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REVIEW

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Targeting nucleus pulposus cell death in the treatment of intervertebral disc degeneration

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Abstract

Background: Intervertebral disc degeneration (IDD) is a progressive age-related disorder characterized by the reduction in the number of nucleus pulposus cells (NPCs) and degradation of extracellular matrix (ECM), thereby leading to chronic pain and disability. The pathogenesis of IDD is multifaceted, and current therapeutic strategies remain limited. The nucleus pulposus (NP), primarily composed of NPCs, proteoglycans, and type II collagen, constitutes essential components for maintaining intervertebral disc (IVD) function and spinal motion. The disturbed homeostasis of NPCs is closely associated with IDD. Accumulating evidence increasingly suggests the crucial role of programmed cell death (PCD) in regulating the homeostasis of NPCs.

Aims: This review aimed to elucidate various forms of PCD and their respective roles in IDD, and investigate diverse strategies targeting the cell death of NPCs for IDD treatment.

Materials & Methods: We collected the relevant literature regarding PCD and their roles in the development of IDD. Subsequently, we comprehensively summarized the intricate association between PCD and IDD, and also explored the potential and application of cell therapy and traditional Chinese medicine (TCM) in the prevention and treatment of IDD.

Results: Current literature indicated that the PCD of NPCs was closely associated with the pathogenesis of IDD. Additionally, the development of targeted pharmaceuticals based on the mechanisms of PCD could effectively impede the loss of NPCs.

Conclusion: This review demonstrated that targeting the PCD of NPCs may be a promising strategy for the treatment of IDD.

KEYWORDS

cell therapy, intervertebral disc degeneration, nucleus pulposus cells, programmed cell death, traditional Chinese medicine

Abbreviations: AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; BSHXD, Bushen Huoxue Decoction; DHJSD, Duhuo Jisheng Decoction; ECM, extracellular matrix; FPN, Ferroportin; GPX4, glutathione peroxidase 4; GSDM, gasdermin; GSH, glutathione; IDD, intervertebral disc degeneration; IL-1β, Interleukin-1β; MAPK, mitogen-activated protein kinase; MLKL, mixed lineage kinase domain like; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; mTOR, mammalian target of rapamycin; ncRNA, noncoding RNA; NF-κB, Nuclear factor-κB; NPCs, nucleus pulposus cells; PCD, programmed cell death; RIPK, receptor-interacting serine/threonine protein kinase; ROS, reactive oxygen species; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor alpha.

Hong Sun and Jiajie Guo contributed equally to this study.

1 | INTRODUCTION

Low back pain (LBP) is a prevalent degenerative disease that significantly impacts individuals' quality of life and can potentially lead to disability, thereby exacerbating the burden on public health.[1] The intervertebral disc (IVD) plays a crucial role in spinal kinematics and provides essential structural support. The degeneration of IVD results in pathological alterations in the spinal structures, thereby increasing susceptibility to LBP.[2,3] Despite substantial research into the origins and development of IDD, the exact triggers behind its onset remain poorly understood, thereby hindering the advancement of efficacious therapeutic and preventive measures. Current treatment options largely revolve around conservative care and surgery. While alleviating symptoms to some extent, these measures show limited capacity in halting or reversing IDD.[4] Consequently, there is a pressing need for the advent of interventions that are safer and more effective, with current research efforts intensely focusing on the exploration of targeted therapeutic approaches.[5,6]

The IVD is composed of the central nucleus pulposus (NP), peripheral annulus fibrosus (AF), and inferior and superior cartilage endplates (CEP). The NP primarily comprises NPCs, proteoglycans, and type II collagen, serving to counteract axial compressive forces along the spinal column.[7] Proteoglycans and type II collagen in the NP are vital for water retention and osmotic pressure balance, ensuring the IVD can efficiently bear loads and preserve its structural stability.[8] The extracellular matrix (ECM) is derived from NPCs and consists of a diverse array of protein components, which contribute to augmenting tensile strength and preserving the integrity of the NP.[9] The AF is constituted by multiple lamellae of resilient fibrous architecture, which are meticulously organized in concentric fashion encircling the NP. This sophisticated arrangement effectively restrains lateral expansion of the NP, while concurrently maintaining the physiological pressure within IVD, thereby upholding its structural integrity and functional capacity.[10] The CEPs, a delicate layer of hyaline cartilage, facilitate the distribution of mechanical loads and prevent herniation of the IVD into adjacent vertebral bodies, while also supplying essential nutrients to the IVD.[11,12] NPCs rely on the intricate blood vessel network within the CEP to obtain essential nutrients, which permeate through the endplate and diffuse throughout the ECM.

Extensive research consistently implicates a multitude of factors, encompassing aging, smoking, mechanical stress, poor nutrition, inflammation, and physical injury collectively contribute to IDD.[5,8,13] The microenvironment of IVD is characterized by limited oxygen availability, scarce nutrient supply, elevated osmotic pressure, and substantial mechanical stress. This challenging microenvironment significantly amplifies the risk of IDD.[14] Additionally, the initiation of IDD typically occurs in the NP, featured by a reduction in water content and metabolic dysregulation. These metabolic imbalances trigger the accumulation of advanced glycation end products in NP tissues, exacerbating deterioration, amplifying oxidative stress, and boosting inflammatory cytokine release. Simultaneously, this fosters an increase in ECM-degrading enzymes, and facilitates ECM degradation, ultimately leading to the senescence or demise of NPCs.[15] IVD, the largest avascular structure in the human body, undergoes degenerative changes that create a microenvironment conducive to the abnormal proliferation of sensory nerves and vasculature, and this in turn initiates discogenic pain.[16,17] According to reports, inadequate nutrient supply to the IVD can lead to elevated lactate levels and reduce oxygen utilization. Subsequently, the cells within the IVD undergo functional alterations and may even undergo programmed cell death (PCD).[18] Moreover, mitochondrial damage or dysfunction can result in the accumulation of diverse stress signals, leading to impaired NPCs function and ultimately triggering PCD.

Degeneration of the NP is a crucial aspect in the pathophysiology of IDD. Extensive research has consistently demonstrated that the PCD of NPCs plays a pivotal role in IDD, therefore, targeting NPCs death could represent a promising therapeutic strategy.[5] This review aims to clarify the mechanisms underlying PCD in NPCs and its contribution to IDD, exploring therapeutic avenues targeting NPCs death as a strategic intervention. Furthermore, it introduces innovative therapies for IDD, offering new perspectives on treatment.

2 | OVERVIEW OF PCD

Cell death is an important biological process that enable organisms to responsively adapt to internal and external stimuli. PCD is integral to this regulation, preserving cellular homeostasis and maintaining equilibrium within the body's internal environment. The different types exhibit unique morphological and biological traits (Table 1). Apoptosis, a genetically regulated cell death that plays a significant role in the life cycles of organisms, is intricately regulated by diverse signaling pathways, which encompassing death receptors, mitochondria, and endoplasmic reticulum stress[19] (Figure 1). Diverse pathways, such as Fas, TNFR1, and TNF-related apoptosis ligands, induce apoptosis in response to extrinsic stimuli.[20] Intrinsic apoptosis can be triggered by diverse stimuli induce the activation of Bcl-2 family proteins in both mitochondria and ER, thereby modulating membrane permeability and initiating the mitochondrial pathway.[21] Pro-apoptotic factors are released, leading to the liberation of cytochrome c and subsequent formation of apoptotic complexes, which ultimately activate caspases and induce apoptosis.[22,23]

Autophagy, a cellular protective mechanism, facilitates the degradation of cytoplasmic components within lysosomes, thereby ensuring organismal homeostasis.[24] Macroautophagy involves the five stages: induction, nucleation, elongation, maturation, and fusion, which encompass the formation of autophagosomes followed by their fusion with lysosomes (Figure 2). In mammals, autophagy is regulated by the kinase complex which consists of the UNC-51-like kinases (ULK1 or ULK2), the homolog of Atg13 protein, and FIP200.[25] The regulation of autophagy is critically governed by 5' AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR).[26] Pyroptosis is an inflammatory modality of cell death characterized by cellular membrane permeabilization and release of intracellular contents, leading to a robust inflammatory response.[27] The gasdermin (GSDM) protein family members facilitate the formation of pores in both mitochondrial

TABLE 1 The list of different cell death forms in nucleus pulposus cells.[19,24,31,34,40,44,45]

Project	Apoptosis	Autophagy	Pyroptosis	Ferroptosis	Necroptosis
Inducing factors	Gene regulation under physiological conditions	Nutritional deficiency or hormone induction	Pathological stimulation	Iron, ROS	Pathological changes or severe damage
Cell morphology	Shrinkage	Generation of Vacuoles	Gradual Swelling	Shrinkage	Swelling
Cell membrane	Plasma membrane blebbing	Involved in autophagosome	Formation of membrane pores, loss of integrity	Membrane rupture	Rupture of plasma membrane
Cytoplasm	Cytoplasm dense, organelles are tightly arranged	Content entering lyosomes	Osmotic swelling, content leakage	Mitochondrial atrophy and membrane rupture	Cytoplasmic and organelle swelling
Nucleus	Pyknosis and rupture	Normal size	Enrichment	Normal size	Nuclear condensation
DNA	Degradeation fragmentation	Random degradation	Random degradation	None	Random degradation
Intermediary	Apoptotic body	Autophagosome	Pyroptosome	None	Necrosomes
Inflammation	No	No	Yes	Yes	Yes
Key role	Caspase-3, Caspase-6, Caspase-7	LC3-II, Atg5, Atg7, Beclin1	Gasdermins	Iron, GPX4, lipid peroxidation	RIPK1/3, MLKL, Necrostatin-1
Signal pathway	Death receptor pathway, mitochondrial pathway, ER pathway	PI3K/AKT/mTOR AMPK/ULK/mTOR	Classic pathway, Caspase-1; non-classic pathway, Caspase-4/5/11	Iron overload, Inhibition of the X_C^- system and GPX4	TNFa-TNFR1, Fas–FasL
ATP requirement	Yes	Yes	Yes	Yes	No

and plasma membranes to promote the release of IL-1β and IL-18.[28,29] The signaling pathways of pyroptosis can be categorized into various types (Figure 3). A classical form is distinguished by the occurrence of caspase-1-mediated pyroptosis. The activation of the inflammasome triggers the activation of caspase-1, which cleaves GSDMD and induces pyroptosis.[29,30] The non-classical form involves the activation of caspase-4/5/11 upon stimulation with LPS in cytoplasm.[31] Additionally, pyroptosis encompasses alternative pathways reliant on caspase-3 and caspase-8.[32,33]

Ferroptosis, an iron-dependent lipid peroxidation process, is triggered by the dysregulation between oxidation and antioxidant systems[34] (Figure 1). This intricate cascade involves lipid peroxidation, iron accumulation, ROS formation, and glutathione (GSH) depletion.[35] Iron overload induces the generation of ROS through the Fenton reaction and activation of iron-containing enzymes, resulting in the oxidation of polyunsaturated fatty acids and subsequent lipid peroxidation, triggering ferroptosis.[36,37] GSH is a vital antioxidant that mitigates oxidative stress, inhibits lipid peroxidation, and shields tissue cells from damage. It is essential for the effective working of GSH peroxidase 4 (GPX4), an enzyme that neutralizes harmful phospholipid hydroperoxides in cell membranes.[38,39] Importantly, GPX4 is the vital regulatory factor governing ferroptosis. The study has demonstrated that the inhibition of GPX4 leads to the accumulation of lipid peroxidation, ultimately resulting in ferroptosis. Necroptosis predominantly occurs through the activation of receptor-interacting serine/threonine protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain like (MLKL).[40,41] Necroptosis, characterized by necrotic features and caspase-independent activity, has been demonstrated the inhibition of caspase fails to hinder cell death when TNFR is activated, instead, it elicits necroptosis[42] (Figure 1). Degterev et al. found that activation of the Fas/TNFR receptor family can initiate the necroptosis pathway in the absence of intracellular apoptotic signals.[43]

Cell death pathways have long been considered to function in parallel with little or no overlap. However, emerging research reveals that the diverse forms of PCD may be seen as a single, coordinated cell death system, in which the individual pathways are intricately interconnected.[44,45] For example, caspase-8 appears to be a central regulatory factor, determining the trajectory of cell death towards apoptosis, necroptosis, or pyroptosis, among other pathways.[46] Different types of cell death can even occur concurrently in a combined manner. A study has demonstrated that the combination of TNF-α and IFNγ or PAMPs can induce a mixed form of cell death, referred to as "PANoptosis," which simultaneously activates pyroptosis, apoptosis, and necroptosis.[47] Furthermore, IFNγ is involved in promoting ferroptosis by decreasing the expression of SCL7A11 and SLC3A2.[48] The release of cytochrome c from mitochondria initiates apoptosis, while the mitochondrial dysfunction leads to the generation of ROS, which are critically involved in the occurrence of ferroptosis.[37] The relationship between autophagy and other forms of PCD is intricate, particularly characterized by an intimate association with apoptosis. The alteration in autophagic flux is associated with the apoptosis of NPCs, and a significant enhancement in autophagic flux may accelerate the apoptotic process.[49] It is evident that various modes of PCD are intercross-regulated, with a network of synergistic interactions existing among them.

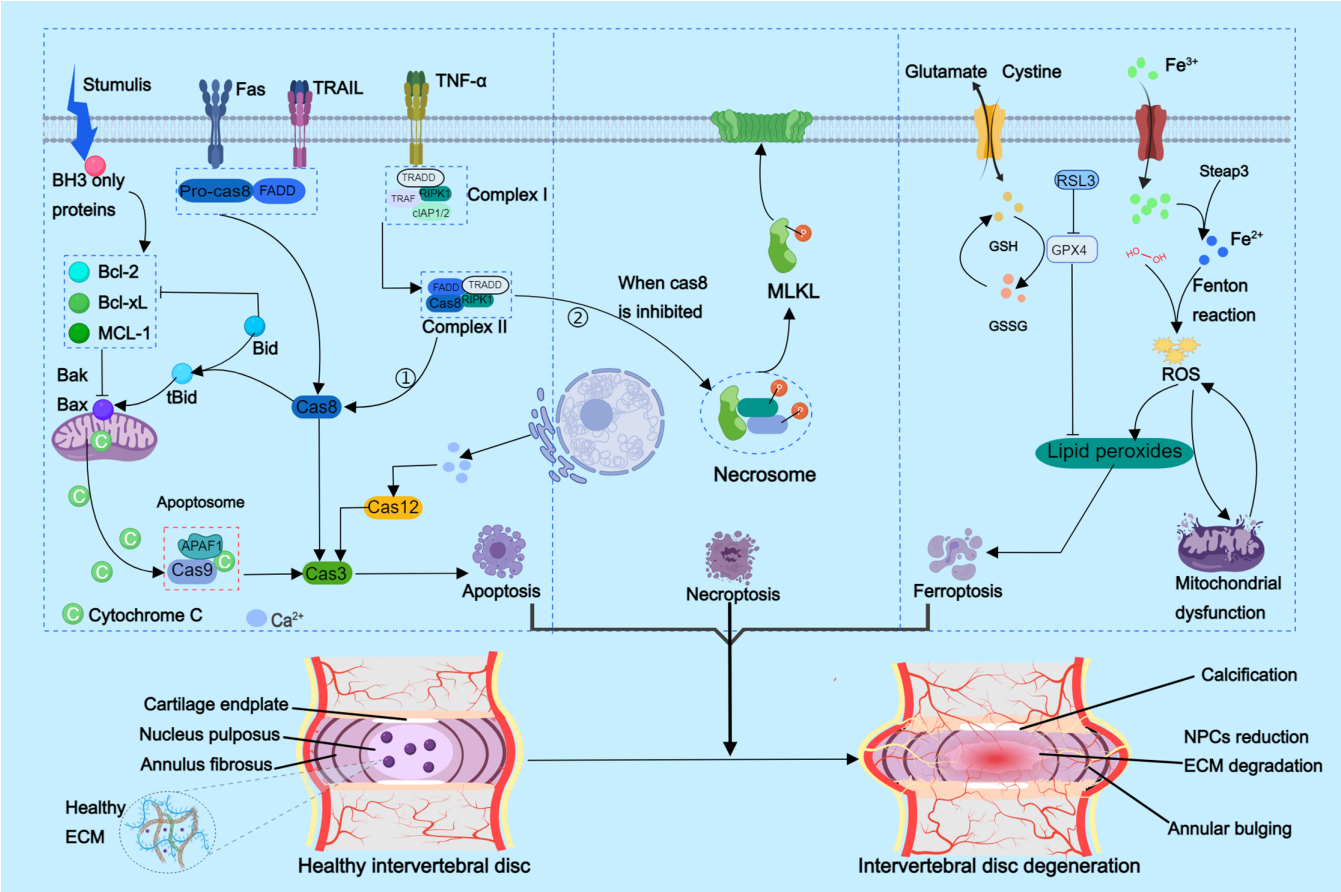

FIGURE 1 Regulatory mechanisms underlying apoptosis (left), necroptosis (middle), and ferroptosis (right) in the context of IDD. (i) Under specific biochemical conditions and stimuli, the cells of the IVD undergo PCD, resulting in the eventual degeneration of the intervertebral disc. Apoptosis-inducing factors primarily activate NPCs through pathways involving death receptors, mitochondria, and endoplasmic reticulum. This leads to caspase activation followed by initiation of apoptosis. (ii) By inhibiting caspase-8 activity, it promotes necrosome formation which subsequently triggers phosphorylation and activation of MLKL. This process induces cell membrane perforation that initiates necroptosis. (iii) The accumulation of free iron within nucleus pulposus cells reacts with H_2O_2 through Fenton reaction mechanism, resulting in lipid peroxidation. However, this process is efficiently countered by GPX4. Excessive lipid peroxidation eventually leads to ferroptosis. Apaf-1, apoptotic protease activating factor-1; BAX/BAK/tBid, pro-apoptotic proteins; BCL-2/BCL-xl/MCL-1, anti-apoptotic proteins; Cas, caspase; FADD, Fas-related death domain; GSSG, oxidized glutathione; MOMP, mitochondrial outer membrane permeability; RIPK, receptor-interacting protein kinase; Steap3, six-transmembrane epithelial antigen of the prostate3; TRADD, TNF receptor associated death domain protein; TRAIL, TNF related apoptosis inducing ligand; TRIF, TIR domain containing adaptor inducing interferon-β.

3 | PCD OF NPCs AND THEIR ROLEs IN IDD

3.1 | Apoptosis

Apoptosis of NPCs has been observed in numerous IDD patients as well as animal models.[50] Studies have demonstrated that apoptosis of NPCs can be simultaneously mediated by two or three of the apoptosis pathways. Further research suggests that targeting various pathways to inhibit apoptosis of NPCs could serve as a valuable therapeutic strategy for delaying IDD. Current studies have specifically focused on elucidating the involvement of inflammatory responses, signaling pathways, and non-coding RNAs in mediating apoptosis of NPCs.

Interleukin-1β (IL-1β) is an inflammatory factor belonging to the IL-1 family, which plays a significant role in various pathological processes associated with IDD.[51] The release of various pro-inflammatory mediators, including tumor necrosis factor alpha (TNF-α), IL-6, and matrix-degrading enzymes, can be triggered by IL-1β, thereby perturbing the equilibrium of ECM metabolism.[52] The nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways serve as crucial regulators of IL-1β-induced inflammation and degradation metabolism.[53] IL-1β induces apoptosis of NPCs through the activation of NF-κB and MAPK signaling pathways, augmentation of Caspase-3 activity, and downregulation of Bcl-2 expression.[53,54] The TNF superfamily is synthesized by various cell types, including macrophages, T cells, granulocytes, and NK cells. The members of the TNF superfamily possess pro-inflammatory properties and

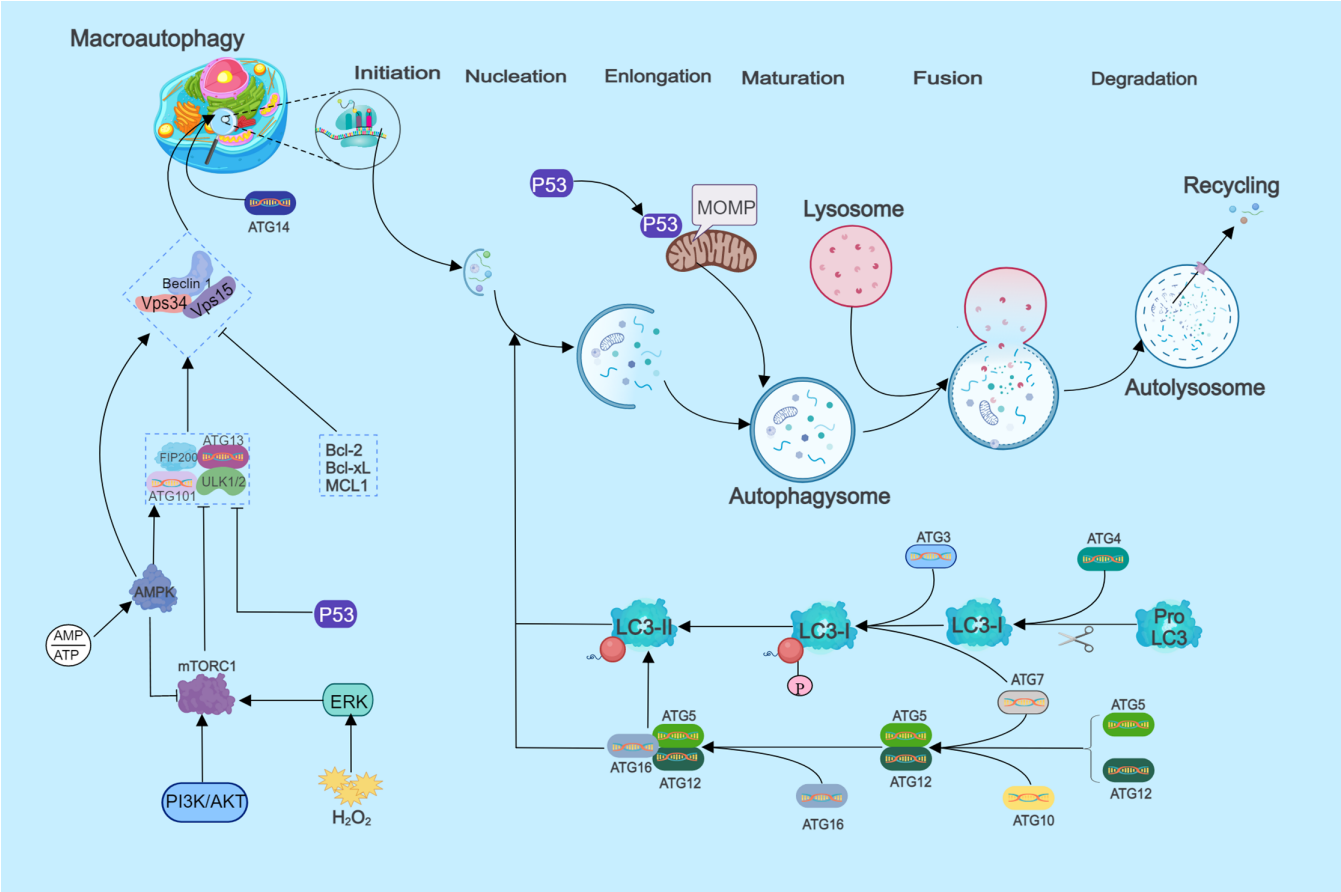

FIGURE 2 Macroautophagy-related regulatory processes. Autophagy is a cellular process that facilitates the recycling of nutrients within the cytoplasm through the degradation of structures or substances, thereby fulfilling metabolic requirements and rejuvenating specific organelles. This intricate phenomenon relies on a series of specialized complexes encompassing initiation, nucleation, elongation, maturation, fusion, and degradation stages. AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; LC3, light chain 3; MOMP: Mitochondrial outer membrane permeability; mTORC1, mechanistic target of rapamycin complex 1; ULK1/2, Unc-51-like kinase 1/2. AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; mTORC1, mechanistic target of rapamycin complex 1; MOMP: Mitochondrial outer membrane permeability; ULK1/2, Unc-51-like kinase 1/2; LC3, light chain 3.

also play an important role in the regulation of apoptosis, which are associated with IDD.[55] The majority of TNF-α's biological functions are mediated by TNF-R1, which triggers apoptosis through activation of the NF-κB, JNK, and MAPK signaling pathways.[56] Li et al. have indicated that the inhibition of NF-κB and MAPK signaling pathways can effectively attenuate apoptosis of NPCs, thereby inhibiting the progression of IDD.[57]

Within the intricate process of modulating IDD progression, non-coding RNAs (ncRNAs), notably featuring microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), exert a pivotal regulatory influence. Evidence suggested that ncRNA contributes to the progression of IDD by affecting the processes of apoptosis, autophagy, ECM degradation, and inflammation.[58] Previous reports have provided evidence supporting the association between miRNA expression and IDD. The miRNA can modulate apoptosis in NPCs through diverse molecular mechanisms. Yan et al. demonstrated that miR-328-5p modulates the proliferation and apoptosis of NPCs by regulating the expression of key apoptosis-related molecules.[59] Instead, the expression of certain miRNAs demonstrates anti-apoptotic properties, such as miR-623 and miR-155-3p.[60,61] The interaction between lnc-MT1DP and miR-365 can attenuate mitochondrial function, thereby facilitating apoptosis in NPCs, thereby facilitating IDD.[62] However, MP1DT activates the mitochondrial pathway in NPCs by downregulating Bcl-2 and upregulating caspase-3.[63] Furthermore, Song et al. demonstrated that circRNA_0000253 exerts its function through the inhibition of miRNA-141-5p, resulting in downregulation of SIRT1. Consequently, this leads to an increase in the expression of apoptosis-related proteins such as caspase3/7/9, thereby driving IDD progression.[64]

Nutrient supply is also a crucial aspect, and alterations in it can induce changes in the microenvironment of NPCs. Research has shown that nutrient deprivation can activate the BNIP3/AIF signaling pathway, leading to apoptosis of NPCs.[65] Additionally, studies have demonstrated an upregulation of Notch signaling pathway activity in NPCs within degenerated IVD tissue. This augmentation in Notch signaling is induced by the presence of IL-1β and TNF-α within NPCs.[66] However, the impact of Notch activation on NPCs remains to be elucidated. Melatonin, a molecule primarily synthesized in the pineal

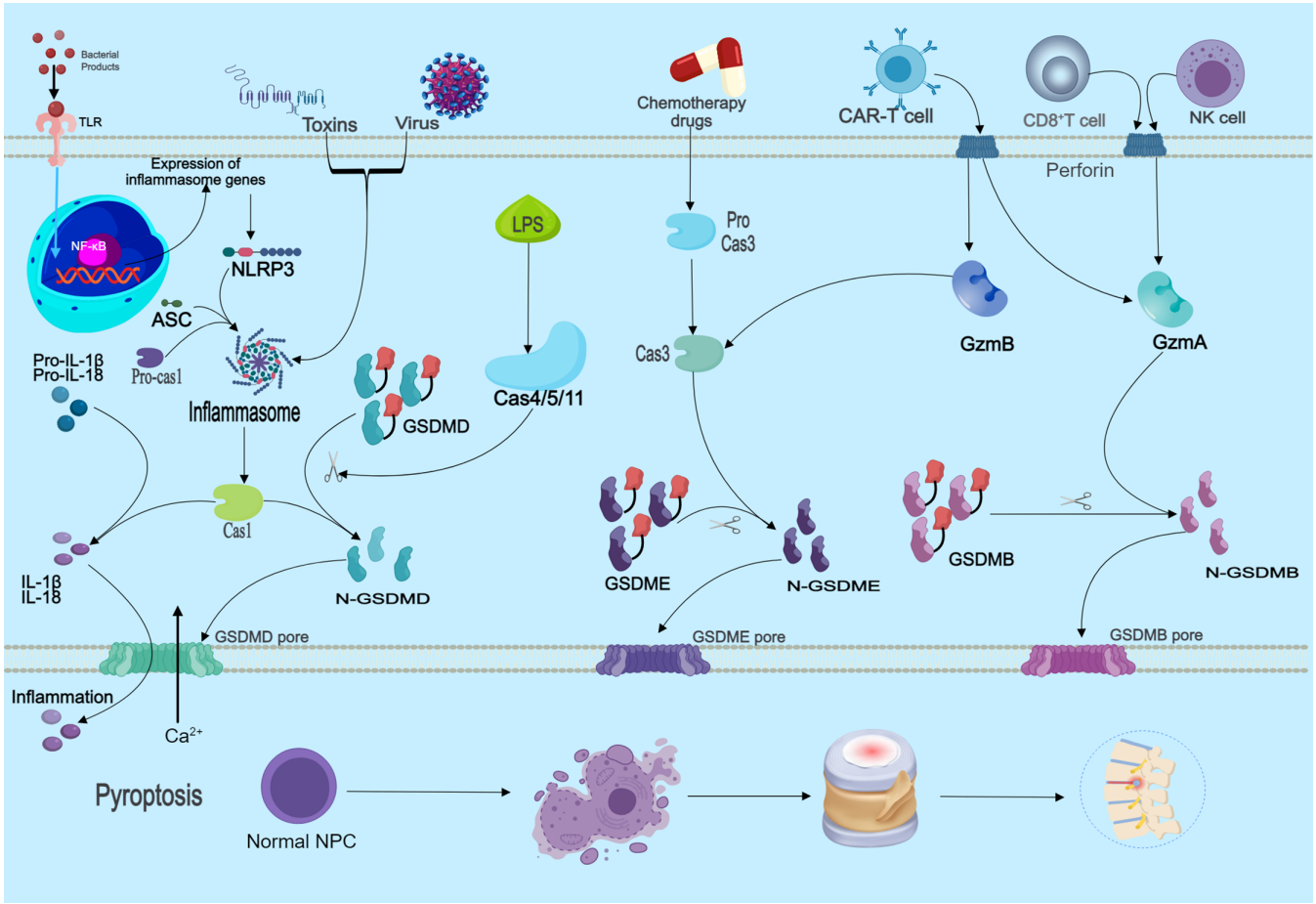

FIGURE 3 Regulatory mechanisms associated with pyroptosis and their implications IDD. (i) Canonical pyroptosis. The inflammasome recruits and activates caspase-1, which cleaves and activates IL-18 and IL-1β. Additionally, it cleaves the N-terminal sequence of GSDMD to facilitate its membrane binding for pore formation, ultimately leading to pyroptosis. (ii) Noncanonical pyroptosis. Cytoplasmic LPS can activate caspase-4/5/11, triggering the cleavage of GSDMD. (iii) Other forms of pyroptosis. Different cell types activate the gasdermin family via caspase-dependent or caspase-independent pathways, ultimately resulting in cellular expansion, membrane perforation, and subsequent release of cytoplasmic contents. Pyroptosis can ultimately result in intervertebral disc degeneration. ADSCs, adipose-derived stem cells; BMSCs, Bone marrow-derived MSCs; CESCs, cartilage endplate stem cells; MVB, multivesicular bodies; PLMSCs, placental-derived MSCs; UMSCs, umbilical cord mesenchymal stem cells.

gland, demonstrates anti-inflammatory and anti-apoptotic properties, serving as a significant mediator in various pathophysiological processes.[67] Recent research suggested that melatonin can attenuate the polarization of macrophages induced by inflammatory stimulation through modulation of the SIRT1/Notch signaling pathway. This leads to enhancements in both in vitro and in vivo inflammation-induced damage of NPCs.[68] In conclusion, apoptosis is a prominent focus in IDD research due to its involvement in numerous intricate signaling pathways. The inhibition of apoptosis emerges as a promising strategy for delaying or reversing IDD progression.

3.2 | Autophagy

Autophagy acts as a critical cell defense mechanism, enabling adaptation to the unfavorable conditions within IVD. Mounting evidence highlights its vital role in IDD, suggesting that targeting autophagy regulation could be novel therapeutic interventions targeting IDD.[49] Activation of the AMPK/mTOR pathway stimulates autophagy in human NPCs, which in turn exacerbates apoptosis, cellular senescence, and degradation of the ECM.[69] Evidence suggests that the inhibition of mTOR signaling pathway can effectively trigger autophagy, thereby mitigating apoptosis and ECM degradation.[70] Autophagy is intimately linked to inflammatory processes, and its regulatory role in inflammation is pivotal in the progression of IDD. TNF-α-induced protein 3 (TNFAIP3) plays a vital role in balancing inflammation and autophagy regulation. It enhances autophagy and reduces inflammation in NPCs under lipopolysaccharide stress, contributing to cell survival by inhibiting mTOR signaling and fostering autophagic processes.[71] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a fundamental transcription factor that plays a central role in cellular defense against oxidative stress and inflammation. The expression of Nrf2 in human NPCs exhibits an inverse correlation with the severity of IDD, and depletion of Nrf2 exacerbates IDD by downregulating the

expression of autophagy-related genes (ATG) in an induced mouse model.[72]

The miRNA plays a significant role in the regulation of autophagy of NPCs. Studies have demonstrated that miR-210 exerts inhibitory effects on autophagy of NPCs through the regulation of ATG7, miR-21 suppresses autophagy of NPCs by activating the PTEN/AKT/mTOR signaling pathway, thereby facilitating ECM degradation.[73,74] The induction of autophagy by lncRNA is not solely achieved, but rather through its interaction with miRNA, thereby establishing the lncRNA-miRNA-mRNA competitive endogenous RNA network.[75] Moreover, circRNAs have been implicated in the pathogenesis of IDD through their role as competing endogenous RNAs and modulation of autophagy.[75,76] An accumulating body of studies have demonstrated the involvement of circRNA-miRNA interactions in the regulation of autophagy associated with IDD. For instance, circRNA-ERCC2 has been shown to enhance IDD progression through modulation of the miR-182-5p/SIRT1 axis, which governs autophagy and apoptosis.[77] Consequently, targeting autophagy via ncRNA may provide valuable perspectives in the treatment of IDD.

The process of autophagy can potentially safeguard against and delay IDD by mitigating apoptosis of NPCs, degradation of ECM, cellular senescence, and inflammatory responses.[78] However, the role of autophagy in IDD remains contentious due to its apparent dual functionality. Activation of autophagy has the potential to alleviate the progression of IDD by modulating its adaptive signaling pathways. This mitigation occurs through diminishing apoptosis and suppressing the degradation of the ECM.[49,79] Reversely, excessive activation of autophagy can induce cellular damage and accelerate the apoptosis of NPCs.[79] Consequently, meticulous control over autophagic activity levels is essential to preserve the balance between autophagy's protective and deleterious roles in IDD.

3.3 | Pyroptosis

Pyroptosis, a paramount immunological response, significantly contributes to pathogen clearance and the recognition of danger signals. It participates in the initiation and advancement of IDD. Consequently, modulation of pyroptosis in NPCs has emerged as a therapeutic avenue for addressing IDD.[80] Inflammasomes, particularly the prominent NLRP3 complex, are integral to the regulation of pyroptosis. Extensive scientific inquiry is presently centered on elucidating the NLRP3 inflammasome's mediated pyroptosis in the onset and progression of IDD.[81] Significant activation of the NLRP3 inflammasome in IDD initiates a cascade of events, including heightened inflammation, pyroptosis, ECM deterioration, and apoptosis, collectively exacerbating disc degeneration. Conversely, suppressing NLRP3 activity effectively mitigates the upregulation of key pyroptotic markers.[29] A study has demonstrated that retinoic acid can suppress the generation of reactive oxygen species (ROS) and inhibiting the signaling of TXNIP/NLRP3 in dNPCs, leading to the suppression pyroptosis.[82]

Pyroptosis can be regulated by acid-sensing ion channels (ASICs). Extracellular lactate modulates intercellular ROS levels through ASIC1 and ASIC3. Zhao et al. have demonstrated that the activation of NLRP3 inflammasome and subsequent release of IL-1β, promoting NP degeneration, is facilitated by ROS-induced activation of the NF-κB signaling pathway.[83] A separate study has revealed that the involvement of thioredoxin-interacting protein (TXNIP) may contribute to the development of IDD. Specifically, under TNF-α stimulation, NPCs undergo pyroptosis via the ROS/TXNIP/NLRP3/caspase-1/IL-1β signaling pathway.[84] Meanwhile, Ma et al. demonstrated that MFG-E8 exerts a protective effect against H_2O_2-induced oxidative stress, mitochondrial dysfunction, and NLRP3 inflammasome activation. This is achieved through the inhibition of pyroptosis of NPCs and ECM degradation via modulation of the Nrf2/TXNIP/NLRP3 axis.[85] Similarly, verapamil can effectively suppress the generation of ROS and inhibit pyroptosis in NPCs through its modulation of this axis.[86]

Investigations have revealed autophagy's capability to selectively inhibit inflammasome activation, thereby restricting the discharge of inflammatory mediators. In contrast, mitochondrial membrane disruption induced by pyroptosis facilitates the release of pro-inflammatory substances and intracellular contents, amplifying the inflammatory response.[80,87] Michelet et al. revealed that lysosomes can actively participate in membrane repair mechanisms following autophagy induction.[88] These findings suggest a protective role of autophagy in the process of pyroptosis. Furthermore, Liao et al. revealed that the autophagic degradation mechanism of GSDMD mediated by P62/SQSTM1 confers protection to NPCs against LPS-induced pyroptosis.[89] In conclusion, the progression of IDD is intricately associated with the pyroptosis of NPCs. Consequently, targeted therapeutic interventions aimed at modulating pyroptosis of NPCs hold immense potential in both preventing and treating IDD.

3.4 | Ferroptosis

An increasing body of evidence has demonstrated the significant role of ferroptosis in the pathogenesis and progression of IDD.[35,37] Zhang et al. employed single-cell RNA-seq analysis to identify a novel subpopulation of chondrocytes within the NP, highlighting the involvement of ferroptosis in human IDD.[90] In a rat model of IL-1β-induced IDD, Yu et al. demonstrated the occurrence of ferroptosis in NPCs and revealed that suppressing ferroptosis can mitigate IDD.[91] These discoveries have provided a clear thought for therapeutic interventions. Currently the inhibition systems of ferroptosis primarily encompass three types, with the Cysteine/GSH/GPX4 axis previously being considered as the exclusive mechanism restraining ferroptosis.[92] In 2019, the groundbreaking discovery of ferroptosis suppressor protein 1 (FSP1) challenged previously perceived limitations, Bersuker et al. provided elucidation on the NAD(P)H/FSP1/CoQ10 axis.[93] Additionally, recent studies have unveiled the presence of an autonomous GCH1/BH4/DHFR axis, distinct from GPX4, in which tetrahydrobiopterin (BH4), functioning as a potent radical-trapping antioxidant, effectively inhibits lipid peroxidation.[94,95]

Consistent evidence from in vitro and in vivo studies underscores the pivotal role of oxidative stress in instigating ferroptosis, a process

implicated in the development of IDD. Hence, the inhibition of ferroptosis emerges as a promising for managing IDD.[37] Ferroportin (FPN) functions to alleviate oxidative stress-induced ferroptosis. Nevertheless, impaired FPN regulation can lead to iron accumulation within cells under oxidative duress, provoking ferroptosis and intensifying IDD. Lu et al. employed TBHP to generate an oxidative stress model, revealing that diminished FPN expression via suppressed MTF1 nuclear translocation induces intracellular iron accumulation and subsequent ferroptosis in NPCs.[96] Moreover, ferroptosis regulation implicates Ras GTPase-activating protein-binding protein 1 (G3BP1). Li et al. demonstrated that G3BP1 in NPCs modulates lysosomal functionality through the TSC/mTOR pathway, which curtails lipid peroxidation and diminishes free iron concentrations, thereby hindering ferroptosis.[97]

The transcription factor BACH1 exerts regulatory control over IDD by modulating oxidative stress, ferroptosis, and lipid metabolism in NPCs through the modulation of HMOX1/GPX4 signaling. Evidence has shown that reducing BACH1 levels successfully reverses the decline of SLC7A11 and GPX4 expression.[98] Ferrostatin-1 (Fer-1), a ferroptosis inhibitor implicated in IDD, inhibits this process via the TLR4/NF-κB pathway. Notably, erastin diminishes melatonin's protective effect against ferroptosis induced by cytokines, whereas Fer-1 enhances the inhibition of ferroptosis.[99] Activating Transcription Factor 3 (ATF3), functioning as a ferroptosis promoter, directly interacts with the SLC7A11 promoter, effectively downregulating SLC7A11 expression in erastin-treated cells.[100] The expression of ATF3 is significantly upregulated in the degenerative IVD tissue of rats, and it has been identified as an inhibitor of GPX4 and a driver of ferroptosis.[101] By inhibiting SLC7A11 and SOD2 activity, ATF3 efficiently curtails ROS production and ECM degradation triggered by TBHP in NPCs, thereby hindering the progression of IDD. These investigations reveal the potential of diverse factors and signaling cascades to alleviate IDD by targeting NPCs ferroptosis.

3.5 | Necroptosis

Necroptosis of NPCs is implicated as a major contributor to IDD progression. Notably, mitochondrial malfunction and disrupted autophagic pathways converge to propel NPCs toward necroptosis, which further exacerbates the IDD. Chen et al. were the first to report necroptosis in rat NPCs post-compression injury, observing elevated key necroptosis proteins, including RIP1, RIP3, and MLKL.[102] Furthermore, a notable study emphasizes the critical role of necroptosis, mediated by the RIPK1/RIPK3/MLKL pathway, in inducing NPCs death under inflammatory conditions.[103] Therefore, targeting the inhibition of necroptosis of NPCs may emerge as a promising therapeutic strategy for the treatment of IDD.

Studies have demonstrated that the specific inhibitors targeting RIPK1 (necrostatin-1), RIPK3 (GSK'872), or MLKL (necrosulfonamide) could effectively reverse the collapse of ultrastructure in NPCs, leading to a substantial reduction in NPCs death.[102] Zhao et al. discovered that H_2O_2 upregulates the expression of RIPK1 and RIPK3, leading to necroptosis in rat NPCs. However, treatment with necrostatin-1 effectively ameliorated the ultrastructural alterations associated with H_2O_2-induced necroptosis.[104] Similarly, Cao et al. observed an upregulation in the expression of necroptosis-associated molecules in NPCs treated with TNF-α or IL-1β. However, the administration of necrostatin-1, GSK872, or necrosulfonamide significantly mitigated NPCs death and enhanced their viability. Furthermore, these interventions attenuated the loss of mitochondrial membrane potential and suppressed the elevation of ROS levels, thereby demonstrating their protective efficacy against necroptosis.[103] Moreover, the necrosulfonamide possesses the capability to counteract the effects of IL-1β in promoting death of NPCs, thereby safeguarding against IDD by inhibiting both necroptosis and apoptosis.[105]

RIPK1-induced oxidative stress and mitochondrial dysfunctions are pivotal in triggering both necroptosis and apoptosis of NPCs following compression injuries. The combined modulation of these processes significantly influences NPCs survival.[106] Chen et al. have demonstrated that the utilization of necrostatin-1and Z-VAD-FMK, a cell apoptosis inhibitor, effectively enhances the viability of NPCs under conditions of mitochondrial dysfunction.[107] The necroptosis of NPCs involves the myeloid differentiation primary response 88 (MyD88). Fan et al. have demonstrated, through in vitro experiments, that inhibition of MyD88 can augment the viability and ATP levels of NPCs while concurrently reducing ROS levels, thereby effectively mitigating necroptosis in NPCs.[108] The results underscore the promise of necroptosis inhibition in NPCs as a therapeutic approach for IDD. While our understanding of necroptosis in NPCs has advanced, more research is essential to unravel the precise mechanisms by which it contributes to IDD progression.

4 | TARGETING NPCs DEATH IN THE TREATMENT OF IDD

4.1 | Cell Therapy

Cell therapy capitalizes on activating resident stem/progenitor cells and transplanting external mesenchymal stem cells (MSCs) into the IVD. These MSCs differentiate into NPCs, reinforcing the existing cell population and enhancing their overall viability and functionality.[109,110] Undoubtedly, MSCs exhibit substantial potential in augmenting NP repair mechanisms and IVD rejuvenation.[111] Various types of MSCs exhibit promising therapeutic potential in IDD due to their diverse characteristics.[112] The results of a systematic review and meta-analysis demonstrated the potential efficacy of MSCs injection therapy in reducing lumbar pain associated with IDD and significantly improving the oswestry disability index among patients suffering from IDD.[113] However, despite the substantial potential demonstrated by MSCs in delaying or reversing IDD, the problem associated with cellular transplant reactions is the significant challenge.[114] In this context, the utilization of exosomes in IDD research has yielded significant advantages.[115]

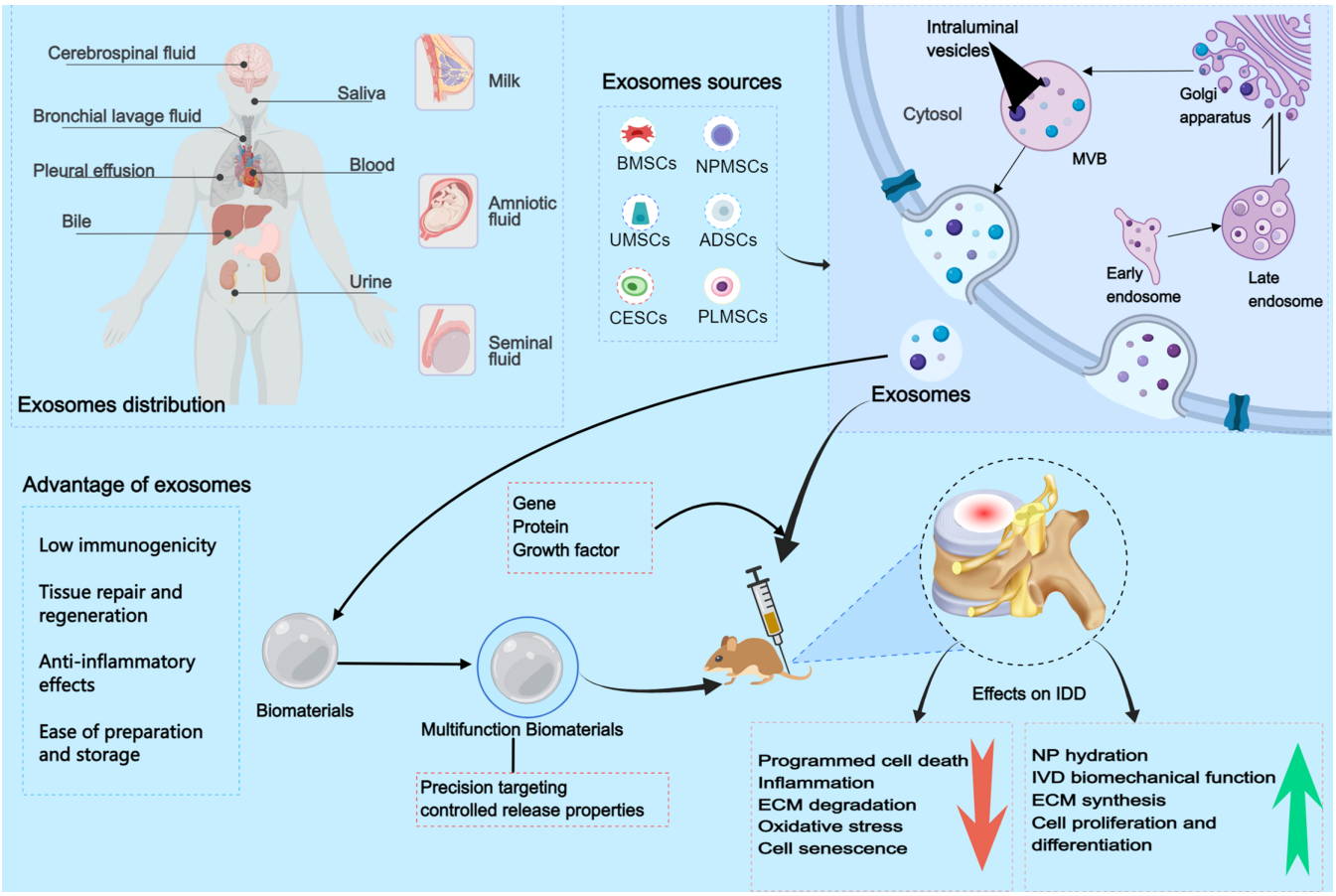

FIGURE 4 Utilization of stem cell-derived exosomes for the treatment of IDD. Annotation: Exosomes exhibit a ubiquitous distribution throughout the human body and originate from diverse populations of stem cells, rendering them promising candidates for therapeutic applications when encapsulated within hydrogels, particularly in the context of addressing intervertebral disc degeneration. ADSCs, adipose-derived stem cells; BMSCs, Bone marrow-derived MSCs; CESCs, cartilage endplate stem cells; MVB, multivesicular bodies; PLMSCs, placental-derived MSCs; UMSCs, umbilical cord mesenchymal stem cells.

Exosomes are ubiquitously present in various bodily fluids within the human organism (Figure 4). Exosomes exhibit diverse biological functions, participating in intercellular communication and material exchange. They are capable of carrying a variety of bioactive molecules, thereby influencing the physiological status and functions of recipient cells.[116] Evidence from preclinical studies suggests that the regenerative effects of stem cell therapy on tissues are mediated through the release of exosomes derived from functional cells.[117] The investigation revealed that NPCs possess the capability to engulf exosomes derived from cartilaginous endplate stem cells, resulting in a diminished expression of both Bax and MMP13. This cellular internalization mechanism consequently mitigates apoptotic activity within the NPCs.[118] In vivo experiments demonstrate that exosomes derived from human embryonic stem cells can effectively suppress NLRP3 inflammasome activation to inhibit excessive pyroptosis of NPCs.[119] Furthermore, the exosomes derived from ADSCs possess the ability to augment the migration and proliferation of NPCs while concurrently suppressing inflammatory activity, thereby exhibiting promising therapeutic potential for IDD.[120]

Due to the promising application of various MSCs in IDD treatment, the utilization of exosomes derived from MSCs (MSC-exos) has emerged as a burgeoning research focus for treating IDD (Figure 4). Currently, a plethora of studies have demonstrated the favorable effects of MSC-exos in the treatment of IDD (Table 2). According to reports, MSC-exos demonstrate the potential to inhibit apoptosis and pyroptosis in NPCs, while concurrently activating autophagy in NPCs, thereby effectively delaying or even reversing the progression of IDD.[121] Exosomes derived from bone marrow-derived MSCs possess the capability to attenuate apoptosis of NPCs. The study has demonstrated that miR-217 in MSC-exos exhibits remarkable efficacy in effectively suppressing apoptosis of NPCs and preventing ECM degradation.[122] Zhang et al. demonstrated that exosomal miR-410 derived from MSCs effectively inhibits NLRP3-mediated pyroptosis.[123] Furthermore, the exosomes derived from human umbilical cord MSCs possess the capacity to selectively target METTL14, thereby augmenting the viability of NPCs and shielding them against pyroptosis.[124] In summary, MSC-exos offer a multitude of advantages, primarily stemming from their capacity to elicit therapeutic effects similar to those of MSCs while circumventing the adverse reactions associated with cell transplantation.[125–127] MSC-exos exhibit

TABLE 2 The stem-cell derived exosomes for IDD therapy.

Exosomes	Experimental subject	Cell origin	Treatment	Study	Effect	Reference
BMSCs-exo	Six-eight week-old Sprague–Dawley male SPF rats	Rat	Intradiscal injection 30 μg once	In vitro and in vivo	Reduce NPCs apoptosis and alleviate IDD by promoting autophagy	Xiao et al., 2022[115]
	Twelve-week-old C57BL/6J male mice	Mice	Tail vein inject 100 μL (3 μg/μL) once a week for 6 weeks	In vitro and in vivo	Inhibit NPCs apoptosis and ECM degradation and attenuate IDD	Yu et al., 2022[125]
	Rabbit	Mice	-	In vitro	Inhibite NLRP3 inflammasome activation and attenuate NPCs apoptosis	Xia et al.,2019[117]
CESCs	Eight week-old male Sprague–Dawley rats	Rat	Intradiscal injection 2 μL (1×10^{10}/mL) once	In vitro	Alleviate IDD by inhibitng TBHP-NPCs apoptosis	Chen et al., 2022[118]
hESCs-exo	Three-month-old Sprague Dawley rats	Human	Intradiscal injection 2 μL (100 μg/mL) once	In vitro	Delay IDD by alleviating NLRP3 inflammasome induced pyroptosis of NPCs	Yu et al., 2023[119]
hASCs-exo	Eight week-old male Sprague–Dawley rats	Human	Intradiscal injection 1.5×10^{6} once a week for 9 weeks	In vitro	Alleviate IDD by targeting TGFβR2 to promote autophagy and reduce pyroptosis	Chen et al., 2023[120]
MSCs-exo	Three-month-old Sprague–Dawley rats	Human	Intradiscal injection 2 μL (1.5×10^{6}) once and repeated 4 weeks later	In vitro and in vivo	Attenuate NPCs apoptosis and ECM degradation through the delivery of miR-217	Hao et al., 2022[122]
	Wild-type C57BL/6 mice	Mice	Tail vein inject 500 μL (20 μg/mL) once	In vitro	Inhibit NPCs pyroptosis via the NLRP3 pathway and alleviate the severity degree of IDD	Zhang et al., 2020[123]
hucMSCs-exo	Human NPCs	Human	-	In vitro	Improve the viability of NPCs and inhibit pyroptosis through targeting METTL14	Yuan et al., 2021[124]
iMSCs-exo	Twelve-week-old Sprague–Dawley rats	Human	Intradiscal injection 2 μL (1×10^{10}) once 2 weeks for 8 weeks	In vitro and in vivo	Rejuvenate the senescence of NPCs and attenuate the development of IDD	Sun et al., 2021[126]
hPLMSC-exo	Fifteen-week-old C57BL/6 male mice	Human	Intradiscal injection 2 μL (1×10^{10} particles/mL) once	In vitro and in vivo	Inhibit the inflammation, apoptosis of NPCs and alleviate IDD	Yuan et al., 2020[127]

additional benefits including precise targeting, personalized treatment options, and an enhanced level of safety.

In recent years, the integration of cellular therapy and biomaterial is becoming an innovative focal point in the realm of stem cell-based regenerative therapy.[128] The efficacy of biomaterials as carriers for cellular therapy has been demonstrated through continuous investigation and experimentation.[129] The integration of exosomes with biomaterials has also been demonstrated to augment the regenerative and reparative potential of NP.[130] A diverse array of biomaterials is available, with hydrogels, microspheres, and nanomaterials being the most frequently employed (Figure 5). Reaching the treatment site for drugs often poses challenges due to the avascular nature of IVD. However, biomaterials possess the capability to deliver drugs, stem cells, growth factors, exosomes, and genes to the NP[131–133] (Figure 5). Biomaterials boast excellent biocompatibility and targeted drug release properties, making them invaluable for NP restoration and regeneration. Cell therapy utilized in conjunction with biomaterials, both can optimize their respective benefits. However, realizing their full potential in clinical regenerative therapies requires further experimental validation.

4.2 | Traditional Chinese medicine

With a legacy exceeding a thousand years, Traditional Chinese Medicine (TCM), a precious treasure of China, has significantly contributed to the prevention and treatment of IDD.[134] The efficacy of TCM in preventing and delaying IDD, as well as providing significant pain relief, has been scientifically validated.[135,136] The practical experience has demonstrated the significant efficacy of acupuncture, moxibustion, and acupressure in managing both acute and chronic pain[136] (Figure 6). In addition to pain relief, these measures can also mitigate IDD through various signaling pathways. The study has demonstrated that moxibustion has the potential to enhance autophagy and attenuate apoptosis of NPCs through activation of the HIF-1α/VEGF pathway, thereby effectively alleviating IDD.[137] Extensive research has demonstrated the potential of herbal compounds and their monomers in the treatment of IDD[138] (Figure 6). Currently, the therapeutic mechanism of TCM in the treatment of IDD primarily involves modulating the release of inflammatory mediators, thereby suppressing inflammatory responses, mitigating oxidative stress, and preventing death of NPCs.[139–141]

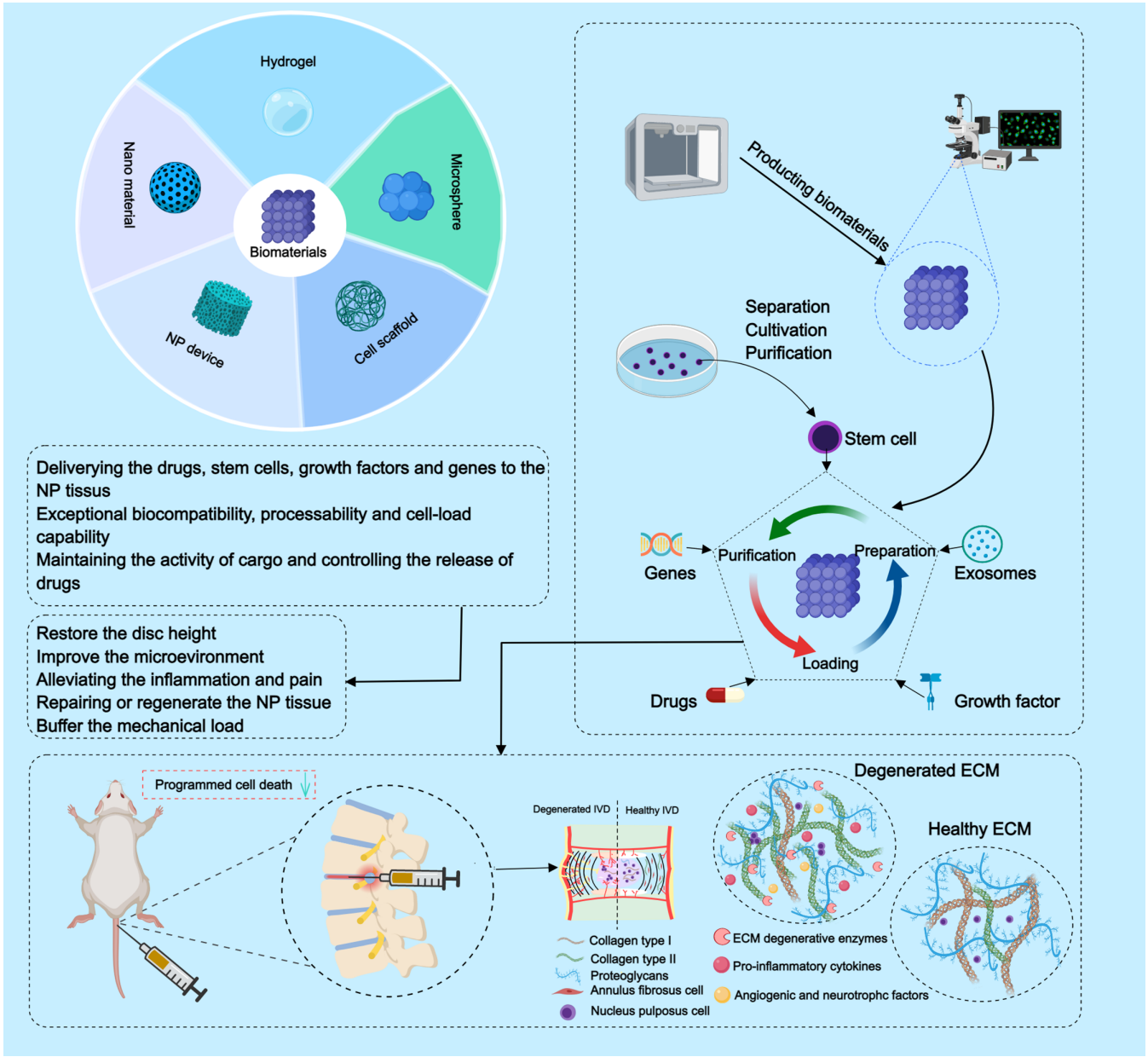

FIGURE 5 Biomaterials utilized for the purpose of treating or regenerating IDD. A diverse range of biomaterials can be utilized for the targeted delivery of stem cells, extracellular vesicles, conventional pharmaceutical agents, genes, and growth factors to the nucleus pulposus, thereby offering promising therapeutic prospects for intervertebral disc degeneration.

Numerous studies have demonstrated the anti-IDD activity of extracts derived from Chinese herbal plants (Table 3). Sodium tanshinone IIA sulfonate demonstrates potent anti-inflammatory and antioxidant properties by effectively inhibiting the p38 MAPK signaling pathway.[142] Scutellarin effectively mitigates the generation of ROS induced by TNF-α stimulation, ameliorates mitochondrial impairment, and inhibits apoptosis in NPCs. Moreover, Scutellarin exerts an antagonistic effect on the activation of both NF-κB and MAPK signaling pathways, thereby suppressing NLRP3 inflammasome activity.[143] Panax notoginseng saponins (PNS) are the primary active constituents of Sanqi. The injection of PNS has been employed to alleviate pain caused by IDD and has demonstrated promising therapeutic efficacy in clinical practice. The PNS exhibits a protective effect on human NPCs against apoptosis through the inhibition of autophagy.[144] Bai et al. demonstrated, through animal experiments, that Cyanidin effectively inhibits the phosphorylation of JAK2 and STAT3 in IL-1β-induced NPCs, thereby suppressing apoptosis and ameliorating IDD.[145] Gong et al. have demonstrated the effective inhibition of NLRP3 activation by maltol, leading to suppression of pyroptosis in NPCs.[146] Zhang et al. demonstrated the inhibitory effect of Cynarin on the metabolic breakdown of NPCs, as well as its capacity to enhance GPX4 and NRF2 expression while suppressing ferroptosis.[147]

The utilization of both Duhuo Jisheng Decoction (DHJSD) and Bushen Huoxue Decoction (BSHXD) has been extensive, showcasing

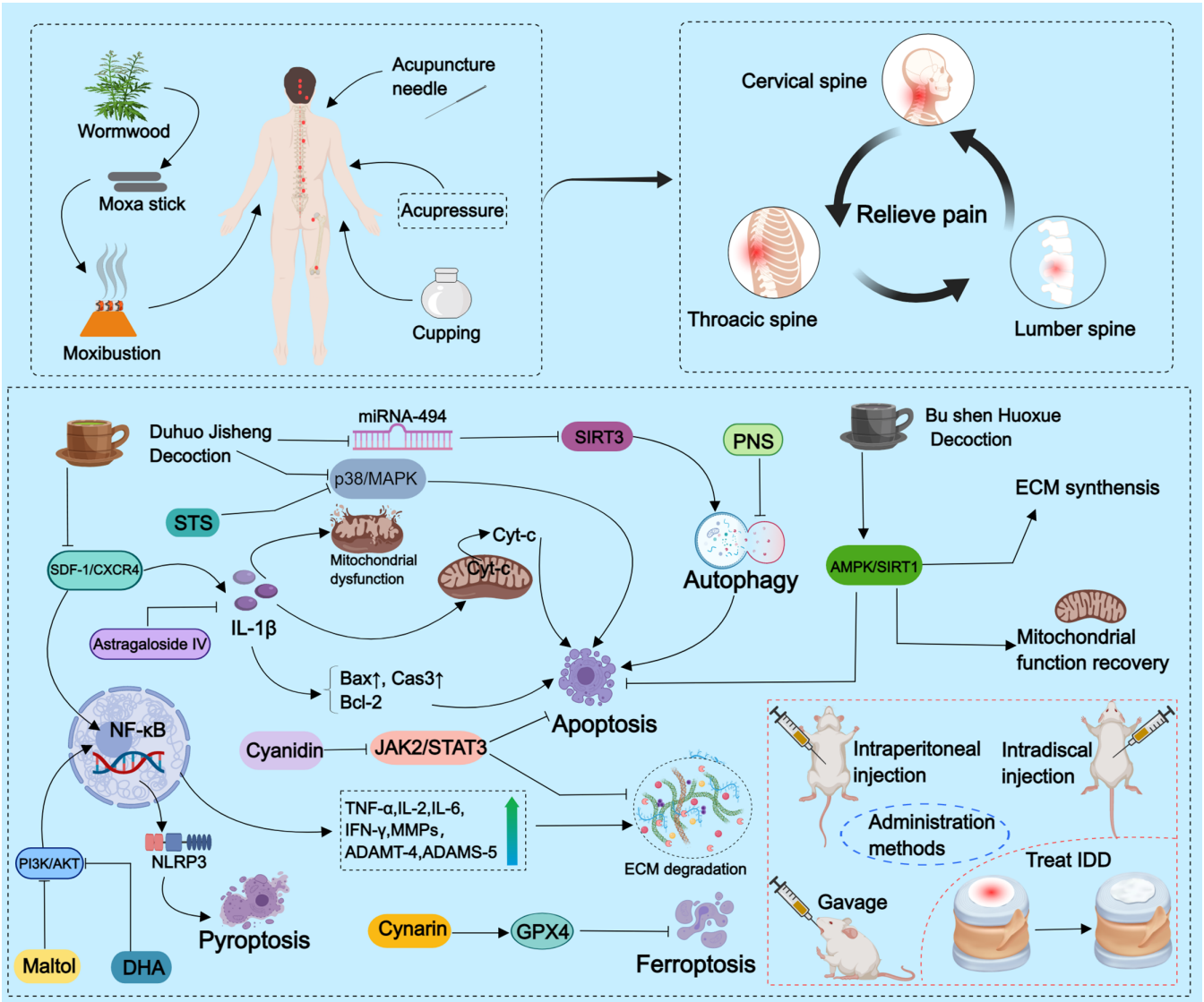

FIGURE 6 The therapeutic approach of traditional Chinese medicine for IDD. Annotation: The therapeutic approach of traditional Chinese medicine can be divided into two components. The upper component, as depicted in the diagram, encompasses physical interventions such as acupuncture, moxibustion, and cupping, which are employed for alleviating pain associated with intervertebral disc degeneration. The lower component focuses on elucidating the mechanisms and administration methods of Chinese herbal formulas and extracts in the treatment of intervertebral disc degeneration. ADAMT, a disintegrin and metalloproteinase with thrombospondin motif; Cas, caspase; DHA, dihydroartemisinin; ECM, extracellular matrix; MMP, matrix metalloproteinase; PNS, panax notoginseng saponins; SIRT1, silent information regulator 1; SIRT3, silent information regulator 3; STS, sodium Tanshinone IIA Sulfonate.

their favorable therapeutic effects through distinct mechanisms.[148,149] The study demonstrates that BSHXD effectively inhibits apoptosis and promotes ECM synthesis through modulation of autophagic flux. Furthermore, it also regulates oxidative stress and facilitates restoration of mitochondrial function by activating the AMPK/SIRT1 pathway.[150] The autophagy flux can be effectively restored by apigenin through modulation of the AMPK/mTOR signaling pathway.[151] Furthermore, BSHXD exhibits a significant inhibitory effect on the development of inflammatory factors, thereby effectively suppressing apoptosis of NPCs and ECM degradation.[152] The DHJSD exhibits potent anti-inflammatory and anti-pyroptotic properties. Recently, a study has demonstrated that DHJSD exerts its therapeutic effects on IDD by effectively suppressing the pyroptosis of NPCs through modulation of the SDF1/CXCR4-NFkB-NLRP3 axis.[153] Furthermore, the DHJSD exerts a modulatory effect on the inflammatory response, leading to a reduction in apoptosis and pyroptosis in NPCs, as well as inhibition of ECM degradation.[154]

TCM has an extensive reservoir of experiential insights and a distinct theoretical framework in addressing IDD. Nonetheless, it simultaneously grapples with the challenges posed by the demand for empirical evidence and efficacy validation within the context of contemporary medical research standards. As advancements in scientific research methodologies progress and intercultural exchanges between Eastern and Western medical practices intensify, the intent

TABLE 3 Extracts derived from Chinese herbal plants demonstrate anti-IDD activity.

Extract	Experimental subject	Treatment	Study	Efficacy	References
Engeletin	Twelve-week-old male Sprague–Dawley rats	Intradiscal injection 50 μL (80 μM) every week for 4 weeks	In vitro and In vivo	Inhibit NPCs apoptosis and inflammation via NF-κB and MAPK Pathways	Li et al., 2022[57]
Eupatilin	Eight-week-old male Sprague Dawley rats	Intradiscal injection 10 μL (12.5 μM and 25 μM) twice a week for 4 weeks	In vitro	Attenuate NPCs senescence and mitigate IDD by inhibiting the MAPK/NF-κB signaling pathways	Yang et al., 2022[139]
Astragaloside IV	Three-month-old Sprague Dawley rats	Intragastric injection 50 mg/kg every day for 4 weeks	In vitro and In vivo	Alleviate inflammation, apoptosis, and ECM degeneration in NPCs	Tian et al., 2022[140]
Mangiferin	Three-month-old male Sprague Dawley rats	Intradiscal injection 0.2 μg once	In vitro and In vivo	Inhibit the NF-κB signaling pathway mitigated the activation of mitochondrial ROS in NPCs	Yu et al., 2021[141]
Sodium Tanshinone IIA Sulfonate	Twelve-week-old male Sprague–Dawley rats	Intraperitoneal injection 10 and 20 mg/kg every day for 4 weeks	In vitro and In vivo	Inhibit the p38 MAPK signaling pathway demonstrated anti-inflammatory and antioxidative	Dai et al., 2021[142]
Scutellarin	Eight-week-old male Sprague Dawley rats	Intradiscal injection 2.5 μL (100 ng/μL) once	In vitro and In vivo	Inhibit the NPCs apoptosis and alleviate the mitochondrial damage	Wang et al., 2022[143]
Panax notoginseng Saponins	Three-month-old male Sprague Dawley rats	Intraperitoneal injection 160 and 200 mg/kg every other day for 4 and 8 weeks	In vitro and In vivo	Decrease the apoptosis of NPCs via autophagy	Guo et al., 2023[144]
Cyanidin	Eight-week-old male Sprague Dawley rats	Intraperitoneal injection 50 mg/kg every day for 8 weeks	In vitro	Attenuate IDD and the apoptosis of NPCs via the JAK2/STAT3 signal pathway	Bai et al., 2022[145]
Maltol	Mice	Gavage 15 or 30 mg/kg twice a week for 12 weeks	In vitro	Inhibit the PI3K/AKT/NF-κB signaling pathway and NLRP3 inflammasome-mediated pyroptosis	Gong et al., 2023[146]
Cynarin	Eight-week-old male Sprague Dawley rats	Intradiscal injection 20 μL (50 μM) twice	In vitro	Inhibit the degradation of the ECM of NPCs and ferroptosis in NPCs	Zhang et al., 2022[147]
Apigenin	Eight-week-old male Sprague Dawley rats	Gavage 10 mg/kg every day for 8 weeks	In vitro and In vivo	Attenuate IDD by restoring autophagy flux in NPCs	Xie et al., 2021[151]

is for TCM to maintain its unique features while enhancing its evidence-based and precision-focused application in IDD therapy. The future endeavors aim to integrate TCM methodologies into a more rigorous and targeted therapeutic approach.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

As a significant disabling disease, IDD has garnered escalating global attention due to its sophisticated nature and chronicity. The escalating prevalence of IDD and the subsequent surge in healthcare expenditures underscore the imperative for advancing therapeutic modalities. The initiation of IDD is intricately linked to the PCD of NPCs. Numerous studies have demonstrated an increasing number of potential targets can be used to effectively prevent the occurrence and progression of IDD. Additionally, the development of targeted pharmaceuticals based on the PCD mechanism of NPCs can effectively impede NPCs loss. The pathways of cell death coexist and frequently engage in intricate crosstalk, therefore, elucidating the interrelationships among diverse types of PCD can offer novel insights into the occurrence and progression of IDD. Cell therapy holds immense potential, however, its implementation in clinical trials is accompanied by ethical concerns and challenges. Although animal models may not precisely reflect the human condition in vivo, if appropriately designed, ncRNAs, cytokines, exosomes, and biomaterials can be utilized as innovative therapeutic strategies for regulating PCD and treating IDD. Future research needs to pay more attention to the combination of cell therapy with biomaterials.

Targeting NPCs PCD as an innovative therapeutic strategy for IDD has witnessed significant theoretical advancements and demonstrated initial efficacy. However, before its broad clinical adoption, several technical and scientific challenges must be surmounted. Uncovering and targeting key molecular mediators of IDD is vital for the development of efficacious therapies. Identifying and precisely targeting selected key targets will be a primary focus of future research.

Furthermore, existing evidence indicates that biomaterials have demonstrated significant potential in drug delivery, and their combination with cell therapies has not only enabled precise targeting but also vastly enhanced therapeutic outcomes. Although preliminary experimental findings hint at the therapeutic potential of targeting NPCs PCD, rigorous clinical trials are required to ascertain long-term effects and detect potential adverse reactions.

AUTHOR CONTRIBUTIONS

Miao Liu: Conceptualization, Funding acquisition, review and editing. **Xu Ning**: Conceptualization, supervision, review and editing. **Hong Sun**: Conceptualization, writing original draft, data collection and reviewing related literature from online databases. **Jiajie Guo**: Writing original draft, data collection and reviewing related literature from online databases, visualization. **Zhilin Xiong**: Visualization, review and editing. The final version of the manuscript was approved by all authors. **Yong Zhuang**: Review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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