Role of non-coding RNAs in cartilage endplate (Review)

XIAOKUN ZHAO[1], JINGHONG YUAN[1], JINGYU JIA[1], JIAN ZHANG[1], JIAHAO LIU[1], QI CHEN[1], TAO LI[1], ZHIWEN WU[1], HUI WU[1], XINXIN MIAO[1], TIANLONG WU[1,2], BIN LI[1,2] and XIGAO CHENG[1-3]

[1]Department of Orthopedics, The Second Affiliated Hospital of Nanchang University; [2]Jiangxi Key Laboratory of Intervertebral Disc Disease, Nanchang University; [3]Institute of Minimally Invasive Orthopedics, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Cartilage endplate (CEP) degeneration is considered one of the major causes of intervertebral disc degeneration (IDD), which causes non-specific neck and lower back pain. In addition, several non-coding RNAs (ncRNAs), including long ncRNAs, microRNAs and circular RNAs have been shown to be involved in the regulation of various diseases. However, the particular role of ncRNAs in CEP remains unclear. Identifying these ncRNAs and their interactions may prove to be is useful for the understanding of CEP health and disease. These RNA molecules regulate signaling pathways and biological processes that are critical for a healthy CEP. When dysregulated, they can contribute to the development disease. Herein, studies related to ncRNAs interactions and regulatory functions in CEP are reviewed. In addition, a summary of the current knowledge regarding the deregulation of ncRNAs in IDD in relation to their actions on CEP cell functions, including cell proliferation, apoptosis and extracellular matrix synthesis/degradation is presented. The present review provides novel insight into the pathogenesis of IDD and may shed light on future therapeutic approaches.

Contents

Correspondence to: Professor Xigao Cheng, Department of Orthopedics, The Second Affiliated Hospital of Nanchang University, 1 Minde Road, Donghu, Nanchang, Jiangxi 330006, P. R. China
E-mail: xigaocheng@hotmail.com

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1. Introduction

At present, the incidence of non-specific neck and lower back pain in the global population is high and the etiology is complex (1,2); this seriously affects the quality of life or even causes disability in affected individuals, reduces life expectancy and increases the economic and social burden (3,4). The total annual expenses associated with lower back pain were ~£12 billion in the UK in 1998 (5), and US$7.4 billion in the USA from 1997 to 2007 (6). Moreover, the total annual costs associated with neck pain were US$686 million in The Netherlands in 1996 (7). Efforts have been made by researchers and clinicians to elucidate the pathogenesis of neck and lower back pain and promote treatment strategies (8,9). One of the main pathogenic factors of these afflictions is intervertebral disc degeneration (IDD) (10-13). Currently, various intervention measures are available for chronic musculoskeletal pain, including psychological based therapies (14-20), pharmacological treatments (21-24), and physical-based therapies (20,25-27). However, satisfactory results have not been achieved in terms of pain relief and functional improvement using these methods.

In recent years, various novel interventions have been used to explore the treatment of IDD, such as stem cell transplantation (28), and nanoparticles (29). At present, stem cell therapy for IDD includes hematopoietic precursor stem cells (30), mesenchymal stem cells (MSCs) and adipose-derived stem cells (31). Among them, MSCs have been well studied, including autologous and allogeneic MSCs. In 2011, Orozco *et al* (32) used autologous MSCs transplantation to treat IDD and showed some pain relief. In 2017, they further used allogeneic MSCs to treat IDD, confirming the feasibility and safety of this method and having some pain relief (33). However, the treatment of IDD with stem cells has yet to achieve satisfactory outcomes, possibly due to unclear treatment mechanisms, low survival rates of stem cells, different sources and injection methods of stem cells and a lack of large-scale clinical studies. Recently, nanoparticles have been increasingly used to treat IDD. Prussian blue nanoparticles relieve intracellular oxidative stress and increases the activity of intracellular antioxidant enzymes to rescue IDD (34); polydopamine nanoparticles alleviate IDD by reactive oxygen species consumption, iron chelation and glutathione peroxidase-4 ubiquitination inhibition (29). However, these treatments remain *in vitro* or have

been tested in animal models and not in appropriate IDD models. Bioreactors are culture systems that can mimic the physiological environment of the IDD and provide an accurate nutritional and mechanical environment for the culture of intervertebral discs (IVD) organs (35). However, current cultivation techniques do not allow for extended reactor cultivation time. According to the research conducted by Šećerović *et al*, the survival rate of fibrous rings decreases by >30% within 3 weeks (35). Additionally, there are still significant differences between the simulated physiological state of the IVD in the current IVD bioreactor and the actual human IVD. Therefore, there are still significant limitations in the research and treatment of IDD using bioreactors.

IVDs are often referred to as the largest avascular structures of the human body (36), which consist of gelatinous nucleus pulposus (NP) as the central structure, surrounded by lamellar annulus fibrosus (AF) and sandwiched by the superior and inferior cartilage endplate (CEP) (37,38). Due to the avascular nature of the IVD, small molecules (such as nutrients) have to reach the cells through the extracellular matrix (ECM) mainly by diffusion (39), from the blood vessels at disc margins via two pathways: The CEP-NP pathway and the AF periphery pathway. Several researchers have reported that the CEP-NP nutritional pathway is primarily responsible for nurturing cells in the NP and inner AF regions, while the AF periphery is mainly for cells in the outer AF region (40-42) (Fig. 1). CEP degeneration can hinder the transport of nutrients and causes the dysfunctions of NP and CEP cells (43-45), including senescence, apoptosis and aberrant cell proliferation. Thus, CEP degeneration is considered one of the major causes of IDD, which causes neck or lower back pain (46-48). At present, there are numerous clinical treatments available for neck and lower back pain; however, these treatments can only partially improve some symptoms of patients and cannot fundamentally delay or reverse the pathological process of IDD (49,50). Therefore, restoring the biological function of the CEP and the nutrient supply of IVD, and preventing or even reversing CEP degeneration at the molecular level are the new aims of treatment for neck and lower back pain.

Non-coding RNAs (ncRNAs) are present in the majority of tissues of different species and account for 99% of the total RNA content (51-54). In addition, ncRNAs, DNA methylation and histone modifications are the main mechanisms in epigenetics (55,56). They have been defined as a class of RNA molecules transcribed from the genome, but not encoding proteins, such as long ncRNAs (lncRNAs) (57,58), microRNAs (miRNAs/miRs) (59,60) and circular RNAs (circRNAs) (61-63), with known biological functions, as well as unknown functions (64). ncRNAs have been found to be involved in the development of various diseases, including cancer, heart failure and even nervous system diseases (65-67). Notably, an increasing number of studies have demonstrated that ncRNAs are involved in chondrocyte degeneration through multiple mechanisms (68,69) (Fig. 2).

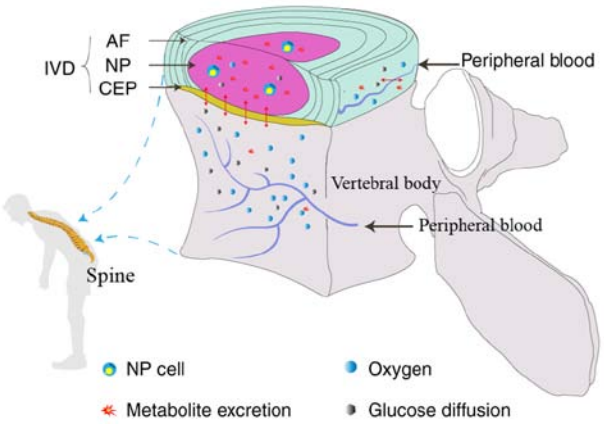

Figure 1. Role of the CEP in the proper nutrition of avascular discs. The IVDs receive nutrients from penetration mainly via the AF and CEP. However, the CEP route is the main route of disc nutrition. Nutrients from the blood vessels in the vertebral body enter the IVD through the CEP and nourish the NP and inner AF. In addition, metabolic waste products from the IVD are excreted into the surrounding capillaries by opposite pathways. CEP, cartilage endplate; IVD, intervertebral disc; AF, annulus fibrosus; NP, nucleus pulposus.

2. miRNAs and CEP

Profile and mechanisms of miRNAs in CEP. Previously, it has been determined that miRNAs play a critical role in complex gene regulatory networks (70). According to statistics, >1,500 miRNAs have been found in the human genome, and each miRNA can target multiple mRNAs; in addition, each mRNA can also be regulated by several miRNAs (71-73). Short RNA molecules of 19-25 nucleotides in size are a class of ncRNAs that regulate the post-transcriptional silencing of target genes by directly binding to the 3'-untranslated region (UTR), 5'-UTR and coding sequence regions of their target mRNAs (74). The majority of miRNA sequences are conserved across species (75). However, miRNA expression varies depending on the time and period examined and tissue type, which indicates that changes in miRNA expression may reflect different cellular composition or activation states (76,77). There is evidence to indicate that miRNAs participate in diverse chondrocyte processes, such as cell proliferation (78), apoptosis (79) and differentiation (80). They are therefore involved in a wider range of processes, such as cartilaginous development, degeneration (81) and regeneration (82). Consequently, CEP degeneration is the primary factor leading to IDD and maintaining the physiological function of CEP is essential for prevention and treatment of IDD (46).

Previous studies have demonstrated that intermittent cyclic mechanical tension (ICMT) can lead to CEP degeneration (83,84). However, the role of miRNAs in regulating chondrocyte responses to ICMT needs to be elucidated. In the study by Feng *et al* (85), CEP chondrocytes from patients without ICMT stimulation were used as controls and specimens were obtained from patients who underwent posterior discectomy and a fusion procedure for IDD. They identified a total of 21 significantly upregulated and 62 downregulated identified compared with the control.

The biological potency of miRNAs has been well-established, with their regulatory effects primarily exerted through sponge target genes, as depicted in Fig. 2, which illustrates the underlying molecular mechanisms.

Roles of miRNAs in CEP. miRNAs are involved in the regulation of multiple mechanisms as a novel subtype ncRNAs.

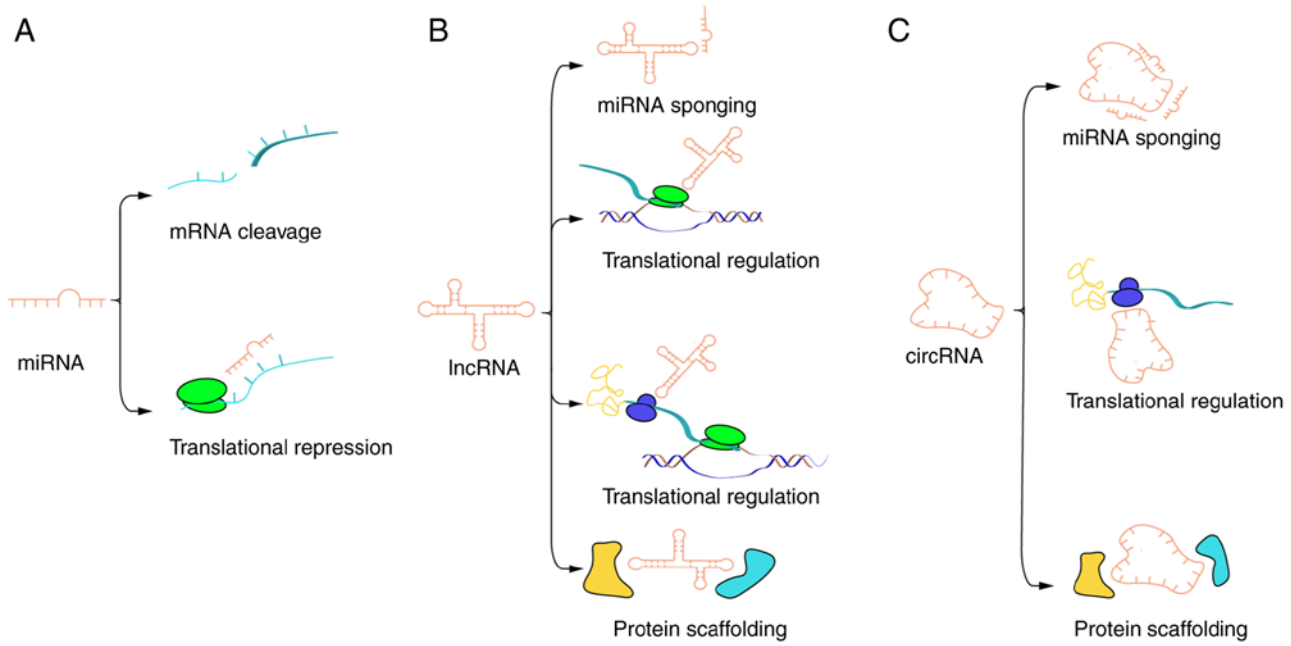

Figure 2. Biological processes and functions of miRNAs, lncRNAs and circRNAs. (A) Functions of miRNAs may include mRNA cleavage and translational repression; (B) the functions of lncRNAs include transcriptional regulation, translational regulation, protein scaffolding and miRNA sponging; (C) the functions of circRNAs include miRNA sponging, protein sponging and translational scaffolding. miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs.

There is evidence to indicate that the apoptosis of chondrocytes in the CEP is implicated in the pathogenesis IDD. Chen *et al* (86) demonstrated that the expression of miR-34a is markedly elevated in human degenerated CEP chondrocytes compared with normal CEP chondrocytes. Furthermore, luciferase assays from the same study indicated that Bcl-2 is a target of miR-34a, while miR-34a represses the expression of Bcl-2. Functionally, the inhibition of miR-34a rescues the fas-induced apoptosis of CEP chondrocytes by releasing Bcl-2, which plays an important role in the development of IDD.

It has been shown that miRNAs are involved in the tension-induced degeneration of endplate chondrocytes by regulating the miR-455-5p/runt-related transcription factor 2 (RUNX2) axis. In the majority of cases, more tension is borne by endplate chondrocytes compared with other cells in human body (87), which is responsible for chondrocyte degeneration (88,89). In chondrocytes, the aberrantly low-expression of miR-455-5p increases the degeneration level of chondrocytes by upregulating RUNX2 expression using ICMT. Furthermore, Xiao *et al* (90) revealed that the up- or downregulation of miR-455-5p does not affect the proliferation or apoptosis of endplate chondrocytes, while RUNX2 expression also exhibits a down- and upregulation, respectively. Therefore, these findings result indicate that miR-455-5p is a therapeutic target for tension-induced degeneration. There is previous evidence to indicate that miRNAs are involved in the calcification of CEP chondrocytes induced by matrix stiffness. For example, it has been shown that the inhibition of miR-20a attenuates calcium deposition and calcification-related gene expression, whereas the overexpression of miR-20a enhances the calcification of CEP chondrocytes on a stiff matrix, which is positively associated with the degree of IDD (91).

The role of CEP chondrocytes in ECM synthesis and catabolism, such as collagens and proteoglycans, plays an important role in maintaining the structural stability of the IVD and in resisting mechanical loads (92,93). In patients with IDD, an imbalance in matrix synthesis and breakdown in the CEP is observed, as shown by the increased expression of breakdown proteins, such as MMP-3 and MMP-9, and a corresponding reduction in the expression of synthetic proteins. Sheng *et al* (94) found that the overexpression of miR-221 in degenerative CEP tissue accelerates apoptosis by downregulating the level of estrogen receptor α. Furthermore, the increased level of miR-221 deteriorates the degradation of the ECM by disrupting the balance in the expression of ECM-degrading and anti-ECM-degrading genes.

Recent studies have demonstrated that cartilage endplate stem cells (CESCs) can maintain the normal function of the NP and CEP through miRNAs. Chen *et al* (95) revealed that miR-637 is expressed in low levels in the degenerative CEP, and the inhibition of miR-637 promotes the osteogenic differentiation ability of degenerative CESCs. However, the upregulation of Wnt family member 5A partially annuls the inhibitory effects of miR-637 overexpression on the osteogenic differentiation of degenerative CESCs. In addition, Chen and Jiang (96) examined the effects of normal CESC-derived exosomes on autophagy, apoptosis and ECM metabolism in the NP. Bioinformatics analysis was used to analyze differences in miRNA expression, and dual-luciferase reporter assays were used to detect target associations. They confirmed that exosomes-derived miR-125-5p from CESCs regulate autophagy and ECM metabolism in the NP by targeting SUV38H1.

There is evidence to indicate that the reduction of the proliferation of CEP chondrocytes is implicated in the

Table I. ncRNA expression, targets and effects in CEP.

ncRNA	Expression	Target	Effect	(Refs.)
miR-34a	Upregulated	Bcl-2	Promotes apoptosis of CEP	(86)
miR-455-5p	Downregulated	RUNX2	Inhibits degeneration of CEP	(90)
miR-20a	Upregulated	ANKH	Mediates the CEP calcification	(91)
miR-221	Upregulated	Erα	Attenuated protective effect of estrogen	(94)
miR-637	Downregulated	WNT5A	Inhibits osteogenic differentiation of CEP	(95)
miR-125-5p	Downregulated	SUV38H1	Regulates autophagy and ECM metabolism in NP	(96)
miR-142-3p	Downregulated	HMGB1	Regulate proliferation, apoptosis, migration, and autophagy of CEP	(97)
MALAT1	Upregulated	ep38/MAPK	Promotes apoptosis of CEP	(124)
CircSNHG5	Downregulated	miR-495-3p	Protect CEP From Degradation	(140)
circRNA_0058097	Upregulated	miR-365a-5p	Promoted morphological changes of endplate chondrocytes, and increased ECM degradation	(136)

ncRNA, non-coding RNA; CEP, cartilage endplate; RUNX2, Runt-related transcription factor 2; ANKH, ankylosis protein homolog; Erα, estrogen receptor alpha; WNT5A, Wnt Family Member 5A; SUV38H1, suppressor of variegation 3-8 homolog 1; HMGB1, high mobility group box 1; MALAT1, lung adenocarcinoma transcript 1; miR, microRNA; circ, circular RNA; SNHG5, small nucleolar RNA host gene 5.

pathogenesis of IDD. Using a double luciferase assay, Wang *et al* (97) indicated that the target gene of miR-142-3p is high mobility group box 1 (HMGB1), the expression of which is significantly increased during the process of IDD. Functionally, the inhibition of chondrocytes proliferation ability follows the addition of a HMGB1 inhibitor.

In conclusion, the aberrant expression of seven miRNAs has been discovered to be involved in various cellular processes, such as proliferation, apoptosis and calcification-induced apoptosis, with their specific regulatory mechanisms and expressions documented in Table I.

3. lncRNAs and CEP

Profile and mechanism of lncRNAs in CEP. From the discovery of the first ncRNA in bacteria in 1980 (98) to a few long-stranded ncRNAs, such as H19 and Xist characterized in the pre-genomic era, to the entry of the genomic era in the 21st century, immense progress has been made in the depth and breadth of research into lncRNAs (99). Previously, lncRNAs were considered as biologically non-functional transcriptional 'noise' (100). However, at present, lncRNAs are considered important regulatory factors with multiple biological functions (99,101), which cannot be translated into protein. The expression patterns of various lncRNAs regulate the different phenotypes of cells (102). In addition, lncRNAs function through a variety of mechanisms, such as acting as a scaffold, bait, signal and guide (103). Of note, lncRNAs play the role of competitive endogenous RNAs (ceRNAs) or small interfering RNA and participate in the lncRNA/circRNA/miRNA/mRNA network as transcriptional regulators (104), which mainly regulate gene expression or control signaling pathways by competitively inhibiting or destroying specific miRNAs (105,106). LncRNAs play an important role in various life processes of organisms, including the cell cycle (101,107-109), differentiation (110-112), and metabolism (57). Furthermore, they participate in the occurrence and development of diseases by affecting gene expression (113), chromatin structure (114) and cell signaling pathways (115).

It has been shown that there is a clear difference in lncRNA expression between degenerated endplate chondrocytes and normal endplate chondrocytes (116). In 2020, the expression profile of lncRNAs was reported for the first time in the endplate of degenerated cartilage. In degenerated chondrocytes, 369 lncRNAs exhibited a differential expression, including 316 upregulated and 53 downregulated lncRNAs, contrasting with the non-degenerated CEP of cervical fractures. In addition, Li *et al* (117) identified the highly selective expression of 34 lncRNAs in human fetal growth plate chondrocytes by employing RNA sequencing. A total of eight lncRNAs were adjacent to the loci of protein coding genes that participate in skeletal development, suggesting that cartilage-selective lncRNAs may be involved in chondrogenesis is through the regulation of protein coding genes.

In summary, the biological functions of lncRNA in chondrocytes can be mediated by various mechanisms, including miRNA sponging, protein scaffolding and translational regulation. Additionally, specific expression patterns of lncRNAs in degenerated endplate chondrocytes have been demonstrated.

Roles of lncRNAs in CEP. Evidence suggests that diabetes causes CEP degeneration by altering endplate thickening and reducing porosity (118-121). Furthermore, chondrocyte apoptosis, characterized by various signaling molecules, is involved in the degeneration of CEPs (122,123). Based on these findings, Jiang *et al* (124) induced CEP cell degeneration with high-glucose medium and revealed that the knockdown of lncRNA MALAT1 reduces the apoptosis of chondrocytes. Furthermore, they demonstrated that lncRNA MALAT1 promotes high glucose-induced rat CEP apoptosis via the p38/MAPK signaling pathway. lncRNAs, as gene expression modulators, are expected to be a novel target for the treatment of disc degeneration; however, to the best of our knowledge,

studies on lncRNAs in CEP degeneration are limited and, thus, further studies on their mechanism of action in CEP degeneration are warranted.

4. circRNAs and CEP

Profile and mechanisms of circRNAs in CEP. circRNAs, which are single-stranded and covalently closed, were first reported as viroids (125), which are pathogens of certain plants in 1976 and were first detected in human HeLa cells by electron microscopy in 1979 (126). Later on, with the development of high-throughput RNA sequencing and bioinformatics tools, circRNAs began to be considered as a general feature of the human transcriptome and are ubiquitous in numerous other metazoans, including mammals (127), unicellular eukaryotes (128), prokaryotes (129) and viruses (130). Previous studies have identified multiple functions of circRNAs, including serving as protein scaffolds or miRNA sponges and being translated into polypeptides (131,132). In addition, the unique covalently closed structure of circRNAs that provides them with a longer half-life and greater resistance to RNase R compared with linear RNAs (133), renders them as potential candidates for use as diagnostic biomarkers and therapeutic targets.

We previously conducted a study to compare degenerative CEP to healthy CEP using a human ceRNA microarray (134). It was revealed that 578 circRNAs were differentially regulated in degenerative CEP samples compared with healthy tissues. Of these, 435 circRNAs were highly expressed, while 143 were significantly repressed. In addition, it has been indicated that biomechanical stimulation is essential for the growth and maintenance of endplate cartilage function (102). Excessive mechanical loading, on the other hand, alters the distribution of the ECM in the CEP, ultimately leading to the destruction of normal cartilage structure and the interruption of nutrient supply (135). By applying an ICMT of 0.5 Hz and an extension of 10% to primitive human endplate chondrocytes, Xiao *et al* (136) verified upregulated expression levels of 17circRNAs and the downregulated expression of another 12 with fold changes 1.5 by using a circRNA microarray technique.

Compared with miRNAs and lncRNAs, circRNAs exhibit an enhanced richness, stability and specific expression (137). Furthermore, various mechanisms such as miRNA sponging, protein scaffolding and translational regulation can be utilized to regulate the chondrocyte process by circRNAs (138) (Fig. 2).

Roles of circRNAs in CEP. Specific circRNAs regulate the ECM and proliferation via a ceRNA mechanism, which contributes to the development of IDD (139). Specifically, circRNA_0058097 and circ small nucleolar RNA host gene 5 (SNHG5) are involved in ECM regulation (136,140). circSNHG5 is related to CEP cell proliferation. miR-495-3p stimulates ECM degradation and inhibits chondrocyte cell proliferation by inhibiting Cbp/P300-interacting transactivator with glu/asp rich carboxy-terminal domain 2, whereas circSNHG5 alleviates the negative effects by sponging miR-495-3p. However, in IDD tissues, the expression of circSNHG5 is repressed, resulting in an aberrantly higher level of miR-495-3p and IDD. The upregulation of circRNA_0058097 expression was observed in the loading group that was subjected to an ICMT of 0.5 Hz and 10% elongation degeneration. Furthermore, circRNA_0058097 can sponge miR-365a-5p and overexpression of miR-365a-5p alleviates tension-induced chondrocyte degeneration (130). These results suggest that the fate of CEP cells in IDD can be modulated by circRNAs, which have the potential to serve as therapeutic targets.

5. Conclusions and future perspectives

Neck and lower back pain is the most prevalent of all musculoskeletal conditions, and it places a major strain on individuals, health systems and social care systems (141). CEP degeneration is one of the primary causes of IDD that leads to neck and lower back pain (46). However, the mechanisms involved have not yet been fully elucidated. Recently, it has been shown that ncRNAs are involved in the degeneration of chondrocytes, including endplate chondrocytes (142).

The present review summarizes the latest evidence concerning the regulation of endplate chondrocytes in IDD based on miRNAs, lncRNAs and circRNAs. In addition, the present review summarizes the mechanisms through which proliferation, calcification, apoptosis and ECM degradation of the CEP can be regulated by regulating downstream target genes (Table I). The data presented herein provides novel insights into the etiology of endplate chondrocyte degeneration and identify ncRNAs as potential novel targets for the treatment of IDD. However, effective therapeutic approaches, such as bone/cartilage targeted hydrogel (143), and exosome-based bone-targeting (144), are hampered by an incomplete understanding of the mechanisms of CEP homeostasis and degeneration. Recently, the advent of novel materials like lipid nanoparticles and cationic polymers has enhanced the targeting specificity of therapy, while also mitigating toxicity and immunogenicity concerns. Furthermore, technological breakthroughs such as CRISPR/Cas gene editing have lowered off-target effects and boosted RNA interference levels. Therefore, injectable hydrogels or nanoparticles (145,146), recombinant adeno-associated viral vector-mediated gene delivery (147), and mesenchymal stem cell-based therapies (148) interfere with RNA expression in endplate chondrocytes to achieve the purpose of treating disc degeneration. At the same time, interfering with the central nodes in the regulatory network allows ncRNAs to provide a future for IDD treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

XKZ, JHY, JYJ, JZ, JHL, QC, TL, ZWW, HW, XXM, TLW, BL and XGC contributed to the conception and design of the study. JHL, QC, TL, ZWW and HW examined the relevant literature, and XKZ wrote the manuscript. JHY, JYJ, JZ, XXM TLW and BL provided advice and are responsible for revising the manuscript. All authors read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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