Ageing Research Reviews 87 (2023) 101902

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Epigenetic modifications of inflammation in intervertebral disc degeneration

Liang Kang [1], Huaqing Zhang [1], Chongyu Jia [1], Renjie Zhang [*], Cailiang Shen [*]

Department of Orthopedics & Spine Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

ARTICLE INFO

Keywords:
Modifications
Inflammation
Intervertebral disc degeneration
DNA methylation
Histone modification
Non-coding RNA regulation

ABSTRACT

Intervertebral disc degeneration (IDD) is a common cause of joint-related chronic disability in elderly individuals worldwide. It seriously impacts the quality of life and inflicts a substantial social and economic burden. The pathological mechanisms underlying IDD have not been fully revealed, leading to less satisfactory clinical treatment outcomes. More studies are urgently needed to reveal its precise pathological mechanisms. Numerous studies have revealed that inflammation is closely related to various pathological processes of IDD, including the continuous loss of extracellular matrix, cell apoptosis, and senescence, indicating the important role of inflammation in the pathological mechanism of IDD. Epigenetic modifications affect the functions and characteristics of genes mainly through DNA methylation, histone modification, non-coding RNA regulation, and other mechanisms, thus having a major effect on the survival state of the body. Recently, the role of epigenetic modifications in inflammation during IDD has been attracting research interest. In this review, we summarize the roles of different types of epigenetic modifications in inflammation during IDD in recent years, to improve our understanding of the etiology of IDD and to transform basic research strategy into a clinically effective treatment for joint-related chronic disability in elderly individuals.

1. Introduction

Joints are anatomical structures that are critical for the flexibility, mobility, and stability of the body. As a result, patients with joint diseases often experience pain in joints and impairment in daily activities (Rustenburg et al., 2018; Tonomura et al., 2020). With the aging of modern society and the continued impact of the accelerated pace of life and daily work stress, the number of patients with degenerative joint diseases is increasing. Intervertebral disc (IVD) degeneration (IDD) is a common underlying cause of joint-related chronic disability in elderly individuals (Madhu et al., 2021). It is the main cause of lower back pain and the common pathological basis for a variety of spinal disorders including lumbar disc herniation and lumbar spinal stenosis. The IVD, composed of nucleus pulposus (NP), annulus fibrosus (AF) and cartilage endplate (CEP), plays an important role in spinal movement and load bearing. The NP located in the center of the IVD contains abundant water and extracellular matrix (ECM),which is essential for the maintenance of IVD function. The AF located at the periphery prevents excessive lateral expansion of the IVD. The CEP located above and below provides a barrier for nutrient penetration of the IVD (Chen et al., 2019). The lack of nutrition to the IVD results in its limited ability to repair itself when damaged. IDD is mainly characterized by decreased disc height, reduced hydration, and a weakened ability to absorb pressure loads. An important pathological feature of IDD is the disruption of the dynamic balance between ECM catabolism and anabolism, with a preference for catabolism. This metabolic imbalance in the ECM is mainly caused by the homeostasis disorder of NP cells in IVD (Li et al., 2021b; Zheng et al., 2021). CEP degeneration hinders nutrient delivery and affects mechanical conduction, which leads to IDD development (Jiang et al., 2019). The damage caused by IDD is a major challenge for patients and healthcare providers, increasing the burden on global health care. Furthermore, the clinical outcomes of IDD have been unsatisfactory.

The current clinical approach for the early treatment of IDD focuses on changes in lifestyle and the use of nonsteroidal anti-inflammatory drugs along with physical therapy, however, these interventions are unable to prevent disease progression. Surgical treatment, specifically spinal fusion, is the preferred treatment option for advanced cases of

* Corresponding authors.
E-mail addresses: zhangrenjie1089@126.com (R. Zhang), shencailiang@ahmu.edu.cn (C. Shen).
[1] These authors have contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.arr.2023.101902
Received 11 October 2022; Received in revised form 17 February 2023; Accepted 2 March 2023
Available online 4 March 2023

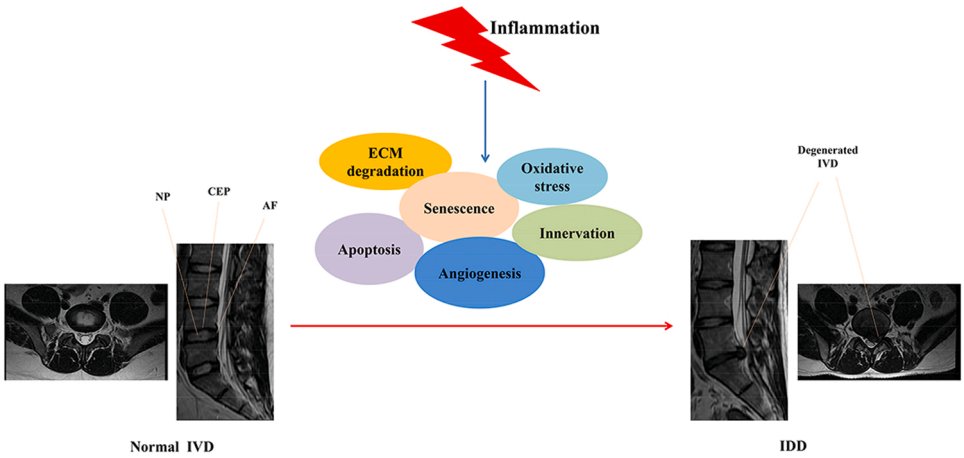

Fig. 1. Inflammation is involved in multiple pathological processes of IDD. Inflammation plays an important role in the occurrence and development of IDD by regulating the continuous loss of extracellular matrix, apoptosis, senescence, oxidative stress, angiogenesis and nerve ingrowth.

IDD. It has been proven to improve pain symptoms in patients in numerous clinical studies; however, its high invasiveness and cost cannot be ignored (Lu et al., 2021; Ma et al., 2019; Zhou et al., 2020). The main reason for these suboptimal outcomes is the fact that the pathogenesis of IDD is not well understood. Although the etiology of IDD is complex, many studies have confirmed the importance of inflammation in disease progression. For example, inflammatory factors promote ECM degradation, senescence and apoptosis, and ultimately lead to the development of IDD (Early et al., 2021; Kang et al., 2017; Zhang et al., 2021a, 2021b). Therefore, identifying the specific mechanisms that trigger and maintain the inflammatory response during IDD would greatly contribute to the clarification of the disease pathology and allow the development of new therapeutic strategies to facilitate more targeted and less invasive treatments. Herein, we focus our discussion on the reasons for the continuous activation of inflammation in the pathogenesis of IDD.

2. Role of inflammation in the course of IDD

Inflammation is closely related to IDD progression (Krupkova et al., 2018; Li et al., 2021a; Silva et al., 2019; Wang et al., 2020b). Several pro-inflammatory cytokines such as TNF-α, IL-1β,IL-17, IL-1α,and IL-8 are significantly increased in the degenerative intervertebral disc. These cytokines have been revealed to play an important role in several key pathophysiological processes in IDD (Johnson et al., 2015; Wang et al., 2020b). The expression levels of inflammatory factors, which form a gradually amplified inflammatory cascade and a continuous inflammatory state, involve a mutual induction process. For example, IL-1β stimulation substantially enhances the expression of IL-6, IL-8, and IL-17 in human IVD cells (Jia et al., 2020; Jimbo et al., 2005). In in vivo experiments, after the IVD was injected with inflammatory factors, degenerative changes including rupture of the AF and degradation of NP ECM were observed (Kang et al., 2015). The anabolism and catabolism of ECM in NP tissues are in balance under the regulation of various cytokines, which is the key factor for the maintenance of healthy IVD. In the microenvironment of degenerative IVD, the expression and activity of catabolic components of ECM are greater than that of synthetic components. Matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS) are the main enzymes that cleave ECM components. Some ECM-degrading enzymes, such as MMP-1/3/7/9 and ADAMTS-1/4/5/9 are significantly increased in degenerative IVD (Le Maitre et al., 2007). Pro-inflammatory cytokines have been shown to promote ECM degradation and the subsequent IVD structural destruction by promoting the expression of ECM-degrading enzymes (Le Maitre et al., 2007; Vo et al., 2013). Excessive IVD cell apoptosis and senescence are important pathological features of IDD. This pathological change leads to a gradual reduction in the number of active cells in the IVD, which eventually leads to the destruction of the structure and loss of function of the IVD (Cazzanelli and Wuertz-Kozak, 2020; Lin et al., 2021). In addition, senescent cells may further destroy the microenvironment of the IVD by secreting ECM-degrading enzymes and inflammatory factors and aggravate the development of IDD (Zhang et al., 2020b). Studies have confirmed that inflammatory factors can promote apoptosis and senescence of IVD cells. Oxidative stress plays an important role in several diseases. In degenerated IVD cells, the imbalance between the increase of reactive oxygen species and the lack of antioxidant capacity leads to oxidative stress, which leads to the damage of various molecules including DNA and protein. Pro-inflammatory factors can induce oxidative damage to IVD cells (Wang et al., 2020b). Healthy IVD is characterized by limited blood vessels in the outer surface of AF. In IDD, vascular invasion has been widely observed, and is believed to play an important role in the development of IDD by activating immune cells and inflammatory cytokines, promoting neuralization, and thus destroying the stability of the IVD. Pro-inflammatory factors can also promote the vascularization of degenerative intervertebral discs, thereby exacerbating degeneration (Kwon et al., 2017). In addition, nerve ingrowth of degenerative intervertebral discs and the low back pain that ensues have also been shown to be related to an inflammatory response (Ohtori et al., 2012a; Ohtori et al., 2012b). In conclusion, inflammation is an important driver of IDD (Fig. 1). However, the factors triggering inflammation in IDD have not been fully elucidated.

3. Effects of epigenetic modifications on inflammation in IDD

Epigenetics refers to reversible and heritable changes in gene function, with no changes in the cellular nuclear DNA. Several types of epigenetic modification are widely studied, including DNA methylation, histone modification, and non-coding RNA regulation (Li et al., 2020a; Lio et al., 2019; Topper et al., 2020; Vaiserman and Lushchak, 2019). Numerous studies have revealed that these changes play an important role in not only the normal physiological processes of cells but also the pathological processes of various diseases (Chang et al., 2022; Sun et al., 2022; Yang et al., 2022; Zhao et al., 2022). In the above section, we describe the role of inflammation in the progression of IDD. Elucidation of the specific mechanisms that trigger and maintain inflammation during IDD would help identify new targets for the treatment of IDD. Epigenetic modifications play a crucial role in controlling inflammation in the pathophysiology of several diseases. Some epigenetic modifications are disease-specific; however, others influence the inflammatory

response during disease progression through complex interactions between multiple epigenetics (Celarain and Tomas-Roig, 2020; Chen et al., 2022c; Evans et al., 2020; Liu et al., 2022; Rasheed et al., 2021; Tan et al., 2022; Zong et al., 2019). During the progression of IDD, some epigenetic modifications exhibit disease-specific changes. Determining the specific mechanisms of epigenetics in a disease can help unravel the pathology of the disease and contribute to therapeutic improvement.

3.1. DNA methylation

DNA methylation is a widely studied mechanism of epigenetic modification in mammals. In the presence of DNA methyltransferases (DNMTs), the methyl group is embedded in the fifth carbon atom of cytosine to form 5-methylcytosine. Methylation of CpG islands regulates gene expression in a variety of ways. For example, DNA methylation can affect the configuration of the promoter in the gene, and then interfere with the binding of transcription factors to promoter regions with hypermethylation; The methylated sequences in the promoter can bind to specific proteins and then competitively inhibit the binding of transcription factors to the promoter; DNA methylation can suppress gene expression via modification of the chromatin structure. Therefore, hypermethylation of gene promoter regions is often associated with gene expression silencing, whereas hypomethylation of genes is associated with increased gene transcriptional activity (Vandenhoeck et al., 2021; Ye et al., 2021; Yu et al., 2022). DNMTs are classified as DNMT1, DNMT3a, and DNMT3b. DNMT1 is the most important methyltransferase in cells and is mainly involved in the maintenance of the methylation state. DNMT3a and DNMT3b are the main enzymes involved in de novo methylation (Arumugam et al., 2021).

In the field of disc degeneration research, Ikunoet al. (Ikuno et al., 2019) mapped genome-wide DNA methylation profiles in NP tissue in the early and late stages of degeneration progression. They identified 220 differentially methylated loci between tissue samples from early and late degeneration stages, with four hypomethylated loci and 216 hypermethylated loci in the late stage. They concluded that there were significant differences in the DNA methylation profiles between the early and late stages of human disc degeneration, suggesting that DNA methylation may be involved in IDD development. In addition, Zhao et al. (Zhao et al., 2017) found that the upregulated expression of miRNA-143 in degenerated disc specimens is associated with the hypomethylation of CpG islands in its promoter region. High expression of miRNA-143 promotes the apoptosis of NP cells by reducing expression of anti-apoptotic factors, suggesting that DNA methylation is involved in regulating the pathological processes in IDD.

In terms of the inflammatory response during IDD, Ikuno et al. (Ikuno et al., 2019) found that the methylation levels of several genes related to inflammatory response changed during the progression of IDD. Nuclear factor-κB (NF-κB) pathway activation has been confirmed to be related to the expression level of many inflammatory factors in IDD development, such as TNF-α, IL-1β, IL-6, and IL-8 (Tak and Firestein, 2001). CARD14, EFHD2, and RTKN2 are involved in the regulation of the NF-κB signaling pathway, and their methylation levels are significantly different in the early and late stages of IDD (Myouzen et al., 2012; Zotti et al., 2018). In addition, the gene methylation levels of *MAPKAPK5 and PRKCZ*, which are related to the MAPK signaling pathway, also changed significantly in IDD development (Monick et al., 2000; Ni et al., 1998; Westhovens et al., 2013). In addition, Luo et al. (Luo et al., 2021)found a significant reduction in the mRNA and protein expression of DNMT3b in degenerated disc tissue, and functional experiments showed that DNMT3b promotes NP cell proliferation and inhibits the expression of inflammatory cytokines TNF-α, IL-6, and IL-8, as well as the ECM-degrading enzymes MMP-3 and MMP-9. It has been proved that inhibiting inflammatory factors can inhibit the catabolism of ECM and thus inhibit the progression of IDD. This finding supports the inhibitory effect of DNMT3b on the development of IDD. Luo et al. also continued their mechanistic studies. Transient receptor potential (TRP) channels

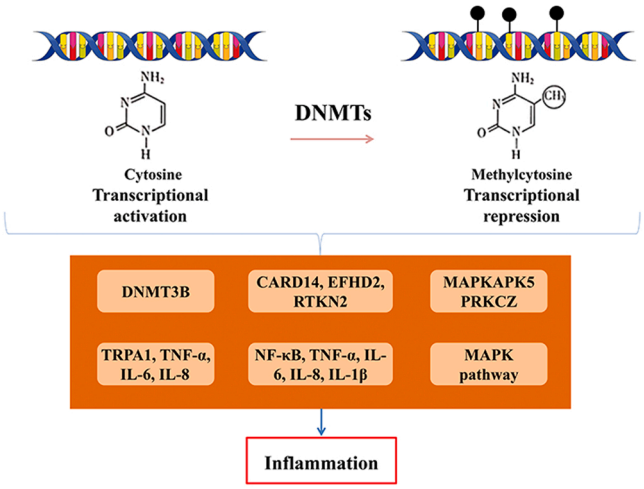

Fig. 2. DNA methylation modulates inflammation in IDD. DNMTs cause the methyl group to embed into the fifth carbon atom of cytosine to form 5-methylcytosine. Subsequent methylation of CpG islands regulates gene expression in multiple ways. The expression level of DNMT3b was significantly decreased in degenerative disc tissue. DNMT3b reduces inflammation in NP cells through TRPA1/COX2 axis. During IDD development, there are DNA methylation changes in CARD14, EFHD2, RTKN2, MAPKAPK5 and PRKCZ in disc tissue. Altered DNA methylation of these key genes leads to changes in the activity of associated molecular networks, which has an important role in the progression of IDD.

have emerged as potential sensors of inflammatory pain, and transient receptor potential ankyrin 1 (TRPA1) is involved in regulating the disc inflammatory response and ECM homeostasis. They showed that DNMT3b inhibits TRPA1 expression by promoting methylation of its promoter, promotes cell proliferation, and reduces ECM degradation and inflammation in a TRPA1-dependent manner.COX-2 is a key link in triggering the inflammatory response.COX-2 activity is extremely low in normal tissue cells; however, when cells are stimulated by inflammatory stimuli, COX-2 activity is substantially increased leading to an inflammatory response and tissue damage. Luo et al. found that DNMT3b could reverse the TRPA1-induced expression of COX2. It was also found that COX2 can increase the expression of IL-6, TNF-α, and IL-8, whereas DNMT3b can reverse this trend. These findings suggest that DNMT3B promotes NP cell proliferation and reduces ECM degradation and inflammation in a TRPA1/COX2-dependent manner (Luo et al., 2021). From these studies, it can be concluded that DNA methylation may play a key regulatory role in disc degeneration and is closely related to the inflammatory response (Fig. 2).

3.2. Histone modification

Histone modification is a post-translational modification of a specific site on histones in chromatin. It can regulate gene expression by affecting chromatin structure, and this has become topic of interest in the epigenetic research field (Huang et al., 2020; Samudyata et al., 2020). The nucleosome is the basic structural unit of chromatin, which is composed of DNA and five histones, such as H1, H2A, H2B, H3, and H4. Two molecules of H2A, H2B, H3, and H4 form a histone octamer, and about 200 bp of DNA molecules coil around the core structure formed by the histone octamer to form a nucleosome core particle. Histone modifications are post-translational modifications of the characteristic sites on chromatin histones, mainly including acetylation, methylation, phosphorylation, and ubiquitination (Su et al., 2020). These post-translational modifications of histones that have been demonstrated are reversible, and there are interactions between different types, culminating in a complex chromatin-based signaling system. By affecting the interaction between histones and DNA, these modifications

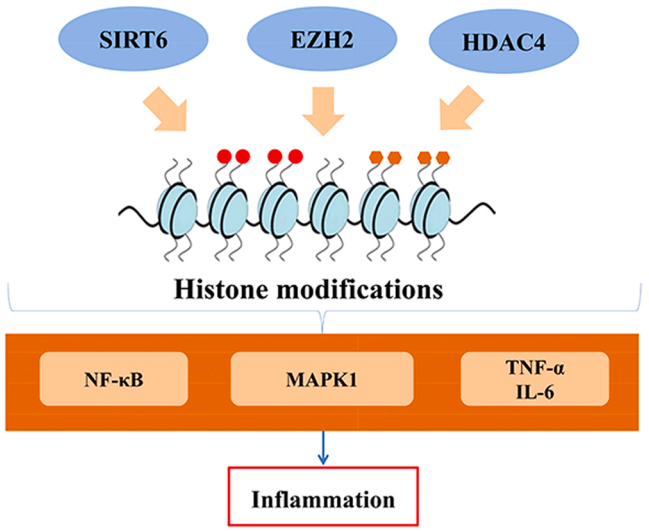

Fig. 3. Histone modification modulates inflammation in IDD. SIRT6 reduces the acetylation level of the downstream target gene promoter, thus inhibiting the transcription activity of NF-κB. EZH2 inhibits the expression of miR-129–5p through H3K27me3 modification, thereby upregulating the expression of MAPK1 and promoting the development of IDD. HDAC4 is related to the expression level of inflammatory factors in the process of IDD.

influence the ability of regulatory complexes to bind to chromatin and chromatin remodeling, ultimately affecting a wide range of cellular functions (Edwards and Johnson, 2021; García-Giménez et al., 2021).

One of the most widely studied modifications is histone acetylation, which is an important and common phenomenon. It regulates the transcriptional activity and modulates fitness through chromatin. Dynamic acetylation and deacetylation are regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HAT-mediated histone acetylation is involved in transcriptional activation of open chromatin structures, whereas deacetylation by HDAC is associated with transcriptional repression of condensed chromatin structures (Desaulniers et al., 2021; Kowluru and Mohammad, 2022). Sirtuins are a class of histone deacetylases. Seven members of the sirtuin family, SIRT1–SIRT7,have been identified, which belong to class III HDAC (Wang et al., 2020a). NF-κB is an inducible stress response transcription factor, and its important role in the inflammatory response has been revealed in detail (Choi et al., 2019; Lepetsos et al., 2019). It is worth noting that its pro-inflammatory effect on IDD has also been recognized by researchers (Zhang et al., 2021a). Under normal conditions, NF-κB is located in the cytoplasm. When stimulated by risk factors, NF-κB rapidly transfers to the nucleus, where it participates in regulating the expression of target genes and promoting the production of inflammatory factors, such as TNF-α, IL-6, and IL-2, by combining the promoter of its downstream target genes (Zhang et al., 2021a). SIRT6 is a member of the sirtuin family, which is mainly located in the nucleus. Studies have confirmed that SIRT6 can be recruited into NF-κB on the promoter of its downstream target gene, thereby deacetylating histone H3K9 in this region and reducing the acetylation level of the promoter, thereby weakening NF-κB signal transduction. In SIRT6 knockdown cells, high acetylation levels in the promoter region of NF-κB downstream target genes and NF-κB occupancy, gene expression level, and cell aging are closely related (Kawahara et al., 2009; Yu et al., 2013). These effects have also been confirmed in the field of IDD (Kang et al., 2017; Xie et al., 2022; Zhang et al., 2020a). *EZH2* encodes a histone lysine N-methyltransferase that functions as a gene silencer by adding three methyl groups to histone H3 lysine 27 (H3K27). The methylation activity of EZH2 promotes the formation of heterochromatin and thus gene silencing, and EZH2 is one of the components of the PRC2 complex. Mutations or overexpression of EZH2 are associated with several types of cancers, such as bladder cancer, prostate cancer, and breast cancer (Huang et al., 2022; Li et al., 2022d; Xiang et al., 2020; Yuan et al., 2020). Abnormal EZH2 activity has also been observed in osteoarthritis and rheumatoid arthritis (Luobu et al., 2022; Wang et al., 2021). Inactivation of EZH2 attenuates chondrocyte dysfunction and osteoarthritis progression by reducing the enrichment of H3K27me3 in the miR-128a promoter (Lian et al., 2018). In the field of disc degeneration research, EZH2 and MAPK1 are overexpressed in specimens and LPS-induced NP cells of patients with disc degeneration (Zhou et al., 2022). In terms of cellular phenotype, EZH2 overexpression increases the release of inflammatory factors and cellular senescence factors from NP cells. Mechanistic studies have confirmed that EZH2 suppresses the expression of miR-129–5p through H3K27me3 modification, thereby upregulating the expression of MAPK1 and promoting the development of disc degeneration (Zhou et al., 2022). In addition, the role of HDAC4 in the inflammatory response of IDD was also observed. Studies have shown that HDAC4 can inhibit TNF-α and IL-6 expression, and then participate in the occurrence and development of IDD (Wu et al., 2020). In summary, the above studies demonstrate the role of histone post-translational modifications in IDD development (Fig. 3).

3.3. *Non-coding RNA*

Most transcripts in the human genome are non-coding RNAs (ncRNAs) that cannot encode proteins. Several ncRNAs have been widely studied, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Numerous studies have revealed that ncRNAs are significantly differentially expressed in different disease states and play a critical role in the development of multiple diseases. The role of ncRNAs in age-related diseases has been extensively studied, such as degenerative musculoskeletal disorders, cancer, neurodegenerative diseases, chronic inflammation, and aging (Li et al., 2021c; Li et al., 2021d; Liu et al., 2022; Rasheed et al., 2021; Vezzani et al., 2022; Yang et al., 2022; Zheng et al., 2021). Importantly, their role in IDD has also been demonstrated.

miRNAs are a large class of short-stranded non-coding RNAs that are approximately 22 nucleotides. miRNAs exert regulatory effects on the expression levels of their target genes at the post-transcriptional level, primarily by directing the RNA-induced silencing complex to the 3′-untranslated region of their downstream target mRNAs. miRNAs are involved in almost all cellular functional processes, and their important roles in various diseases have been revealed (Cazzanelli and Wuertz-Kozak, 2020; Chi et al., 2021; Lin et al., 2020). miRNAs are closely related to the inflammatory response and can contribute to the inflammatory response through dysregulated cytokines (Chunlei et al., 2020). Kong et al. (Kong et al., 2018)confirmed that miR-194 plays an important role in the inflammatory response during the progression of IDD. MiR-194 can inhibit the expression level of inflammatory cytokines, such as TNF-α, IL-1, IL-6, and PGE2. This effect is related to its inhibitory effect on TNF receptor-associated factor 6 (TRAF6) and downstream signal molecule NF-κB. Sun et al. found that the upregulation of miR-181a inactivates the ERK pathway by inhibiting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in mice with IDD, thereby inhibiting TNF-α, IL-6, and IL-1β expression (Sun et al., 2020). MiRNA-495–3p has been proven to play a protective role by inhibiting the inflammatory response of human NP cells by targeting Interleukin 5 receptor subunit alpha (IL5RA) pathway (Lin and Lin, 2020). Overexpression of miR-140 inhibits Toll-like receptor 4 (TLR4), thereby inhibiting TNF-α, IL-1β, and IL-6 expression and NF-κB activation (Zhang et al., 2018).

LncRNAs are another class of ncRNAs that are more than 200 nucleotides in length and significantly longer than miRNAs. LncRNAs are derived from genomic regions but lack open reading frames. With the advances in sequencing technology, more than 14,000 lncRNAs have been identified (Derrien et al., 2012). lncRNAs are mainly classified into long intergenic ncRNAs (lincRNAs), intronic lncRNAs, antisense

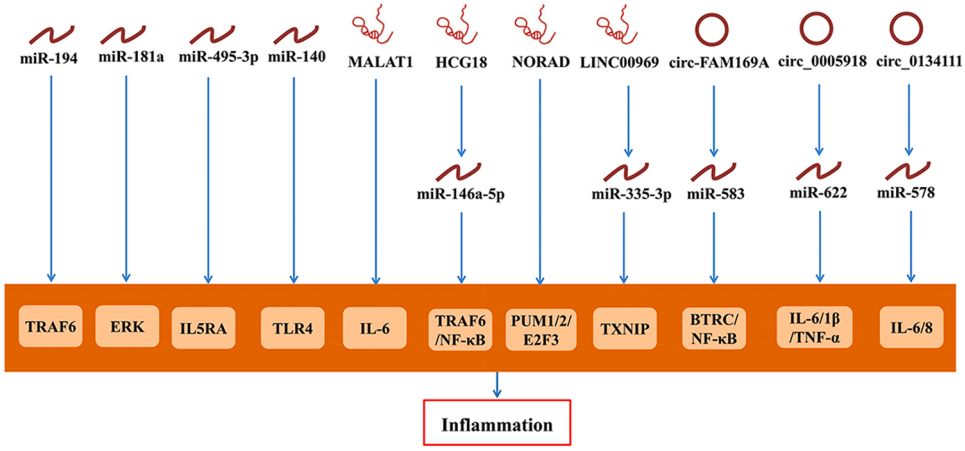

Fig. 4. Non-coding RNA regulation modulates inflammation in IDD. miRNA regulates inflammation by inhibiting the expression level of downstream specific targets. LncRNA or circRNA mainly regulate the expression level of target genes through the mechanism of competitive endogenous RNA, or directly interact with target proteins, thereby regulating inflammation.

lncRNAs, enhancer RNAs, and pseudogene lncRNAs, based on their genomic localization relative to protein-coding genes. In terms of its regulatory functions, lncRNAs have many ways of action. For example, interacting with transcription factors and chromatin modifiers to regulate gene expression; or acting as endogenous miRNA sponges, which absorb miRNAs through multiple specific binding sites, thereby reducing the inhibition of downstream target genes and thus regulating the expression of downstream target genes (Jung et al., 2020). Notably, studies have shown that lncRNAs are involved in a variety of physiological and pathological processes (Kyriazi et al., 2020; Li et al., 2020b; Shi et al., 2021; Zhang et al., 2021c). In the IDD study, Li et al. reviewed articles related to the expression profile of lncRNAs and summarized the number of differentially expressed lncRNAs. The number of up-regulated lncRNAs ranged from 67 to 2234, while the number of down-regulated lncRNAs ranged from 49 to 938 (Li et al., 2018). During IDD, Zhang et al. found reduced lncRNA MALAT1 expression in degenerating NP cells. MALAT1 can downregulate IL-1 and IL-6 expression levels in NP cells (Zhang et al., 2017). In addition, Jiang et al. found that MALAT1 promotes the degeneration of rat CEP cells induced by high glucose by activating p38/MAPK signal pathway (Jiang et al., 2020). Xi et al. found that HCG18 can absorb miR-146a-5p as competitive endogenous RNA, thereby regulating the TRAF6/NF-κB pathway in NP cells and playing an important role in IDD (Xi et al., 2017). In addition, lncRNA zinc finger antisense 1 (ZFAS1) expression was significantly upregulated in degenerated NP tissues, and ZFAS1 was positively correlated with TNF-α and IL-6 expression levels (Deng et al., 2019). Yu et al. found that inhibition of LINC00969 decreased thioredoxin-interacting protein (TXNIP) and IL-1β levels, but increased miR-335–3p expression compared with the control. *TXNIP*, a target gene of miR-335–3p, may promote the release of inflammatory factors such as IL-1β and induce apoptosis in NP cells during IDD (Yu et al., 2019). N6-methyladenosine (m^6A) is the most prevalent RNA modification at the post-transcriptional level in eukaryotic cells and is closely involved in various biological and pathological processes (Chen et al., 2022b; Zhang et al., 2019). The m^6A modification of lncRNA has been proved to be associated with IDD. The m^6A modification is catalyzed by "writers", including METTL3, METTL4, and WTAP, while the demethylases ALKBH5 and FTO act as "erasers" to reverse this process. The transcripts modified with m^6Acan be recognized by "readers", such as YTHDF1–3, YTHDC1, and IGF2BPs, to perform a specific functional regulation (Li et al., 2022a; Qin et al., 2021). NORAD is a lncRNA that responds to DNA damage and is critical for genome integrity. Li et al. found that WTAP upregulation promoted m^6A modification of NORAD and induced degradation of NORAD transcripts through YTHDF2 recognition. Less NORAD leads to less sequestered RNA-binding proteins PUM1/2, which leads to more binding of PUM1/2 to E2F3 mRNA, and ultimately promotes the NP cell senescence (Li et al., 2022b). Senescent NP cells can further damage the microenvironment of degenerative IVD by secreting inflammatory factors and ECM degrading enzymes.

circRNAs are a class of ncRNAs characterized by a covalent closed-loop structure and are thus more metabolically stable to exonucleases than linear ones. In addition, circRNAs are widely expressed in mammalian cells. They have drawn increasing attention to the study of biomarkers and as therapeutic targets for a variety of human diseases (Chen et al., 2022a; Han et al., 2022; Li et al., 2022c). circRNAs have been studied to reveal different biological functions, and the most studied molecular mechanism of action is that of competing endogenous RNA as miRNA molecule "sponge". Other mechanisms of circRNAs include interacting with chromatin and acting as protein scaffolds. CircRNAs play a crucial role in the pathophysiological processes of various human diseases and have great potential for the clinical treatment of diseases (Chen et al., 2021; Yang et al., 2021). Among them, their relationship with the inflammatory response in IDD is gradually being revealed. Guo et al. (Guo et al., 2020) found that circ-FAM169A upregulates Beta-Transducin Repeat Containing E3 Ubiquitin Protein Ligase (BTRC) in NP cells, resulting in NF-kappaB inhibitor alpha (IKBα) degradation. In turn, this leads to the upregulation of the expression of a variety of pro-inflammatory cytokines (IL-1β and TNF-α). The levels of type II collagen and aggrecan decreased, and the levels of MMP-13 and ADAMTS-5 increased, resulting in an imbalance between the anabolic and catabolic activities of NP cells. These adverse factors cause or accelerate IDD. Cui et al. (Cui et al., 2022) found that the expression of circ_0005918 in IVD samples was positively correlated with the degree of IDD. Functional studies show that circ_0005918 overexpression can induce IL-1β, IL-6, and TNF-α secretion and MMP-13 and MMP-9 expression. Mechanism study shows that circ_0005918 plays a role in promoting IDD by sponging miR-622. Yan et al. found that circ_0134111 overexpression promotes IDD by inhibiting miR-578, which in turn induces inflammation and ECM degradation in NP cells (Yan et al., 2022). These evidences above suggest that ncRNAs play an important regulatory role in the inflammatory response to IDD (Fig. 4).

4. Epigenetics provides a potential therapeutic target for the control of inflammation in IDD

The above studies suggest that epigenetic modifications in genes associated with inflammatory responses are abnormally regulated during IDD process, promoting inflammation and IDD development. Targeted modulation of such epigenetic changes, therefore, holds promise for the treatment of IDD. HDAC inhibitors can inhibit histone

Table1
Epigenetic modifications of inflammation in IDD.

Gene/Target	Experimental design	Key findings	References
DNA methylation			
MAPKAPK5/ PRKCZ	Human NP tissue samples; Genome-wide DNA methylation profiling	Advanced vs. Early degenerated human NP tissue samples: Hypermethylation; Regulated MAPK signaling pathway	Ikuno et al. (2019); Monick et al. (2000); Ni et al. (1998); Westhovens et al. (2013)
CARD14/ EFHD2/ RTKN2	Human NP tissue samples; Genome-wide DNA methylation profiling	Advanced vs. Early degenerated human NP tissue samples: Hypomethylation, CARD14; Hypermethylation, EFHD2/RTKN2; Regulated NF-κB signaling pathway	Ikuno et al. (2019); Myouzen et al. (2012); Zotti et al. (2018)
DNMT3b	Puncture-induced rat IDD model; rat NP cells	IVD samples of IDD rats vs. sham rats: Downregulation; Suppressed inflammation and alleviated IDD through TRPA1/COX2/YAP axis	Luo et al. (2021)
Histone modifications			
SIRT6	Human NP tissue samples; IL-1β induced human NP cells	Degenerated vs. Normal human NP tissue samples: Downregulation; Inhibited NF-κB signaling pathway	Kang et al. (2017)
EZH2	Human NP tissue samples; LPS induced human NP cells	Degenerated vs. Normal human NP tissue samples: Upregulation; Upregulated MAPK signaling pathway	Zhou et al. (2022)
HDAC4	IL-1β induced human NP cells	IL-1β induced human NP cells vs. Normal control: Downregulation; Inhibited the TNF-α and IL-6 expression	Wu et al. (2020)
Non-coding RNA regulation			
miR-194	LPS induced rat NP cells	LPS induced rat NP cells vs. Normal control: Downregulation; Inhibited LPS-Induced inflammatory response by targeting TRAF6	Kong et al. (2018)
miR-181a	Mouse IDD model	Mouse IDD model vs. Normal control: Downregulation; Exerted anti-inflammatory effects via inhibition of the ERK pathway	Sun et al. (2020)
miR-495–3p	TNF-α induced human NP cells	TNF-α induced human NP cells vs. Normal control: Downregulation; Attenuated TNF-α induced inflammation in human NP cells by targeting IL5RA	Lin et al. (2020)
miR-140	Human NP tissue samples; LPS induced human NP cells	High degeneration group vs. Low degeneration group: Downregulation; Inhibited LPS-induced inflammation by downregulating TLR4	Zhang et al. (2018)
MALAT1	Human NP cells	Degenerated human NP cells vs. Normal control: Downregulation; Suppressed the expression of IL-6	Zhang et al. (2017)
HCG18	Human NP tissue samples; Human NP cells	Degenerated vs. Control human NP tissue samples: Upregulation; Promoted IDD by sponging miR-146a-5p and regulating TRAF6 expression	Xi et al. (2017)
NORAD	Human NP tissue samples; Human NP cells	Degenerated vs. Control human NP tissue samples: Downregulation; Regulated IDD development through PUM1/2/E2F3 axis	Li et al. (2022b)
LINC00969	Human NP tissue samples; Human NP cells	Degenerated vs. Control human NP tissue samples: Upregulation; Promoted inflammation through miR-335–3P/TXNIP	Yu et al. (2019)
circ-FAM169A	Human NP tissue samples; Human NP cells	Degenerated vs. Control human NP tissue samples: Upregulation; Promoted inflammation by miR-583/BTRC/NF-κB signaling	Guo et al. (2020)
circ_0005918	Human NP tissue samples; IL-1β and TNF-α induced human NP cells	Degenerated vs. Control human NP tissue samples: Upregulation; Induced inflammation via sponging miR-622	Cui et al. (2022)
circ_0134111	Human NP tissue samples; Human NP cells	Degenerated vs. Control human NP tissue samples: Upregulation; Induced inflammation through inhibiting miR-578	Yan et al. (2022)

deacetylases and thereby regulate gene expression levels. Suberoylanilide hydroxamic acid (SAHA) is an HDAC inhibitor and has been approved by the U.S. Food and Drug Administration (FDA)for the treatment of cutaneous T-cell lymphoma (Kim et al., 2019). In addition, SAHA has been shown to treat rheumatoid arthritis (Kim et al., 2019). Park et al. showed that M808, a novel specific HDAC6 inhibitor, inhibited the inflammatory and destructive activity of fibroblast-like synoviocytes and reduced the severity of arthritis (Park et al., 2021). Azacitidine, a DNA methyltransferase inhibitor, became the first FDA-approved drug for myelodysplastic syndrometreatment in 2004 (Kaminskas et al., 2005). For non-coding RNAs, their expression can now be blocked or knocked down by antisense oligonucleotides or small interfering RNA, and these approaches have been tested clinically with proven results (Liu et al., 2022). The role of Traditional Chinese Medicine (TCM) in disease treatment has become a research topic of interest in recent years (Kang et al., 2022). The classical TCM, Wutou Decoction (WTD) has been used clinically for thousands of years. It also has been studied and proven to be useful in the treatment of arthritis. Further studies have revealed that WTD exerts anti-inflammatory effects by regulating DNA methylation and histone modification. Liu et al. found

that the DNMT1 mRNA level and DNA methylation were significantly downregulated and the level of H3 acetylation was significantly increased in peripheral blood mononuclear cells of collagen-induced arthritis rats treated with WTD (Liu et al., 2016). As mentioned above, these types of epigenetic modifications are all associated with excessive activation of inflammation during IDD. They are already being used clinically to treat a variety of diseases with targeted drugs, although they have not yet been studied in the clinical management of IDD. Therefore, a more systematic study of epigenetic changes in the over-activation of the inflammatory response in IDD is needed, which will help to identify clinical therapeutic targets for IDD in the future (Table 1).

5. Conclusion and prospect

In general, epigenetics plays an important regulatory role in the regulation of gene expression levels and is closely related to the pathogenesis of numerous diseases. Among them, the relationship between epigenetics and the inflammatory response in the process of IDD has been initially revealed. Considering the important role of the inflammatory response in IDD and the fact that epigenetics is still at a preliminary stage of research in this field, more attention needs to be placed on the study of this aspect in the future. Several specific issues require our attention. First, functions of the epigenetics in diseases are mainly based on adjustments to expression levels of specific genes. To comprehensively consider epigenetic changes as well as functions of specific genes in disease development can help to identify key pathogenic molecules. Second, some biological inhibitors, such as deacetylase inhibitors, have shown optimal inhibition of IDD in both in vitro cellular experiments and in vivo animal experiments, but more experiments are needed to validate their clinical efficacy in patients. Third, while experiments are designed to verify the therapeutic effects of drugs on disease, their side effects on patients should also be taken into account. This has led to another question on how to deliver the drugs to the disease-causing sites has also surfaced. Fourth, while research on TCM components is in full swing, the reality of the complexity of TCM components is also an issue that cannot be ignored, so a more targeted use of the active ingredients in the drug is essential. Finally, a deeper understanding of the epigenetic regulatory mechanisms of the inflammatory response in IDD will help identify new markers, signaling pathways, and targeted drugs/herbal medicines, providing new strategies for diagnosing and treating IDD.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81772408).

CRediT authorship contribution statement

LK, RZ, and CS conceptualized the review. LK, HZ, CJ drafted the manuscript. LK, HZ, CJ, RZ, CS revised and supplemented the manuscript. All the authors participated in writing and giving feedback on the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

These authors have no conflict of interest to declare.

References

Arumugam, T., Ramphal, U., Adimulam, T., Chinniah, R., Ramsuran, V., 2021. Deciphering DNA methylation in HIV infection. Front. Immunol. 12, 795121.
Cazzanelli, P., Wuertz-Kozak, K., 2020. MicroRNAs in intervertebral disc degeneration, apoptosis, inflammation, and mechanobiology. Int. J. Mol. Sci. 21.
Celarain, N., Tomas-Roig, J., 2020. Aberrant DNA methylation profile exacerbates inflammation and neurodegeneration in multiple sclerosis patients. J. Neuroinflamm. 17, 21.
Chang, C., Xu, L., Zhang, R., Jin, Y., Jiang, P., Wei, K., Xu, L., Shi, Y., Zhao, J., Xiong, M., Guo, S., He, D., 2022. MicroRNA-mediated epigenetic regulation of rheumatoid arthritis susceptibility and pathogenesis. Front. Immunol. 13, 838884.
Chen, C., Xia, C., Tang, H., Jiang, Y., Wang, S., Zhang, X., Huang, T., Yuan, X., Wang, J., Peng, L., 2022a. Circular RNAs Involve in Immunity of digestive cancers from bench to bedside: a review. Front. Immunol. 13, 833058.
Chen, F., Xie, X., Chao, M., Cao, H., Wang, L., 2022b. The potential value of m6A RNA methylation in the development of cancers focus on malignant glioma. Front. Immunol. 13, 917153.
Chen, J., Yang, J., Fei, X., Wang, X., Wang, K., 2021. CircRNA ciRS-7: a novel oncogene in multiple cancers. Int. J. Biol. Sci. 17, 379–389.
Chen, N., Peng, C., Li, D., 2022c. Epigenetic underpinnings of inflammation: a key to unlock the tumor microenvironment in glioblastoma. Front. Immunol. 13, 869307.
Chen, S., Liu, S., Ma, K., Zhao, L., Lin, H., Shao, Z., 2019. TGF-β signaling in intervertebral disc health and disease. Osteoarthr. Cartil. 27, 1109–1117.
Chi, M., Ma, K., Li, Y., Quan, M., Han, Z., Ding, Z., Liang, X., Zhang, Q., Song, L., Liu, C., 2021. Immunological involvement of MicroRNAs in the key events of systemic lupus erythematosus. Front. Immunol. 12, 699684.
Choi, M.C., Jo, J., Park, J., Kang, H.K., Park, Y., 2019. NF-κB signaling pathways in osteoarthritic cartilage destruction. Cells 8.
Chunlei, H., Chang, Z., Sheng, L., Yanchun, Z., Lulin, L., Daozhang, C., 2020. Down-regulation of MiR-138-5p protects chondrocytes ATDC5 and CHON-001 from IL-1 β-induced inflammation via up-regulating SOX9. Curr. Pharm. Des. 25, 4613–4621.
Cui, Y., Zhao, X., Wu, Y., 2022. Circ_0005918 Sponges miR-622 to aggravate intervertebral disc degeneration. Front. Cell Dev. Biol. 10, 905213.
Deng, R.Y., Hong, T., Li, C.Y., Shi, C.L., Liu, C., Jiang, F.Y., Li, J., Fan, X.M., Feng, S.B., Wang, Y.F., 2019. Long non-coding RNA zinc finger antisense 1 expression associates with increased disease risk, elevated disease severity and higher inflammatory cytokines levels in patients with lumbar disc degeneration. Medicine 98, e18465.
Derrien, T., Johnson, R., Bussotti, G., Tanzer, A., Djebali, S., Tilgner, H., Guernec, G., Martin, D., Merkel, A., Knowles, D.G., Lagarde, J., Veeravalli, L., Ruan, X., Ruan, Y., Lassmann, T., Carninci, P., Brown, J.B., Lipovich, L., Gonzalez, J.M., Thomas, M., Davis, C.A., Shiekhattar, R., Gingeras, T.R., Hubbard, T.J., Notredame, C., Harrow, J., Guigó, R., 2012. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 22, 1775–1789.
Desaulniers, D., Vasseur, P., Jacobs, A., Aguila, M., Ertych, N., Jacobs, M., 2021. Integration of epigenetic mechanisms into non-genotoxic carcinogenicity hazard assessment: focus on DNA methylation and histone modifications. Int. J. Mol. Sci. 22.
Early, J.O., Fagan, L.E., Curtis, A.M., Kennedy, O.D., 2021. Mitochondria in injury, inflammation and disease of articular skeletal joints. Front. Immunol. 12, 695257.
Edwards, C., Johnson, R., 2021. Targeting histone modifications in bone and lung metastatic cancers. Curr. Osteoporos. Rep. 19, 230–246.
Evans, L.W., Stratton, M.S., Ferguson, B.S., 2020. Dietary natural products as epigenetic modifiers in aging-associated inflammation and disease. Nat. Prod. Rep. 37, 653–676.
García-Giménez, J.L., Garcés, C., Romá-Mateo, C., Pallardó, F.V., 2021. Oxidative stress-mediated alterations in histone post-translational modifications. Free Radic. Biol. Med. 170, 6–18.
Guo, W., Mu, K., Zhang, B., Sun, C., Zhao, L., Dong, Z.Y., Cui, Q., 2020. The circular RNA FAM169A functions as a competitive endogenous RNA and regulates intervertebral disc degeneration by targeting miR-583 and BTRC. Cell Death Dis. 11, 315.
Han, J.J., Wang, X.Q., Zhang, X.A., 2022. Functional interactions between lncRNAs/circRNAs and miRNAs: insights into rheumatoid arthritis. Front. Immunol. 13, 810317.
Huang, B., Zhong, D., Zhu, J., An, Y., Gao, M., Zhu, S., Dang, W., Wang, X., Yang, B., Xie, Z., 2020. Inhibition of histone acetyltransferase GCN5 extends lifespan in both yeast and human cell lines. Aging Cell 19, e13129.
Huang, C., Hu, F., Song, D., Sun, X., Liu, A., Wu, Q., She, X., Chen, Y., Chen, L., Hu, F., Xu, F., Luo, X., Feng, Y., Yang, X., Hu, J., Wang, G., 2022. EZH2-triggered methylation of SMAD3 promotes its activation and tumor metastasis. J. Clin. Investig. 132.
Ikuno, A., Akeda, K., Takebayashi, S., Shimaoka, M., Okumura, K., Sudo, A., 2019. Genome-wide analysis of DNA methylation profile identifies differentially methylated loci associated with human intervertebral disc degeneration. PloS One 14, e0222188.
Jia, J., Nie, L., Liu, Y., 2020. Butyrate alleviates inflammatory response and NF-κB activation in human degenerated intervertebral disc tissues. Int. Immunopharmacol. 78, 106004.
Jiang, C., Guo, Q., Jin, Y., Xu, J.J., Sun, Z.M., Zhu, D.C., Lin, J.H., Tian, N.F., Sun, L.J., Zhang, X.L., Wu, Y.S., 2019. Inhibition of EZH2 ameliorates cartilage endplate degeneration and attenuates the progression of intervertebral disc degeneration via demethylation of Sox-9. EBioMedicine 48, 619–629.
Jiang, Z., Zeng, Q., Li, D., Ding, L., Lu, W., Bian, M., Wu, J., 2020. Long non-coding RNA MALAT1 promotes high glucose-induced rat cartilage endplate cell apoptosis via the p38/MAPK signalling pathway. Mol. Med. Rep. 21, 2220–2226.
Jimbo, K., Park, J.S., Yokosuka, K., Sato, K., Nagata, K., 2005. Positive feedback loop of interleukin-1beta upregulating production of inflammatory mediators in human intervertebral disc cells in vitro. J. Neurosurg. Spine 2, 589–595.
Johnson, Z.I., Schoepflin, Z.R., Choi, H., Shapiro, I.M., Risbud, M.V., 2015. Disc in flames: roles of TNF-α and IL-1β in intervertebral disc degeneration. Eur. Cells Mater. 30, 104–116 discussion 116-107.
Jung, G., Hernández-Illán, E., Moreira, L., Balaguer, F., Goel, A., 2020. Epigenetics of colorectal cancer: biomarker and therapeutic potential. Nat. Rev. Gastroenterol. Hepatol. 17, 111–130.

Kaminskas, E., Farrell, A.T., Wang, Y.-C., Sridhara, R., Pazdur, R., 2005. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza™) for injectable suspension. Oncologist 10, 176–182.
Kang, L., Hu, J., Weng, Y., Jia, J., Zhang, Y., 2017. Sirtuin 6 prevents matrix degradation through inhibition of the NF-κB pathway in intervertebral disc degeneration. Exp. Cell Res. 352, 322–332.
Kang, L., Zhang, H., Jia, C., Zhang, R., Shen, C., 2022. Targeting oxidative stress and inflammation in intervertebral disc degeneration: therapeutic perspectives of phytochemicals. Front. Pharmacol. 13, 956355.
Kang, R., Li, H., Rickers, K., Ringgaard, S., Xie, L., Bünger, C., 2015. Intervertebral disc degenerative changes after intradiscal injection of TNF-α in a porcine model. Eur. Spine J.: Off. Publ. Eur. Spine Soc., Eur. Spinal Deform. Soc., Eur. Sect. Cerv. Spine Res. Soc. 24, 2010–2016.
Kawahara, T.L., Michishita, E., Adler, A.S., Damian, M., Berber, E., Lin, M., McCord, R.A., Ongaigui, K.C., Boxer, L.D., Chang, H.Y., Chua, K.F., 2009. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell 136, 62–74.
Kim, D., Min, H., Kim, E., Yang, S., Na, H., Lee, S., Choi, J., Jung, K., Kwok, S., Park, S., Cho, M., 2019. Suberoylanilide hydroxamic acid attenuates autoimmune arthritis by suppressing Th17 cells through NR1D1 inhibition. Mediat. Inflamm. 2019, 5648987.
Kong, L., Sun, M., Jiang, Z., Li, L., Lu, B., 2018. MicroRNA-194 Inhibits lipopolysaccharide-induced inflammatory response in nucleus pulposus cells of the intervertebral disc by targeting TNF receptor-associated factor 6 (TRAF6). Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 24, 3056–3067.
Kowluru, R.A., Mohammad, G., 2022. Epigenetic modifications in diabetes. Metab.: Clin. Exp. 126, 154920.
Krupkova, O., Sadowska, A., Kameda, T., Hitzl, W., Hausmann, O.N., Klasen, J., Wuertz-Kozak, K., 2018. p38 MAPK facilitates crosstalk between endoplasmic reticulum stress and IL-6 release in the intervertebral disc. Front. Immunol. 9, 1706.
Kwon, W.K., Moon, H.J., Kwon, T.H., Park, Y.K., Kim, J.H., 2017. The role of hypoxia in angiogenesis and extracellular matrix regulation of intervertebral disc cells during inflammatory reactions. Neurosurgery 81, 867–875.
Kyriazi, A.A., Papiris, E., Kitsos Kalyvianakis, K., Sakellaris, G., Baritaki, S., 2020. Dual effects of non-coding RNAs (ncRNAs) in cancer stem cell biology. Int. J. Mol. Sci. 21.
Le Maitre, C.L., Pockert, A., Buttle, D.J., Freemont, A.J., Hoyland, J.A., 2007. Matrix synthesis and degradation in human intervertebral disc degeneration. Biochem. Soc. Trans. 35, 652–655.
Lepetsos, P., Papavassiliou, K.A., Papavassiliou, A.G., 2019. Redox and NF-κB signaling in osteoarthritis. Free Radic. Biol. Med. 132, 90–100.
Li, G., Luo, R., Zhang, W., He, S., Wang, B., Liang, H., Song, Y., Ke, W., Shi, Y., Feng, X., Zhao, K., Wu, X., Zhang, Y., Wang, K., Yang, C., 2022a. m6A hypomethylation of DNMT3B regulated by ALKBH5 promotes intervertebral disc degeneration via E4F1 deficiency. Clin. Transl. Med. 12, e765.
Li, G., Ma, L., He, S., Luo, R., Wang, B., Zhang, W., Song, Y., Liao, Z., Ke, W., Xiang, Q., Feng, X., Wu, X., Zhang, Y., Wang, K., Yang, C., 2022b. WTAP-mediated mA modification of lncRNA NORAD promotes intervertebral disc degeneration. Nat. Commun. 13, 1469.
Li, L., Wei, K., Ding, Y., Ahati, P., Xu, H., Fang, H., Wang, H., 2021a. M2a macrophage-secreted CHI3L1 promotes extracellular matrix metabolic imbalances via activation of IL-13Rα2/MAPK pathway in rat intervertebral disc degeneration. Front. Immunol. 12, 666361.
Li, Y., Zhou, S., Peng, P., Wang, X., Du, L., Huo, Z., Xu, B., 2020a. Emerging role of circular RNA in intervertebral disc degeneration: knowns and unknowns (Review). Mol. Med. Rep. 22, 3057–3065.
Li, Y., Liu, S., Pan, D., Xu, B., Xing, X., Zhou, H., Zhang, B., Zhou, S., Ning, G., Feng, S., 2021b. The potential role and trend of HIF-1α in intervertebral disc degeneration: friend or foe? (Review). Mol. Med. Rep. 23.
Li, Y., Pan, D., Liu, S., Xing, X., Zhou, H., Zhang, B., Zhang, D., Li, B., Li, G., Tao, B., Ning, G., Feng, S., 2021c. Identification of circ-FAM169A sponges miR-583 involved in the regulation of intervertebral disc degeneration. J. Orthop. Transl. 26, 121–131.
Li, Y., Wang, X., Xu, H., Li, G., Huo, Z., Du, L., Zhang, K., Shen, L., Li, H., Xu, B., 2021d. Circ_0040039 may aggravate intervertebral disk degeneration by regulating the MiR-874-3p-ESR1 pathway. Front. Genet. 12, 656759.
Li, Y., Wu, X., Li, J., Du, L., Wang, X., Cao, J., Li, H., Huo, Z., Li, G., Pan, D., Xu, H., Xu, B., 2022c. Circ_0004354 might compete with circ_0040039 to induce NPCs death and inflammatory response by targeting miR-345-3p-FAF1/TP73 axis in intervertebral disc degeneration. Oxid. Med. Cell. Longev. 2022, 2776440.
Li, Z., Li, X., Chen, C., Li, S., Shen, J., Tse, G., Chan, M.T.V., Wu, W.K.K., 2018. Long non-coding RNAs in nucleus pulposus cell function and intervertebral disc degeneration. Cell Prolif. 51, e12483.
Li, Z., Huang, C., Yang, B., Hu, W., Chan, M.T., Wu, W.K.K., 2020b. Emerging roles of long non-coding RNAs in osteonecrosis of the femoral head. Am. J. Transl. Res. 12, 5984–5991.
Li, Z., Li, B., Yu, H., Wang, P., Wang, W., Hou, P., Li, M., Chu, S., Zheng, J., Mao, L., Bai, J., 2022d. DNMT1-mediated epigenetic silencing of TRAF6 promotes prostate cancer tumorigenesis and metastasis by enhancing EZH2 stability. Oncogene.
Lian, W.S., Ko, J.Y., Wu, R.W., Sun, Y.C., Chen, Y.S., Wu, S.L., Weng, L.H., Jahr, H., Wang, F.S., 2018. MicroRNA-128a represses chondrocyte autophagy and exacerbates knee osteoarthritis by disrupting Atg12. Cell Death Dis. 9, 919.
Lin, X., Lin, Q., 2020. MiRNA-495-3p attenuates TNF-α induced apoptosis and inflammation in human nucleus pulposus cells by targeting IL5RA. Inflammation 43, 1797–1805.
Lin, Z., Lu, S., Xie, X., Yi, X., Huang, H., 2020. Noncoding RNAs in drug-resistant pancreatic cancer: a review. Biomed. Pharmacother. = Biomed. Pharmacother. 131, 110768.
Lin, Z., Lu, F., Ma, X., Xia, X., Zou, F., Jiang, J., 2021. Roles of circular RNAs in the pathogenesis of intervertebral disc degeneration (Review). Exp. Ther. Med. 22, 1221.
Lio, C.J., Yuita, H., Rao, A., 2019. Dysregulation of the TET family of epigenetic regulators in lymphoid and myeloid malignancies. Blood 134, 1487–1497.
Liu, Y., Wen, C., Chen, Z., Wang, Y., Huang, Y., Hu, Y., Tu, S., 2016. Effects of wutou decoction on DNA methylation and histone modifications in rats with collagen-induced arthritis. Evid. -Based Complement. Altern. Med.: eCAM 2016, 5836879.
Liu, Y., Cheng, X., Li, H., Hui, S., Zhang, Z., Xiao, Y., Peng, W., 2022. Non-coding RNAs as novel regulators of neuroinflammation in Alzheimer's disease. Front. Immunol. 13, 908076.
Lu, L., Xu, A., Gao, F., Tian, C., Wang, H., Zhang, J., Xie, Y., Liu, P., Liu, S., Yang, C., Ye, Z., Wu, X., 2021. Mesenchymal stem cell-derived exosomes as a novel strategy for the treatment of intervertebral disc degeneration. Front. Cell Dev. Biol. 9, 770510.
Luo, Z., Ma, Y., Di, T., Ma, B., Li, H., An, J., Wang, Y., Zhang, H., 2021. DNMT3B decreases extracellular matrix degradation and alleviates intervertebral disc degeneration through TRPA1 methylation to inhibit the COX2/YAP axis. Aging 13, 20258–20276.
Luobu, Z., Wang, L., Jiang, D., Liao, T., Luobu, C., Qunpei, L., 2022. CircSCAPER contributes to IL-1β-induced osteoarthritis in vitro via miR-140-3p/EZH2 axis. Bone Jt. Res. 11, 61–72.
Ma, K., Chen, S., Li, Z., Deng, X., Huang, D., Xiong, L., Shao, Z., 2019. Mechanisms of endogenous repair failure during intervertebral disc degeneration. Osteoarthr. Cartil. 27, 41–48.
Madhu, V., Guntur, A.R., Risbud, M.V., 2021. Role of autophagy in intervertebral disc and cartilage function: implications in health and disease. Matrix Biol. 100–101, 207–220.
Monick, M.M., Carter, A.B., Flaherty, D.M., Peterson, M.W., Hunninghake, G.W., 2000. Protein kinase C zeta plays a central role in activation of the p42/44 mitogen-activated protein kinase by endotoxin in alveolar macrophages. J. Immunol. (Baltim., Md.: 1950) 165 4632–4639.
Myouzen, K., Kochi, Y., Okada, Y., Terao, C., Suzuki, A., Ikari, K., Tsunoda, T., Takahashi, A., Kubo, M., Taniguchi, A., Matsuda, F., Ohmura, K., Momohara, S., Mimori, T., Yamanaka, H., Kamatani, N., Yamada, R., Nakamura, Y., Yamamoto, K., 2012. Functional variants in NFKBIE and RTKN2 involved in activation of the NF-κB pathway are associated with rheumatoid arthritis in Japanese. PLoS Genet. 8, e1002949.
Ni, H., Wang, X.S., Diener, K., Yao, Z., 1998. MAPKAPK5, a novel mitogen-activated protein kinase (MAPK)-activated protein kinase, is a substrate of the extracellular-regulated kinase (ERK) and p38 kinase. Biochem. Biophys. Res. Commun. 243, 492–496.
Ohtori, S., Miyagi, M., Eguchi, Y., Inoue, G., Orita, S., Ochiai, N., Kishida, S., Kuniyoshi, K., Nakamura, J., Aoki, Y., Ishikawa, T., Arai, G., Kamoda, H., Suzuki, M., Takaso, M., Furuya, T., Kubota, G., Sakuma, Y., Oikawa, Y., Toyone, T., Takahashi, K., 2012a. Efficacy of epidural administration of anti-interleukin-6 receptor antibody onto spinal nerve for treatment of sciatica. Eur. Spine J.: Off. Publ. Eur. Spine Soc., Eur. Spinal Deform. Soc., Eur. Sect. Cerv. Spine Res. Soc. 21, 2079–2084.
Ohtori, S., Miyagi, M., Eguchi, Y., Inoue, G., Orita, S., Ochiai, N., Kishida, S., Kuniyoshi, K., Nakamura, J., Aoki, Y., Ishikawa, T., Arai, G., Kamoda, H., Suzuki, M., Takaso, M., Furuya, T., Toyone, T., Takahashi, K., 2012b. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study. Spine 37, 439–444.
Park, J., Shon, S., Yoo, H., Suh, D., Bae, D., Shin, J., Jun, J., Ha, N., Song, H., Choi, Y., Pap, T., Song, Y., 2021. Inhibition of histone deacetylase 6 suppresses inflammatory responses and invasiveness of fibroblast-like-synoviocytes in inflammatory arthritis. Arthritis Res. Ther. 23, 177.
Qin, S., Mao, Y., Wang, H., Duan, Y., Zhao, L., 2021. The interplay between m6A modification and non-coding RNA in cancer stemness modulation: mechanisms, signaling pathways, and clinical implications. Int. J. Biol. Sci. 17, 2718–2736.
Rasheed, M., Liang, J., Wang, C., Deng, Y., Chen, Z., 2021. Epigenetic regulation of neuroinflammation in Parkinson's disease. Int. J. Mol. Sci. 22.
Rustenburg, C.M.E., Emanuel, K.S., Peeters, M., Lems, W.F., Vergroesen, P.-P.A., Smit, T. H., 2018. Osteoarthritis and intervertebral disc degeneration: quite different, quite similar. JOR. SPINE 1, e1033.
Samudyata, Castelo-Branco, G., Liu, J., 2020. Epigenetic regulation of oligodendrocyte differentiation: from development to demyelinating disorders. Glia 68, 1619–1630.
Shi, T., Morishita, A., Kobara, H., Masaki, T., 2021. The role of long non-coding RNA and microRNA networks in hepatocellular carcinoma and its tumor microenvironment. Int. J. Mol. Sci. 22.
Silva, A.J., Ferreira, J.R., Cunha, C., Corte-Real, J.V., Bessa-Gonçalves, M., Barbosa, M. A., Santos, S.G., Gonçalves, R.M., 2019. Macrophages Down-regulate gene expression of intervertebral disc degenerative markers under a pro-inflammatory microenvironment. Front. Immunol. 10, 1508.
Su, Y., Liu, X., Lian, J., Deng, C., 2020. Epigenetic histone modulations of PPARγ and related pathways contribute to olanzapine-induced metabolic disorders. Pharm. Res 155, 104703.
Sun, L., Zhang, H., Gao, P., 2022. Metabolic reprogramming and epigenetic modifications on the path to cancer. Protein Cell 13, 877–919.
Sun, Y., Shi, X., Peng, X., Li, Y., Ma, H., Li, D., Cao, X., 2020. MicroRNA-181a exerts anti-inflammatory effects via inhibition of the ERK pathway in mice with intervertebral disc degeneration. J. Cell. Physiol. 235, 2676–2686.
Tak, P.P., Firestein, G.S., 2001. NF-kappaB: a key role in inflammatory diseases. J. Clin. Investig. 107, 7–11.

Tan, S.Y.X., Zhang, J., Tee, W.W., 2022. Epigenetic regulation of inflammatory signaling and inflammation-induced cancer. Front. Cell Dev. Biol. 10, 931493.
Tonomura, H., Nagae, M., Takatori, R., Ishibashi, H., Itsuji, T., Takahashi, K., 2020. The potential role of hepatocyte growth factor in degenerative disorders of the synovial joint and spine. Int. J. Mol. Sci. 21.
Topper, M.J., Vaz, M., Marrone, K.A., Brahmer, J.R., Baylin, S.B., 2020. The emerging role of epigenetic therapeutics in immuno-oncology. Nat. Rev. Clin. Oncol. 17, 75–90.
Vaiserman, A., Lushchak, O., 2019. Developmental origins of type 2 diabetes: focus on epigenetics. Ageing Res. Rev. 55, 100957.
Vandenhoeck, J., van Meerbeeck, J.P., Fransen, E., Raskin, J., Van Camp, G., Op de Beeck, K., Lamote, K., 2021. DNA methylation as a diagnostic biomarker for malignant mesothelioma: a systematic review and meta-analysis. J. Thorac. Oncol.: Off. Publ. Int. Assoc. Study Lung Cancer 16, 1461–1478.
Vezzani, B., Carinci, M., Previati, M., Giacovazzi, S., Della Sala, M., Gafà, R., Lanza, G., Wieckowski, M.R., Pinton, P., Giorgi, C., 2022. Epigenetic regulation: a link between inflammation and carcinogenesis. Cancers 14, 1221.
Vo, N.V., Hartman, R.A., Yurube, T., Jacobs, L.J., Sowa, G.A., Kang, J.D., 2013. Expression and regulation of metalloproteinases and their inhibitors in intervertebral disc aging and degeneration. Spine J.: Off. J. North Am. Spine Soc. 13, 331–341.
Wang, J., Wang, X., Ding, X., Huang, T., Song, D., Tao, H., 2021. EZH2 is associated with cartilage degeneration in osteoarthritis by promoting SDC1 expression via histone methylation of the microRNA-138 promoter. Lab. Investig. ; a J. Tech. Methods Pathol. 101, 600–611.
Wang, T., Wang, Y., Liu, L., Jiang, Z., Li, X., Tong, R., He, J., Shi, J., 2020a. Research progress on sirtuins family members and cell senescence. Eur. J. Med. Chem. 193, 112207.
Wang, Y., Che, M., Xin, J., Zheng, Z., Li, J., Zhang, S., 2020b. The role of IL-1β and TNF-α in intervertebral disc degeneration. Biomed. Pharmacother. = Biomed. Pharmacother. 131, 110660.
Westhovens, R., Keyser, F.D., Rekalov, D., Nasonov, E.L., Beetens, J., Van der Aa, A., Wigerinck, P., Namour, F., Vanhoutte, F., Durez, P., 2013. Oral administration of GLPG0259, an inhibitor of MAPKAPK5, a new target for the treatment of rheumatoid arthritis: a phase II, randomised, double-blind, placebo-controlled, multicentre trial. Ann. Rheum. Dis. 72, 741–744.
Wu, Y.D., Guo, Z.G., Deng, W.J., Wang, J.G., 2020. SD0006 promotes nucleus pulposus cell proliferation via the p38MAPK/HDAC4 pathway. Eur. Rev. Med. Pharmacol. Sci. 24, 10966–10974.
Xi, Y., Jiang, T., Wang, W., Yu, J., Wang, Y., Wu, X., He, Y., 2017. Long non-coding HCG18 promotes intervertebral disc degeneration by sponging miR-146a-5p and regulating TRAF6 expression. Sci. Rep. 7, 13234.
Xiang, W., Lyu, L., Huang, T., Zheng, F., Yuan, J., Zhang, C., Jiang, G., 2020. The long non-coding RNA SNHG1 promotes bladder cancer progression by interacting with miR-143-3p and EZH2. J. Cell. Mol. Med. 24, 11858–11873.
Xie, T., Yuan, J., Mei, L., Li, P., Pan, R., 2022. Luteolin suppresses TNF-α-induced inflammatory injury and senescence of nucleus pulposus cells via the Sirt6/NF-κB pathway. Exp. Ther. Med. 24, 469.
Yan, P., Sun, C., Luan, L., Han, J., Qu, Y., Zhou, C., Xu, D., 2022. Hsa_circ_0134111 promotes intervertebral disc degeneration via sponging miR-578. Cell Death Discov. 8, 55.
Yang, C., Li, D., Teng, D., Zhou, Y., Zhang, L., Zhong, Z., Yang, G.J., 2022. Epigenetic regulation in the pathogenesis of rheumatoid arthritis. Front. Immunol. 13, 859400.
Yang, X., Ye, T., Liu, H., Lv, P., Duan, C., Wu, X., Jiang, K., Lu, H., Xia, D., Peng, E., Chen, Z., Tang, K., Ye, Z., 2021. Expression profiles, biological functions and clinical significance of circRNAs in bladder cancer. Mol. Cancer 20, 4.
Ye, Z., Li, Y., Xie, J., Feng, Z., Yang, X., Wu, Y., Pu, Y., Gao, J., Xu, X., Zhu, Z., Li, W., Chen, W., Xing, C., 2021. Integrated bioinformatics identifies the dysregulation induced by aberrant gene methylation in colorectal carcinoma. Genes Dis. 8, 521–530.
Yu, H., Tuminello, S., Alpert, N., van Gerwen, M., Yoo, S., Mulholland, D., Aaronson, S., Donovan, M., Oh, W., Gong, Y., Wang, L., Zhu, J., Taioli, E., 2022. Global DNA methylation of WTC prostate cancer tissues show signature differences compared to non-exposed cases. Carcinogenesis 43, 528–537.
Yu, L., Hao, Y., Xu, C., Zhu, G., Cai, Y., 2019. LINC00969 promotes the degeneration of intervertebral disk by sponging miR-335-3p and regulating NLRP3 inflammasome activation. IUBMB Life 71, 611–618.
Yu, S.S., Cai, Y., Ye, J.T., Pi, R.B., Chen, S.R., Liu, P.Q., Shen, X.Y., Ji, Y., 2013. Sirtuin 6 protects cardiomyocytes from hypertrophy in vitro via inhibition of NF-κB-dependent transcriptional activity. Br. J. Pharmacol. 168, 117–128.
Yuan, B., Sun, R., Du, Y., Jia, Z., Yao, W., Yang, J., 2020. STAT3-induced upregulation of lncRNA CASC9 Promotes the progression of bladder cancer by interacting with EZH2 and affecting the expression of PTEN. OncoTargets Ther. 13, 9147–9157.
Zhang, C., Fu, J., Zhou, Y., 2019. A review in research progress concerning m6A methylation and immunoregulation. Front. Immunol. 10, 922.
Zhang, G., Liu, M., Chen, H., Wu, Z., Gao, Y., Ma, Z., He, X., Kang, X., 2021a. NF-κB signalling pathways in nucleus pulposus cell function and intervertebral disc degeneration. Cell Prolif. 54, e13057.
Zhang, G.-Z., Deng, Y.-J., Xie, Q.-Q., Ren, E.-H., Ma, Z.-J., He, X.-G., Gao, Y.-C., Kang, X.-W., 2020a. Sirtuins and intervertebral disc degeneration: roles in inflammation, oxidative stress, and mitochondrial function. Clin. Chim. Acta 508, 33–42.
Zhang, H., Li, J., Duan, D., She, W., Wang, L., Zhang, F., 2017. The role of lncRNA MALAT1 in intervertebral degenerative disc disease. Int. J. Clin. Exp. Pathol. 10, 10611–10617.
Zhang, H.J., Liao, H.Y., Bai, D.Y., Wang, Z.Q., Xie, X.W., 2021b. MAPK /ERK signaling pathway: A potential target for the treatment of intervertebral disc degeneration. Biomed. Pharmacother. = Biomed. Pharmacother. 143, 112170.
Zhang, Q., Weng, Y., Jiang, Y., Zhao, S., Zhou, D., Xu, N., 2018. Overexpression of miR-140-5p inhibits lipopolysaccharide-induced human intervertebral disc inflammation and degeneration by downregulating toll-like receptor 4. Oncol. Rep. 40, 793–802.
Zhang, Y., Yang, B., Wang, J., Cheng, F., Shi, K., Ying, L., Wang, C., Xia, K., Huang, X., Gong, Z., Yu, C., Li, F., Liang, C., Chen, Q., 2020b. Cell senescence: a nonnegligible cell state under survival stress in pathology of intervertebral disc degeneration. Oxid. Med. Cell. Longev. 2020, 9503562.
Zhang, Y., Mao, Q., Xia, Q., Cheng, J., Huang, Z., Li, Y., Chen, P., Yang, J., Fan, X., Liang, Y., Lin, H., 2021c. Noncoding RNAs link metabolic reprogramming to immune microenvironment in cancers. J. Hematol. Oncol. 14, 169.
Zhao, J., Wei, K., Chang, C., Xu, L., Jiang, P., Guo, S., Schrodi, S.J., He, D., 2022. DNA methylation of T lymphocytes as a therapeutic target: implications for rheumatoid arthritis etiology. Front. Immunol. 13, 863703.
Zhao, K., Zhang, Y., Kang, L., Song, Y., Wang, K., Li, S., Wu, X., Hua, W., Shao, Z., Yang, S., Yang, C., 2017. Epigenetic silencing of miRNA-143 regulates apoptosis by targeting BCL2 in human intervertebral disc degeneration. Gene 628, 259–266.
Zheng, Y.L., Song, G., Guo, J.B., Su, X., Chen, Y.M., Yang, Z., Chen, P.J., Wang, X.Q., 2021. Interactions among lncRNA/circRNA, miRNA, and mRNA in musculoskeletal degenerative diseases. Front. Cell Dev. Biol. 9, 753931.
Zhou, M., He, S.J., Liu, W., Yang, M.J., Hou, Z.Y., Meng, Q., Qian, Z.L., 2022. EZH2 upregulates the expression of MAPK1 to promote intervertebral disc degeneration via suppression of miR-129-5p. J. Gene Med. 24, e3395.
Zhou, Q., Cai, Y., Jiang, Y., Lin, X., 2020. Exosomes in osteoarthritis and cartilage injury: advanced development and potential therapeutic strategies. Int. J. Biol. Sci. 16, 1811–1820.
Zong, D., Liu, X., Li, J., Ouyang, R., Chen, P., 2019. The role of cigarette smoke-induced epigenetic alterations in inflammation. Epigenetics Chromatin 12, 65.
Zotti, T., Polvere, I., Voccola, S., Vito, P., Stilo, R., 2018. CARD14/CARMA2 signaling and its role in inflammatory skin disorders. Front. Immunol. 9, 2167.