Research progress on long non-coding RNAs in non-infectious spinal diseases (Review)

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Abstract. Spinal diseases, including intervertebral disc degeneration (IDD), ankylosing spondylitis, spinal cord injury and other non-infectious spinal diseases, severely affect the quality of life of patients. Current treatments for IDD and other spinal diseases can only relieve symptoms and do not completely cure the disease. Therefore, there is an urgent need to explore the causes of these diseases and develop new treatment approaches. Long non-coding RNA (lncRNA), a form of non-coding RNA, is abundant in diverse sources, has numerous functions, and plays an important role in the occurrence and development of spinal diseases such as IDD. However, the mechanism of action of lncRNAs has not been fully elucidated, and significant challenges remain in the use of lncRNAs as new therapeutic targets. The present article reviews the sources, classification and functions of lncRNAs, and introduces the role of lncRNAs in spinal diseases, such as IDD, and their therapeutic potential.

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1. Introduction

The spine is one of the most common sites of lesions in middle-aged and older individuals (>45 years of age) (1). Conditions such as intervertebral disc degeneration (IDD), ankylosing spondylitis (AS) and spinal cord injury (SCI) are common non-infectious spinal diseases that impair the quality of life of patients, and cause a huge economic burden on families and society (2). In addition to causing financial stress, IDD and other spinal disorders are important causes of pain and disability in patients (3). Notably, the incidence of spinal diseases such as IDD has increased, with a trend towards younger individuals (13-20 years of age) (4). Reportedly, ~80% of individuals experience lower back pain due to IDD during their lifetime (5). Unfortunately, the current treatment for these spinal diseases encompasses pain reduction and symptom improvement (6), and does not reverse or cure the diseases (7). Therefore, a more comprehensive understanding of the pathology of these diseases is of great significance for developing new therapeutic drugs, improving and optimising treatment programmes, and curing the diseases.

Although the human genome is expansive, only ~1% of the genome is involved in coding proteins (5), with >98% not directly involved in protein translation (8). RNAs transcribed from these genes not directly involved in protein translation is called non-coding RNAs (ncRNAs). Although ncRNAs are not involved in protein synthesis, they play important roles in regulating gene expression, cell function and development (9). NcRNAs can be divided into numerous categories, including microRNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), small interfering RNAs and PIWI-interacting RNA (10). lncRNAs are RNAs with a length of >200 nucleotides that cannot encode proteins and have various biological functions (11). The functions of lncRNAs include gene regulation, RNAs processing and splicing regulation, cell cycle and proliferation, cell signal transduction, chromosome structure and nucleoplasmic transport (12). The present article reviews the functional classification of lncRNAs and their roles in IDD, AS and SCI, and discusses the potential of lncRNAs for treating spinal diseases such as IDD.

2. Introduction to lncRNAs

Sources and classification of lncRNAs. The majority of lncRNAs are similar in origin to mRNAs and are transcribed by RNA polymerase II. They also have the same structure as mRNAs (13); however, lncRNAs also have certain characteristics, although these are not unique to lncRNAs. lncRNAs account for >60% of all ncRNAs [certain studies report rates of >70% (14) or 70-90% (15)], and most lncRNAs contain >2 exons (16). Some lncRNAs, owing to their reverse splicing or lack of a 5' cap, are readily connected with their own 3' poly-A tail, generating circRNA (17). Numerous lncRNA genes have miRNA sequences embedded in their exons or introns, making them a source of miRNAs (13). A number of chemical modification methods exist for lncRNAs, including adenosine methylation, cytosine modification, uridine isomerisation, guanosine methylation and ribose modification (18), resulting in more complex ncRNA biogenesis.

To date >900 lncRNAs have been identified (19), resulting in different methods of classifying lncRNAs (Fig. 1). Based on their location, they can be divided into nuclear, cytoplasmic and mitochondrial lncRNAs (20). According to their shape, lncRNAs can be divided into linear and circular lncRNAs (21). lncRNAs can also be categorised by source as follows: i) Sense transcript; ii) antisense transcript; iii) bidirectional transcript; iv) long intergenic ncRNAs (22); v) intron region; vi) promoter region (14); and vii) enhancer region (23). Finally, lncRNAs can be categorised by function as follows: i) Functional lncRNAs, ii) non-functional lncRNAs; and iii) lncRNAs for which transcription alone is sufficient to exert their effects and those that do not need to rely on transcripts to function (24). In general, the classification of lncRNAs is regarded as imperfect, as functional interactions and overlaps exist among different classifications of lncRNAs (5). In the future, a better lncRNA classification system will be required.

Functions of lncRNAs. The function of lncRNAs varies depending on their spatial structure and location. lncRNAs have two functional forms including spliced and unspliced (25). The biological genetic information in mRNAs is mainly transmitted through 'linear' coding, while the biological information in lncRNAs mainly works through its different 'spatial' structural mechanisms (26). The main pathways through which lncRNAs function include epigenetic, transcriptional and post-transcriptional regulation (27). When lncRNAs perform their functions, they usually combine with DNA, RNAs and proteins to form the corresponding complexes. First, lncRNAs bind with DNA and play a role in decompressing chromatin (28). They can also affect chromatin accessibility (29), and the R-loop can make lncRNAs an ideal regulatory centre (30). Next, lncRNAs bind to RNAs. The lncRNAs regulate mRNA expression through competitive endogenous RNA mechanisms (31). Finally, lncRNAs bind with proteins to form complexes, regulating protein structure and function (32). Some lncRNAs directly bind to proteins, affecting cellular signal transduction and gene expression.

The functions of lncRNAs vary depending on their location (Fig. 2). The functions of lncRNAs in the nucleus include: i) Providing scaffolding for DNA (33), RNAs and proteins (34); ii) recruiting chromatin-remodelling complexes to remodel the chromatin (35); iii) preventing RNA polymerase II from attaching to the gene promoter and interfering with transcription (36); and iv) alternative splicing (37). The functions of lncRNAs in the cytoplasm include the following: i) Recruiting proteins that promote mRNA degradation and affect the stability of mRNAs (13); ii) sequestering specific miRNAs through the competing endogenous RNA (ceRNA) mechanism to regulate translation (38); iii) interfering with post-translational modifications; and iv) affecting the structure and function of proteins (39). Although the function of lncRNAs is understood to a certain extent, it cannot be inferred from its primary structure, unlike mRNAs. Therefore, further in-depth exploration of lncRNA functions is required.

3. Research progress of lncRNAs in IDD

Introduction to IDD. The intervertebral disc (IVD) is the largest non-blood supply tissue in the human body (40). The IVD is composed of three parts: i) The cartilage endplate (CEP) on the upper and lower sides; ii) the surrounding annulus fibrosus (AF); and iii) the nucleus pulposus (NP) in the middle (41). The CEP is ~1-mm thick and contains a number of micropores for material exchange in the NP, but contains no nerve tissue. The AF is divided into outer and inner rings, and the front and sides are twice as thick as the back. Nerve endings are only distributed in the outer ring (42). The AF is very strong and plays a major role in supporting and stabilising the spine (42). The NP is a gel-like tissue with a high water content, containing collagen, proteoglycans, NP cells and water (43). The composition and structure change with age, accounting for 50-60% of the IVD cross-section (44). The toughness and elasticity of the IVD enable it to perform important physiological functions, such as supporting the spine, buffering pressure and providing spine mobility (45).

As the IVD has no blood vessels, its self-repair ability is poor, making it prone to degeneration (40). IDD initiates in NP cells (46), and this is hypothesised to be primarily due to the joint action of genetic and environmental factors. Smoking, physical activity and poor living habits are contributing factors to IDD, although genetic factors are the most important (47). It is estimated that >70% of cases are caused by genetics and the programmed cell death drives the occurrence of IDD (48). After the onset of IDD, the water content in the IVD decreases, and the extracellular matrix (ECM), including type II collagen and proteoglycans, degrades (49). After the CEP and AF are destroyed, the barrier between the IVD, and the circulatory and immune systems is broken, triggering an inflammatory reaction (50). Under the influence of these pathogenic factors and changes in the microenvironment, the proliferative ability of the NP cells decreases, causing cell apoptosis, autophagy and senescence, ultimately resulting in IDD (5). Surgical treatment of IDD also has challenges, including infection (51), recurrence (52) and adjacent spondylosis (53). Therefore, understanding the pathogenesis of IDD and exploring new therapeutic targets are crucial.

Expression differences of lncRNAs in IDD. Compared with normal tissues, IDD exhibits numerous differentially expressed ncRNAs, including lncRNAs, which play an important role in the occurrence and development of IDD. Wan *et al* (54) used

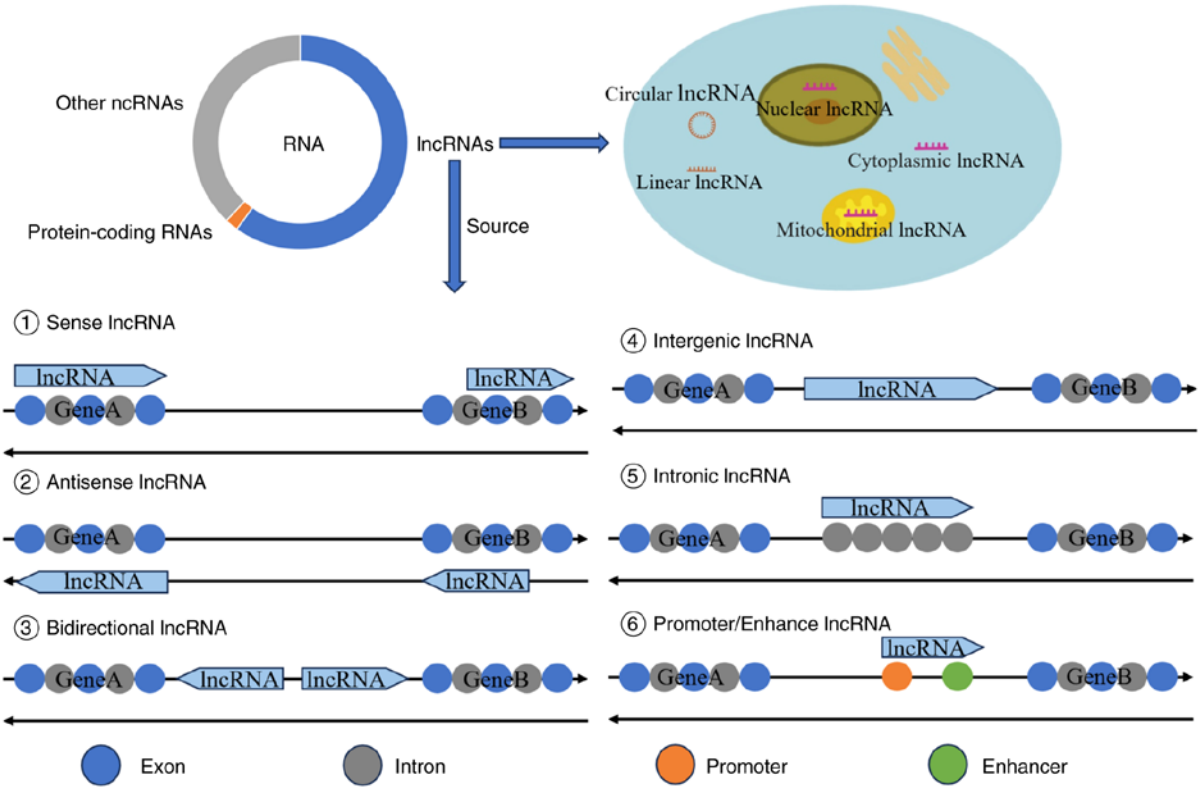

Figure 1. Classification of lncRNAs by location, shape and source. lncRNAs account for >60% of the genome. According to their location, they can be classified as nuclear lncRNA, cytoplasmic lncRNA or mitochondrial lncRNA. According to their shape, they can be classified as linear lncRNA or circular lncRNA. Finally, according to their source, they can be classified as i) sense transcript, ii) antisense transcript, iii) bidirectional transcript, iv) long intergenic ncRNA, v) intron region or vi) promoter region and enhancer region lncRNA. ncRNA, non-coding RNA; lncRNA, long non-coding RNA.

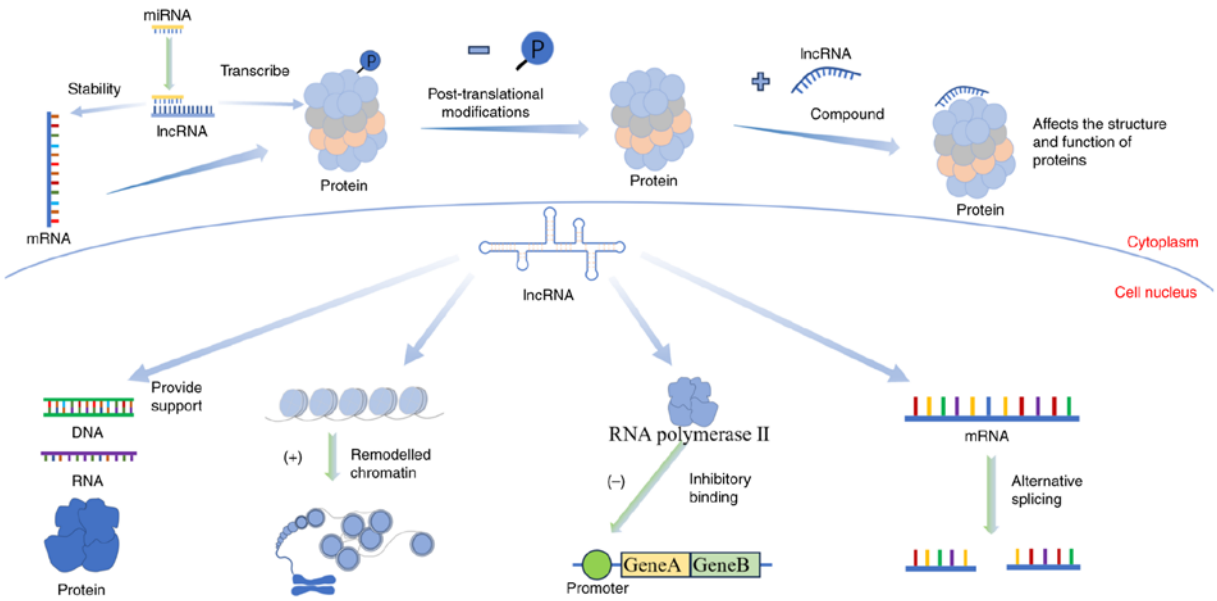

Figure 2. Functions of lncRNA. The functions of lncRNA in the nucleus include providing scaffolding for DNA, RNA and proteins, recruiting chromatin remodelling complexes to remodel chromatin, preventing RNA polymerase II from attaching to the gene promoter and interfering with transcription, and alternative splicing. The functions of lncRNA in the cytoplasm include recruiting proteins that promote mRNA degradation and affect mRNA stability, sequestering specific miRNAs through the competing endogenous RNA mechanism to regulate translation, interfering with post-translational modifications, and affecting the structure and function of proteins. lncRNA, long non-coding RNA; miRNA, microRNA.

lncRNA-mRNA microarrays to study lncRNA expression in NP specimens from human degenerative NP tissue and normal groups. The results revealed that the expression levels of 67 lncRNAs increased and those of 49 decreased. In another study, the same lncRNA-mRNA microarray technology was used to analyse the lncRNA expression in NP specimens of

human degenerative NP tissue and normal groups, and 135 significantly upregulated and 170 downregulated lncRNAs were found (55). A similar study found that 2,418 mRNAs and 528 lncRNAs were differentially expressed in the IDD group compared with the control group (56). Shi *et al* (57) recently constructed a ceRNA network containing 15 lncRNAs, 9 miRNAs and 103 mRNAs, and discovered a lncRNA/miRNA/mRNA axis, which affects the progression of IDD, namely, the small nucleolar RNA host gene 5/miR-299-5p/activating transcription factor 2 axis. However, further experimental verification is still needed. In another study, a ceRNA network was constructed using 15 lncRNAs and 21 miRNAs, and identified the two hub genes MAPK8 and CAPN1 in this regulatory network as key biomarkers of IDD (58). These studies demonstrate that there are obvious differences in lncRNA expression in IDD and that lncRNAs do not function independently but form an extensive ceRNA network system with other ncRNAs.

Association between NP cell phenotypic dysregulation and IDD. As aforementioned, IDD originates primarily from NP cells. As early as 2006, researchers found that transplantation of human NP cells into degenerated IVDs in rabbits could improve the degree of disc degeneration (59). A subsequent similar study showed that transplantation of NP stem cells into degenerated IVDs can more effectively improve IDD than transplantation of NP cells (60). These studies indicate that NP cells play a crucial role in the occurrence and development of IDD. The state of NP cells is influenced by the ECM, inflammation, apoptosis, necrosis and ageing factors. Under a series of negative influences, this ultimately leads to dysregulation of the NP cell phenotype, thereby participating in the occurrence and development of IDD (61). Jiang *et al* (62) reported that miR-365 can alleviate the development of IDD by regulating the synthesis and degradation of the ECM in NP cells. *Propionibacterium acnes* has been shown to induce the apoptosis of NP cells through the TLR2/JNK pathway, which can alter the process of IDD (63). Inflammation in NP cells also affects IDD, whereby extracellular lactate can promote activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, increasing inflammatory levels in the NP cells and thereby promoting IDD (64). Experimental results from Du *et al* (65) suggested that activation of cannabinoid receptor type 2 can delay the ageing of NP cells, restore the balance of ECM metabolism and attenuate IDD. Overall, changes in the ECM, cell death, cell inflammation and cell ageing are all part of the complex mechanisms underlying the occurrence and development of IDD. They interact with each other, collectively influencing the process of IDD.

Role of lncRNAs in the ECM. The ECM, type II collagen and proteoglycan (aggrecan) are the main components of the NP. The ECM is produced by NP cells, and the balance between ECM synthesis and degradation contributes to the biomechanical balance and structural stability of the IVD, which is also considered a key indicator for evaluating NP cell function (66). Subsequent studies indicate that lncRNAs can affect the synthesis and degradation of the ECM through a ceRNA mechanism and can directly regulate hub genes or signalling pathways. Gao *et al* (67) studied degenerated human tissues and cells, and found that prostate androgen-regulated transcript 1 (PART1) was upregulated in degenerated NP tissues. By contrast, PART1 knockdown led to increased ECM synthesis, reduced degradation and enhanced proliferation of NP cells. Growth arrest specific 5 has been shown to be expressed at abnormally high levels in human degenerative NP tissues (68). After downregulation, angiopoietin 2 has been shown to be inhibited in a miR-17-3p-dependent manner, promoting ECM remodelling, inhibiting NP cell apoptosis and improving IDD (68). A recent study showed that the transcription factor FOXO3 may enhance the competitive binding of HOXA transcript at the distal tip (HOTTIP) and miR-615-3p by activating HOTTIP transcription, increasing the expression of the target gene collagen type II α1 of miR-615-3p, inducing NP cell proliferation, and reducing apoptosis to prevent ECM degradation (69). Krüppel-like factor 3 antisense RNA 1 (KLF3-AS1), like HOTTIP, was also shown to be expressed at low levels in degenerative NP tissues. Overexpression of KLF3-AS1 can increase NP cell viability, prevent cell apoptosis and increase ECM synthesis (70).

Shang *et al* (71) showed that docosahexaenoic acid, which plays a protective role in numerous chronic diseases, can alleviate excessive ECM degradation by reducing nuclear paraspeckle assembly transcript 1 overexpression in degenerative NP tissues. This previous study also revealed that ZNFX1 antisense RNA 1 (ZFAS1) was upregulated in degenerative NP tissues and NP cells treated with IL-1β, and that ZFAS1 competitively bound to miR-4711-5p through a ceRNA mechanism, thereby affecting the expression of adaptor-associated kinase 1, which is the target of miR-4711-5p. Silencing ZFAS1 may inhibit IDD progression by reducing NP apoptosis and ECM degradation (72). Similar to most lncRNAs, long intergenic nonprotein coding RNA 284 was revealed to be upregulated in IDD tissues and IL-1β-induced NP cells, and it activated the Wnt/β-catenin pathway by sponging miR-205-3p, thereby inhibiting NP cell proliferation and ECM synthesis (73). Zhan *et al* (74) showed that Hox transcript antisense intergenic RNA (HOTAIR) expression was positively associated with the IDD grade. Oe-HOTAIR enhanced NP cell autophagy, and promoted NP cell ECM degradation, apoptosis and senescence (74). A subsequent study found that HOTAIR regulates ECM synthesis and degradation in NP cells (75). In addition, inhibiting HOTAIR in *in vivo* animal models can effectively reduce IDD symptoms (75). In general, lncRNAs, miRNAs and circRNAs form an intricate regulatory network that jointly affects the synthesis and degradation of the ECM in IDD and IDD progression (Table I and Fig. 3).

Role of lncRNAs in cell death. Owing to different damage factors, NP cells die through a number of the same mechanisms as other cells, such as apoptosis, pyroptosis, autophagy, ferroptosis and necrosis (76). Currently, the most studied process is NP cell apoptosis. As aforementioned, PART1 not only affects the synthesis and degradation of the ECM through the miR-93/matrix metalloproteinase-2 signalling axis, but increased PART1 expression in degenerated tissues can also promote the apoptosis of NP cells and promote IDD (67). Similarly, HOTTIP, while preventing ECM degradation through a ceRNA mechanism, can also inhibit the apoptosis of NP cells and promote proliferation, improving the progression

Table I. Roles of lncRNAs in IDD.

LncRNA	Direction of aberrant expression	Signaling pathway	Cell changes	(Refs.)
MALAT1	Reduced	miR-217/SIRT1	ECM (+); pyroptosis (+)	(80)
HOTTIP	Reduced	miR-615-3p/COL2A1	ECM (-); apoptosis (-); propagation (+)	(69)
HCG18	Increased	miR-495-3p/FSTL1	Apoptosis (+); inflammation (+)	(85)
MEG3	Reduced	miR-15a-5p/ PGC-1α/SIRT1	Apoptosis (+); inflammation (+)	(86)
KLF3-AS1	Reduced	miR-10a-3p/ZBTB20	ECM (+); apoptosis (+); propagation (-)	(70)
NEAT1	Increased	-	ECM (+)	(71)
MAGI2-AS3	Reduced	miR-374b-5p/IL-10	ECM (+); apoptosis (+); inflammation (+)	(78)
HCG18	Increased	MIR4306/EPAS1	ECM (+)	(114)
CAHM	Reduced	-	ECM (+); inflammation (+)	(87)
ZFAS1	Increased	miR-4711-5p/AAK1	ECM (+); apoptosis (+)	(72)
LINC00284	Increased	miR-205-3p	ECM (+); propagation (-)	(73)
NORAD	Reduced	PUMILIO/E2F3	Ageing (+)	(90)
HOTAIR	Increased	miR-130b	Propagation (-)	(115)
PART1	Increased	miR-93/MMP2	ECM (+); apoptosis (+); propagation (-)	(67)
ADIRF-AS1	Reduced	miR-214-3p	Apoptosis (+); aging (+); propagation (-)	(88)
GAS5	Increased	miR-17-3p	ECM (+); apoptosis (+); propagation (-)	(68)
FAM83H-AS1	Reduced	miR-22-3p	ECM (+); inflammation (+); propagation (-)	(84)
HOTAIR	Increased	Wnt/β-catenin	ECM (+); apoptosis (+); ageing (+)	(75)
SNHG6	Increased	miR-101-3p	Apoptosis (+); propagation (-)	(77)
MIR155HG	Increased	miR-223-3p	Pyroptosis (+)	(79)
H19	Increased	miR-139-3p/CXCR4/ NF-κB	Apoptosis (+); autophagy (+)	(82)
TRPC7-AS1	Increased	miR-4769-5p	ECM (+); propagation (+); ageing (+)	(89)

lncRNA, long non-coding RNA; AS1, antisense RNA 1; ECM, extracellular matrix; miR, microRNA; IDD, intervertebral disc degeneration; (+), promoting/promoting degradation; (-), inhibiting/inhibiting degradation; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SIRT1, silent information regulator sirtuin 1; HOTTIP, HOXA transcript at the distal tip; COL2A1, collagen type II α1; HCG18, HLA complex group 18; FSTL1, follistatin-like protein 1; MEG3, maternally expressed gene 3; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; KLF3, Krüppel-like factor 3; ZBTB20, zinc finger and BTB domain-containing protein 20; NEAT1, nuclear paraspeckle assembly transcript 1; MAGI2, membrane associated guanylate kinase, WW and PDZ domain containing 2; EPAS1, endothelial PAS domain protein 1; CAHM, colon adenocarcinoma hypermethylated; ZFAS1, ZNFX1 antisense RNA 1; AAK1, adaptor-associated kinase 1; LINC00284, long intergenic nonprotein coding RNA 284; NORAD, long non-coding RNA activated by DNA damage; PUMILIO, Pumilio-homology domain; E2F3, E2F transcription factor 3; HOTAIR, HOX antisense intergenic RNA; PART1, prostate androgen-regulated transcript 1; MMP2, matrix metalloproteinase 2; ADIRF, adipogenesis regulatory factor; GAS5, growth arrest specific 5; FAM83H, family with sequence similarity 83 member H; SNHG6, small nucleolar RNA host gene 6; MIR155HG, miR155 host gene; H19, H19 imprinted maternally expressed transcript; CXCR4, C-X-C chemokine receptor type 4; NF-κB, nuclear factor-κB; TRPC7, transient receptor potential canonical 7.

of IDD (69). In degenerated NP cells, small nucleolar RNA host gene 6 (SNHG6) expression has been reported to be upregulated and SNHG6 can induce NP cell apoptosis by targeting miR-101-3p (77). Chen *et al* (70) illustrated the possible impact of KLF3-AS1 on IDD. Oe-KLF3-AS1 enhanced NP cell viability and prevented apoptosis. The experimental results confirmed that KLF3-AS1 overexpression improved degenerative changes in NP cells through the

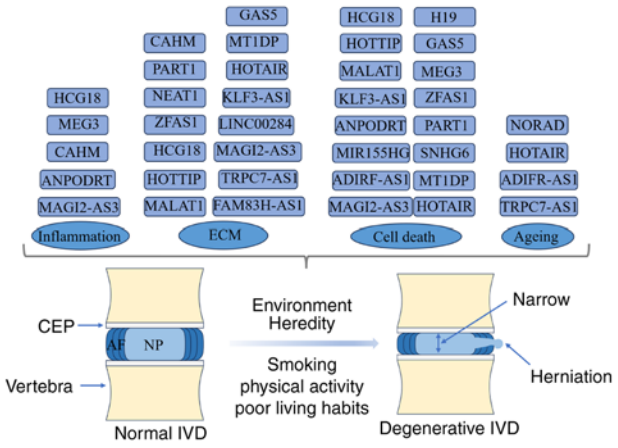

Figure 3. Research progress of lncRNAs in IDD. The intervertebral disc is composed of CEP, AF and NP. Under the combined action of environment, heredity, smoking, physical activity and poor living habits, degeneration occurs, leading to NP protrusion and a decrease in intervertebral space height. lncRNAs mainly regulate the progression of IDD by affecting inflammation, the ECM, cell death and ageing of NP cells. lncRNA, long non-coding RNA; IDD, intervertebral disc degeneration; CEP, cartilage endplate; AF, annulus fibrosus; NP, nucleus pulposus; IVD, intervertebral disc; ECM, extracellular matrix.

miR-10a-3p/zinc finger and BTB domain-containing protein 20 (ZBTB20) axis. Yu and Li (78) detected low expression of membrane associated guanylate kinase, WW and PDZ domain containing 2 (MAGI2)-AS3 and IL-10, and high expression of miR-374b-5p in lipopolysaccharide (LPS)-induced NP cells. Notably, miR-374b-5p is a target of MAGI2-AS3 and IL-10. MAGI2-AS3 can increase the expression of IL-10 by competing with miR-374b-5p, thereby reducing the inflammatory response and cell apoptosis. Thus, the regulation of NP cell apoptosis by lncRNAs is mainly based on the ceRNA mechanism.

LncRNAs regulate the apoptosis of NP cells and affect pyroptosis and autophagy. For instance, MIR155 host gene (MIR155HG) has been shown to be upregulated in degenerated human NP tissues, and further experiments revealed that MIR155HG sponges miR-223-3p and promotes NLRP3 expression, thereby inducing pyroptosis in NP cells (79). Furthermore, platelet-rich plasma-derived extracellular vesicles may inhibit tert-butyl hydroperoxide-induced NP cell injury by upregulating metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression; MALAT1 regulates the miR-217/silent information regulator sirtuin 1 (SIRT1) signalling axis, and its overexpression can alleviate NP cell pyroptosis (80). As aforementioned, HOTAIR can affect the synthesis and decomposition of the ECM in NP cells and the apoptosis of NP cells. Simultaneously, HOTAIR can also affect autophagy and alter the progression of IDD (75). As the first lncRNA discovered (81), H19 imprinted maternally expressed transcript (H19) is highly conserved and widely expressed in mammals. Sun *et al* (82) found that H19 was highly expressed in degenerated NP tissues, and experimentally verified that H19 can promote autophagy and apoptosis in NP cells through the miR-139-3p/C-X-C motif chemokine receptor type 4/nuclear factor-κB (NF-κB) signalling axis, thereby affecting IDD (Table I and Fig. 3).

Role of lncRNAs in cellular inflammation. Inflammation can accelerate the process of IDD and cause damage and dehydration of the IVD tissue, resulting in loss of its original elasticity and function. Therefore, preventing and controlling inflammation is crucial for treating IDD (83). LncRNAs are important molecules that regulate inflammatory responses. Jiang *et al* (84) found that IDD tissues showed decreased expression of family with sequence similarity 83 member H (FAM83H)-AS1 compared with normal tissues, and Oe-FAM83H-AS1 could promote NP-cell proliferation, and reduce inflammatory responses and ECM degradation. In addition, miR-22-3p mediated the effect of FAM83H-AS1 on degenerated NP tissue (84). In IL-1β-stimulated NP cells, the expression of HLA complex group 18 (HCG18) and follistatin-like protein 1 (FSTL1) has been shown to be increased. Subsequent overexpression experiments demonstrated the impact of the HCG18/miR-495-3p/FSTL1 signalling axis on NP tissue inflammation and apoptosis (85). Zhang *et al* (86) showed that melatonin can reduce inflammation and apoptosis in NP cells while upregulating maternally expressed gene 3 (MEG3) expression, whereas MEG3 expression was shown to be downregulated in the degenerated NP. The study revealed that melatonin can reduce NP cell inflammation and apoptosis through the MEG3/miR-15a-5p/peroxisome proliferator-activated receptor γ coactivator 1α/SIRT1 pathway. Similar to most lncRNAs described previously, MAGI2-AS3 also affects IDD progression through a ceRNA mechanism. MAGI2-AS3 has been reported to be poorly expressed in degenerated NP cells, whereas oe-MAGI2-AS3 can downregulate miR-374b-5p and upregulate IL-10 expression to improve inflammation and ECM degradation in NP cells (78). Exosomes derived from bone marrow mesenchymal stem cells (BMSC-Exos) have therapeutic effects on IDD. In co-culture experiments, BMSC-Exos delivered colon adenocarcinoma hypermethylated (CAHM) to inhibit the polarisation of M1 macrophages, thereby reducing the apoptosis of degenerated NP cells, ECM degradation and the expression of inflammatory factors, and improving IDD (87). In addition to the aforementioned lncRNAs, numerous lncRNAs discovered in previous studies also have important effects on the occurrence and development of IDD (56), requiring further verification experiments (Table I and Fig. 3).

Role of lncRNAs in cellular senescence. Senescence of NP cells plays an important role in the development of IDD. During ageing, the regenerative capacity of NP cells weakens, apoptosis and inflammation increase, and cell metabolism becomes abnormal (65), ultimately promoting the occurrence of IDD under the combined action of various factors. *In vivo* and *in vitro* experiments have shown that the expression levels of adipogenesis regulatory factor (ADIRF)-AS1 and SERPINA1 are downregulated in high-grade degenerated NP tissues and that both have binding sites for miR-214-3p. Subsequent experiments revealed that ADIRF-AS1 can bind to miR-214-3p, thereby increasing SERPINA1 expression and ultimately delaying NP cell ageing and apoptosis (88). As aforementioned, HOTAIR can promote the apoptosis and ECM degradation of NP cells, and accelerate the ageing of NP cells, which can comprehensively affect the progress of IDD in these numerous aspects (74). Furthermore, transient receptor

potential canonical 7 RNA 1-AS1 adsorbs miR-4769-5p through the classical ceRNA mechanism, inhibiting HPN and regulating ageing, vitality and ECM synthesis in NP cells (89). The methylation level of lncRNA activated by DNA damage (NORAD) has been shown to be significantly increased in ageing NP cells, and the expression of WTAP was revealed to be increased in the degenerated NP, significantly promoting the m6 modification of NORAD; the lack of NORAD can promote cellular senescence by affecting the expression of Pumilio-homology domain (90).

In general, research on the mechanisms of lncRNAs in IDD has made great progress since the discovery of the first lncRNAs, H19, and the mechanisms of numerous lncRNAs in IDD have been clarified step-by-step. The same lncRNAs can control IDD through different signalling channels. Different lncRNAs can also function through the same signalling pathway. The impact of lncRNAs on NP cells has also impacted a number of aspects, such as apoptosis, ECM degradation and synthesis, inflammatory response, autophagy and ageing. lncRNAs form a large and complex regulatory network with miRNAs, circRNAs and proteins. To date, most studies have focused on the role of lncRNAs in nucleus pulposus, and there has been little research on CEP and AF. Future research should endeavour to further the understanding of CEP and AF (Table I and Fig. 3).

4. Research progress on lncRNA expression in AS

AS is a chronic systemic disease caused by autoimmunity (91). The main affected population is adolescents or young adults (20-40 years of age), with a higher prevalence in men (92). AS mainly manifests as pain and stiffness in the lower back, gradually worsening and seriously affecting quality of life (93). At present, the pathogenesis of AS is not completely clear; treatment is mainly controlled by drugs, and the condition cannot be completely cured (94).

Cen *et al* (95) compared mesenchymal stem cells from patients with AS (ASMSCs) and healthy donors (HDMSCs) and found that HDMSCs had a stronger adipogenic differentiation ability. A total of 263 lncRNAs showed differential expression during adipogenesis in ASMSCs, and reverse transcription quantitative-polymerase chain reaction results showed that the expression of the top 10 lncRNAs was consistent with the high-throughput sequencing results. This is expected to provide new targets for future interventions in adipogenic metaplasia in AS (95). Another study found 200 upregulated and 70 downregulated lncRNAs in a comparison between patients with AS and healthy individuals (96). Wang *et al* (97) identified lncRNA 122K13.12 and lncRNA 326C3.7 from 205 lncRNAs that were differentially expressed in patients with AS and healthy individuals, and found that 30 miRNAs and 5 mRNAs formed a ceRNA signaling network together with these 2 lncRNAs; this signaling network may regulate the TNF-α signalling pathway in AS (97).

There are numerous differences in lncRNA expression between patients with AS and healthy individuals, thus warranting studies into the specific mechanisms governing this. Fang *et al* (98) found that NONHSAT227927.1 (a type of lncRNA) and tumour necrosis factor receptor-associated factor 2 (TRAF2) were significantly increased in the peripheral blood cells of patients with AS, and were positively associated with clinical inflammatory indicators. Xinfeng capsules, a traditional Chinese medicine, reduced immune inflammation in AS by inhibiting lncRNA NONHSAT227927.1/TRAF2. Furthermore, NONHSAT227927.1 was shown to activate the nuclear factor-κB-p65 pathway by promoting TRAF2 expression, thereby affecting the inflammatory process of AS (98). Osteoblasts are important regulators of bone formation; however, their specific mechanisms of action in AS remain unclear. Liu *et al* (99) collected serum and mesenchymal stem cells from patients with AS and healthy donors and found that MEG3 and TNFα-induced protein 3 (TNFAIP3) were downregulated, whereas miR-125a-5p was upregulated. Overexpression and knockdown experiments showed that MEG3 reduced osteogenic differentiation and inhibited AS progression through the miR-125a-5p/TNFAIP3/Wnt/β-catenin axis (99). As the first lncRNA discovered, H19 plays a regulatory role in diseases such as tumours and IDD, and affects the progression of inflammatory diseases such as AS. A total of three molecules, H19, VDR and TGF-β, can bind to miR22-5p and miR675-5p, and experiments have shown that H19 can regulate AS through the miR22-5p/miR675-5p/VDR-IL-17A/IL-23 signalling pathway (100). As a chronic spinal disease, AS causes severe pain, and understanding the role of lncRNAs in AS regulation provides a potential therapeutic strategy for AS (Table II).

5. Research progress on lncRNAs in SCI

SCI is a severe consequence of trauma to the spinal cord. The spinal cord is affected by external forces or chronic compression, and the corresponding sensory, motor and autonomic nervous functions are impaired owing to factors such as inflammation and apoptosis (101). Nerve cells have poor regenerative ability and cannot be cured after being damaged; therefore, treatment and rehabilitation after SCI are challenging (102). Differentially expressed lncRNAs play a regulatory role in SCI, providing new ideas for its treatment (103). Notably, menstrual blood-derived stem cells (MenSCs) have important therapeutic effects in degenerative and traumatic diseases, such as premature ovarian failure in mice (104) and cutaneous wound (105). Compared with SCI rats, rats treated with MenSCs exhibited significant upregulation of 89 lncRNAs and other RNAs, and significant downregulation of 65 lncRNAs and other RNAs. The lncRNA-miRNA-mRNA and circRNA-miRNA-mRNA ceRNA networks of SCI indicated that the role of lncRNAs in SCI may be mediated by a large interconnected regulatory network (103). Liu *et al* (106) examined changes in the expression of lncRNAs in the proximal tissue of the T10 layer at different time points during the right hemisection of T10 laminectomy. The expression of 68 lncRNAs first increased and then remained high 3 days after injury. Meanwhile, the expression of 56 lncRNAs decreased initially and remained low 3 days after injury. In a similar study, circulating exosomes were extracted from the blood of rats with SCI and control rats, and ncRNAs in the exosomes were identified, ultimately showing that the expression of ENSRN0T00000067908, XR_590093, XR_591455, XR_360081 and XR_346933 was upregulated, whereas the expression of XR_351404, XR_591426, XR_353833, XR_590076 and XR_590719

Table II. Role of lncRNAs in AS and SCI.

LncRNA	Condition/ direction of aberrant expression	Cell/tissue type	Signaling pathway	Cell/tissue changes	(Refs.)
NONHSAT227927.1	AS/increased	Monocytes	TRAF2	Inflammation (+)	(98)
MEG3	AS/reduced	Mesenchymal stem cells	miR-125a-5p/ TNFAIP3/Wnt/β-catenin	Osteogenic differentiation (+)	(99)
MALAT1	AS/increased	Chondrocytes	miR-558	Apoptosis (+); inflammation (+)	(116)
H19	AS/increased	Monocytes	miR22-5p/ miR675-5p	Inflammation (+)	(100)
Vof16	SCI/increased	SD rat	miR-185-5p-GAP43	Axonal regeneration (+)	(108)
TCTN2	SCI/reduced	Mouse NSC-34 cells	miR-125a-5p/ DUSP1	Apoptosis (+); inflammation (+)	(109)
MALAT1	SCI/reduced	Human umbilical cord mesenchymal stem cells	miRNA-22-3p/ SIRT1/AMPK	Apoptosis (-)	(110)
TUG1	SCI/reduced	Bone marrow-derived macrophages	miR-1192	Inflammation (-)	(111)

lncRNA, long non-coding RNA; AS, ankylosing spondylitis; SCI, spinal cord injury; IDD, intervertebral disc degeneration; (+), promotion; (-), inhibition; NONHSAT227927.1, a type of lncRNA; TRAF2, TNF receptor associated factor 2; MEG3, maternally expressed gene 3; TNFAIP3, tumor necrosis factor α inducible protein 3; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; H19, H19 imprinted maternally expressed transcript; Vof16, ischemia-related factor Vof-16; GAP43, growth-associated protein 43; TCTN2, tectonic family member 2; DUSP1, dual-specificity phosphatase 1; SIRT1, silent information regulator sirtuin 1; TUG1, taurine upregulated gene 1.

was downregulated. These 10 lncRNAs were at the centre of the constructed lncRNA-miRNA-mRNA co-expression network (107). These studies indicated that lncRNAs form important regulatory networks in SCI.

Growth-associated protein 43 (GAP43) is important for axonal growth and elongation. Hu *et al* (108) reported the protective role of vof16 (ischemia-related factor Vof-16) in SCI through the miR-185-5p-GAP43 regulatory network. Tanshinone IIA (TSIIA), a traditional Chinese medicine ingredient, can protect against SCI and tectonic family member 2 (TCTN2) expression has been shown to be low in an LPS-induced cell injury model. By contrast, TSIIA reduced cell damage and increased the expression of TCTN2; follow-up experiments demonstrated that TCTN2 may act as a regulator of dual-specificity phosphatase 1 (DUSP1) expression through miR-125a-5p; that is, TSIIA may regulate SCI through the TCTN2/miR-125a-5p/DUSP1 axis (109). In another previous study (110), researchers injected small extracellular vesicles (sEVs) derived from human umbilical cord mesenchymal stem cells induced by micro-electric field stimulation (EF-sEVs) and normally conditioned human umbilical cord mesenchymal stem cells-derived sEVs. Within the lesions of rats with SCI, MALAT1 expression was elevated in tissues treated with EF-sEVs. In addition, a luciferase reporter gene assay showed that MALAT1 can competitively bind to miR-22-3p and reduce its inhibitory effect on SIRT1, thereby improving SCI (110). A study has indicated that photobiomodulation (PBM) reduces inflammation by inhibiting bone marrow-derived macrophages. Transcriptome sequencing and bioinformatics analyses indicated that taurine upregulated gene 1 (TUG1) may be a target of PBM, and that TUG1 could competitively bind to miR-1192 and reduce miR-1192-induced inhibition of TLR3, leading to increased TLR3 expression and promotion of nerve survival and motor recovery (111) (Table II).

6. Treatment of spinal diseases based on lncRNAs

The role of lncRNAs in treating spinal diseases is mostly exerted by reducing or increasing the effective expression of the corresponding lncRNAs. Several methods can reduce the expression of lncRNAs. Firstly, silencing lncRNAs, such as siPART1, can enhance the growth of NP cells and increase the synthesis of the ECM, which can be used to treat IDD (67). Secondly, in a previous study, changing the chemical modification of lncRNAs increased WTAP expression in degenerated NP cells and significantly promoted the m6 modification of NORAD, promoting cell senescence. Therefore, therapeutic purposes can be achieved by reducing the m6 modification

of NORAD (90). Finally, the formation of a complex with lncRNAs can interfere with its function; for example, some small molecule inhibitors can hide the functional sites of lncRNAs and interfere with their functions. Notably, BRD4 can bind to the HOTAIR promoter, affect HOTAIR function and control glioblastoma (112).

Methods to increase lncRNA expression include lncRNA mimics transfection. A previous study reported that KLF3-AS1 overexpression may improve IDD through the miR-10a-3p/ZBTB20 axis (70). Another method includes exogenously supplementing lncRNAs. Li *et al* (87) revealed that BMSC-Exo delivered exogenous CAHM can regulate macrophage polarisation and improve IDD (87). LncRNAs have therapeutic potential in spinal diseases, such as IDD, but some problems remain to be solved. When regulating the expression of lncRNAs, their impact cannot be accurately controlled, and their effect is not permanent and may decrease over time. Therefore, treating spinal diseases using lncRNAs requires further research to promote their progress.

7. Conclusions and outlook

Numerous lncRNAs have complex functions. The present article explains the classification and functions of lncRNAs and their roles in IDD, AS and SCI. In spinal diseases such as IDD, lncRNAs affect different aspects of disease progression, such as the ECM, cell death, inflammation and ageing. Taking IDD as an example, thousands of lncRNAs show differential expression in IDD compared with normal tissues. However, only a handful of lncRNAs have been studied. Increased research is required to fully understand the role of lncRNAs in spinal diseases, and experiments are needed to explore, supplement and improve ceRNA regulatory networks. Application of lncRNA in treating spinal diseases, such as IDD, is still in the preclinical experimental stage. However, lncRNAs have been used in the treatment of some malignant diseases (113) and have shown good efficacy; therefore, lncRNAs show great potential for clinical application in treating spinal diseases such as IDD.

In summary, lncRNAs are important regulatory factors affecting the occurrence and development of spinal diseases, such as IDD. However, current research on lncRNAs in spinal diseases has mainly focused on cells, rats and human degenerative tissues, and studies on more advanced large animals such as monkeys are lacking. Experimental and clinical treatments are meaningful directions for future research.

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Authors' contributions

ZM collected the literature and wrote the article; ZL and JA revised the article; ZM and ZL designed the study; and XL, XZ and SL prepared the figures and tables. ZM, XL, XZ, SL, JA and ZL contributed to data analysis, drafted and critically revised the paper, and agreed to be accountable for all aspects of the work. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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