Epigenetic crossroads in intervertebral disc degeneration: Unlocking novel therapeutic avenues (Review)

YANG HOU, LEI LIU, YONGFEI GUO and JIANGANG SHI

Department of Orthopaedic Surgery, Changzheng Hospital, Second Military Medical University, Shanghai 200003, P.R. China

Received June 25, 2025; Accepted October 20, 2025

DOI: 10.3892/mmr.2026.13823

Abstract. Intervertebral disc degeneration (IDD) is a major pathological basis for spinal degenerative diseases, involving mechanisms such as abnormal mechanical loading, inflammatory responses, and genetic and environmental factors. The role of epigenetic regulation in IDD has gained attention as a potential therapeutic target. The present review systematically explores the contributions of DNA methylation, histone modifications, non-coding RNAs (ncRNAs) and metabolic regulation to IDD progression, and elucidates their molecular mechanisms. Specific examples include: DNA methyltransferase 3β-mediated DNA methylation promoting ferroptosis and oxidative stress in nucleus pulposus cells; enhancer of zeste homolog 2 (EZH2)-mediated trimethylation of histone H3 lysine 27 modification inhibiting SOX9 expression, leading to cellular senescence and extracellular matrix degradation; and ncRNAs (such as microRNA-143 and LINC01121) regulating gene transcription to affect inflammation and apoptosis. Additionally, metabolic products (such as NAD^+, α-ketoglutarate and lactate) interact with epigenetic pathways to influence IDD. Specifically, NAD^+ acts as a cofactor for sirtuin deacetylases, thereby regulating histone and non-histone protein acetylation; α-ketoglutarate serves as a cofactor for TET DNA demethylases and Jumonji-C histone demethylases, influencing DNA and histone demethylation; and lactate induces histone lactylation, which modulates gene transcription related to inflammation and extracellular matrix metabolism in IDD. Based on these mechanisms, novel therapies targeting epigenetics (such as DNA methylation inhibitors, EZH2 inhibitors and RNA interference) show therapeutic potential. Future research should further explore the crosstalk between epigenetic and metabolic regulation to advance the development of personalized and precision medicine strategies for IDD intervention.

Correspondence to: Professor Yongfei Guo or Professor Jiangang Shi, Department of Orthopaedic Surgery, Changzheng Hospital, Second Military Medical University, 415 Fengyang Road, Shanghai 200003, P.R. China
E-mail: junjiespine@sina.com
E-mail: alexzandersuper@163.com

Key words: intervertebral disc degeneration, epigenetics, DNA methylation, histone modifications, non-coding RNA

Contents

1. Introduction

Intervertebral disc degeneration (IDD) is a major pathological basis of spinal degenerative diseases, and a key factor leading to lumbar disc herniation, spinal stenosis and chronic low back pain (1). Epidemiological studies have shown that the prevalence of IDD increases with age, and is influenced by genetic factors, mechanical load, inflammatory responses and environmental conditions (2,3). Due to the complex pathogenesis of IDD, there is currently no effective treatment to reverse or halt its progression. Existing therapeutic approaches primarily focus on symptom relief, including pain medications, physical therapy and surgical interventions. However, with advancements in molecular biology, the role of epigenetic regulation in IDD has gained increasing attention and is considered a promising avenue for potential therapeutic targets at present, as it offers opportunities to modulate gene expression involved in extracellular matrix (ECM) metabolism, inflammation and cell senescence without altering the underlying DNA sequence. By targeting these reversible epigenetic changes, such as DNA methylation, histone modifications and non-coding RNAs, future therapies may be able to slow or even reverse disc degeneration rather than merely alleviate symptoms (4).

Epigenetics refers to regulatory mechanisms that influence gene expression without altering the DNA sequence, mainly through reversible chemical modifications or changes in nucleosome structure. These mechanisms include DNA methylation, histone modifications, non-coding RNA

(ncRNA)-mediated regulation and chromatin remodeling (5). These regulatory pathways serve crucial roles in the onset and progression of IDD (6). For example, DNA methylation can influence the expression of genes such as MMPs and type II collagen (COL2A1), histone modifications can alter the transcriptional state of intervertebral disc cells, and ncRNAs are involved in regulating apoptosis, inflammatory responses and ECM metabolism (7-9). Additionally, IDD is often associated with chronic inflammation and oxidative stress, where epigenetic modifications serve a key role in regulating inflammatory mediators and metabolic pathways (6).

The present review systematically explores the role of epigenetic regulation in IDD, focusing on how mechanisms such as DNA methylation, histone modifications, and ncRNAs-mediated regulation influence IDD, and how metabolic disorders may modulate these epigenetic processes. Furthermore, the present review discusses the potential therapeutic implications of targeting these epigenetic mechanisms in IDD treatment.

2. Role of DNA methylation in IDD

Overall association between DNA methylation and IDD. A previous study employing genome-wide methylation analysis identified hypermethylation in advanced degenerative discs compared with early-stage discs (10). Further evidence has demonstrated that numerous genes related to stress responses, matrix catabolism and cell death are regulated by aberrant DNA methylation in degenerative discs (11).

In particular, the upregulation of the DNA methyltransferase (DNMT)3B has received considerable attention. DNMT3B expression is regarded as a prominent feature of degenerative nucleus pulposus (NP) cells (12). In both *in vitro* and *in vivo* models, blocking DNMT activity [e.g., using the inhibitor 5-azacytidine (5-AZA)] can reduce ferroptosis and oxidative stress, ultimately slowing NP cell degeneration and ECM breakdown (12), as schematically illustrated in Fig. 1, which depicts the regulatory roles of DNMTs and TET enzymes in methylation-mediated ferroptosis and ECM metabolism.

Abnormal methylation of key genes. Research has indicated that secreted protein acidic and cysteine rich (SPARC), an important regulator of ECM homeostasis, is hypermethylated in aging and degenerative discs, leading to suppressed SPARC expression, which disrupts matrix integrity and is closely associated with chronic pain (13). Growth differentiation factor 5 (GDF5) has a critical CpG site in its 5' untranslated region (UTR), where increased methylation alters transcription factor (SP1/SP3) binding, reducing GDF5 expression and increasing the risk of multiple musculoskeletal disorders, including lumbar disc degeneration (14).

Regarding ferroptosis and oxidative stress, silencing of the solute carrier family 40 member 1 (SLC40A1) gene by DNMT3B-mediated hypermethylation makes NP cells more vulnerable to ferroptosis and oxidative stress (12). Conversely, restoring SLC40A1 expression by inhibiting DNMT3B can ease disc damage (15). In addition, epigenetic regulation of apoptotic pathways is evident in the methylation-dependent upregulation of certain microRNAs (miRNAs/miRs; for example, miR-143), which suppress BCL2 and increase NP cell apoptosis (16).

Autophagy and senescence pathways also display altered methylation patterns. For instance, miR-129-5p is downregulated in degenerative discs due to hypermethylation in its promoter region; consequently, its reduced suppression of Beclin-1 affects normal autophagy homeostasis (17). E4F transcription factor 1, another key factor in cell senescence, is also epigenetically inhibited when DNMT3B is upregulated by ALKBH5-mediated N^6-methyladenosine (m^6A) demethylation, compounding the degenerative process (18).

Regulatory mechanisms and network interactions. DNA methylation not only affects gene transcription but also interacts with other epigenetic processes, such as histone modifications, ncRNA-mediated regulation and RNA methylation, to amplify injury from senescence, inflammation and oxidative stress (6). Inflammatory signals can stimulate DNMT and ten-eleven translocation (TET) enzyme expression, while oxidative stress can modulate the activity of methyltransferases via the p38/MAPK pathway, increasing catabolic enzyme expression (19).

3. Histone modifications and IDD

Histone modifications, including acetylation, methylation, phosphorylation and ubiquitination, are essential epigenetic mechanisms that influence chromatin structure and gene expression (6). In the context of IDD, growing evidence indicates that dysregulation of these modifications contributes to pathological processes such as ECM degradation, inflammation, cellular senescence and apoptosis (20,21). Among these various modifications, histone acetylation/deacetylation and histone methylation/demethylation have been most prominently studied (18). This section summarizes the findings on these two major modifications and their regulatory factors in IDD (Fig. 2), which are supported by recent studies (21,22).

Role of histone acetylation/deacetylation [histone acetyltransferases (HATs)/histone deacetylases (HDACs)] in IDD. Histone acetylation, mediated by HATs, reduces the positive charge of lysine residues, leading to chromatin relaxation and promoting gene transcription (23). Conversely, HDACs remove acetyl groups, resulting in chromatin condensation and transcriptional repression. Emerging evidence suggests that dysregulation of HDACs serves a crucial role in IDD (22).

Studies have demonstrated that HDAC9 expression is reduced in degenerative NP cells (22,24). Under normal conditions, HDAC9 deacetylates and stabilizes RUNX family transcription factor 3 (RUNX3) to maintain cell viability. Loss of HDAC9 expression in IDD diminishes RUNX3 stability, thereby promoting NP cell apoptosis (22). By contrast, HDAC4 has been shown to promote IDD progression by upregulating the Krüppel-like factor 5 (KLF5) and apoptosis signal-regulating kinase 1 signaling axis, which accelerates ECM degradation (24). These findings highlight the complex role of histone acetylation/deacetylation in IDD pathogenesis and suggest that selective HDAC inhibition may offer novel therapeutic potential for mitigating disc degeneration.

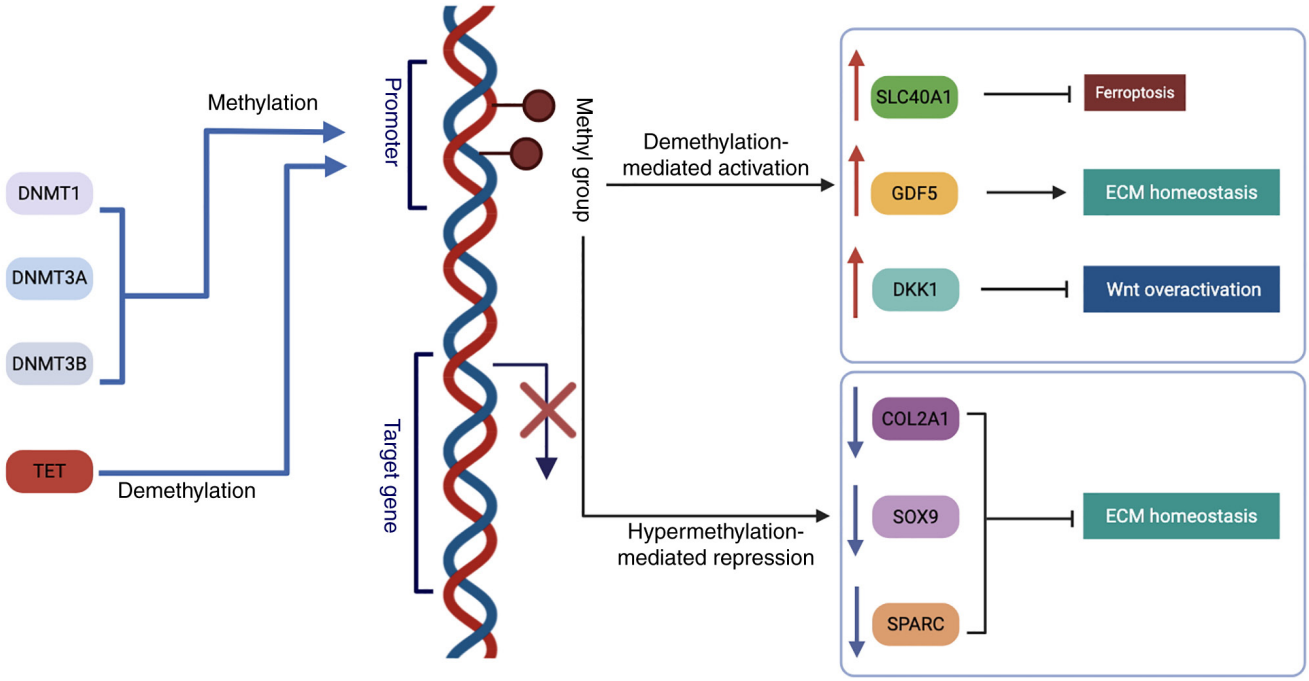

Figure 1. Critical role of DNA methylation regulation in IDD. DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) mediate promoter methylation and repress target genes, whereas TET enzymes promote demethylation and transcriptional activation. Demethylation of SLC40A1 and GDF5 restores their expression, thereby regulating ferroptosis resistance and ECM homeostasis. Demethylation-mediated upregulation of DKK1, a Wnt antagonist, inhibits Wnt signaling activity. By contrast, hypermethylation of COL2A1, SOX9 and SPARC represses their expression, leading to ECM degradation and accelerating IDD progression. COL2A1, type II collagen; DKK1, dickkopf Wnt signaling pathway inhibitor 1; DNMT, DNA methyltransferase; ECM, extracellular matrix; GDF5, growth differentiation factor 5; IDD, intervertebral disc degeneration; SLC40A1, solute carrier family 40 member 1; SPARC, secreted protein acidic and cysteine rich; TET, ten-eleven translocation.

Role of histone methylation and its regulatory factors in IDD. In the pathogenesis and progression of IDD, histone methylation has been shown to serve a crucial regulatory role in key processes such as ECM homeostasis, cellular senescence, autophagy and inflammation (21). This modification is primarily mediated by methyltransferases [such as enhancer of zeste homolog 2 (EZH2), lysine methyltransferase 2A (KMT2A) and SUV39H2] and demethylases [such as lysine demethylase (KDM)2/7, KDM4B and KDM3A], which add or remove methyl groups on specific lysine or arginine residues of histones, thereby influencing chromatin conformation and gene transcription (25,26).

Multiple studies have demonstrated that EZH2, a methyltransferase responsible for trimethylation of histone H3 lysine 27 (H3K27), is elevated in degenerative discs (27,28). By enriching trimethylation of histone H3 lysine 27 (H3K27me3) in specific gene promoter regions, EZH2 suppresses gene expression, accelerating the senescence of NP cells and promoting ECM degradation (28). For example, inhibition of EZH2 can remove H3K27me3 marks at the SOX9 promoter, upregulate cartilage phenotype-related genes such as SOX9, and curb ECM breakdown, thus counteracting endplate and NP degeneration (27). Additionally, EZH2-mediated H3K27me3 can silence key regulatory factors such as dickkopf Wnt signaling pathway inhibitor 1 or miR-129-5p, thereby activating the NLRP3, NLR family apoptosis inhibitory protein/NLR family CARD domain containing 4 or MAPK1 pathways, and further exacerbating pyroptosis and inflammation in NP cells (21,28). These findings suggest that inhibiting EZH2 expression or activity may be a potential strategy to delay disc degeneration.

Besides EZH2, other methyltransferases also serve essential roles in the pathological progression of IDD. SUV39H2 can specifically monomethylate protein phosphatase 1 catalytic subunit α at K141, disrupting its interaction with transcription factor EB (TFEB), and hampering TFEB nuclear translocation and autophagy gene activation, ultimately inducing cell senescence and disc degeneration (29). KMT2A (MLL1) enhances METTL3 expression via H3K4me3 enrichment at the METTL3 promoter, which increases m^6A modification and downregulates autophagy related (ATG)4a transcription. This leads to impaired autophagy, GATA binding protein 4 activation and a senescent phenotype in NP cells (30). Such findings highlight the interplay among histone methylation, autophagy and cellular senescence, offering novel insights into IDD mechanisms.

In contrast to methyltransferases, histone demethylases (for example, the KDM2, KDM4 and KDM3 families) remove methyl groups from specific residues, thus either activating or repressing target genes (31). Research has shown that targeted inhibition of KDM2/7, using either gene editing or pharmacological approaches, may promote the differentiation of human induced pluripotent stem cells into notochord-like cells, potentially opening novel avenues for regenerative therapy against IDD (32). Furthermore, in a 400 mOsm environment, KDM4B upregulates NP marker genes and enhances stem cell differentiation into NP-like cells (33). This finding highlights the crucial role

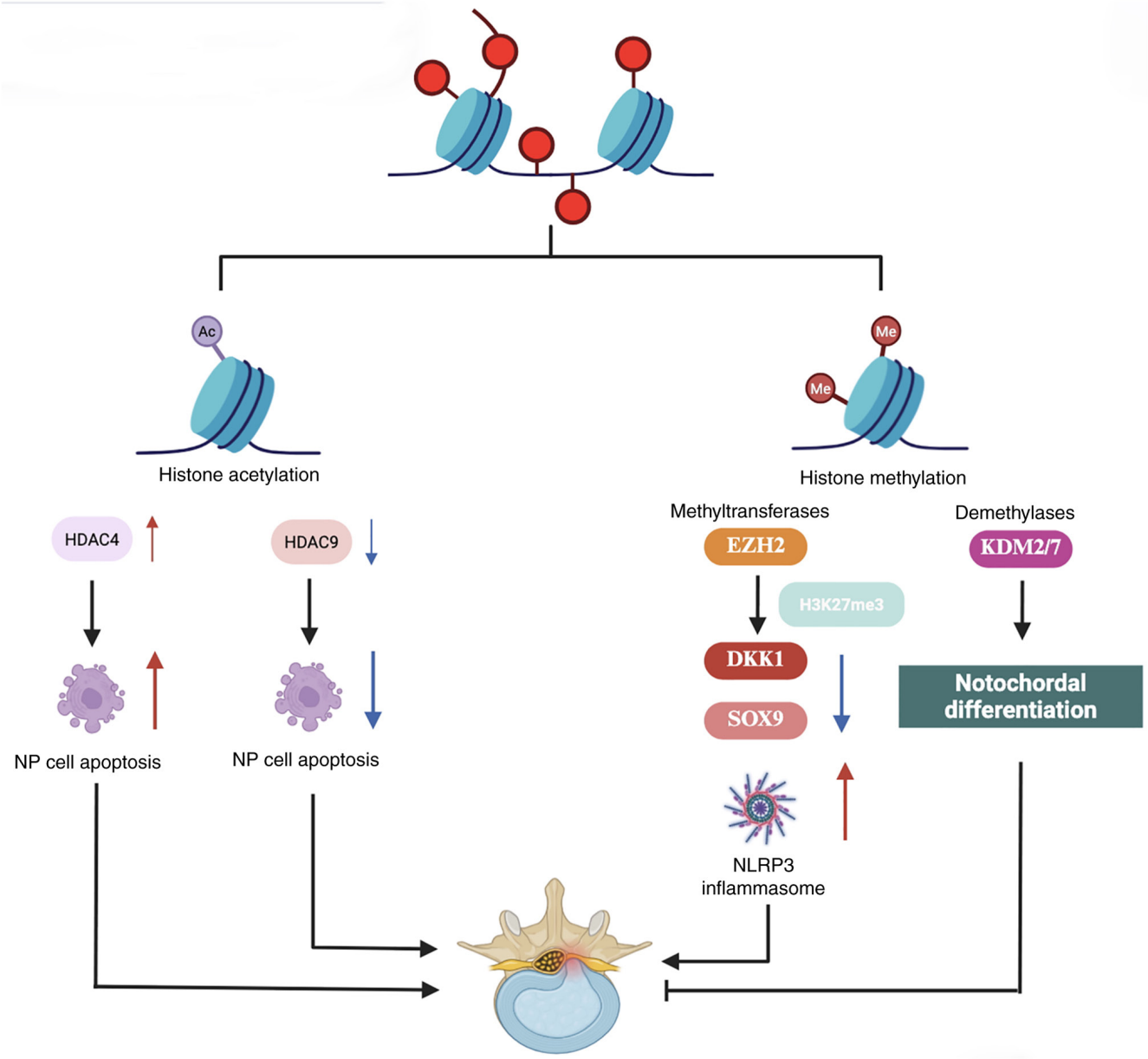

Figure 2. Role of histone modifications in IDD. Histone acetylation and methylation influence IDD pathogenesis. HDAC4 promotes NP cell apoptosis, whereas HDAC9 exerts protective effects. EZH2-mediated H3K27me3 suppresses SOX9 expression, enhancing NLRP3 inflammasome activation and extracellular matrix degradation. By contrast, KDM2/7 promotes notochordal differentiation, suggesting a potential therapeutic approach for IDD. DKK1, dickkopf Wnt signaling pathway inhibitor 1; EZH2, enhancer of zeste homolog 2; H3K27me3, trimethylation of histone H3 lysine 27; HDAC, histone deacetylase; IDD, intervertebral disc degeneration; KDM2/7, lysine demethylase 2/7; NLRP3, NLR family pyrin domain containing 3; NP, nucleus pulposus; Me, methyl group.

of histone demethylation in maintaining disc cell identity under osmotic stress, a key pathological factor in IDD. By promoting notochordal and NP-like differentiation, KDM4B-mediated demethylation may help restore the regenerative potential of degenerated discs. Therefore, targeting KDM4B activity or mimicking its epigenetic effects could represent a promising therapeutic approach for disc repair and regeneration. However, excessive demethylase activity could trigger abnormal regulation of downstream genes. For instance, increased KDM3A may elevate hypoxia-inducible factor 1α levels, provoking disturbances in autophagy and apoptosis among NP cells; thus, precisely regulating demethylase activities remains a crucial therapeutic goal (34).

4. Role of ncRNAs in IDD

ncRNAs have attracted attention in the study of IDD. ncRNAs, including miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), regulate various cellular processes related to IDD, including ECM metabolism, inflammation, oxidative stress, apoptosis and ferroptosis (35).

Role of miRNAs in IDD. miRNAs are endogenous small RNAs, 20-22 nucleotides in length, and regulate gene expression by binding to the 3'UTR of target mRNAs, thereby inhibiting translation or promoting degradation (36,37). During IDD, miRNAs serve key regulatory roles in NP cells, annulus fibrosus cells and inflammation-related processes (38). Studies

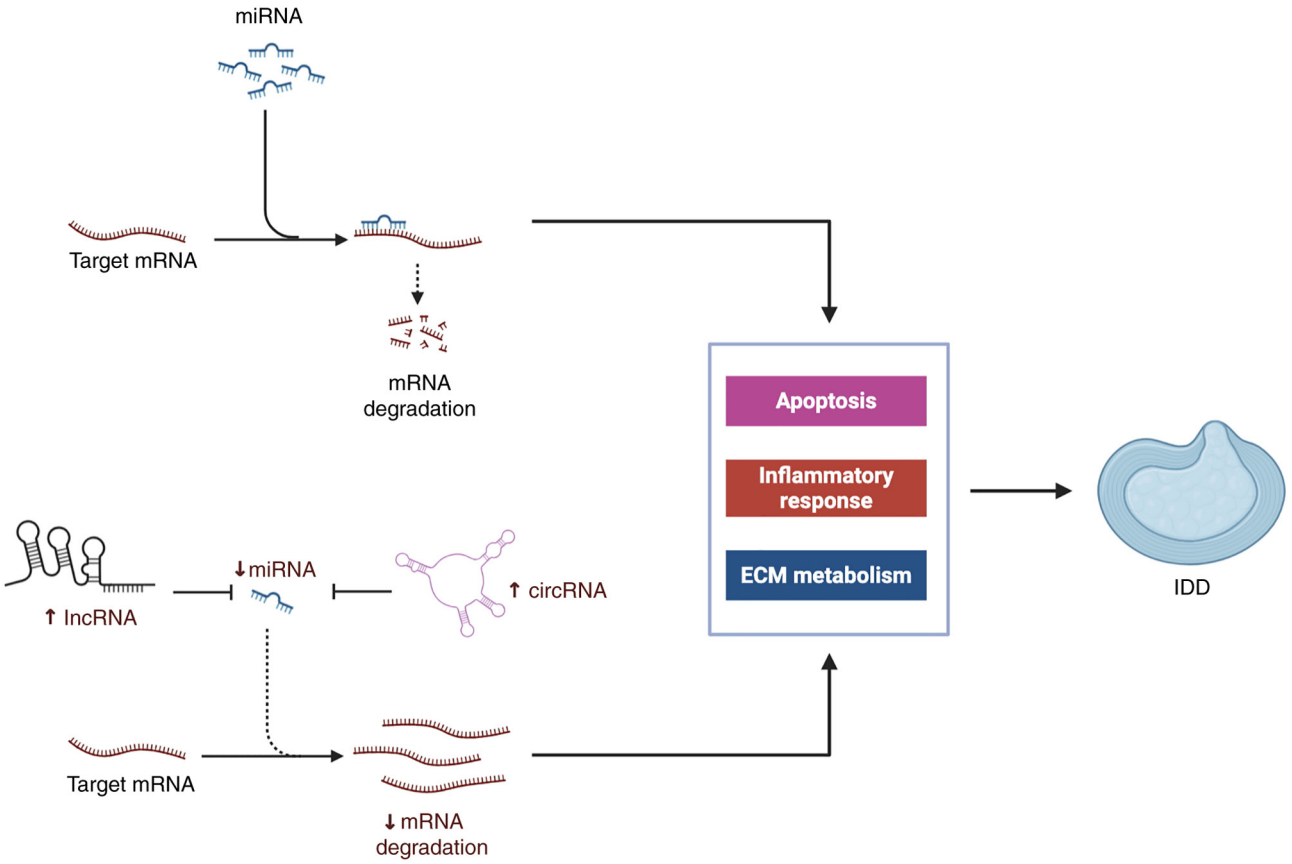

Figure 3. Role of Non-Coding RNAs in IDD. miRNAs repress target mRNAs, thereby regulating apoptosis, inflammation and ECM metabolism in IDD. lncRNAs and circRNAs act as competing endogenous RNAs that modulate miRNA activity, further influencing IDD pathogenesis. circRNA, circular RNA; ECM, extracellular matrix; IDD, intervertebral disc degeneration; lncRNA, long non-coding RNA; miRNA, microRNA.

have demonstrated that miRNAs, through their specific targeting mechanisms, influence ECM synthesis, autophagy and inflammatory pathways (39,40). For example, a regulatory network involving multiple miRNAs has been identified as crucial in IDD progression (41).

During IDD pathogenesis, some miRNAs affect matrix metabolism and apoptosis. For instance, miR-141-5p promotes IDD progression by regulating circRNA_0000253 (42). Additionally, miR-141 has been shown to accelerate IDD by inhibiting the sirtuin (SIRT)1/NF-κB pathway (43).

In IDD-related inflammation regulation, studies have indicated that miRNAs influence the expression of inflammatory factors by modulating specific pathways (44,45). For example, miRNA-222 serves a role in IDD progression by regulating MMP1 expression (46). Furthermore, the interaction between miRNAs and autophagy is also considered a key factor in IDD progression (47).

Notably, the function of certain miRNAs may depend on different stages of IDD or specific microenvironments (38). This regulatory complexity suggests that miRNAs could serve as potential therapeutic targets for IDD (48). As illustrated in Fig. 3, miRNAs repress target messenger RNAs (mRNAs), thereby regulating key biological processes such as apoptosis, inflammation, and ECM metabolism. In addition, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) act as competing endogenous RNAs (ceRNAs) that modulate miRNA activity, further influencing IDD pathogenesis (49).

lncRNAs in IDD. lncRNAs, which are transcripts longer than 200 nucleotides without significant protein-coding potential, serve pivotal roles in IDD. By acting as competing endogenous RNAs (ceRNAs), interacting with proteins or regulating RNA modifications (such as m^6A), lncRNAs influence key processes such as NP cell proliferation, apoptosis, ECM catabolism and inflammatory responses (50,51). Current studies have identified a variety of lncRNAs that either promote or ameliorate IDD (52,53).

Several lncRNAs have been shown to aggravate IDD by promoting NP cell apoptosis, inflammation or ECM degradation. For instance, OIP5-AS1 is highly expressed in degenerative discs and exacerbates these pathological changes by sponging miR-25-3p (54). LINC01121 is also induced by IL-1 and TNF-α, and accelerates disc degeneration through the miR-150-5p/MMP16 axis, elevating inflammation-related enzymes such as MMP-3 and ADAM metallopeptidase with thrombospondin type 1 motif 5 (ADAMTS5) (55). Similarly, LINC00324 is upregulated in IDD and enhances Fas ligand expression, thereby exacerbating NP cell apoptosis (56). HOTAIR promotes pro-degenerative events by targeting miR-130b and inhibiting the PTEN/AKT pathway, leading to reduced CyclinD1 expression and impaired NP-cell proliferation (57). In addition, HCG18 augments apoptosis and inflammation via the miR-495-3p/follistatin like 1 axis (58), while FAF1 (referring to a lncRNA transcript in that region) is associated with advanced degeneration grades and activates

the Erk signaling pathway (59). Beyond ceRNA interactions, aberrant m^6A modification also contributes to IDD. WTAP-mediated hypermethylation of NORAD accelerates its degradation via YTH N^6-methyladenosine RNA binding protein F2, reducing the ability of NORAD to restrain PUMILIO and thereby promoting cellular senescence (51).

By contrast, some lncRNAs exhibit protective functions against IDD. KLF3-AS1 is downregulated in degenerative discs but can improve NP cell viability and suppress apoptosis and ECM breakdown by sequestering miR-10a-3p, thereby upregulating zinc finger and BTB domain containing 20 (60). RP11-81H3.2 also serves a protective role by binding miR-1539, relieving its inhibitory effect on COL2A1 and mitigating NP cell apoptosis (61). Additionally, LINC00689 counters disc degeneration by sponging miR-3127-5p and activating the autophagy-related gene ATG7, which promotes autophagy and diminishes apoptosis in NP cells (62).

circRNAs in IDD. ncRNAs, particularly circRNAs, have attracted attention in studies of IDD. With their high stability and resistance to degradation, circRNAs can bind to proteins or miRNAs in ways that influence NP-cell proliferation, apoptosis, ECM metabolism and inflammatory responses, thereby contributing to the development and progression of IDD (63,64).

Multiple studies have demonstrated that circRNAs frequently show aberrant expression in degenerative NP tissues and can aggravate IDD by regulating crucial pathways. For example, Chen *et al* (65) found that circGPATCH2L was highly expressed in degenerated NP tissues when in a hypomethylated (m^6A) state, enabling it to bind to and block the phosphorylation of tripartite motif containing 28, thereby inhibiting P53 degradation and promoting DNA damage and apoptosis. Du *et al* (66) reported that hsa_circ_0083756 was upregulated in degenerative NP tissues and cells and, by sponging miR-558, it upregulated triggering receptor expressed on myeloid cells 1 expression, ultimately suppressing NP cell proliferation and ECM formation. Meng and Xu (67) demonstrated that hsa_circ_0001658 exerted a protective effect in IDD by sponging miR-181c-5p and enhancing FAS expression, thereby inhibiting degeneration. Wang *et al* (68) identified circEYA3 as a key regulator of intervertebral disc degeneration. circEYA3 acts as a sponge for miR-196a-5p to upregulate EBF1 (early B-cell factor 1), thereby activating NF-κB signaling and promoting NP cell apoptosis and ECM degradation. Yan *et al* (69) reported that hsa_circ_0134111 was upregulated in IDD tissues and could bind to miR-578, thereby increasing the levels of ADAMTS5 and MMP-9 to promote ECM degradation and inflammation.

These findings collectively indicate that circRNAs serve pivotal regulatory roles in IDD. They often serve as miRNA 'sponges' or interact with specific proteins to disrupt the dynamic balance of ECM metabolism, cell proliferation and apoptosis, and inflammatory responses (70). At the same time, they offer novel avenues for potential clinical interventions. Strategies, such as inhibiting the upregulation of particular circRNAs or enhancing their physiological degradation, could represent promising approaches for slowing or preventing disc degeneration in the future.

5. Interaction between metabolic regulation and epigenetics in IDD

In the development and progression of IDD, cellular metabolic disorders often interact with epigenetic modifications, forming a complex regulatory network that jointly drives degeneration (6). Studies have shed light on the close relationship between the two in the following aspects (Fig. 4). Specifically, recent research indicates that reactive oxygen species (ROS), NAD^+, lactate, and α-ketoglutarate regulate histone and DNA modifications, thereby influencing cellular senescence, ECM homeostasis, and inflammation, ultimately driving the initiation and progression of IDD (6,71).

Oxidative stress and epigenetic modifications. Excessive reactive oxygen species (ROS) can activate p38/MAPK, ERK and other signaling pathways, thereby affecting the stability and transcriptional activity of histone methyltransferases (such as KMT2D) and other epigenetic factors (for example, DNMTs and HDACs). This leads to the upregulation of matrix-degrading genes (MMPs and ADAMTS) and exacerbates ECM degradation (19). Notably, oxidative stress is not only a product of metabolic imbalance but also amplifies degeneration via DNA and histone modifications (19).

Regulation of epigenetic enzyme activity by key metabolic substrates. NAD^+ is a cofactor for the SIRT family, directly influencing the catalytic efficiency of deacetylases such as SIRT1 and SIRT6. When NAD^+ levels decline, SIRT activity is diminished, weakening the resilience of intervertebral disc cells against external stress. Conversely, maintaining higher NAD^+ levels helps regulate autophagy and ECM homeostasis (72). Additionally, α-ketoglutarate (α-KG) can serve as a cofactor for TET demethylases, influencing DNA and histone demethylation (73). Recent findings suggest that α-KG inhibits excessive expression of inflammatory or fibrotic genes in disc cells and possibly slows degenerative processes by upregulating demethylase activity (74).

Novel modifications linked to metabolic products. Lysine lactylation (Kla), a histone modification dependent on the intracellular lactate concentration, is increasingly recognized (75). In the hypoxic environment of the disc, anaerobic glycolysis leads to lactate accumulation, and the resulting Kla modifications may regulate key biological processes such as cellular aging, ECM metabolic imbalance and inflammatory responses. Recent evidence from NP cells further confirms that Kla is dynamically regulated under hypoxic and high-lactate conditions, highlighting its critical role in intervertebral disc degeneration (76). Additionally, m^6A RNA modification intersects with various metabolic pathways (including ferroptosis and oxidative stress): ALKBH5 and FTO can alter the stability or translation of key gene mRNAs, thereby affecting the cellular stress response and degenerative progression (18).

Taken together, IDD is no longer viewed merely as a structural degradation resulting from mechanical loading and inflammation, but rather as a disease driven by the bidirectional regulatory network involving metabolic intermediates and pathways, including those associated with NAD^+ metabolism, α-ketoglutarate-dependent reactions, and

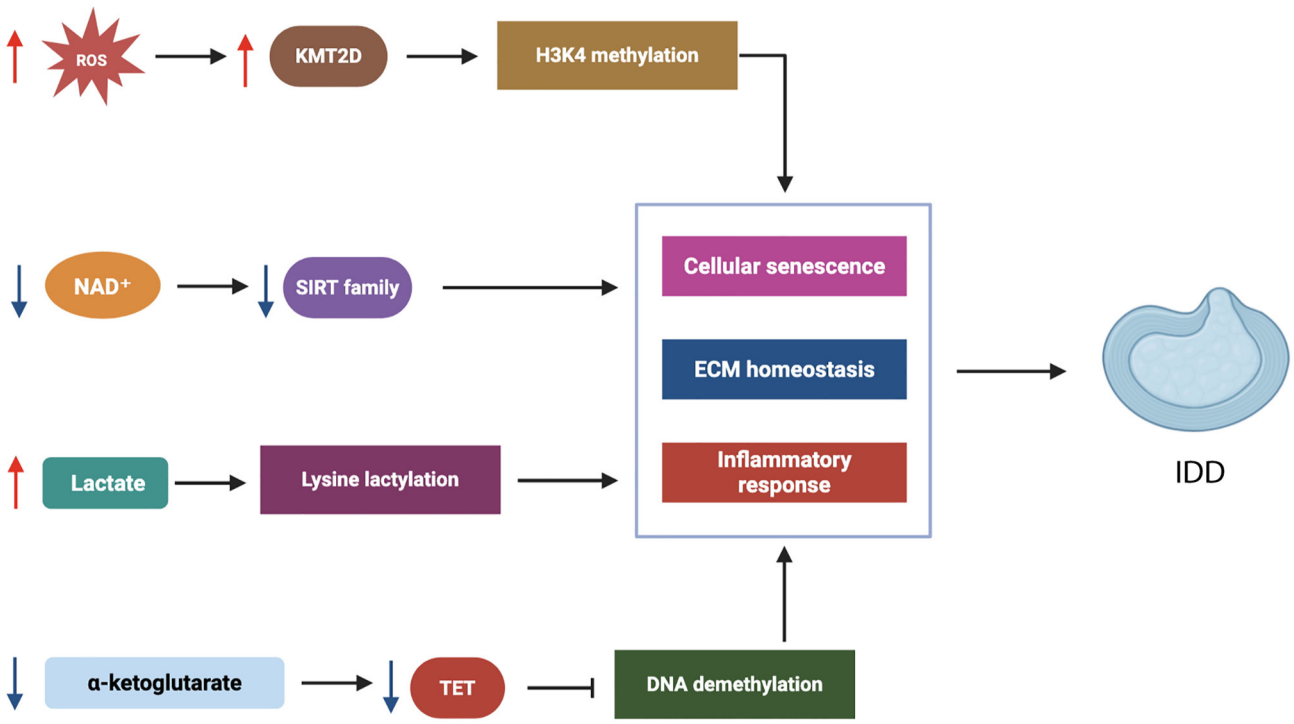

Figure 4. Interaction between metabolic regulation and epigenetics in IDD. ROS, NAD^+, lactate and α-ketoglutarate regulate histone and DNA modifications, thereby affecting cellular senescence, ECM homeostasis and inflammation. These metabolism-epigenetics interactions drive the initiation and progression of IDD. ECM, extracellular matrix; H3K4, histone H3 lysine 4; IDD, intervertebral disc degeneration; KMT2D, lysine methyltransferase 2D; ROS, reactive oxygen species; SIRT, sirtuin; TET, ten-eleven translocation.

lactate-mediated signaling, as well as epigenetic modifications (including DNA/histone methylation, m^6A, and Kla) (76). A deeper understanding of these 'metabolism-epigenetics' interactions will aid in identifying novel molecular targets and strategies for early intervention or even potential reversal of disc degeneration (77).

6. Potential clinical translational applications

Drug and epigenetic intervention strategies. Targeting epigenetic modifications offers novel therapeutic approaches for IDD. DNA methylation inhibitors, such as 5-AZA, have been shown to restore the expression of key genes involved in disc homeostasis by reversing hypermethylation-induced silencing (12). Similarly, histone modification regulators, such as EZH2 inhibitors, have demonstrated the ability to attenuate inflammation and ECM degradation, offering another promising avenue for treatment (6,27).

RNA modifications, particularly m^6A methylation, serve a crucial role in IDD progression by influencing mRNA stability and translation (78). The modulation of key m^6A enzymes, such as METTL3, FTO and ALKBH5, may provide an effective means to regulate NP cell apoptosis and ECM homeostasis (18). RNA-based therapies, including small interfering RNA and antisense oligonucleotides, could offer precise interventions to correct abnormal RNA modifications and restore gene function (79).

Combined biological therapies. Epigenetic regulation can be combined with biological therapies, such as stem cell transplantation and gene editing, to enhance IDD treatment outcomes. For instance, mesenchymal stem cell (MSC) transplantation has been explored as a regenerative therapy for IDD, but its efficacy is often limited by the harsh degenerative microenvironment (80,81). Preconditioning stem cells with epigenetic modulators, such as DNMT3A or EZH2 inhibitors, could improve their survival and therapeutic potential in IDD treatment (6,27).

Another promising approach involves integrating epigenetic regulation with nanotechnology-based drug delivery systems. Nanocarriers, such as liposomes and biodegradable polymers, could facilitate the targeted delivery of epigenetic drugs, reducing systemic side effects while enhancing local efficacy (82). Additionally, gene-editing technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), offer the potential to directly modify epigenetic regulatory genes, providing a long-term therapeutic solution for IDD (83).

Beyond these approaches, bioengineered nanomaterials have been applied to co-deliver MSCs and epigenetic modulators for disc regeneration. Novel nanofibrous spongy microspheres (NF-SMS) enhanced MSC seeding, proliferation and differentiation compared with conventional microcarriers. A hyperbranched polymer (HP) with strong miRNA-binding affinity was used to complex with anti-miR-199a, forming 'double shell' polyplexes with high transfection efficiency. Encapsulation of these polyplexes within biodegradable nanospheres (NS) enabled sustained release of anti-miR-199a. The composite system (MSC/HP-anti-miR-199a/NS/NF-SMS) promoted NP-like phenotypes, resisted calcification *in vitro* and *in vivo*, and, in a rabbit lumbar degeneration model, preserved disc

Table I. Candidate epigenetic interventions for IDD.

Drug/strategy	Primary target	Model system (*in vitro*/*in vivo*)	Outcomes	Reported adverse effects	Delivery options
5-AZA	DNMTs (DNA methylation)	NP cells; rat IDD models	Restores SLC40A1 expression, reduces ferroptosis, attenuates ECM degradation	Cytotoxicity at high doses	Intraperitoneal injection; potential local hydrogel-based delivery
EZH2 inhibitors (such as GSK126 and EPZ6438)	EZH2 (H3K27me3)	Human NP cells; cartilage endplate degeneration models	Increases SOX9 expression, improves ECM integrity, reduces inflammatory signaling	Off-target effects; altered immune responses	Systemic administration; nanoparticle delivery explored
HDAC inhibitors (such as trichostatin A and SAHA/ vorinostat)	Class I/II HDACs	Human NP cells; rat puncture IDD model	Suppresses apoptosis, restores ECM markers, reduces inflammation	Broad inhibition leads to risk of toxicity	Systemic injection; possible local delivery
SIRT1/SIRT6 activators (such as resveratrol and NAD^+ boosters)	SIRT1, SIRT6 (deacetylases)	Human NP cells; rabbit IDD models	Enhances autophagy, reduces oxidative stress, preserves disc structure	Generally low toxicity; bioavailability issues	Oral; intradiscal injection; NAD^+ precursor supplementation
siRNA/antisense oligonucleotides	miRNAs, lncRNAs, circRNAs (such as miR-143, LINC01121 and circ_0001658)	Human NP cells; mouse/rat IDD models	Suppresses apoptosis, inflammation or ECM catabolism depending on target	Off-target silencing; immune activation	Local hydrogel, liposome or viral vector delivery
CRISPR/dCas9-based epigenetic editing	Gene-specific methylation/ acetylation marks	Proof-of-concept in NP cells (pre-clinical)	Precise modulation of target gene expression (e.g., SOX9 and COL2A1)	Off-target genome editing; safety not established	Viral vectors; nanoparticle systems (under development)

5-AZA, 5-azacytidine; circRNA, circular RNA; COL2A1, type II collagen; dCas9, deactivated clustered regularly interspaced short palindromic repeats-associated protein 9; DNMT, DNA methyltransferase; ECM, extracellular matrix; EZH2, enhancer of zeste homolog 2; H3K27me3, trimethylation of histone H3 lysine 27; HDAC, histone deacetylase; IDD, intervertebral disc degeneration; lncRNA, long non-coding RNA; miRNA/miR, microRNA; NP, nucleus pulposus; siRNA, small interfering RNA; SIRT, sirtuin; SLC40A1, solute carrier family 40 member 1.

height, maintained ECM function and prevented IDD calcification (84).

Personalized and precision medicine. Advances in epigenomic profiling have paved the way for personalized IDD treatment strategies. By analyzing epigenetic signatures, such as DNA methylation patterns and histone modification profiles, clinicians can stratify patients based on their molecular characteristics and tailor treatment plans accordingly (13,27,85). For example, patients with elevated EZH2 expression and suppressed SOX9 levels may benefit from EZH2 inhibitors in combination with MSC therapy, whereas those with increased DNMT3b activity might respond better to DNA methylation inhibitors (18).

Dynamic monitoring of epigenetic modifications during treatment could enable real-time adjustments to therapeutic strategies. This 'precise-dynamic-reversible' approach refers to the concept of precisely targeting disease-related epigenetic modifications, dynamically monitoring their changes during treatment and reversibly modulating these marks in response to therapeutic needs. In the context of IDD, this strategy emphasizes individualized, adaptable interventions that can fine-tune gene expression and cellular responses in real time, potentially improving both safety and efficacy in clinical management (15,49).

To synthesize the aforementioned translational insights, Table I (6,81,86-88) summarizes the major candidate epigenetic interventions for IDD. Table I compiles current strategies, their targets, experimental systems, therapeutic outcomes, adverse effects and delivery options, providing a comprehensive overview of the preclinical landscape and guiding future clinical development.

Translational bottlenecks. Despite encouraging preclinical findings, several translational bottlenecks hinder the clinical application of epigenetic therapies for IDD. First, off-target effects remain a major concern. Epigenetic modulators such as DNA methylation inhibitors or HDAC inhibitors often act broadly rather than in a locus-specific manner, potentially leading to dysregulation of unrelated genes and adverse biological outcomes in non-disc tissues (89). Second, immune responses induced by RNA-based therapies or CRISPR/deactivated Cas9 epigenetic editors can activate innate immunity or exacerbate inflammation, which is particularly problematic in the already inflamed disc microenvironment (90,91). Third, long-term safety is insufficiently understood. While epigenetic modifications are theoretically reversible, persistent or cumulative alterations may increase the risk of tumorigenesis, ectopic tissue remodeling or interference with normal aging pathways (92). Finally, the lack of standardized outcome measures complicates translational progress. Preclinical studies employ heterogeneous endpoints, from disc height index and MRI signals to histological and molecular markers, making cross-study comparisons difficult and limiting their predictive value for clinical outcomes such as pain relief and functional improvement (93).

Overcoming these challenges will require the development of precision-targeted delivery systems, immune-evasive biomaterials, long-term safety monitoring protocols and consensus-driven standardized evaluation criteria to guide both preclinical and clinical research (94).

7. Conclusion

Epigenetic modifications serve a crucial role in maintaining intervertebral disc homeostasis, regulating NP cell fate and modulating local inflammatory responses. Targeting DNA methylation, histone modifications and RNA methylation at the molecular level has been demonstrated to have the potential to mitigate IDD progression, offering novel therapeutic strategies (6,95).

Further research is needed to fully understand the mechanisms underlying epigenetic regulation in IDD and to identify optimal intervention timing and dosages. Multidisciplinary collaboration will be essential to translate these findings into clinical applications, ensuring that epigenetic therapies are both effective and safe.

Epigenetic therapies should be integrated with existing treatments, including stem cell transplantation, gene editing, biomaterial scaffolds and physical therapy, to enhance overall treatment efficacy. With continuous advancements in high-throughput sequencing, gene editing and regenerative medicine, personalized epigenetic therapies hold great promise for the future of IDD treatment, potentially offering long-term relief for patients suffering from chronic low back pain.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YH and LL drafted the manuscript and prepared the figures and tables. YG conducted an in-depth literature review, contributed to the conception and design of the review structure, and participated substantially in manuscript revision, including critical evaluation of the scientific content, organization of updated references, and language refinement after peer-review. JS conceived and supervised the study, provided critical revisions for important intellectual content, and approved the final version of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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

1. Diwan AD and Melrose J: Intervertebral disc degeneration and how it leads to low back pain. JOR Spine 6: e1231, 2022.
2. Teraguchi M, Yoshimura N, Hashizume H, Yamada H, Oka H, Minamide A, Nagata K, Ishimoto Y, Kagotani R, Kawaguchi H, *et al*: Progression, incidence, and risk factors for intervertebral disc degeneration in a longitudinal population-based cohort: The Wakayama Spine Study. Osteoarthritis Cartilage 25: 1122-1131, 2017.
3. Hassett G, Hart DJ, Manek NJ, Doyle DV and Spector TD: Risk factors for progression of lumbar spine disc degeneration: The Chingford Study. Arthritis Rheum 48: 3112-3117, 2003.
4. Li G, Zhang W, Liang H and Yang C: Epigenetic regulation in intervertebral disc degeneration. Trends Mol Med 28: 803-805, 2022.
5. Clark J and Rager JE: Chapter 1-Epigenetics: An overview of CpG methylation, chromatin remodeling, and regulatory/noncoding RNAs. In: Fry RC (ed.), Environmental Epigenetics in Toxicology and Public Health, Academic Press, pp3-32, 2020.
6. Kang L, Zhang H, Jia C, Zhang R and Shen C: Epigenetic modifications of inflammation in intervertebral disc degeneration. Ageing Res Rev 87: 101902, 2023.
7. Razmara E, Bitaraf A, Yousefi H, Nguyen TH, Garshasbi M, Cho WC and Babashah S: Non-coding RNAs in cartilage development: An updated review. Int J Mol Sci 20: 4475, 2019.
8. Kiełbowski K, Herian M, Bakinowska E, Banach B, Sroczyński T and Pawlik A: The role of genetics and epigenetic regulation in the pathogenesis of osteoarthritis. Int J Mol Sci 24: 11655, 2023.
9. Ma Z, Liu X, Zhang X, Li S, An J and Luo Z: Research progress on long non-coding RNAs in non-infectious spinal diseases (Review). Mol Med Rep 30: 164, 2024.
10. Ikuno A, Akeda K, Takebayashi SI, Shimaoka M, Okumura K and Sudo A: Genome-wide analysis of DNA methylation profile identifies differentially methylated loci associated with human intervertebral disc degeneration. PLoS One 14: e0222188, 2019.
11. Hong JY, Kim H, Jeon WJ, Lee J, Yeo C, Lee YJ and Ha IH: Epigenetic changes within the annulus fibrosus by DNA methylation in rat intervertebral disc degeneration model. Cells 11: 3547, 2022.
12. Chen J, Yang X, Li Q, Ma J, Li H, Wang L, Chen Z and Quan Z: Inhibiting DNA methyltransferase DNMT3B confers protection against ferroptosis in nucleus pulposus and ameliorates intervertebral disc degeneration via upregulating SLC40A1. Free Radic Biol Med 220: 139-153, 2024.
13. Tajerian M, Alvarado S, Millecamps M, Dashwood T, Anderson KM, Haglund L, Ouellet J, Szyf M and Stone LS: DNA methylation of SPARC and chronic low back pain. Mol Pain 7: 65, 2011.
14. Reynard LN, Bui C, Syddall CM and Loughlin J: CpG methylation regulates allelic expression of GDF5 by modulating binding of SP1 and SP3 repressor proteins to the osteoarthritis susceptibility SNP rs143383. Hum Genet 133: 1059-1073, 2014.
15. Esteras N, Blacker TS, Zherebtsov EA, Stelmashuk OA, Zhang Y, Wigley WC, Duchen MR, Dinkova-Kostova AT and Abramov AY: Nrf2 regulates glucose uptake and metabolism in neurons and astrocytes. Redox Biol 62: 102672, 2023.
16. Zhao K, Zhang Y, Kang L, Song Y, Wang K, Li S, Wu X, Hua W, Shao Z, Yang S and Yang C: Epigenetic silencing of miRNA-143 regulates apoptosis by targeting BCL2 in human intervertebral disc degeneration. Gene 628: 259-266, 2017.
17. Zhao K, Zhang Y, Kang L, Song Y, Wang K, Li S, Wu X, Hua W, Shao Z, Yang S and Yang C: Methylation of microRNA-129-5P modulates nucleus pulposus cell autophagy by targeting Beclin-1 in intervertebral disc degeneration. Oncotarget 8: 86264-86276, 2017.
18. Li G, Luo R, Zhang W, He S, Wang B, Liang H, Song Y, Ke W, Shi Y, Feng X, *et al*: m6A hypomethylation of DNMT3B regulated by ALKBH5 promotes intervertebral disc degeneration via E4F1 deficiency. Clin Transl Med 12: e765, 2022.
19. Xu W, Zhang X, Liu G, Zhu M, Wu Y, Jie Z, Xie Z, Wang S, Ma Q, Fan S and Fang X: Oxidative stress abrogates the degradation of KMT2D to promote degeneration in nucleus pulposus. Biochim Biophys Acta Mol Basis Dis 1866: 165888, 2020.
20. Zheng J, Ma Z, Liu P, Wei J, Min S, Shan Y, Zhang J, Li Y, Xue L, Tan Z and Wang D: EZH2 inhibits senescence-associated inflammation and attenuates intervertebral disc degeneration by regulating the cGAS/STING pathway via H3K27me3. Osteoarthritis Cartilage 33: 548-559, 2025.
21. Yao Q, Lei Y, Zhang Y, Chen H, Dong X, Ye Z and Liang H: EZH2-H3K27me3-mediated epigenetic silencing of DKK1 induces nucleus pulposus cell pyroptosis in intervertebral disc degeneration by activating NLRP3 and NAIP/NLRC4. Inflammation 48: 902-918, 2025.
22. Lei M, Lin H, Shi D, Hong P, Song H, Herman B, Liao Z and Yang C: Molecular mechanism and therapeutic potential of HDAC9 in intervertebral disc degeneration. Cell Mol Biol Lett 28: 104, 2023.
23. Kouzarides T: Chromatin modifications and their function. Cell 128: 693-705, 2007.
24. Xiao L, Gong D, Liang L, Liang A, Liang H, Xu X and Teng H: Inhibition of HDAC4 by GSK3β leads to downregulation of KLF5 and ASK1 and prevents the progression of intravertebral disc degeneration. Clin Epigenetics 13: 53, 2021.
25. Bennett RL: The epigenetic underpinnings of lower back pain. Clin Transl Med 12: e868, 2022.
26. Zhu D, Liang H, Tong B, Du Z, Li G, Zhang W, Wu D, Zhou X, Lei J, Zhang X, *et al*: DDX1 methylation mediated MATR3 splicing regulates intervertebral disc degeneration by initiating chromatin reprogramming. Nat Commun 16: 6153, 2025.
27. Jiang C, Guo Q, Jin Y, Xu JJ, Sun ZM, Zhu DC, Lin JH, Tian NF, Sun LJ, Zhang XL and Wu YS: Inhibition of EZH2 ameliorates cartilage endplate degeneration and attenuates the progression of intervertebral disc degeneration via demethylation of Sox-9. EBioMedicine 48: 619-629, 2019.
28. Zhou M, He SJ, Liu W, Yang MJ, Hou ZY, Meng Q and Qian ZL: EZH2 upregulates the expression of MAPK1 to promote intervertebral disc degeneration via suppression of miR-129-5p. J Gene Med 24: e3395, 2022.
29. Liang H, Luo R, Li G, Zhang W, Zhu D, Wu D, Zhou X, Tong B, Wang B, Feng X, *et al*: Lysine methylation of PPP1CA by the methyltransferase SUV39H2 disrupts TFEB-dependent autophagy and promotes intervertebral disc degeneration. Cell Death Differ 30: 2135-2150, 2023.
30. Wu O, Jin Y, Zhang Z, Zhou H, Xu W, Chen L, Jones M, Kwan KYH, Gao J, Zhang K, *et al*: KMT2A regulates the autophagy-GATA4 axis through METTL3-mediated m^6A modification of ATG4a to promote NPCs senescence and IVDD progression. Bone Res 12: 67, 2024.
31. Kooistra SM and Helin K: Molecular mechanisms and potential functions of histone demethylases. Nat Rev Mol Cell Biol 13: 297-311, 2012.
32. Diaz-Hernandez ME, Murakami K, Murata S, Khan NM, Shenoy SPV, Henke K, Yamada H and Drissi H: Inhibition of KDM2/7 promotes notochordal differentiation of hiPSCs. Cells 13: 1482, 2024.
33. Zhang Y, Wang Y, Zhou X, Wang J, Shi M, Wang J, Li F and Chen Q: Osmolarity controls the differentiation of adipose-derived stem cells into nucleus pulposus cells via histone demethylase KDM4B. Mol Cell Biochem 472: 157-171, 2020.
34. Zhou X, Li J, Teng J, Liu Y, Zhang D, Liu L and Zhang W: microRNA-155-3p attenuates intervertebral disc degeneration via inhibition of KDM3A and HIF1α. Inflamm Res 70: 297-308, 2021.
35. Li Z, Li X, Chen C, Li S, Shen J, Tse G, Chan MTV and Wu WKK: Long non-coding RNAs in nucleus pulposus cell function and intervertebral disc degeneration. Cell Prolif 51: e12483, 2018.
36. Lytle JR, Yario TA and Steitz JA: Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. Proc Natl Acad Sci USA 104: 9667-9672, 2007.
37. Haas U, Sczakiel G and Laufer SD: MicroRNA-mediated regulation of gene expression is affected by disease-associated SNPs within the 3'-UTR via altered RNA structure. RNA Biol 9: 924-937, 2012.
38. Wang C, Cui L, Gu Q, Guo S, Zhu B, Liu X, Li Y, Liu X, Wang D and Li S: The mechanism and function of miRNA in intervertebral disc degeneration. Orthop Surg 14: 463-471, 2022.
39. Yu Z, Fan C, Mao Y, Wu X and Mao H: Autophagy activation alleviates annulus fibrosus degeneration via the miR-2355-5p/mTOR pathway. J Orthop Surg Res 20: 86, 2025.
40. Chen D, Jiang X and Zou H: hASCs-derived exosomal miR-155-5p targeting TGFβR2 promotes autophagy and reduces pyroptosis to alleviate intervertebral disc degeneration. J Orthop Translat 39: 163-176, 2023.
41. Hu P, Feng B, Wang G, Ning B and Jia T: Microarray based analysis of gene regulation by microRNA in intervertebral disc degeneration. Mol Med Rep 12: 4925-4930, 2015.

42. 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.
43. Ji ML, Jiang H, Zhang XJ, Shi PL, Li C, Wu H, Wu XT, Wang YT, Wang C and Lu J: Preclinical development of a microRNA-based therapy for intervertebral disc degeneration. Nat Commun 9: 5051, 2018.
44. Lin H, Zhang W, Zhou T, Li W, Chen Z, Ji C, Zhang C and He F: Mechanism of microRNA-21 regulating IL-6 inflammatory response and cell autophagy in intervertebral disc degeneration. Exp Ther Med 14: 1441-1444, 2017.
45. Gu SX, Li X, Hamilton JL, Chee A, Kc R, Chen D, An HS, Kim JS, Oh CD, Ma YZ, *et al*: MicroRNA-146a reduces IL-1 dependent inflammatory responses in the intervertebral disc. Gene 555: 80-87, 2015.
46. Ge C and Li C: Expression and regulatory role of miRNA-222 in intervertebral disc degeneration (IDD). Biotechnol Biotechnol Equip 33: 1553-1559, 2019.
47. Lan T, Shiyu-Hu, Shen Z, Yan B and Chen J: New insights into the interplay between miRNAs and autophagy in the aging of intervertebral discs. Ageing Res Rev 65: 101227, 2021.
48. Li Z, Sun Y, He M and Liu J: Differentially-expressed mRNAs, microRNAs and long noncoding RNAs in intervertebral disc degeneration identified by RNA-sequencing. Bioengineered 12: 1026-1039, 2021.
49. Cazzanelli P and Wuertz-Kozak K: MicroRNAs in intervertebral disc degeneration, apoptosis, inflammation, and mechanobiology. Int J Mol Sci 21: 3601, 2020.
50. 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.
51. Li G, Ma L, He S, Luo R, Wang B, Zhang W, Song Y, Liao Z, Ke W, Xiang Q, *et al*: WTAP-mediated m^6A modification of lncRNA NORAD promotes intervertebral disc degeneration. Nat Commun 13: 1469, 2022.
52. Chen HW, Zhou JW, Zhang GZ, Luo ZB, Li L and Kang XW: Emerging role and therapeutic implication of mTOR signalling in intervertebral disc degeneration. Cell Prolif 56: e13338, 2023.
53. Sun Z, Tang X, Wang H, Sun H, Chu P, Sun L and Tian J: LncRNA H19 aggravates intervertebral disc degeneration by promoting the autophagy and apoptosis of nucleus pulposus cells through the miR-139/CXCR4/NF-κB axis. Stem Cells Dev 30: 736-748, 2021.
54. Che Z, Xueqin J and Zhang Z: LncRNA OIP5-AS1 accelerates intervertebral disc degeneration by targeting miR-25-3p. Bioengineered 12: 11201-11212, 2021.
55. Chen X, Li Z, Xu D and Li S: LINC01121 induced intervertebral disc degeneration via modulating miR-150-5p/MMP16 axis. J Gene Med 22: e3231, 2020.
56. Chen Y, Wu Y, Chen R, Xu C and Chen Q: LncRNA LINC00324 is upregulated in intervertebral disk degeneration and upregulates FasL in nucleus pulposus cells. Mol Cell Biochem 476: 1995-2000, 2021.
57. Chen WK, Zhang HJ, Zou MX, Wang C, Yan YG, Zhan XL, Li XL and Wang WJ: LncRNA HOTAIR influences cell proliferation via miR-130b/PTEN/AKT axis in IDD. Cell Cycle 21: 323-339, 2022.
58. Luo Y, He Y, Wang Y, Xu Y and Yang L: LncRNA HCG18 promotes inflammation and apoptosis in intervertebral disc degeneration via the miR-495-3p/FSTL1 axis. Mol Cell Biochem 479: 171-181, 2024.
59. Mi D, Cai C, Zhou B, Liu X, Ma P, Shen S, Lu W and Huang W: Long non-coding RNA FAF1 promotes intervertebral disc degeneration by targeting the Erk signaling pathway. Mol Med Rep 17: 3158-3163, 2018.
60. Chen S, Zhuang Q, Li P, Zeng J, Peng Y, Ding Z, Cao H, Zheng R and Wang W: The long non-coding RNA KLF3-AS1/miR-10a-3p/ZBTB20 axis improves the degenerative changes in human nucleus pulposus cells. Cell Tissue Res 393: 97-109, 2023.
61. Qiao L, Peng SY, Zhou YP, Yin J, Xu JP, Chen B, Zhang H, Zhu C and Yu XD: Long non-coding RNA RP11-81H3.2 suppresses apoptosis by targeting microRNA-1539/COL2A1 in human nucleus pulposus cells. Exp Ther Med 22: 884, 2021.
62. Wang C, Chen R, Zhu X and Zhang X: Long non-coding RNAs LINC00689 inhibits the apoptosis of human nucleus pulposus cells via miR-3127-5p/ATG7 axis-mediated autophagy. Open Med (Wars) 17: 1821-1832, 2022.
63. Li Y, Zhou S, Hu X and Lu S: The pathological mechanisms of circRNAs in mediating intervertebral disc degeneration. Noncoding RNA Res 8: 633-640, 2023.
64. 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.
65. 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.
66. 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.
67. Meng GD and Xu BS: Circular RNA hsa_circ_0001658 inhibits intervertebral disc degeneration development by regulating hsa-miR-181c-5p/FAS. Comput Math Methods Med 2021: 7853335, 2021.
68. 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-κB signaling. Commun Biol 7: 390, 2024.
69. 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.
70. Cheng X, Zhang L, Zhang K, Zhang G, Hu Y, Sun X, Zhao C, Li H, Li YM and Zhao J: Circular RNA VMA21 protects against intervertebral disc degeneration through targeting miR-200c and X linked inhibitor-of-apoptosis protein. Ann Rheum Dis 77: 770-779, 2018.
71. Zhu D, Liang H, Du Z, Liu Q, Li G, Zhang W, Wu D, Zhou X, Song Y and Yang C: Altered metabolism and inflammation driven by post-translational modifications in intervertebral disc degeneration. Research (Wash D C) 7: 0350, 2024.
72. Shi C, Wu H, Du D, Im HJ, Zhang Y, Hu B, Chen H, Wang X, Liu Y, Cao P, *et al*: Nicotinamide phosphoribosyltransferase inhibitor APO866 prevents IL-1β-induced human nucleus pulposus cell degeneration via autophagy. Cell Physiol Biochem 49: 2463-2482, 2018.
73. Sandalova E, Goh J, Lim ZX, Lim ZM, Barardo D, Dorajoo R, Kennedy BK and Maier AB: Alpha-ketoglutarate supplementation and BiologicaL agE in middle-aged adults (ABLE)-intervention study protocol. Geroscience 45: 2897-2907, 2023.
74. Xu HW, Fang XY, Liu XW, Zhang SB, Yi YY, Chang SJ, Chen H and Wang SJ: α-Ketoglutaric acid ameliorates intervertebral disk degeneration by blocking the IL-6/JAK2/STAT3 pathway. Am J Physiol Cell Physiol 325: C1119-C1130, 2023.
75. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, *et al*: Metabolic regulation of gene expression by histone lactylation. Nature 574: 575-580, 2019.
76. Sheng L, Xu H, Wang Y, Ni J, Xiang T, Xu H, Zhou X, Wei K and Dai J: Systematic analysis of lysine lactylation in nucleus pulposus cells. iScience 27: 111157, 2024.
77. Xu WN, Yang RZ, Zheng HL, Yu W, Zheng XF, Li B, Jiang SD and Jiang LS: PGC-1α acts as an mediator of Sirtuin2 to protect annulus fibrosus from apoptosis induced by oxidative stress through restraining mitophagy. Int J Biol Macromol 136: 1007-1017, 2019.
78. Lei Y, Zhan E, Chen C, Hu Y, Lv Z, He Q, Wang X, Li X and Zhang F: ALKBH5-mediated m^6A demethylation of Runx2 mRNA promotes extracellular matrix degradation and intervertebral disc degeneration. Cell Biosci 14: 79, 2024.
79. Hofman CR and Corey DR: Targeting RNA with synthetic oligonucleotides: Clinical success invites new challenges. Cell Chem Biol 31: 125-138, 2024.
80. Zhang W, Wang D, Li H, Xu G, Zhang H, Xu C and Li J: Mesenchymal stem cells can improve discogenic pain in patients with intervertebral disc degeneration: A systematic review and meta-analysis. Front Bioeng Biotechnol 11: 1155357, 2023.
81. Zhao Y, He J, Qiu T, Zhang H, Liao L and Su X: Epigenetic therapy targeting bone marrow mesenchymal stem cells for age-related bone diseases. Stem Cell Res Ther 13: 201, 2022.
82. Li T, Chen Y and Li S: The advances in the development of epigenetic modifications therapeutic drugs delivery systems. Int J Nanomedicine 19: 10623-10637, 2024.
83. Fadul SM, Arshad A and Mehmood R: CRISPR-based epigenome editing: Mechanisms and Applications. Epigenomics 15: 1137-1155, 2023.
84. Feng G, Zhang Z, Dang M, Rambhia KJ and Ma PX: Nanofibrous spongy microspheres to deliver rabbit mesenchymal stem cells and anti-miR-199a to regenerate nucleus pulposus and prevent calcification. Biomaterials 256: 120213, 2020.

85. Cheng P, Wei HZ, Chen HW, Wang ZQ, Mao P and Zhang HH: DNMT3a-mediated methylation of PPARγ promote intervertebral disc degeneration by regulating the NF-κB pathway. J Cell Mol Med 28: e18048, 2024.
86. Yan X, Wang X, Che Y, Feng P and Zhang T: Immunological mechanisms and immunoregulatory strategies in intervertebral disc degeneration. arXiv: 2506.09336, 2025.
87. Milheiro C, Moura ML, Amendola M, Barbosa MA and Caldeira J: Harnessing CRISPR potential for intervertebral disc regeneration strategies. Front Bioeng Biotechnol 13: 1562412, 2025.
88. Zhang Y, Wang J, Hua D, Fan C, He W, Deng Y, Tang M, Geng D, Wu X and Mao H: Histone modifications: Unveiling the epigenetic enigma of degenerative skeletal diseases. J Orthop Translat 55: 245-266, 2025.
89. 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.
90. Keshavarz S, Alavi CE, Aghayan H, Jafari-Shakib R and Vojoudi E: Advancements in degenerative disc disease treatment: a regenerative medicine approach. Stem Cell Rev Rep 21: 1252-1282, 2025.
91. Ma W, Wang W, Zhao L, Fan J, Liu L, Huang L, Peng B, Wang J, Xu B, Liu H, *et al*: Reprogramming to restore youthful epigenetics of senescent nucleus pulposus cells for mitigating intervertebral disc degeneration and alleviating low back pain. Bone Res 13: 35, 2025.
92. Li X, Chang H, Cai F, Zhang Y, Li A, Yang X, Cai Z, Cui W and Liu X: Progress of gene-functionalized regenerative material repair intervertebral disc degeneration. Small Sci 4: 2300355, 2024.
93. Samanta A, Lufkin T and Kraus P: Intervertebral disc degeneration-current therapeutic options and challenges. Front Public Health 11: 1156749, 2023.
94. Ma L, Pan J, Zhang J and Liu F: Innovative strategies in combating intervertebral disc degeneration: pathological mechanisms and biomaterial advancements. Front Bioeng Biotechnol 13: 1643222, 2025.
95. Zhu B, Chen HX, Li S, Tan JH, Xie Y, Zou MX, Wang C, Xue JB, Li XL, Cao Y and Yan YG: Comprehensive analysis of N6-methyladenosine (m^6A) modification during the degeneration of lumbar intervertebral disc in mice. J Orthop Translat 31: 126-138, 2021.