

Circular RNAs in intervertebral disc degeneration: Current insights into mechanisms and therapeutic potentials (Review)

LUYAN WANG¹, KE YANG¹, HOUJUN ZHU², DACHUAN WANG¹, FENG WANG¹ and XIANFA DU¹

¹Department of Orthopaedics, The Second Qilu Hospital of Shandong University, Jinan, Shandong 250033, P.R. China;

²Department of Orthopaedics, Penglai People's Hospital, Yantai, Shandong 265600, P.R. China

Received July 18, 2025; Accepted December 23, 2025

DOI: 10.3892/mmr.2026.13821

Abstract. Low back pain (LBP) is a leading cause of productivity loss worldwide and a major contributor to disability, imposing an economic burden on society. Intervertebral disc degeneration (IVDD) as a principal pathological driver of LBP remains a formidable therapeutic challenge, given that existing conservative and surgical interventions frequently fall short of achieving long-term efficacy or halting disease progression. Advancements in molecular biology have revealed that circular RNAs (circRNAs) play a pivotal role in the intricate gene regulatory networks governing IVDD. The most extensively studied function of circRNAs is their ability to act as microRNA sponges. In addition, they participate in protein interactions, regulate gene transcription and serve as templates for protein translation. The present review provided a comprehensive overview of the current understanding of circRNA characteristics and functions, elucidated their involvement in IVDD pathogenesis and examined the therapeutic potential of emerging biomaterials for IVDD treatment. By consolidating existing research, the aim of this review was to offer theoretical foundations for innovative therapeutic strategies targeting IVDD.

Contents

1. Introduction
2. Normal anatomic structure of IVD and the pathogenesis of IVDD
3. Characteristics, history, synthesis, mechanism and function of circRNA
4. Regulatory role of circRNA in IVDD
5. Potential clinical application
6. Conclusions and future prospects

Correspondence to: Professor Xianfa Du, Department of Orthopaedics, The Second Qilu Hospital of Shandong University, 247 Beiyuan Street, Jinan, Shandong 250033, P.R. China
E-mail: duxfa3@email.sdu.edu.cn

Key words: circular RNA, nucleus pulposus, intervertebral disc degeneration, mechanisms, therapeutic potentials

1. Introduction

Low back pain (LBP) is a prevalent worldwide health issue, which not only impairs patient mobility, but also leads to a loss of productivity and imposes a notable economic burden on society (1). According to a previous study, 84% of global population experience LBP in their daily lives (2), and a 2019 systematic analysis covering 369 diseases across 204 countries identified LBP as the fourth leading cause of disability among individuals aged 25-74 years (3). The etiology of LBP is multifactorial, with intervertebral disc degeneration (IVDD) considered to be the main underlying cause of LBP among the various etiological factors (4).

IVDD is characterized by structural deterioration of the IVD, often resulting in premature disc aging (5). With the progression of IVDD, the level of inflammatory cytokines increases, the degradation of collagen increases and the phenotype of intervertebral disc cells change (6). According to previous evidence-based research, multiple factors including mechanical, genetic, traumatic, inflammatory and biological factors cause or accelerate the development of IVDD (7). However, genetic predisposition is particularly notable, with increasing evidence highlighting the involvement of long non-coding RNAs (lncRNAs) in IVDD pathophysiology (8).

Circular RNAs (circRNAs), a prominent class of ncRNAs, have emerged as pivotal regulators in IVDD pathogenesis, with their complex mechanisms becoming increasingly elucidated through advancing experimental investigations and in-depth research (9). As circRNAs are substantiated by robust statistical analyses and biochemical evidence, they have been established as integral components of spliced transcripts across hundreds of genes, underscoring their fundamental biological significance (10). Despite their demonstrated involvement in diverse pathological processes, the precise molecular mechanisms and functional implications of circRNAs in IVDD pathogenesis remain incompletely characterized. The present comprehensive review systematically examined previous and recent advances in understanding circRNA-mediated regulatory networks in IVDD progression, particularly evaluating their emerging potential as diagnostic biomarkers and therapeutic targets, and identified current research limitations to inform future investigative directions.

2. Normal anatomic structure of IVD and the pathogenesis of IVDD

Structure and function of IVD. The IVD is a fibrocartilaginous structure positioned between adjacent vertebrae, comprising three primary components: i) The nucleus pulposus (NP); ii) the annulus fibrosus (AF); and iii) the cartilaginous endplate (CEP) (11). The gelatinous NP resides at the core of the disc and is primarily composed of water, a dense network of type II collagen and proteoglycans (12). This composition creates a hydrated, gel-like structure that generates substantial osmotic pressure, which is essential for maintaining disc height, distributing mechanical loads and ensuring overall disc integrity (13).

Encapsulating the NP is the organized AF, which consists of 15-25 concentric lamellae of collagen fibers (14). This structure exhibits a morphological gradient: The inner AF is rich in type II collagen, providing elasticity and integration with the NP, whereas the outer AF is composed of robust type I collagen fibers, offering tensile strength and resistance to mechanical stress (15). This anisotropic, multi-lamellar architecture effectively contains the NP and provides structural stability to the disc (16).

The CEP are layers of hyaline cartilage situated superiorly and inferiorly to the NP. In adults, these avascular structures serve as the critical interface for nutrient diffusion and metabolic waste exchange between the vascular-rich vertebral bodies and the avascular disc interior (17).

The functional integrity of the IVD relies on the precise structural and biochemical equilibrium among the NP, AF and CEP. The disruption of this delicate homeostasis is a hallmark of IVDD pathogenesis.

Pathophysiology of IVDD. IVDD is influenced by multiple risk factors, including smoking, alcohol consumption, occupational standing height, socioeconomic status, sleep disturbances, hypertension, type II diabetes and obesity. Of note, metabolic dysregulation appears to have a more profound impact on IVDD progression than biomechanical stress (18). The pathological process of IVDD is characterized by extracellular matrix dysregulation, leading to progressive proteoglycan loss and dehydration of the NP (19). In addition, excessive mechanical loading and aging impair cartilage endplate function, further exacerbating disc degeneration (20). Apoptosis and autophagy of nucleus pulposus cells (NPCs) contribute markedly to IVDD pathophysiology, whereas hypoxia and an acidic microenvironment deplete essential nutrients, ultimately resulting in AF fissures and NP herniation (21). Inflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukins-1 α/β (IL-1 α/β), IL-6 and IL-17, play a critical role in promoting disc degeneration by inducing metabolic imbalances within the IVD (2).

In general, the molecular mechanisms affecting IVDD are varied, but the main factors involved are apoptosis, the release of inflammatory factors and the degradation of extracellular matrix (ECM) (22). The depletion of ECM components results from metabolic disturbances, leading to a marked reduction in type II collagen, proteoglycans and water content. Concurrently, the activity of ECM-degrading enzymes, such as matrix metalloproteinases (MMPs), aggrecanases and A disintegrin and

MMP with thrombospondin motifs (ADAMTS), is increased, further accelerating ECM degradation (23). Along with ECM degradation, the activation and infiltration of immune cells, including CD4⁺ and CD8⁺ T cells, M1 macrophages, mast cells and neutrophils, as well as pyroptosis and apoptosis of NP cells, contribute to the release of pro-inflammatory cytokines and chemokines, perpetuating a self-reinforcing inflammatory cascade. These mediators, such as TNF- α , IL-1 β , IL-6, IL-8 and prostaglandin E2, further accelerate ECM breakdown, thus forming a vicious cycle (24). At the same time, metabolic imbalances in ECM and the production of inflammatory substances promote the aging and death of NP cells (25). As a result, apoptosis, ECM degradation and inflammatory cytokine production are interrelated and interdependent and together lead to the degradation of IVD (Fig. 1).

3. Characteristics, history, synthesis, mechanism and function of circRNA

ncRNAs, comprising primarily microRNAs (miRNAs), lncRNAs and circRNAs, have emerged as crucial regulators in various cellular processes through extensive research over the past decades (26). Among these ncRNA subtypes, circRNAs have attracted particular scientific attention due to their unique covalently closed circular structure and regulatory potential (27). The investigation of circRNAs has undergone notable evolution since their initial discovery, marking important milestones in the understanding of RNA biology.

From the beginning, in 1976, Sanger *et al.* (28) discovered viroids containing single-stranded and covalently closed circular RNA molecules in higher plants. Then in the 1990s, there was a noticeable decline in interest and enthusiasm for circRNA. The discovery of the human estrogen sulfotransferase 1 gene and the deletion of the colon cancer gene were attributed to atypical splicing events during transcription. In addition, the human cytochrome P450, rat androgen binding protein and rat cytochrome P450 2C 24 genes were found to generate other circRNAs. Although the existence of circRNA has been verified, the value of circRNA has been markedly underestimated (28). It was only discovered in 2012 that circRNAs exist in a variety of human cell types, and that they can be derived from the reverse splicing of precursor mRNAs (pre-mRNAs) (29); since then, the research on circRNA has been markedly increased. Due to the circRNA ring structure and long half-life, circRNA has become a biological marker for the examination of cancer cells, and provides a new target and direction for future cancer treatment (30). In addition, the success of circRNA synthesis *in vitro* has made it possible for the stability, low cytotoxicity and long antigen-producing ability of circRNA to play a role in vaccine research (31). As RNA technology continues to advance, it is highly likely that the considerable potential of circRNAs in therapeutic interventions for various diseases will be further substantiated.

CircRNAs, as a subset of ncRNAs, are formed through the back-splicing of pre-mRNA (32). This results in a closed-loop structure that lacks 3' and 5' termini, rendering circRNA resistant to exonuclease degradation and conferring remarkable stability (33); however, circRNAs are generally synthesized at the expense of their linear equivalents (Fig. 2C) (34). CircRNA

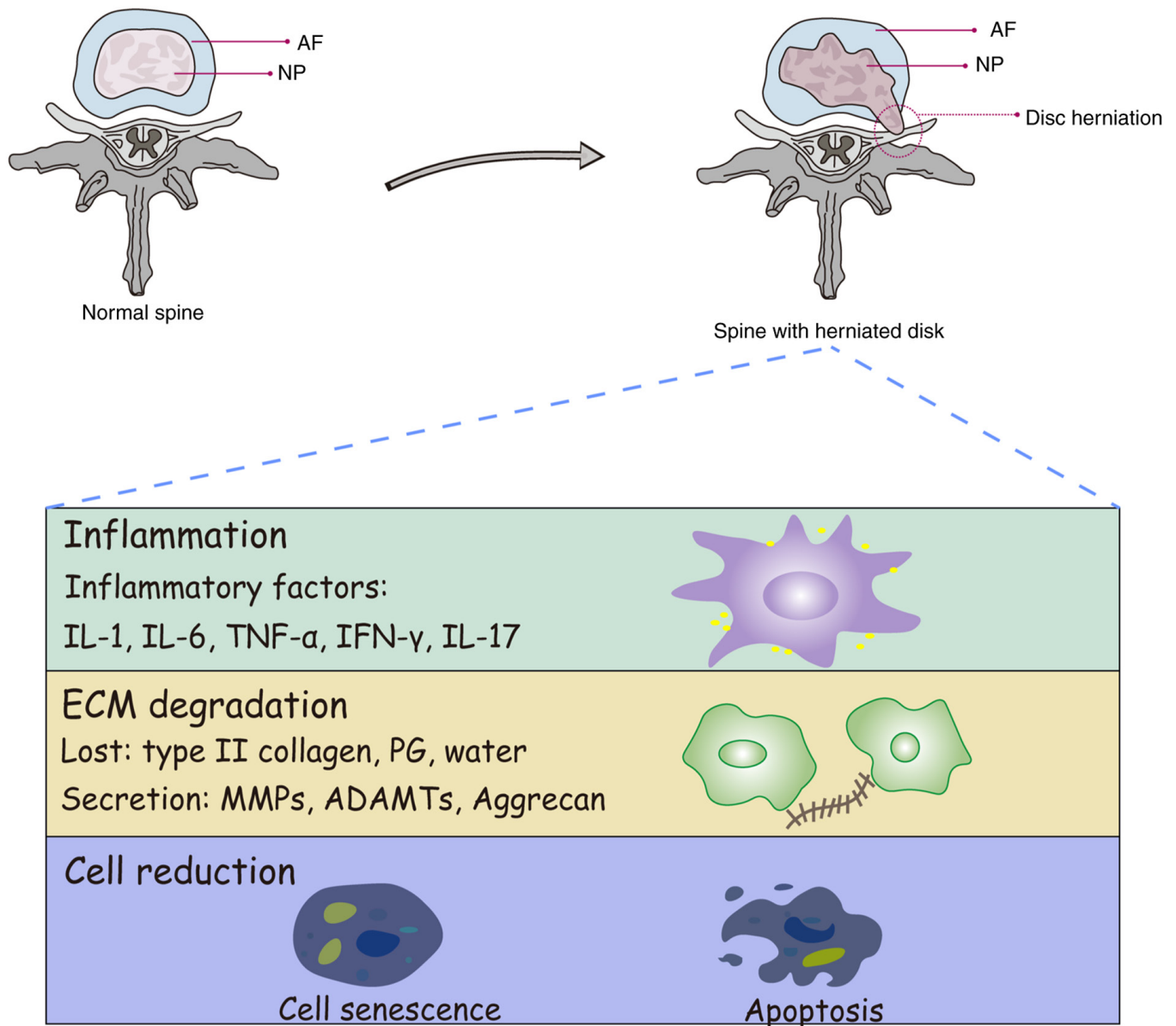


Figure 1. Pathophysiology of IVDD. The IVD, composed of the NP, AF and nutrient-supplying CEP, undergoes degeneration through multifactorial etiologies. Risk modulators including lifestyle factors, biomechanical stress, socioeconomic parameters and metabolic disorders collectively drive pathological cascades. These stimuli induce cellular apoptosis, ECM degradation and inflammatory mediator release, ultimately progressing to disc structural failure. Advanced degeneration manifests as disc height loss, annular rupture with NP herniation and nerve root compression, establishing a direct mechanistic basis for chronic low back pain. IVDD, intervertebral disc degeneration; NP, nucleus pulposus; AF, annulus fibrosus; CEP, cartilaginous endplates; ECM, extracellular matrix; MMP, matrix metalloproteinase; ADAMTs, A disintegrin and MMP with thrombospondin motifs.

has been reported to be involved in physiological and pathological processes in a variety of ways. circRNAs can act as miRNA sponges (Fig. 2A) or decoys to enhance the activity of target RNA translation. Furthermore, circRNAs can interact with RNA-binding proteins (RBPs) through distinct mechanisms: they can act as protein ‘sponges’ to sequester RBPs and indirectly regulate their function, or they can bind to specific proteins directly to enhance their activity. Some circRNAs serve as molecular scaffolds, facilitating interactions between enzymes and substrates to modulate reaction kinetics (Fig. 2D). Furthermore, circRNAs can recruit specific proteins to distinct cellular compartments, thereby influencing various physiological and pathological processes (35). Emerging evidence reveals that circRNAs exhibit protein-coding potential, even

though protein-coding genes constitute <2% of the entire genome (Fig. 2B) (36).

CircRNA is similar to linear mRNA in that circRNA is derived from the linear pre-mRNA transcribed by RNA polymerase II and can be produced by reverse splicing (37). Based on their composition, circRNAs can be divided into three types: Exonic circRNAs (ecircRNAs), exon-intron circRNA (eicircRNA) and circular intronic RNA (ciRNA) (Fig. 3). EcircRNAs are composed of ≥ 1 exons, and represent ~85% of all circRNAs (38); they predominantly localize to the cytoplasm, where they play crucial roles in post-transcriptional regulation. By contrast, eicircRNAs and ciRNAs are typically retained in the nucleus, where they modulate gene transcription (39). In addition, ecircRNAs localized in the cytoplasm

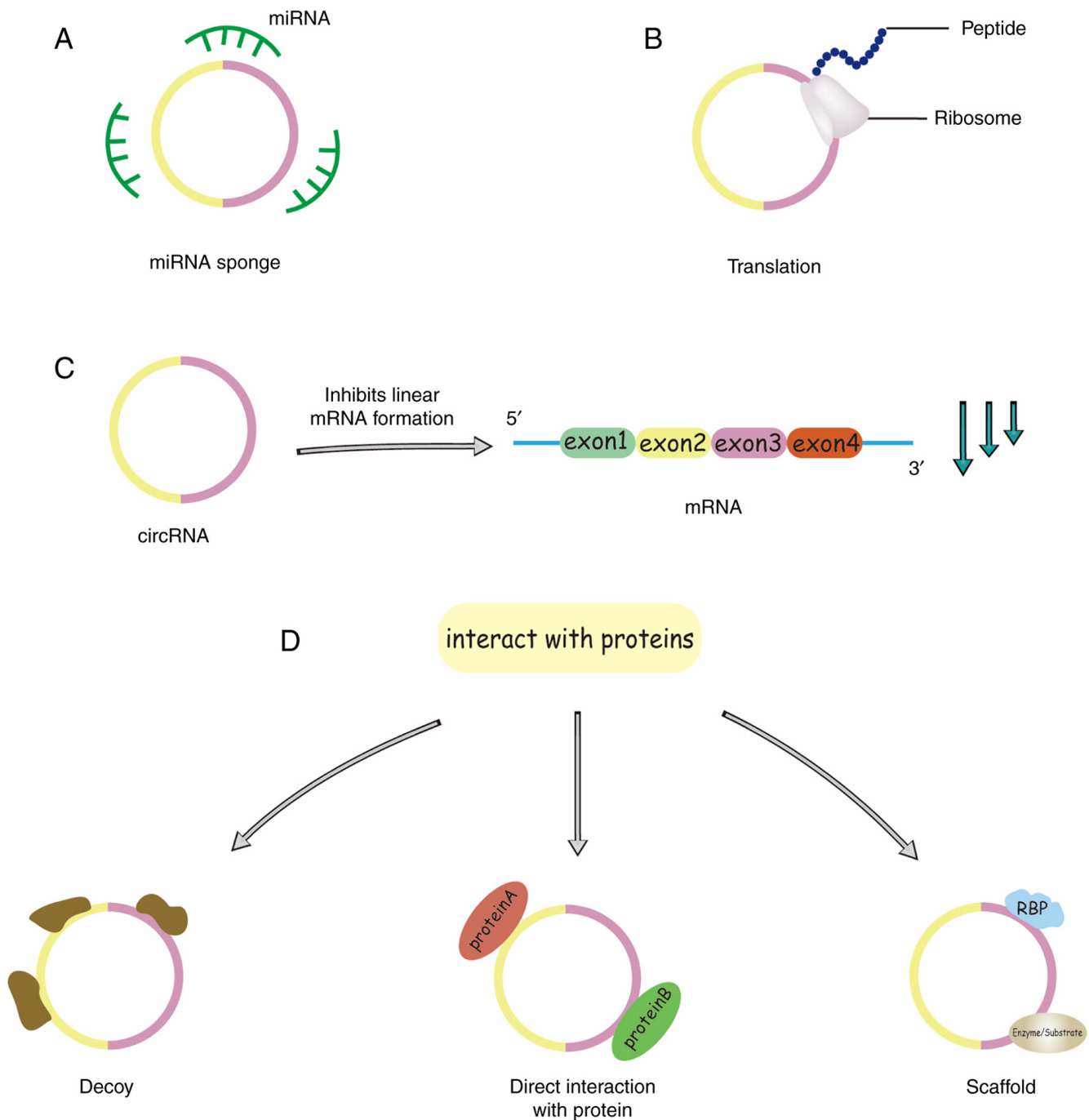


Figure 2. Function of circRNA. CircRNAs exert multifaceted regulatory functions critical for cellular homeostasis. Key mechanisms include: (A) miRNA sponging through complementary base-pairing; (B) certain circRNAs can translate proteins; (C) competitive splicing regulation that suppresses canonical mRNA maturation; and (D) multimodal protein interactions, functioning as scaffolds for ribonucleoprotein complexes, modulating enzymatic activity through direct binding and serving as molecular decoys for RBPs. circRNA, circular RNA; miRNA, microRNA; RBPs, RNA-binding proteins.

are very stable in the cell, with a half-life four times longer than the average half-life of mRNA (10). Due to their cytoplasmic localization and structural stability, ecircRNAs have been the most extensively studied to date (40). At present, >1 million reliable circRNAs have been identified across various species (41), with numerous studies having demonstrated that circRNAs exhibit tissue and developmental stage-specific expression patterns and are implicated in diverse cellular

processes and disease pathogenesis (42,43). Of note, despite the canonical miRNA sponge theory, recent studies have revealed a spectrum of alternative mechanisms for circRNAs, including their role as dynamic molecular scaffolds that facilitate enzyme-substrate interactions, their capacity to modulate transcription in the nucleus and their potential for cap-independent translation to generate functional peptides (44). This expanded functional repertoire markedly enhances

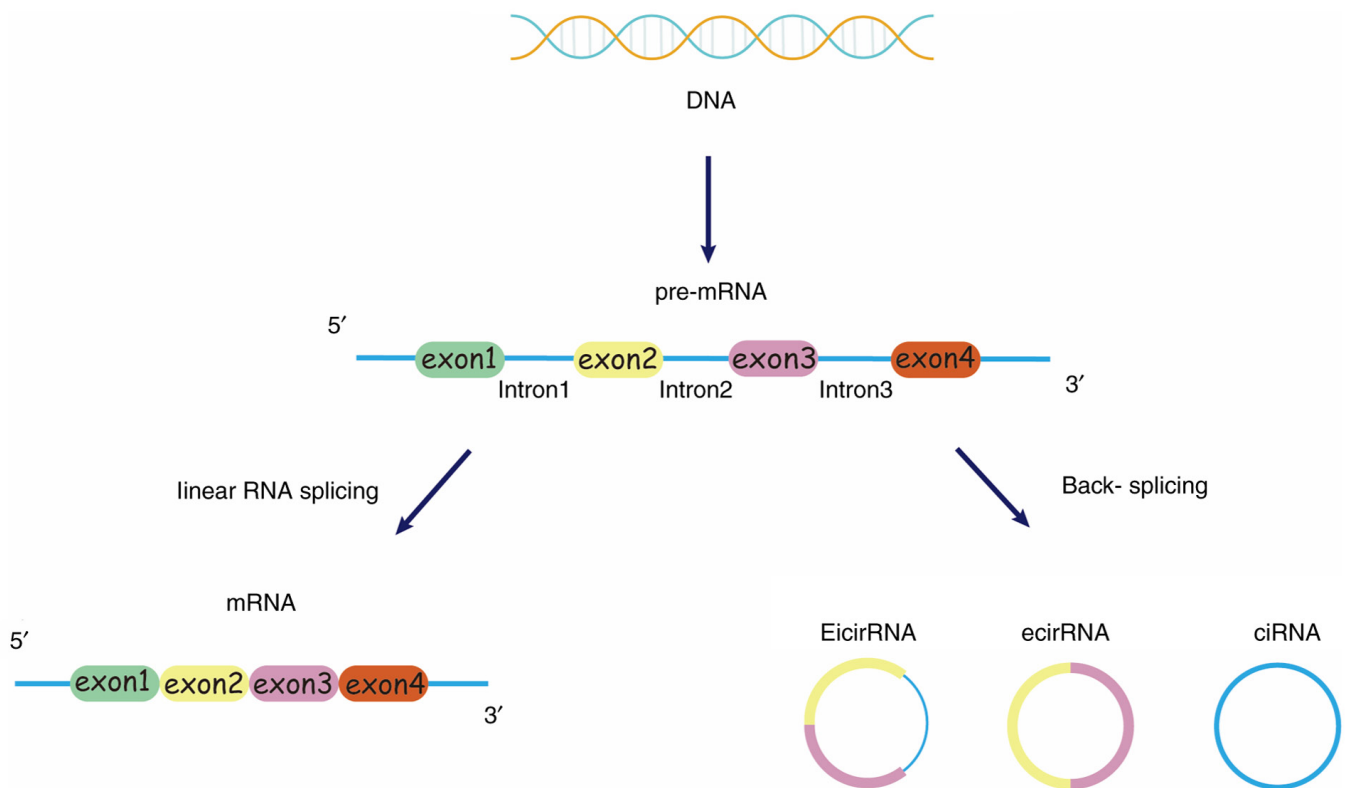


Figure 3. Formation and classification of circRNA. CircRNA biogenesis initiates with transcription-generated precursor mRNA containing exon-intron sequences. While canonical splicing produces linear mRNA through exon joining, circRNAs form via back-splicing mechanisms. Three structural subtypes exist: EicirRNA (exon-derived), eicirRNA (exon-intron hybrid) and ciRNA (intron-retained), each exhibiting distinct functional properties. circRNA, circular RNA; eicirRNA, exonic circRNA; eicirRNA, exon-intron circRNA; ciRNA, circular intronic RNA.

their regulatory complexity in cellular processes and disease pathogenesis (45). However, despite their recognized roles in various diseases, the precise functions of circRNAs in IVDD remain incompletely understood.

4. Regulatory role of circRNA in IVDD

As previously discussed, circRNAs modulate cellular functions through diverse mechanisms. To better elucidate their role in IVDD, a comprehensive review of existing literature was conducted, and circRNA functions were categorized into four distinct mechanisms based on their influence on IVDD. This classification not only facilitates a deeper understanding of individual circRNA-mediated regulatory pathways but also provides insights for future research directions and potential clinical applications.

CircRNA can act as miRNA sponges. Due to their closed-loop structure, circRNAs lack free 3' and 5' ends, rendering them stable and evolutionarily conserved in eukaryotic cells (28). As a direct target of circRNAs and as a member of ncRNAs, miRNAs function as key post-transcriptional regulators by binding to the 3'-untranslated region of target mRNAs, leading to translation inhibition or transcript degradation (46). Since miRNA and its target RNA have complementary binding sites, and both circRNAs and miRNAs are mainly located in the cytoplasm, circRNAs can regulate the translation rate of target mRNA and affect its stability by pairing with the complementary sequence of miRNA (47).

With the increased understanding of and research on ncRNAs, the intricate interactions between circRNAs and miRNAs, along with their biological implications, have become progressively clearer. The ability of circRNAs to act as miRNA sponges has been implicated in various disease processes, including IVDD. CircRNAs can modulate disc degeneration by sequestering miRNA regulatory factors, thereby suppressing the translation of target mRNAs (48).

For instance, circEYA3 has been identified as a key regulator in IVDD, promoting ECM degradation, inflammatory responses and apoptosis in NP cells. By integrating circRNA/miRNA/mRNA interactions, researchers established a circRNA/miRNA/mRNA regulatory network centered on circEYA3/miR-196a-5p/early B-cell factor 1 (EBF1). Experimental validation demonstrated that miR-196a-5p expression was inversely associated with circEYA3 and EBF1 expression levels (49). Further *in vivo* studies confirmed that circEYA3 acts as a sponge for miR-196a-5p, indirectly regulating EBF1 expression. In addition, Wang *et al* (49) demonstrated that EBF1 binds to the promoter region of inhibitor of nuclear factor kappa B kinase β , thereby enhancing its transcription. The encoded protein I- κ B kinase 1 facilitates the phosphorylation of inhibitor of κ B α , disrupting NF- κ B pathway homeostasis, leading to the activation of NF- κ B target genes and subsequent pathological changes that drive IVDD progression.

Through systematic screening, hsa_circ_0083756 was identified as a key regulator in NP cells (50). Experimental evidence demonstrated its role in promoting NP cell apoptosis

and IL-1 β production, while modulating ECM synthesis and degradation. Mechanistic studies revealed that circ_0083756 functions as a molecular sponge for miR-558, which in turn regulates triggering receptor expressed on myeloid cells 1 (TREM1) expression. This circ_0083756/miR-558/TREM1 axis was shown to notably influence NP cell proliferation, apoptosis, ECM homeostasis and inflammatory responses. The findings were further validated in animal models, confirming the relevance of the pathway in disc degeneration (50).

Inflammatory cytokines such as IL-1 β and TNF- α have been shown to upregulate circ_0005918 expression in a time-dependent manner, contributing to IVDD. By designing a controlled study, research findings established a link between circ_0005918 upregulation and IVDD progression. This circRNA was found to promote NP cell proliferation, ECM degradation and inflammatory cytokine secretion, including IL-1 β , IL-6 and TNF- α , through the sponging of miR-622. Compared with the control group, the degree of disc degeneration was associated with miR-622 expression levels but exhibited an inverse relationship with circ_0005918 expression (51).

Further investigation into circ_0134111 identified a binding site for miR-578, which was found to counteract the effects of circ_0134111 on NP cell proliferation and inflammatory factor expression, including IL-6, IL-8, MMP-9 and ADAMTS-5. In addition, miR-578 reversed the circ_0134111-induced downregulation of type II collagen and aggrecan (ACAN). These findings indicated that circ_0134111 contributes to disc degeneration by modulating miR-578 expression; however, whether VEGF, a gene associated with miR-578, plays a role in this pathway remains to be explored (52).

The functional role of circ-FAM169A in IVDD progression was investigated, demonstrating its activity as a competing endogenous RNA (ceRNA) targeting miR-583. Considering that key regulatory genes in IVDD affect ECM composition through SRY-box transcription factor 9 (SOX9) regulation, the study further confirmed SOX9 as a direct target of miR-583, showing an inverse association with IVDD severity. Pathway analysis suggested that miR-583 potentially mediates its effects through epidermal growth factor receptor, phosphatidylinositol 3-kinase-protein kinase B and bone morphogenetic protein pathways, although the specific mechanism of the circ-FAM169A-miR-583 pathway in IVDD requires further investigation (53).

CEP, an integral component of the IVD, facilitates nutrient diffusion, and its degradation accelerates IVDD progression (54). The study on intermittent cyclic mechanical tension revealed its association with cytoskeletal morphology and ECM protein secretion in CEP cells (55). The selection of circ_0022382 as a research target was based on its 4-fold higher expression in experimental groups compared with the controls. Further functional analysis indicated that circRNA_0022382 mitigates pressure-induced degeneration in CEP chondrocytes, as demonstrated through control group comparisons and cell staining assays. Additional findings established an antagonistic relationship between circ_0022382 and miR-4726-5p, confirming the role of circ_0022382 as a miRNA sponge that regulates TGF- β 3 expression. Finally, *in vivo* experiments using a rat model provided evidence that

the circRNA_0022382/miR-4726-5p/TGF- β 3 axis alleviates disc degeneration by enhancing ECM synthesis in CEP chondrocytes (56).

Xiang *et al.* (8) identified Hsa_circ_0044722 (circCIDN) as a target gene through heat map and microarray analyses, and showed that it had a protective effect on NP cells exposed to stress load by transfecting them. Subsequently, it was verified that circRNA-CIDN directly binds to miR-34a-5p through complementary target sites, suggesting that it may act as a miRNA sponge for miR-34a-5p in NP cells, in which sirtuin (SIRT1) is the target mRNA of miR-34a-5p. Finally, reverse transcription-quantitative PCR (RT-qPCR) was used to verify that circRNA-CIDN overexpression inhibited the expression of miR-34a-5p and weakened the inhibitory effect of miR-34a-5p on target mRNA, thereby inhibiting the compression-induced apoptosis of NP cells and ECM degradation to delay the process of disc degeneration.

The expression of circ-4099 in NP cells is influenced by TNF- α in a dose- and time-dependent manner through the MAPK and NF- κ B pathways. Experimental validation indicated that circ-4099 enhances collagen II and ACAN levels, thereby restoring ECM synthesis in NP cells. Concurrently, investigations into miR-616-5p revealed its opposing role in modulating inflammatory gene expression and ECM synthesis, supporting the hypothesis that circ-4099 functions as a competitive endogenous RNA. Further findings demonstrated that circ-4099 exerts its regulatory effects by counteracting miR-616-5p's suppression of SOX9, a pivotal NP cell regulator known to mitigate IVDD by promoting matrix protein expression and reducing inflammatory responses. This highlighted circ-4099 as a promising research avenue and therapeutic target (57).

Investigations into circSNHG5 identified its downregulation in IVDD, with functional studies showing that silencing this circRNA led to decreased chondrocyte proliferation and increased ECM degradation. Fluorescence *in situ* hybridization and luciferase reporter assays confirmed that circSNHG5 acts as an miR-495-3p sponge, inhibiting its activity. CBP/p300-Interacting Transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2), a downstream target of miR-495-3p, was found to play a role in IVDD attenuation by reducing MMP13 levels while enhancing collagen II and ACAN expression. Ultimately, findings suggested that the circSNHG5/miR-495-3p/CITED2 axis serves as a protective mechanism against CEP degradation (58).

CircGLCE was stably present in the cytoplasm of NP cells, but circGLCE was found by microarray analysis and RT-qPCR to be notably downregulated in IVDD. CircGLCE silencing led to the increased apoptosis and ECM degradation of NP cells, which was verified by immunofluorescence and flow cytometry, suggesting that circGLCE exerts a regulatory effect on NP cells. Subsequently, it was determined that circGLCE served as an miR-587 sponge in NP cells, and signal transducing adaptor family member 1 (STAP1) was the target mRNA of miR-587. Silencing miR-587 could reverse the circGLCE downregulation-induced IVDD, whereas STAP1 could promote the expression of collagen II and ACAN. Finally, animal IVDD models were established to verify that circGLCE alleviates IVDD by targeting miR-587/STAP1 (59).

Emerging evidence underscores the pivotal role of circRNAs as miRNA sponges, regulating target mRNAs and influencing IVDD pathogenesis. These insights offer valuable guidance for exploring the molecular mechanisms of IVDD and developing novel therapeutic strategies.

Through the study of the sponge mechanism, circRNAs have been identified as key regulators in IVDD by acting as ceRNAs. By sequestering specific miRNAs, circRNAs modulate the expression of target genes, thereby influencing apoptosis, inflammation and ECM metabolism in NP cells and chondrocytes. However, existing studies focus on different circRNAs, each associated with distinct signaling pathways and target molecules, highlighting the complexity and heterogeneity of their regulatory roles in IVDD.

Given the pivotal role of circRNAs in IVDD pathogenesis, further research is required to elucidate their molecular mechanisms in greater depth. Expanding investigations into the circRNA-miRNA-mRNA regulatory network, particularly in relation to inflammation and mechanical stress pathways, is crucial. Furthermore, exploring the upstream and downstream regulatory mechanisms of specific circRNAs will provide deeper insights into their functional significance in IVDD.

Due to their stability and tissue specificity, circRNAs hold great promise as non-invasive diagnostic biomarkers for IVDD. Future research should focus on developing targeted therapeutic strategies, such as circRNA inhibitors or miRNA mimics, to modulate their expression effectively. There are currently a large number of ongoing research projects in this field, and significant progress has been made. Furthermore, the application of nanotechnology for the precise and stable delivery of RNA molecules presents an innovative avenue to enhancing therapeutic efficacy.

Collectively, the molecular sponge mechanism remains the most extensively studied and characterized function of circRNAs. Current evidence demonstrates that circRNA-mediated miRNA sponging exerts regulatory effects on multiple pathological processes in IVDD, including ECM metabolism, inflammatory factor expression and NP cell apoptosis, with analogous regulatory functions observed in the cartilage endplate. Nevertheless, the majority of circRNAs remain uncharacterized, and their potential involvement in IVDD pathogenesis, particularly through sponge-mediated mechanisms, requires systematic investigation. These unresolved questions represent critical directions for future research in this field.

CircRNAs can be transported by exosomes to influence the normal structure of IVD. Exosomes are extracellular vesicles with diameters ranging from 40-160 nm. They encapsulate various cellular components, including DNA, RNA, metabolic byproducts and proteins, and facilitate intercellular communication through diverse mechanisms, thereby triggering complex biological responses (60). Studies have demonstrated that circRNAs exhibit exceptional stability and are abundantly expressed in exosomes. As a novel class of genetic information molecules, exosomal circRNAs have gained considerable research attention due to their intrinsic stability, high abundance and widespread distribution. Their unique characteristics position them as promising candidates for further investigation in intercellular communication and disease biomarker discovery (61,62).

Extensive research has demonstrated that exosomes play a pivotal role in disease pathogenesis and offer novel therapeutic avenues. For instance, exosomal miRNAs are implicated in oxidative stress and immune dysregulation, serving as potential biomarkers for assessing vitiligo activity (63). In addition, exosomes contribute to the progression of cancer and cardiovascular diseases (64). In the musculoskeletal system, they have also been demonstrated to be involved in IVDD.

Chen *et al* (65) isolated and cultured primary human NP cells from degenerated IVDs. RT-qPCR analysis revealed a marked downregulation of circ_0036763 and U2 small nuclear RNA auxiliary factor 2 (U2AF2), whereas miR-583 was upregulated. Transfection experiments and western blotting confirmed that circ_0036763 promotes the expression of ACAN. The study further identified the U2AF2/circ_0036763/miR-583/ACAN axis as a key regulatory pathway in IVDD, wherein U2AF2 facilitates circ_0036763 maturation, and circ_0036763 sponges miR-583 to enhance ACAN expression. In addition, exosomal U2AF2 derived from bone marrow mesenchymal stem cells was shown to mitigate IVDD, highlighting the therapeutic potential of exosome-mediated RNA delivery.

Investigations have demonstrated notable findings through comparative analysis of exosomes derived from normal and degenerative disc cells, employing electron microscopy and western blotting for morphological characterization and molecular marker identification. Through comprehensive circRNA microarray profiling and subsequent PCR validation, circRNA_0000253 was identified as markedly upregulated in degenerative disc cells, and computational bioinformatics analysis established miR-141-5p as a putative target of circRNA_0000253. Mechanistic studies revealed that circRNA_0000253 regulates cellular proliferation and apoptotic processes through the modulation of SIRT1 and ECM-associated components, including collagen II and ACAN. *In vivo* validation using a rat IVDD model, incorporating MRI, X-ray imaging and histological staining techniques, provided compelling evidence that circRNA_0000253 promotes disc degeneration through its miR-141-5p sponge function and subsequent downregulation of SIRT1 (66).

These findings suggest that the exosome-mediated delivery of specific circRNAs holds promise as a targeted therapy for IVDD. However, challenges remain in translating laboratory findings into clinical applications. Of note, studies lack in-depth analysis of the stability and delivery efficiency of exosomes *in vivo*. In addition, the limited sample sizes may affect the generalizability of their conclusions, underscoring the need for further research (Table I).

CircRNAs interact with proteins. As discussed earlier, circRNAs regulate DD primarily by acting as ceRNAs to sponge miRNAs; however, studies on the direct interaction between circRNAs and proteins in IVDD remain limited. This section provides an overview of the mechanisms through which circRNAs interact with proteins and their potential implications in IVDD.

CircRNAs can function in multiple ways: As protein sponges, altering the physiological functions of proteins; as protein scaffolds, facilitating interactions between proteins; or as molecular recruiters, directing proteins to specific cellular locations (67). These interactions play a critical role in

Table I. CircRNAs act as miRNA sponges in IVDD.

CircRNA	Pathway	Function	Expression	(Refs.)
EYA3	circEYA3/miR-196a-5p/EBF1/IKK β	ECM degradation in NP cells \uparrow Secretion of inflammatory cytokines \uparrow Apoptosis in NP cells \uparrow	Upregulated	(49)
0083756	circ_0083756/miR-558/TREM1	NP cells proliferation \downarrow Secretion of inflammatory cytokines \uparrow ECM degradation in NP cells \uparrow	Upregulated	(50)
0005918	circ_005918/miR-622	NP cells growth \uparrow ECM degradation in NP cells \uparrow Secretion of inflammatory cytokines \uparrow	Upregulated	(51)
0134111	circ_0134111/miR-578	NP cells proliferation \uparrow Pro-inflammatory cytokines secretion \uparrow ECM degradation in NP cells \uparrow	Upregulated	(52)
FAM169A	circ-FAM169A-miR-583	ECM synthesis in NP cells \uparrow MMP expression \downarrow	Upregulated	(53)
0022382	circ_0022382/miR-4726-5p/TGF- β 3	Degeneration of chondrocytes \downarrow Endplate chondrocyte ECM synthesis \uparrow	Downregulated	(56)
CIDN (0044722)	circ-CIDN/miR-34a-5p/SIRT1	Compression-induced NP cells apoptosis \downarrow ECM degradation in NP cells \downarrow	Downregulated	(8)
4099	circ-4099/miR-616-5p/SOX9	ECM degradation in NP cells \downarrow Inflammation \downarrow	Upregulated	(57)
SNHG5 (0077254)	circSNHG5/miR-495-3p/CITED2	Chondrocytes proliferation \uparrow ECM degradation in chondrocytes \downarrow	Downregulated	(58)
GLCE	circGLCE/miR-587/STAP1	Apoptosis in NP cells \downarrow ECM degradation in NP cells \downarrow	Downregulated	(59)

IVDD, intervertebral disc degeneration; circRNA, circular RNA; miR, microRNA; ECM, extracellular matrix; NP, nucleus pulposus; MMP, matrix metalloproteinase; EBF1, early B-cell factor 1; IKK β , inhibitor of nuclear factor kappa B kinase β ; TREM1, triggering receptor expressed on myeloid cells 1; SIRT1, sirtuin; SOX9, SRY-box transcription factor 9; CITED2, carboxy-terminal domain 2; AP-1, activator protein 1.

regulating cellular processes such as proliferation, apoptosis, angiogenesis, mRNA translation, energy metabolism and differentiation (68). Of note, RBPs, which recognize and bind RNA through specific structural motifs, form intricate regulatory networks with circRNAs (69). RBPs orchestrate various aspects of circRNA biology, including biogenesis, degradation, nucleocytoplasmic transport and translational regulation, thereby fine-tuning circRNA function (70). In the context of IVDD, emerging evidence underscores the significance of circRNA-protein interactions in disease pathogenesis, particularly through their modulation of specific cellular processes.

CircFUNDCl ameliorates IVDD by promoting PTEN-induced kinase 1 (PINK1)-dependent mitophagy in NPCs under oxidative stress. It executes this function not as a miRNA sponge, but by directly interacting with and stabilizing the cyclin dependent kinase (CDK)9 protein. This interaction enhances the phosphorylation of RNA polymerase II, thereby facilitating the transcription of the key mitophagy gene PINK1. This mechanism establishes a novel paradigm wherein a circRNA directly regulates a kinase to control transcriptional activation in disc homeostasis (71).

The reduced m6A methylation and elevated expression of circGPATCH2L in degenerated human IVD tissues have garnered notable attention from researchers. Overexpression

and knockdown experiments revealed that circGPATCH2L promotes the degeneration of NPCs by inducing apoptosis. Furthermore, circGPATCH2L interacts with tripartite motif containing 28 to inhibit its phosphorylation, resulting in P53 accumulation and DNA damage. Furthermore, it was found that circGPATCH2L is recognized and degraded by the YTH N6-methyladenosine RNA binding protein F2 (YTHDF2)-ribosomal protein L10 (RPL10)-ribonuclease P/RNases P/mitochondrial RNA processing ribonuclease complex, which helps maintain homeostasis in normal NPCs. Finally, a mouse model study confirmed that the knockdown of circGPATCH2L can alleviate IVDD. However, the small sample size of patients in the study (4 patients in the degenerative group and 4 in the control group) may affect its statistical power. The dynamic regulation of m6A modification has not been deeply discussed in this study. The potential interactions of circGPATCH2L with other DNA damage-related proteins have also not been fully analyzed (9).

Another study identified circATXN1 as notably upregulated in NPCs from aged individuals (>70 years old) of degenerated intervertebral discs. To investigate its role, researchers constructed a circATXN1 overexpression vector and confirmed its activation of aging markers CDK inhibitor 2A, specifically the P16 isoform and P21. Further analysis

revealed that circATXN1 downregulated collagen type II α 1 chain and SOX9, impacting ECM homeostasis and mitochondrial function. Using RNA immunoprecipitation (RIP), RNA affinity purification and mass spectrometry, heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) was identified as a direct binding partner of circATXN1. HNRNPA2B1 facilitates the biogenesis of circATXN1 by regulating the splicing of its precursor transcript, while concurrently reducing ATXN1 mRNA levels. In a therapeutic approach, researchers developed a small interfering RNA-embedded DNA tetrahedral nanogel to efficiently silence circATXN1, leading to improvements in tissue structure and ECM content in an aged mouse IVDD model. However, while the interaction between circATXN1 and HNRNPA2B1 has been characterized, the precise mechanism through which it regulates protein mislocalization remains unclear and warrants further investigation (72).

In the musculoskeletal system, Chen *et al* (73) revealed that the overexpression of circTMEFF1 aggravated muscle atrophy, while the inhibition of its expression alleviated the atrophy. circTMEFF1 mainly promotes muscular atrophy through two mechanisms; the first is by binding to TAR DNA-binding protein 43 protein, inducing mitochondrial DNA release and activating cyclic GMP-AMP synthase-stimulator of interferon gene signaling pathway, thus promoting atrophy. The other mechanism is by encoding a new protein, TMEFF1-339aa, which has a pro-atrophy effect. It was revealed that this works through a dual mechanism: Binding proteins and translation proteins. In addition, circ-Foxo3 blocks the cell cycle by binding to CDK2 and cyclin dependent kinase inhibitor 1 to form a ternary complex (74). In oncology research, circZKSCAN1 has been found to suppress cancer stemness by acting as an RBP sponge, modulating the function of fragile X mental retardation protein. The characterization of circZKSCAN1 provided a new perspective on the role of circRNAs in tumor biology (75).

Although the above studies have indicated that circRNAs interact with proteins to influence IVDD, the precise molecular mechanisms remain largely unexplored. This knowledge gap may be attributed to the complexity of protein-circRNA interactions, the technical challenges of *in vitro* and *in vivo* studies, and the early stage of research in this area. In addition, the experimental validation of circRNA-protein interactions is hindered by notable technical challenges and high costs. Furthermore, the limited availability of specialized databases and analytical tools for circRNA-protein interactions poses a substantial barrier to advancing research in this field. These objective factors collectively impede the progress of related experimental studies. Most of the existing research on circRNA-protein interactions focuses on cancer, while their role in musculoskeletal disorders, including IVDD, requires further investigation.

CircRNA may influence IVDD through its translation function. To date, there has been no direct evidence linking the protein-coding function of circRNAs to IVDD. However, the emerging mechanisms through which circRNAs encode proteins are noteworthy and may represent a promising new research direction in understanding the pathophysiology of disc degeneration.

Initially regarded as mere splicing byproducts, circRNAs have been increasingly recognized for their diverse physiological functions (29); among them, their capacity to encode proteins has garnered marked attention (76). CircRNAs contain ≥ 1 open reading frames (ORFs), which, due to their circular structure, can facilitate the translation of short peptides or even proteins >100 amino acids in length (77).

This translational mechanism has been explored in the musculoskeletal system. For example, Yin *et al* (78) identified an ORF in circFAM188B and demonstrated its ability to encode a novel protein, circFam188B-103AA, which regulates the proliferation and differentiation of chicken skeletal muscle satellite cells. Legnini *et al* (79) discovered that circ-ZNF609, containing an ORF, plays a role in myoblast proliferation and protein translation. Despite these advances, the molecular activities of such proteins and their interactions with linear mRNA counterparts remain poorly understood. Similarly, Zhu *et al* (80) identified a circRNA, circDdb1, that promotes muscle atrophy; their pivotal finding was that circDdb1 is translated into a novel protein, circDdb1-867aa. This protein executes the function by entering the nucleus to inhibit Pax7, a master transcription factor for muscle regeneration. This work crucially establishes a paradigm where a coding circRNA directly disrupts myogenic transcription.

While current research on circRNA-encoded proteins primarily focuses on cancer and tumor biology, this field is still in its infancy (30,81,82). Numerous circRNAs with protein-coding potential remain undiscovered, and the underlying translation mechanisms require further exploration (83). To date, no studies have directly implicated circRNA-mediated protein translation in IVDD; this gap may be attributed to the rarity of circRNAs with functional ORFs, the small molecular weight of the encoded proteins and the technical challenges associated with their detection. Nevertheless, given the established role of circRNAs in the musculoskeletal system, it is plausible that they may also influence disc degeneration, although this hypothesis awaits experimental validation.

5. Potential clinical application

Currently, the management of IVDD relies on two traditional approaches: Non-surgical conservative treatment and surgical intervention (84). However, neither strategy can fully restore degenerated disc tissue or reverse the pathological progression of IVDD (85). The development of biomaterials has opened new avenues for addressing these limitations. Researchers have increasingly focused on leveraging biomaterials to mitigate oxidative stress, reduce inflammatory factors, regulate ECM homeostasis and modulate cellular functions in animal models; however, evidence from human studies remains limited (23). In the following section, advancements in biomaterial-based therapies for IVDD are summarized, their mechanisms of action were elucidated and future research directions and therapeutic strategies were highlighted.

Gao *et al* (86) developed an injectable kaempferol-fibrin glue, combining kaempferol with fibrinogen to create a biomaterial with low immunogenicity and high stability. Animal studies demonstrated its efficacy in promoting NP cell proliferation and reducing cellular inflammation. Lu *et al* (87) investigated Physalin A, a natural

bioactive withanolide extracted from *Physalis alkekengi* var, which enhances NP cell autophagy by inhibiting the PI3K/AKT/mTOR pathway and mitigates tissue fibrosis by suppressing the SMAD2/3 pathway. Chen *et al.* (88) designed a zinc-oxidized sodium alginate-gelatin (ZOG) hydrogel loaded with antagomir-204-3p (AM). This composite material leverages the anti-apoptotic properties of AM, the antibacterial effects of zinc ions and the mechanical strength of ZOG to restore disc height and correct ECM metabolic imbalances. Wang *et al.* (89) developed oxymatrine-loaded liposomes (OMT-LIP), where oxymatrine exerts anti-fibrotic and anti-inflammatory effects, and liposomes enable sustained drug release. Animal experiments confirmed that OMT-LIP reduces ECM degradation in NP cells and suppresses the expression of MMP-319 and IL-6, thereby alleviating IVDD. Zhang *et al.* (90) constructed MnO₂-based nanoassemblies that decompose H₂O₂, alleviate oxidative stress and improve the hypoxic and acidic microenvironment of NPCs, while also enabling controlled drug release to slow IVDD progression.

In summary, emerging biomaterials, including nanomaterials, inorganic compounds and hydrogels, have shown promise in mitigating IVDD. Antioxidant and anti-inflammatory agents play a pivotal role in preserving ECM integrity and NP cell function; however, the specific molecular pathways through which these materials exert their effects remain incompletely understood. Furthermore, it is unclear whether combining multiple materials and drugs to target different pathways could yield superior therapeutic outcomes compared with single-pathway interventions. These questions represent critical areas for future research and exploration. At the same time, there is a scarcity of studies on the integration of circRNA with biomaterials, particularly for IVDD therapy. This limited research can be attributed to several key factors. First, the gene regulatory mechanisms of circRNA in IVDD remain unclear, complicating its therapeutic application. Secondly, developing biomaterials for circRNA delivery requires balancing biocompatibility, stability and targeting, which poses notable technical challenges. Despite these challenges, biomaterial research remains one of the fields most closely tied to clinical applications. The combination of circRNA with advanced biomaterials continues to hold great promise, making it a potential research hotspot for future IVDD therapies.

6. Conclusions and future prospects

The present review provided a comprehensive overview of the historical context, biogenesis and functional roles of circRNAs, with a particular focus on their involvement in IVDD. The current understanding of circRNA-mediated mechanisms in IVDD was elucidated, highlighting their regulatory roles as miRNA sponges, their interactions with proteins and their potential involvement in exosome-mediated signaling pathways. These findings underscore the critical role of circRNAs in modulating key cellular processes, including apoptosis, inflammation and ECM metabolism, which are central to the pathogenesis of IVDD.

The predominant mechanism through which circRNAs influence IVDD is through their function as ceRNAs, where they sequester specific miRNAs to regulate the expression

of target genes. This miRNA sponge mechanism has been extensively studied, with several circRNAs identified as either promoters or protectors of disc degeneration. For instance, circRNAs such as circEYA3 and circ_0083756 have been shown to exacerbate IVDD by promoting ECM degradation and inflammatory responses, while others, such as circRNA-CIDN and circGLCE exhibit protective effects by mitigating apoptosis and ECM disruption. However, current research on circRNAs in IVDD exhibits several methodological limitations that warrant critical appraisal. The field is heavily reliant on *in vitro* models utilizing cytokine-induced NP cells, an approach that fails to recapitulate the complex pathophysiology of the human disc environment. Consequently, findings from these simplified systems may lack *in vivo* relevance. Furthermore, the mechanistic exploration is predominantly confined to the competitive ceRNA network paradigm. While valuable, this focus often overlooks alternative functions of circRNAs, such as interactions with RBPs or protein translation, and is frequently unsupported by robust *in vivo* functional validation. Finally, clinical translation is hampered by studies with limited human sample sizes and the frequent use of suboptimal control tissues. Future investigations should prioritize the use of sophisticated *in vivo* models, larger and well-defined clinical cohorts and more specific genetic tools to unequivocally establish causal relationships and explore the full mechanistic spectrum of circRNAs in IVDD.

Furthermore, the role of circRNAs in protein interactions and their potential to encode functional peptides remains an underexplored area. While preliminary evidence suggests that circRNAs can interact with RBPs and even encode small peptides, the implications of these interactions in IVDD are yet to be fully elucidated. The development of advanced techniques, such as RNA RIP and mass spectrometry, will be crucial in uncovering the molecular mechanisms underlying circRNA-protein interactions. In addition, the exploration of circRNA-encoded peptides and their functional roles in disc degeneration represents a promising avenue for future research, potentially opening new therapeutic avenues.

Another critical area for future investigation is the application of circRNAs as non-invasive diagnostic biomarkers for IVDD. Given their stability and tissue-specific expression patterns, circRNAs hold notable promise for early detection and monitoring of disc degeneration. Furthermore, the development of targeted therapeutic strategies, such as circRNA inhibitors or miRNA mimics, could offer novel approaches to modulate circRNA expression and function. The integration of nanotechnology for the precise delivery of RNA-based therapeutics may further enhance the efficacy of these interventions.

In conclusion, while marked progress has been made in understanding the role of circRNAs in IVDD, several knowledge gaps remain. Current research predominantly focuses on the mechanism of circRNA as miRNA sponges, while investigations into circRNA-protein interactions and the translation potential of circRNAs remain in their nascent stages. Furthermore, research exploring the integration of circRNAs with biomaterials is particularly limited. These underexplored areas represent critical directions for future research breakthroughs. In the present review, emerging trends were highlighted and promising research directions were outlined, which may help bridge the current knowledge gap regarding

the role of circRNAs in IVDD and facilitate the development of improved therapeutic strategies to alleviate the associated socioeconomic burden. By addressing these challenges, new innovative diagnostic tools and therapeutic strategies can be developed, ultimately improving the management of IVDD and enhancing patient outcomes.

Acknowledgements

Not applicable.

Funding

The present review was funded by the National Natural Science Foundation of China (grant no. 82202753) and the Shandong Provincial Natural Science Foundation (grant no. ZR2022QH282).

Availability of data and materials

Not applicable.

Authors' contributions

XFD conceived the study. LYW and KY designed the study and wrote the manuscript. HJZ, DCW and FW contributed to the critical revision of the manuscript for important intellectual content. All authors contributed to perform the literature search. All authors read and approved the final manuscript. Data authentication 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.

References

- Knezevic NN, Candido KD, Vlaeyen JWS, Van Zundert J and Cohen SP: Low back pain. *Lancet* 398: 78-92, 2021.
- Risbud MV and Shapiro IM: Role of cytokines in intervertebral disc degeneration: Pain and disc content. *Nat Rev Rheumatol* 10: 44-56, 2014.
- Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, Horst C, Kaldjian A, Matyas T, Scott KW, *et al*: US health care spending by payer and health condition, 1996-2016. *JAMA* 323: 863-884, 2020.
- Jöud A, Petersson IF and Englund M: Low back pain: Epidemiology of consultations. *Arthritis Care Res (Hoboken)* 64: 1084-1088, 2012.
- Xu D, Ma X, Sun C, Han J, Zhou C, Wong SH, Chan MTV and Wu WKK: Circular RNAs in intervertebral disc degeneration: An updated review. *Front Mol Biosci* 8: 781424, 2022.
- Roberts S, Evans H, Trivedi J and Menage J: Histology and pathology of the human intervertebral disc. *J Bone Joint Surg Am* 88 (Suppl 2): S10-S14, 2006.
- Xie G, Wu T, Ji G, Wu H, Lai Y, Wei B and Huang W: Circular RNA and intervertebral disc degeneration: Unravelling mechanisms and implications. *Front Mol Biosci* 10: 1302017, 2023.
- Xiang Q, Kang L, Wang J, Liao Z, Song Y, Zhao K, Wang K, Yang C and Zhang Y: CircRNA-CIDN mitigated compression loading-induced damage in human nucleus pulposus cells via miR-34a-5p/SIRT1 axis. *EBioMedicine* 53: 102679, 2020.
- Chen Z, Song J, Xie L, Xu G, Zheng C, Xia X, Lu F, Ma X, Zou F, Jiang J and Wang H: N6-methyladenosine hypomethylation of circGPATCH2L regulates DNA damage and apoptosis through TRIM28 in intervertebral disc degeneration. *Cell Death Differ* 30: 1957-1972, 2023.
- Jeck WR and Sharpless NE: Detecting and characterizing circular RNAs. *Nat Biotechnol* 32: 453-461, 2014.
- Leão Monteiro R: Future of low back pain: Unravelling IVD components and MSCs' potential. *Cell Regen* 13: 1, 2024.
- Zhou D, Liu H, Zheng Z and Wu D: Design principles in mechanically adaptable biomaterials for repairing annulus fibrosus rupture: A review. *Bioact Mater* 31: 422-439, 2023.
- Zehra U, Tryfonidou M, Iatridis JC, Illien-Jünger S, Mwale F and Samartzis D: Mechanisms and clinical implications of intervertebral disc calcification. *Nat Rev Rheumatol* 18: 352-362, 2022.
- Zhang A, Cheng Z, Chen Y, Shi P, Gan W and Zhang Y: Emerging tissue engineering strategies for annulus fibrosus therapy. *Acta Biomater* 167: 1-15, 2023.
- Mohd Isa IL, Teoh SL, Mohd Nor NH and Mokhtar SA: Discogenic low back pain: Anatomy, pathophysiology and treatments of intervertebral disc degeneration. *Int J Mol Sci* 24: 208, 2022.
- Kirnaz S, Capadona C, Wong T, Goldberg JL, Medary B, Sommer F, McGrath LB Jr and Härtl R: Fundamentals of intervertebral disc degeneration. *World Neurosurg* 157: 264-273, 2022.
- Ma Z, Liu X, Zhang M, Wu Z, Zhang X, Li S, Li S, An J and Luo Z: Research progress on the role of cartilage endplate in intervertebral disc degeneration. *Cell Biochem Funct* 42: e4118, 2024.
- Guo W, Li BL, Zhao JY, Li XM and Wang LF: Causal associations between modifiable risk factors and intervertebral disc degeneration. *Spine J* 24: 195-209, 2024.
- Xia Q, Zhao Y, Dong H, Mao Q, Zhu L, Xia J, Weng Z, Liao W, Hu Z, Yi J, *et al*: Progress in the study of molecular mechanisms of intervertebral disc degeneration. *Biomed Pharmacother* 174: 116593, 2024.
- Adams MA and Roughley PJ: What is intervertebral disc degeneration, and what causes it? *Spine (Phila Pa 1976)* 31: 2151-2161, 2006.
- Roh EJ, Darai A, Kyung JW, Choi H, Kwon SY, Bhujel B, Kim KT and Han I: Genetic therapy for intervertebral disc degeneration. *Int J Mol Sci* 22: 1579, 2021.
- Clouet J, Vinatier C, Merceron C, Pot-Vaucel M, Hamel O, Weiss P, Grimandi G and Guicheux J: The intervertebral disc: From pathophysiology to tissue engineering. *Joint Bone Spine* 76: 614-618, 2009.
- Mohd Isa IL, Mokhtar SA, Abbah SA, Fauzi MB, Devitt A and Pandit A: Intervertebral disc degeneration: Biomaterials and tissue engineering strategies toward precision medicine. *Adv Healthc Mater* 11: e2102530, 2022.
- Wang J, Markova D, Anderson DG, Zheng Z, Shapiro IM and Risbud MV: TNF- α and IL-1 β promote a disintegrin-like and metalloprotease with thrombospondin type I motif-5-mediated aggrecan degradation through syndecan-4 in intervertebral disc. *J Biol Chem* 286: 39738-39749, 2011.
- Wang F, Cai F, Shi R, Wang XH and Wu XT: Aging and age related stresses: A senescence mechanism of intervertebral disc degeneration. *Osteoarthritis Cartilage* 24: 398-408, 2016.
- Zhu J, Zhang X, Gao W, Hu H, Wang X and Hao D: lncRNA/circRNA-miRNA-mRNA ceRNA network in lumbar intervertebral disc degeneration. *Mol Med Rep* 20: 3160-3174, 2019.
- Yin X, Lin H, Lin L, Miao L, He J and Zhuo Z: LncRNAs and CircRNAs in cancer. *MedComm* (2020) 3: e141, 2022.
- Sanger HL, Klotz G, Riesner D, Gross HJ and Kleinschmidt AK: Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. *Proc Natl Acad Sci U S A* 73: 3852-3856, 1976.
- Zhao X, Zhong Y, Wang X, Shen J and An W: Advances in circular RNA and its applications. *Int J Med Sci* 19: 975-985, 2022.
- Conn VM, Chinnaiyan AM and Conn SJ: Circular RNA in cancer. *Nat Rev Cancer* 24: 597-613, 2024.
- Niu D, Wu Y and Lian J: Circular RNA vaccine in disease prevention and treatment. *Signal Transduct Target Ther* 8: 341, 2023.

32. Yang Y, Yujiao W, Fang W, Linhui Y, Ziqi G, Zhichen W, Zirui W and Shengwang W: The roles of miRNA, lncRNA and circRNA in the development of osteoporosis. *Biol Res* 53: 40, 2020.
33. Li Q, Ren X, Wang Y and Xin X: CircRNA: A rising star in leukemia. *PeerJ* 11: e15577, 2023.
34. Kelly S, Greenman C, Cook PR and Papantonis A: Exon skipping is correlated with exon circularization. *J Mol Biol* 427: 2414-2417, 2015.
35. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB and Kjems J: The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet* 20: 675-691, 2019.
36. Wang M, Yu F, Wu W, Zhang Y, Chang W, Ponnusamy M, Wang K and Li P: Circular RNAs: A novel type of non-coding RNA and their potential implications in antiviral immunity. *Int J Biol Sci* 13: 1497-1506, 2017.
37. Chen L, Wang C, Sun H, Wang J, Liang Y, Wang Y and Wong G: The bioinformatics toolbox for circRNA discovery and analysis. *Brief Bioinform* 22: 1706-1728, 2021.
38. Di Agostino S, Riccioli A, De Cesaris P, Fontemaggi G, Blandino G, Filippini A and Fazi F: Circular RNAs in embryogenesis and cell differentiation with a focus on cancer development. *Front Cell Dev Biol* 8: 389, 2020.
39. Hsiao KY, Lin YC, Gupta SK, Chang N, Yen L, Sun HS and Tsai SJ: Noncoding effects of circular RNA CCDC66 promote colon cancer growth and metastasis. *Cancer Res* 77: 2339-2350, 2017.
40. Altesha MA, Ni T, Khan A, Liu K and Zheng X: Circular RNA in cardiovascular disease. *J Cell Physiol* 234: 5588-5600, 2019.
41. Wu W, Ji P and Zhao F: CircAtlas: An integrated resource of one million highly accurate circular RNAs from 1070 vertebrate transcriptomes. *Genome Boil* 21: 101, 2020.
42. Nguyen DT: An integrative pipeline for circular RNA quantitative trait locus discovery with application in human T cells. *Bioinformatics* 39: btad667, 2023.
43. Wang Q, Yang D, Zuo Y, Wang D and Li W: Emerging roles of circular RNAs in tuberculosis. *Front Immunol* 13: 995701, 2022.
44. Fischer JW and Leung AKL: CircRNAs: A regulator of cellular stress. *Crit Rev Biochem Mol Biol* 52: 220-233, 2017.
45. Xu F, Xiao Q, Du WW, Wang S and Yang BB: CircRNA: Functions, applications and prospects. *Biomolecules* 14: 1503, 2024.
46. Hausser J and Zavolan M: Identification and consequences of miRNA-target interactions-beyond repression of gene expression. *Nat Rev Genet* 15: 599-612, 2014.
47. Liu Y, Xue M, Du S, Feng W, Zhang K, Zhang L, Liu H, Jia G, Wu L, Hu X, *et al*: Competitive endogenous RNA is an intrinsic component of EMT regulatory circuits and modulates EMT. *Nat Commun* 10: 1637, 2019.
48. Militello G, Weirick T, John D, Döring C, Dimmeler S and Uchida S: Screening and validation of lncRNAs and circRNAs as miRNA sponges. *Brief Bioinform* 18: 780-788, 2017.
49. Wang T, Yan X, Song D, Li Y, Li Z and Feng D: CircEYA3 aggravates intervertebral disc degeneration through the miR-196a-5p/EBF1 axis and NF- κ B signaling. *Commun Boil* 7: 390, 2024.
50. Du X, Chen S, Cui H, Huang Y, Wang J, Liu H, Li Z, Liang C, Zheng Z and Wang H: Circular RNA hsa_circ_0083756 promotes intervertebral disc degeneration by sponging miR-558 and regulating TREM1 expression. *Cell Prolif* 55: e13205, 2022.
51. Cui Y, Zhao X and Wu Y: Circ_0005918 sponges miR-622 to aggravate intervertebral disc degeneration. *Front Cell Dev Biol* 10: 905213, 2022.
52. Yan P, Sun C, Luan L, Han J, Qu Y, Zhou C and Xu D: Hsa_circ_0134111 promotes intervertebral disc degeneration via sponging miR-578. *Cell Death Discov* 8: 55, 2022.
53. Li Y, Pan D, Liu S, Xing X, Zhou H, Zhang B, Zhang D, Li B, Li G, Tao B, *et al*: Identification of circ-FAM169A sponges miR-583 involved in the regulation of intervertebral disc degeneration. *J Orthop Translat* 26: 121-131, 2020.
54. Urban JP, Smith S and Fairbank JCT: Nutrition of the intervertebral disc. *Spine (Phila Pa 1976)* 29: 2700-2709, 2004.
55. Feng C, Liu M, Fan X, Yang M, Liu H and Zhou Y: Intermittent cyclic mechanical tension altered the microRNA expression profile of human cartilage endplate chondrocytes. *Mol Med Rep* 17: 5238-5246, 2018.
56. Hu B, Xiao L, Wang C, Liu C, Zhang Y, Ding B, Gao D, Lu Y and Xu H: Circ_0022382 ameliorated intervertebral disc degeneration by regulating TGF- β 3 expression through sponge adsorption of miR-4726-5p. *Bone* 154: 116185, 2022.
57. Wang H, He P, Pan H, Long J, Wang J, Li Z, Liu H, Jiang W and Zheng Z: Circular RNA circ-4099 is induced by TNF- α and regulates ECM synthesis by blocking miR-616-5p inhibition of Sox9 in intervertebral disc degeneration. *Exp Mol Med* 50: 1-14, 2018.
58. Zhang J, Hu S, Ding R, Yuan J, Jia J, Wu T and Cheng X: CircSNHG5 sponges Mir-495-3p and modulates CITED2 to protect cartilage endplate from degradation. *Front Cell Dev Biol* 9: 668715, 2021.
59. Chen Z, Zhang W, Deng M, Li Y and Zhou Y: CircGLCE alleviates intervertebral disc degeneration by regulating apoptosis and matrix degradation through the targeting of miR-587/STAP1. *Aging (Albany NY)* 12: 21971-21991, 2020.
60. Kalluri R and LeBleu VS: The biology, function, and biomedical applications of exosomes. *Science* 367: eaau6977, 2020.
61. Zhang F, Jiang J, Qian H, Yan Y and Xu W: Exosomal circRNA: Emerging insights into cancer progression and clinical application potential. *J Hematol Oncol* 16: 67, 2023.
62. Xue Q, Huang Y, Chang J, Cheng C, Wang Y, Wang X and Miao C: CircRNA-mediated ceRNA mechanism in osteoarthritis: Special emphasis on circRNAs in exosomes and the crosstalk of circRNAs and RNA methylation. *Biochem Pharmacol* 212: 115580, 2023.
63. Li W, Pang Y, He Q, Song Z, Xie X, Zeng J and Guo J: Exosome-derived microRNAs: Emerging players in vitiligo. *Front Immunol* 15: 1419660, 2024.
64. He C, Zheng S, Luo Y and Wang B: Exosome theranostics: Biology and translational medicine. *Theranostics* 8: 237-255, 2018.
65. Chen X, Cai D, Li H, Wei Q, Li X, Han Z, Liang J, Xie J, Ruan J, Liu J, *et al*: Exosomal U2AF2 derived from human bone marrow mesenchymal stem cells attenuates the intervertebral disc degeneration through circ_0036763/miR-583/ACAN axis. *Regen Ther* 25: 344-354, 2024.
66. Song J, Chen ZH, Zheng CJ, Song KH, Xu GY, Xu S, Zou F, Ma XS, Wang HL and Jiang JY: Exosome-transported circRNA_0000253 competitively adsorbs MicroRNA-141-5p and increases IDD. *Mol Ther Nucleic Acids* 21: 1087-1099, 2020.
67. Huang A, Zheng H, Wu Z, Chen M and Huang Y: Circular RNA-protein interactions: Functions, mechanisms, and identification. *Theranostics* 10: 3503-3517, 2020.
68. Das A, Sinha T, Shyamal S and Panda AC: Emerging role of circular RNA-protein interactions. *Noncoding RNA* 7: 48, 2021.
69. Shaath H, Vishnubalaji R, Elango R, Kardousha A, Islam Z, Qureshi R, Alam T, Kolatkar PR and Alajez NM: Long non-coding RNA and RNA-binding protein interactions in cancer: Experimental and machine learning approaches. *Semin Cancer Biol* 86: 325-345, 2022.
70. Zheng S, Zhang X, Odame E, Xu X, Chen Y, Ye J, Zhou H, Dai D, Kyei B, Zhan S, *et al*: CircRNA-protein interactions in muscle development and diseases. *Int J Mol Sci* 22: 3262, 2021.
71. Gu T, He Y, Zhou J, Qiu X, Yang W, Zhu Q, Liang Y, Zheng Y, Yik JHN, Haudenschild DR, *et al*: CircFUNDCl interacts with CDK9 to promote mitophagy in nucleus pulposus cells under oxidative stress and ameliorates intervertebral disc degeneration. *Cell Death Dis* 16: 94, 2025.
72. Yu C, Zhao J, Cheng F, Chen J, Chen J, Xu H, Shi K, Xia K, Ding S, Wang K, *et al*: Silencing circATXN1 in aging nucleus pulposus cell alleviates intervertebral disc degeneration via correcting progerin mislocalization. *Research (Wash D C)* 7: 0336, 2024.
73. Chen R, Yang T, Jin B, Xu W, Yan Y, Wood N, Lehmann HI, Wang S, Zhu X, Yuan W, *et al*: CircTmeff1 promotes muscle atrophy by interacting with TDP-43 and encoding A novel TMEFF1-339aa protein. *Adv Sci (Weinh)* 10: e2206732, 2023.
74. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P and Yang BB: Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. *Nucleic Acids Res* 44: 2846-2858, 2016.
75. Zhu YJ, Zheng B, Luo GJ, Ma XK, Lu XY, Lin XM, Yang S, Zhao Q, Wu T, Li ZX, *et al*: Circular RNAs negatively regulate cancer stem cells by physically binding FMRP against CCAR1 complex in hepatocellular carcinoma. *Theranostics* 9: 3526-3540, 2019.
76. Cheng J, Li G, Wang W, Stovall DB, Sui G and Li D: Circular RNAs with protein-coding ability in oncogenesis. *Biochim Biophys Acta Rev Cancer* 1878: 188909, 2023.

77. Wu P, Mo Y, Peng M, Tang T, Zhong Y, Deng X, Xiong F, Guo C, Wu X, Li Y, *et al*: Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. *Mol Cancer* 19: 22, 2020.
78. Yin H, Shen X, Zhao J, Cao X, He H, Han S, Chen Y, Cui C, Wei Y, Wang Y, *et al*: Circular RNA CircFAM188B encodes a protein that regulates proliferation and differentiation of chicken skeletal muscle satellite cells. *Front Cell Dev Biol* 8: 522588, 2020.
79. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, Fatica A, Santini T, Andronache A, Wade M, *et al*: Circ-ZNF609 Is a circular RNA that can be translated and functions in myogenesis. *Mol Cell* 66: 22-37.e9, 2017.
80. Zhu X, Yang T, Zheng Y, Nie Q, Chen J, Li Q, Ren X, Yin X, Wang S, Yan Y, *et al*: EIF4A3-induced circular RNA CircDdb1 promotes muscle atrophy through encoding a novel protein CircDdb1-867aa. *Adv Sci (Weinh)* 11: e2406986, 2024.
81. Chen S, Cao X, Zhang J, Wu W, Zhang B and Zhao F: circVAMP3 drives CAPRN1 phase separation and inhibits hepatocellular carcinoma by suppressing c-Myc translation. *Adv Sci (Weinh)* 9: e2103817, 2022.
82. Margvelani G, Maquera KAA, Welden JR, Rodgers DW and Stamm S: Translation of circular RNAs. *Nucleic Acids Res* 53: gkae1167, 2025.
83. Yi Q, Feng J, Lan W, Shi H, Sun W and Sun W: CircRNA and lncRNA-encoded peptide in diseases, an update review. *Mol Cancer* 23: 214, 2024.
84. Kim MW, Kang CN and Choi SH: Update of the natural history, pathophysiology, and treatment strategies of degenerative cervical myelopathy: A narrative review. *Asian Spine J* 17: 213-221, 2023.
85. Chen X, Zhang A, Zhao K, Gao H, Shi P, Chen Y, Cheng Z, Zhou W and Zhang Y: The role of oxidative stress in intervertebral disc degeneration: Mechanisms and therapeutic implications. *Ageing Res Rev* 98: 102323, 2024.
86. Gao W, Bao J, Zhang Y, He D, Zhang L, Zhang J, Pan H and Wang D: Injectable kaempferol-loaded fibrin glue regulates the metabolic balance and inhibits inflammation in intervertebral disc degeneration. *Sci Rep* 13: 20001, 2023.
87. Lu R, Xu H, Deng X, Wang Y, He Z, Xu S, Liang S, Huang X, You H, Guo F, *et al*: Physalin A alleviates intervertebral disc degeneration via anti-inflammatory and anti-fibrotic effects. *J Orthop Translat* 39: 74-87, 2023.
88. Chen T, Qian Q, Makvandi P, Zare EN, Chen Q, Chen L, Zhang Z, Zhou H, Zhou W, Wang H, *et al*: Engineered high-strength biohydrogel as a multifunctional platform to deliver nucleic acid for ameliorating intervertebral disc degeneration. *Bioact Mater* 25: 107-121, 2023.
89. Wang H, Ding Y, Zhang W, Wei K, Pei Y, Zou C, Zhang C, Ding J, Fang H and Tan S: Oxymatrine liposomes for intervertebral disc treatment: Formulation, in vitro and vivo assessments. *Drug Des Devel Ther* 14: 921-931, 2020.
90. Zhang W, Yang M, Sun T, Zhang J, Zhao Y, Li J and Li Z: Can manganese dioxide microspheres be used as intermediaries to alleviate intervertebral disc degeneration with strengthening drugs? *Front Bioeng Biotechnol* 10: 866290, 2022.



Copyright © 2026 Wang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.