD, transcription factor jun-D; MMP, matrix metalloprotein; IL-6, interleukin-6; Bcl-2, B-cell lymphoma-2; ANKH, ankylosis protein homolog; RUNX2, Runt-related transcription factor 2; ECM, extracellular matrix; NP, nucleus pulposus; CEP, cartilage endplates.
observation of proliferation and apoptosis of NP cells and the expression of miR-17-3p and ECM-related gene compared with the control group. Functionally, through gain- and loss-of-function studies, circRNA_104670 was demonstrated to inhibit proliferation of NP cells and expression of collagen II, and promote apoptosis and the expression of MMP-2 by targeting miR-17-3p and MMP-2. Xiao et al (90) reported that circRNA_0058097 may promote morphological changes of endplate chondrocytes and enhance ECM degradation and degeneration of IVDs by upregulating the expression of histone deacetylase 4 through sponging miR-365a-5p. Thus, circRNA_0058097 promotes the pathological process of intervertebral disc degeneration.

### Table II. Characteristics of lncRNAs involved in the process of intervertebral disc degeneration.

| lncRNAs | Specimen | Expression | Target | Function | Author, year (Refs.) |
|---------|----------|------------|--------|----------|----------------------|
| SNHG1   | NP       | Up         | miR-326| Proliferation↑ | Tan et al, 2018 (39) |
| HOTAIR  | NP       | Down       | miR-34a| Apoptosis↓  | Yu et al, 2018 (76)  |
| IncPolE | NP       | Up         | PolE1  | Apoptosis↑  | Li et al, 2019 (77)  |
| GAS5    | NP       | Up         | miR-155| Apoptosis↑  | Wang et al, 2019 (78) |
| LINC00969 | NP | Up       | miR-335-3p| Apoptosis↑ | Yu et al, 2019 (79)  |
| HCG18   | NP       | Up         | miR-146a-5p| Apoptosis↑ | Xi et al, 2017 (80)  |
| RMRP    | NP       | Up         | miR-206| Proliferation↑, ECM-degradation↑ | Wang et al, 2018 (81) |
| FAM83H-AS1 | NP | Up       | Notch 1| Proliferation↑, ECM-degradation↑ | Wei et al, 2019 (82)  |
| NEAT1   | NP       | Up         | ERK/MAPK| ECM-degradation↑ | Ruan et al, 2018 (83) |
| linc-ADAMTS5 | NP | Down    | ADAMTS5| ECM-degradation↓ | Wang et al, 2017 (84) |
| TUG1    | NP       | Up         | Wntβ-catenin| Senescence↑, ECM-degradation↑, Apoptosis↑ | Chen et al, 2017 (85) |
| H19     | NP       | Up         | miR-22 | Senescence↑, ECM-degradation↑ | Wang et al, 2018 (86) |
| LINC00641 | NP | Up       | miR-153-3| Autophagy↑ | Wang et al, 2019 (87) |

| circRNA   | Specimen | Expression | Target | Function | Author, year (Refs.) |
|-----------|----------|------------|--------|----------|----------------------|
| circVMA21 | NP       | Down       | miR-200c| Apoptosis↓, ECM-degradation↓ | Cheng et al, 2018 (40) |
| circRNA_104670 | NP  | Up       | miR-17-3p| Apoptosis↑, Proliferation↑, ECM-degradation↑ | Song et al, 2018 (41) |
| circSEMA4B | NP       | Down       | miR-431| Proliferation↑, ECM-degradation↑, Senescence↓ | Wang et al, 2018 (89) |
| circRNA_0058097 | CEP | Up       | miR-365a-5p| ECM-degradation↑ | Xiao et al, 2019 (90) |

↑, promotion; ↓, inhibition. IncRNAs, long non-coding RNAs; ECM, extracellular matrix; NP, nucleus pulposus; SNHG1, small nuclear RNA host gene 1; HOTAIR, homeobox transcript antisense intergenic RNA; GAS5, growth arrest specific 5; LINC00969, long intergenic non-protein coding RNA 969; HCG18, HLA complex group 18; RMRP, RNA component of mitochondrial RNA processing endoribonuclease; FAM83H-AS1, IQ motif and ankyrin repeat containing; NEAT1, nuclear paraspeckle assembly transcript 1; linc, long intergenic non-protein coding RNA; ADAMTS5, A disintegrin and metalloproteinase with thrombospondin motif 5; TUG1, taurine upregulated gene 1; H19, H19 imprinted maternally expressed transcript; LINC00641, long intergenic non-protein coding RNA 641; PolE1, DNA polymerase E catalytic subunit A; miR, microRNA; MAPK, mitogen-activated protein kinase.

### Table III. Characteristics of circRNAs involved in the process of intervertebral disc degeneration.

| circRNA | Specimen | Expression | Target | Function | Author, year (Refs.) |
|---------|----------|------------|--------|----------|----------------------|
| circVMA21 | NP       | Down       | miR-200c| Apoptosis↓, ECM-degradation↓ | Cheng et al, 2018 (40) |
| circRNA_104670 | NP  | Up       | miR-17-3p| Apoptosis↑, Proliferation↑, ECM-degradation↑ | Song et al, 2018 (41) |
| circSEMA4B | NP       | Down       | miR-431| Proliferation↑, ECM-degradation↑, Senescence↓ | Wang et al, 2018 (89) |
| circRNA_0058097 | CEP | Up       | miR-365a-5p| ECM-degradation↑ | Xiao et al, 2019 (90) |

↑, promotion; ↓, inhibition. circRNA, circular RNA; ECM, extracellular matrix; NP, nucleus pulposus; CEP, cartilage endplates; miR, microRNA.
IVDD by regulating tension-induced degeneration of endplate chondrocytes. CircRNAs modulate the development of IVDD by functioning as ceRNAs (90) and may serve as a potential novel therapeutic target of IVDD, similar to miRNAs and lncRNAs (Fig. 5).

5. Conclusions

As one of the most prevalent diseases among the elderly population, NLBP has caused tremendous pressure on medical resources and the economy. Several studies have demonstrated that IVDD is responsible for the pathogenesis of NLBP; however, its underlying molecular and cellular mechanisms remain unclear. Recently, the role of non-coding RNAs in several diseases emerged, including IVDD.

In the present review, the role of miRNAs, lncRNAs and circRNAs in the progression of IVDD is summarized. Furthermore, it presents a summary of how to modulate the proliferation, senescence, apoptosis and ECM degradation of NP and CEP by regulating downstream target genes (Tables I-III). The data presented in the current review provide novel insights into the etiology of IVDD and identifies non-coding RNAs as a potential novel target for the treatment of IVDD. However, there is still a lack of relevant studies on miRNAs and circRNAs as therapeutic targets for IVDD. With the development of nanoparticle technology and an in-depth understanding of the pathogenesis of IVDD, research on non-coding RNAs, particularly miRNAs, lncRNAs and circRNAs as therapeutic targets for the treatment of IVDD has potential to become a novel research focus.

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HW and LW designed the present review. JJ, YS and GX performed the literature review and drafted the initial manuscript. HW and LW critically revised the manuscript for important intellectual content. All authors have read and approved the manuscript.

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