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REVIEW

Targeting Inflammatory Cell Death: A Strategy for Discogenic Pain Relief

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Abstract: Low back pain caused by intervertebral disc degeneration (IVDD) remains a major challenge in clinical management, and its underlying mechanisms have not yet been fully elucidated. Beyond apoptosis, recent studies have shown that pyroptosis, ferroptosis, and necroptosis—as key inflammatory programmed cell death pathways—actively contribute to the pathological progression of IVDD and the development of pain. Currently, effective clinical solutions for discogenic pain are still lacking. This review systematically elaborates on the mechanisms of pyroptosis, ferroptosis, and necroptosis, and explains their activation in different anatomical regions of the intervertebral disc (nucleus pulposus, annulus fibrosus, and endplate). These processes promote pain by altering the local microenvironment, such as through the release of inflammatory factors and the disruption of tissue structure. Furthermore, the article summarizes potential therapeutic strategies targeting these specific cell death pathways, including molecular inhibitors, natural compounds (eg, hesperidin, melatonin), and traditional formulations, with a focus on their prospects for alleviating IVDD-related pain by modulating core cell death mechanisms. By systematically reviewing these novel cell death mechanisms and related therapeutic strategies, this work aims to provide new insights and evidence for the clinical management of discogenic pain.

Keywords: pain, intervertebral disc degeneration, pyroptosis, ferroptosis, necroptosis

Introduction

Epidemiological studies estimate that approximately 540 million individuals are affected by low back pain annually, making it the main cause of disability worldwide.[1] Intervertebral disc degeneration (IVDD), a common degenerative disc disease, is the most common cause of lower back pain.[2] In clinical settings, pain stands as the predominant symptom of driving IVDD patients to seek medical help, substantially impairing their daily functioning and well-being. Lesions such as disc herniation, spinal stenosis, instability, spondylolisthesis, radiculopathy, and scoliosis can cause acute or chronic pain in the neck and waist.[3] Lower back pain can be categorized into several subtypes: nociceptive pain stemming directly from tissue injury, neuropathic (radicular) pain, and the nociceptive pain associated with central sensitization (typically classified as non-specific lower back pain). These subtypes frequently coexist. Patients with disc herniation who suffer from back pain may have radicular pain and nociceptive pain.[4]

IVDD is mainly treated by non-invasive methods (drugs and physical therapy) and invasive surgery (discectomy and spinal fusion), with the goal of providing immediate relief of severe pain.[5–7] At present, conservative treatment includes rest, physical therapy, drugs and rehabilitation exercise to relieve pain, improve function and promote recovery. Traditional conservative treatment has a good effect in the early stage of the disease, but the effect gradually weakens as the disease progresses. Surgical intervention, encompassing both minimally invasive and open procedures (eg, discectomy, disc replacement, or artificial disc implantation), is generally indicated for patients refractory to conservative therapy or with severe pathology. Surgical intervention enables most patients to achieve significant pain relief and

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a marked improvement in their quality of life. However, surgery may lead to serious intraoperative or postoperative complications. IVD fusion results in restricted spinal mobility and elevated stress on adjacent segments, thereby accelerating their degeneration. These inherent drawbacks of conventional treatments have driven spine researchers to pursue more effective, durable, and safer therapeutic alternatives.

The Intervertebral disc (IVD) structure is composed of annulus fibrosus (AF), nucleus pulposus (NP) and cartilaginous endplates on the upper and lower surfaces. Their cellular changes may be the beginning of disc degeneration and lower back pain.[8] Inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), matrix metalloproteinases (MMPs), nitric oxide, cyclooxygenase 2 (COX-2) and nerve growth factor (NGF), are critically involved in the pathogenesis of IVDD, primarily through the activation of NF-κB and p38/MAPK signaling pathways. They enhance inflammation and promote catabolism in human nucleus pulposus cells (NPCs); Disrupting the metabolic homeostasis of extracellular matrix leads to chronic inflammation, which in turn leads to structural and biochemical changes of the IVD; and may induce the production of painrelated compounds to promote nerve proliferation in the IVD. This review aims to first elucidate the mechanisms through which disc degeneration leads to pain, with a specific focus on the role of various cell death modalities. Furthermore, it evaluates how therapeutic agents modulate cell death processes, thereby informing the development of novel clinical interventions (Table 1).

Mechanism of IVDD Pain

The generation and maintenance of low back pain associated with IVDD are related to its structural destruction, inflammatory response and nerve sensitization. The pain caused by IVDD is complex. The nature, location, duration and intensity of pain change with the progression of the disease.

Tissue Structure Changes and Biomechanical Imbalance

Anatomically, the IVD consists of the central NP, the peripheral AF, and the superior/inferior cartilage endplates. The NP is a hydrophilic, proteoglycan-rich gel that sustains the disc's hydration and internal pressure via its osmotically driven water-binding capacity. Meanwhile, the cartilaginous endplates—thin hyaline cartilage layers—serve as crucial metabolic interfaces. They govern the exchange of solutes and fluids, central to maintaining the nutritional equilibrium and waste removal essential for the viability of the avascular NP. Because the IVD is avascular tissue, only the outermost layer of the AF is supplied by arterioles, and the rest relies on the vertebral vessels under the endplate and the peripheral AF for material exchange, this limited nutrient supply and self-healing ability make it more prone to degenerative changes.[21,22]

Table 1 General Treatment and Application of IVDD

Treatment		Application	Ref
Physical therapy	Exercise (Pilates therapy, strength training)	Improvement of pain status and gait disorder	[7]
Medications	NSAIDs	Reduction of inflammatory factors in pain pathways, improving symptoms of depression	[9–11]
	Opioids	Severe pain that is not improved by over-the-counter painkillers	[12]
	Topical patches (lidocaine and capsaicin)	Peripheral neuropathic pain	[11]
	Platelet-rich plasma	Pain in degenerative diseases of the spine, accelerating bone union during spinal fusion surgery	[13]
	Glucocorticoids	Inhibits expression of pro-inflammatory cytokines and induces apoptosis in inflammatory cells	[14]
Interventional Measures	Selective nerve root blocks	Conservative treatment is not effective, managing radiculopathy or spinal stenosis	[15,16]
	Transcutaneous electrical nerve stimulation	Providing analgesia by delivering activating stimuli of different frequencies to afferent nerve fibers	[17]
Surgery	Discectomy	Conservative treatment is not effective, disease duration of at least two to three months	[18,19]
	Spinal fusion		[20]

Central to the pathophysiology of IVDD is a progressive deterioration in the disc's biological and biomechanical properties, leading to a loss of structural integrity and function. This degenerative milieu is driven by abnormal secretion of pro-inflammatory cytokines (eg, TNF-α, IL-1β, IL-6, IL-17) from NPCs and AFCs, which in turn directly upregulate key matrix-degrading enzymes like ADAMTS-4/5 and MMPs. These enzymes degrade collagen and proteoglycan structures, leading to the loss of disc structural integrity (eg, annular tears and nucleus pulposus herniation). The structural breakdown of the disc disrupts biomechanics and directly or indirectly induces pain. Herniated discs can compress the spinal cord and nerve roots. Additionally, mechanical compression can directly damage or indirectly affect spinal nerve roots and the spinal cord through inflammation.[23] Chronic compression may lead to neuronal death and irreversible nerve injury, resulting in persistent pain. Calcification of the cartilaginous endplate impedes nutrient diffusion, and death of NPCs accelerates extracellular matrix degradation. Loss of disc height increases loading on the facet joints, precipitating arthrogenic pain.[24,25]

Neurovascular Invasion and Nerve Sensitization

The expression of SEMA3A in healthy discs is restricted to the outer AF, where it functions to prevent nerve and vascular ingrowth, while being virtually undetectable in the NP. The degenerative disc microenvironment is defined by a constellation of pathological changes, including aberrant neovascularization and ingrowth of nociceptive fibers, coexisting with conditions such as hypoxia, acidosis, mechanical stress, and hyperosmolarity. These stressors drive progressive deterioration of the disc milieu and accelerate the degenerative cascade. Several studies have demonstrated that depletion of proteoglycans promotes annular degradation and vascular invasion of the cartilaginous end plate, and—synergistically with NGF—facilitates the ingrowth of nociceptive fibers (eg, C-fibers) into the NP, thereby generating discogenic pain.[26,27] These nociceptive fibers express pain-related receptors such as TRPV1, enabling them to respond directly to local inflammatory cues and thereby initiate pain.[28] For instance, SEMA3A serves as a key nerve growth inhibitory factor in the IVD microenvironment. In healthy discs, SEMA3A is highly expressed in the outer AF, where it suppresses nerve and vascular ingrowth, while its expression is nearly absent in the NP. However, in degenerated discs, SEMA3A expression in the AF significantly decreases, lifting this inhibition and allowing aberrant nerve and vascular invasion into the inner regions. Concurrently, SEMA3A expression in the degenerated NP markedly increases, which may represent a compensatory response to the loss of SEMA3A in the AF, attempting to hinder further neural infiltration.[29]

Besides nerve ingrowth, pain sensitization serves as another crucial mechanism underlying discogenic pain resulting from IVDD, which can be categorized into peripheral sensitization and central sensitization. In the peripheral context, vascular endothelial growth factor (VEGF) levels are significantly elevated in degenerated discs, thereby promoting the expression of pro-inflammatory cytokine TNFα and matrix metalloproteinase MMP-13, which exacerbates inflammatory responses and tissue destruction. Studies have demonstrated that selective activation of VEGFR-1 constitutes a key pathway in the development of nociceptive hypersensitivity: in models of disc degeneration, silencing vegfr-1 markedly suppresses VEGF-induced expression of pain markers.[30] Furthermore, NGF and various inflammatory cytokines can sensitize TRPV1 and ASIC3 receptors respectively, lowering pain thresholds and leading to hyperalgesia and allodynia. Hypoxic metabolism within degenerated discs also results in the accumulation of lactate and protons, which activates acid-sensing ion channels (ASIC3) and directly stimulates nociceptive nerve endings. Additionally, sustained mechanical overload can elevate prostaglandin E2 (PGE2) levels, which activates TRPV1 channels in sensory neurons via the EP4 receptor. This transmits pain signals to the hypothalamus, further modulating sympathetic nerve tone and enhancing pain sensitivity.[31]

At the central level, sustained input of peripheral nociceptive signals can induce significant neuroplastic changes in the spinal dorsal horn.[32] Meanwhile, spinal neurons become hyperexcitable and synaptic efficacy is enhanced, a process characterized by massive activation of NMDA receptors. This leads to calcium influx, which triggers a cascade of intracellular signaling events that lower neuronal excitation thresholds and enhance the transmission and response to pain signals. Concurrently, brain-derived neurotrophic factor (BDNF) released from regions such as the periaqueductal gray not only facilitates glutamatergic transmission but also enhances synaptic plasticity by modulating postsynaptic TrkB receptors, thereby further amplifying and prolonging nociceptive signaling. Additionally, microglia and astrocytes are activated and release various cytokines (eg, TNF-α, IL-1β), sustaining a central inflammatory microenvironment that collectively contributes to a persistent state of central sensitization.[33] This functional and structural remodeling places the

pain transmission pathway in a heightened state of sensitivity, enabling pain to become self-sustaining even after the original peripheral stimulus has diminished, ultimately leading to chronic low back pain (Figure 1).

Inflammatory Response and Pain Mediators

IVDD is a chronic, non-infectious inflammatory condition marked by the upregulated expression of various inflammatory factors, including IL-1β, IL-6, and TNF-α. These cytokines promote the abnormal ingrowth of nerve fibers into degenerated discs, ultimately leading to clinical symptoms like low back pain.[34] Substantial evidence indicates that tissue levels of IL-1β and TNF-α are markedly increased in painful discs and exhibit a positive correlation with pain intensity on VAS scales.[35] The NF-κB signaling pathway serves as a primary regulator for the production and activation of these inflammatory mediators, playing a central role in IVDD and discogenic pain. In particular, TNF-α amplifies local inflammation and impairs extracellular matrix metabolism by activating the NF-κB/MAPK pathway, thereby accelerating disc degeneration.[36] Moreover, studies in rat models have revealed that TNF-α suppresses SHOX2 gene expression in disc cells via the NF-κB pathway, a mechanism that further promotes degenerative changes and pain sensitization.[37]

In addition to the aforementioned factors, the TGFβ1/NF-κB signaling axis also plays a critical role in IVDD, mediating inflammatory responses and contributing to NPC dysfunction. Studies have revealed significantly elevated expression of both TGFβ1 and the chemokines CCL3/4 in degenerated nucleus pulposus tissues. TGFβ1 may negatively regulate CCL4 expression in NPCs through activation of the ERK1/2 signaling pathway, thereby delaying the progression of lumbar disc degeneration, attenuating inflammatory responses in dorsal root ganglia (DRG), and reducing pain generation.[38] On the other hand, the deacetylase SIRT1 inhibits the nuclear translocation of NF-κB by deacetylating the RelA/p65 protein, thereby attenuating the inflammatory response in IVDD. Furthermore, SIRT1 suppresses IL-1β-

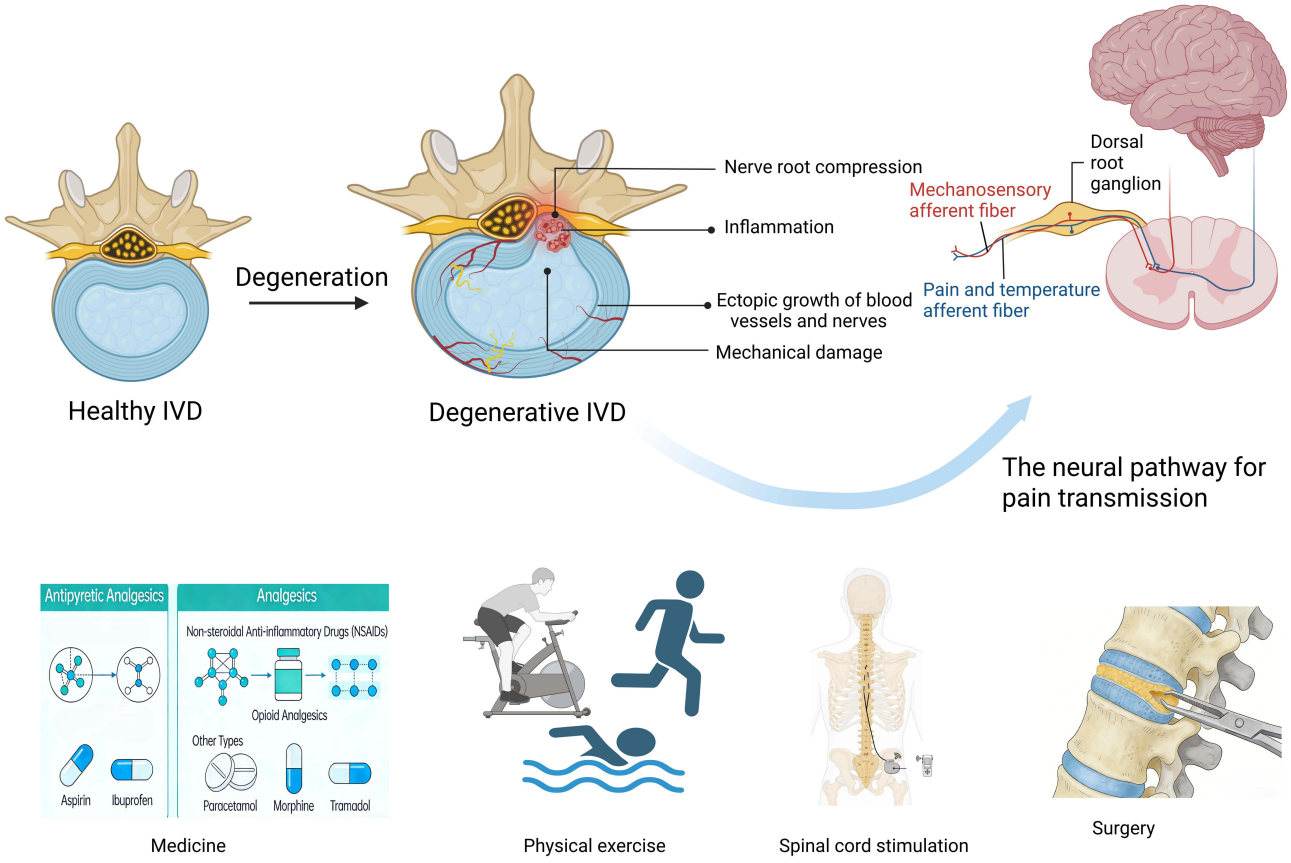

Figure 1 Mechanisms of IVDD pain production and its treatment. The mechanism of IVDD pain generation may be related to nerve root compression, inflammatory response, inward ectopic growth of blood vessels and nerves, and mechanical damage to the IVD, which in turn causes pain symptoms through the nociceptive pathway uploaded to the central nervous system. The treatment of IVDD pain is generally divided into conservative and surgical treatments, which can reduce mechanical damage, inhibit inflammation, reduce nerve compression, and reduce the transmission of pain signals.

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mediated inflammation via the TLR2/SIRT1/NF-κB pathway. Functioning as a SIRT1 agonist, resveratrol has been demonstrated in vitro to suppress pro-inflammatory cytokine production, thereby underscoring its promise as a therapeutic agent for pain associated with NPC degeneration.[39] Conversely, the alarmin S100A8/A9 promotes the progression of IVDD by activating the TLR4 and NF-κB signaling pathways.[40] These findings highlight the critical roles of multiple signaling pathways—including TGFβ1/NF-κB, SIRT1, and S100A8/A9—in IVDD. Although their clinical translation requires further validation, this knowledge may provide theoretical clues and experimental evidence for future development of novel therapeutic strategies targeting IVDD and associated inflammatory pain.

Linking IVDD Pain Subtypes to Inflammatory Cell Death Pathways

The inflammatory mediators and signaling pathways described above do not act in isolation; rather, they are intrinsically linked to specific modes of inflammatory cell death, which in turn shape distinct clinical pain phenotypes. Emerging evidence underscores that the dysregulated release of cytokines such as IL-1β and TNF-α—central to IVDD pathology—is often a direct consequence of pyroptosis, ferroptosis, and necroptosis. Low back pain associated with IVDD can be clinically categorized into distinct subtypes based on the predominant underlying mechanisms: nociceptive pain arising from tissue injury, neuropathic (radicular) pain related to nerve root pathology, and central sensitization-associated pain involving neural plasticity. These subtypes frequently coexist and interact in patients, with their diverse clinical manifestations closely linked to differential pathological processes within the degenerative disc microenvironment. Growing evidence reveals that inflammatory cell death pathways—namely pyroptosis, ferroptosis, and necroptosis—contribute distinctly to the development and maintenance of these pain phenotypes by acting on specific targets within the disc structures and the nervous system.

Nociceptive pain originates directly from structural disruption and local inflammation within the degenerated disc. Pyroptosis plays a central role in this process, as the release of large amounts of inflammatory cytokines such as IL-1β and IL-18 directly sensitizes peripheral nociceptors (eg, TRPV1, ASIC3), leading to a decreased pain threshold. Concurrently, ferroptosis-driven lipid peroxidation and reactive oxygen species (ROS) burst not only exacerbate nucleus pulposus cell death and extracellular matrix degradation but also directly stimulate nerve endings via oxidative stress byproducts, synergistically amplifying nociceptive signaling.

Neuropathic pain is commonly associated with nerve root compression or inflammatory infiltration. Evidence indicates that necroptosis holds significant importance in this pain subtype. Necroptosis occurring in pain-sensitive structures such as the outer annulus fibrosus releases damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines, activating signaling pathways like TLR4/NF-κB and directly inducing immune-inflammatory responses and hyperalgesia around the nerve roots. Furthermore, the release of mediators such as nerve growth factor (NGF) promoted by pyroptosis creates conditions for aberrant ingrowth of nociceptive fibers, collectively forming the pathological basis of neuropathic pain.

Central sensitization-associated pain represents a state of pain chronification and self-sustenance. Its development and maintenance rely not only on persistent peripheral nociceptive input but are also deeply linked to neuroimmune dysregulation at the spinal level. Research suggests (as illustrated in Implications From Bone Tumor-Related Pain Models) that pyroptosis and ferroptosis can also occur in neurons and glial cells (eg, microglia) within the spinal dorsal horn. Inflammatory mediators released from these cell death events can persistently activate central immune cells, enhance synaptic efficacy, and potentially impair descending inhibitory functions, thereby collectively driving and solidifying the state of central sensitization.

Different Cell Fates in IVDD

Routine Programmed Cell Death

As a fundamental biological phenomenon, cellular death denotes the end of a cell's life cycle and constitutes the final endpoint in diverse pathophysiological contexts. Various cell death types engage in complex interactions and conversions. Programmed cell death is a vital process in higher organisms, crucial for orchestrating tissue homeostasis through the selective clearance of redundant, injured, and senescent cells.[41] Taking apoptosis as an example, it is a form of

programmed cell death precisely regulated by relevant genes in response to specific physiological or pathological stimuli. Its characteristics include cytoplasmic condensation, nuclear fragmentation, formation of apoptotic bodies, and eventual phagocytosis and degradation by neighboring cells via the lysosomal pathway.[42] This process does not involve the exposure of DAMPs to the immune system, thus averting an inflammatory response. Studies indicate that the transcription factor SOX4 promotes NPCs apoptosis, thereby exacerbating IVDD and associated low back pain. Conversely, the therapeutic benefits of acetylshikonin in alleviating IVDD pain are linked to its activation of the PI3K/Akt pathway, which suppresses SOX4 expression and subsequently curbs NPC apoptosis.[43] The exact mechanisms by which apoptosis contributes to pain in bone-related pathologies remain elusive. Meanwhile, other forms of programmed cell death, such as pyroptosis, ferroptosis, and necroptosis, are increasingly implicated in the initiation and exacerbation of pain in these contexts.[44,45] Consequently, investigating novel forms of cell death—including pyroptosis, ferroptosis, and necroptosis—to identify novel therapeutic interventions for pain in IVDD merits high priority in future research.

Cellular Senescence in IVDD and Pain

Cellular senescence refers to an irreversible state of cell cycle arrest that occurs after a limited number of divisions or upon exposure to various stressors. Rather than undergoing death, senescent cells transition into a metabolically active yet non-dividing state, characterized by sustained expression of cyclin-dependent kinase inhibitors such as p16INK4a/p21CIP1/WAF1, elevated activity of senescence-associated beta-galactosidase (SA-β-gal), and substantial secretion of a broad spectrum of mediators including inflammatory cytokines, chemokines, and matrix-degrading enzymes. This secretory profile is collectively termed the senescence-associated secretory phenotype (SASP).[46–48]

During IVDD, nucleus pulposus cells, annulus fibrosus cells, and cartilaginous endplate cells can undergo senescence under pressures such as oxidative stress, mechanical loading, and inflammatory cytokines. The accumulation of senescent cells represents a core hallmark of disc aging and degeneration. SASP factors released by these cells, including IL-1β, IL-6, TNF-α, MMPs, VEGF, and others, directly disrupt extracellular matrix homeostasis, promote pathological nerve and vascular ingrowth, and thereby establish a self-sustaining chronic inflammatory microenvironment. Together, these processes participate directly in the initiation and amplification of nociceptive signaling. For example, SASP-derived IL-1β and TNF-α can directly sensitize peripheral nociceptors, while VEGF and NGF drive aberrant innervation within the disc, collectively forming the structural basis of discogenic pain.[49,50]

Furthermore, close functional interplay and signaling crosstalk exist between cellular senescence and programmed cell death pathways such as pyroptosis and ferroptosis.[51,52] On the one hand, the inherent oxidative stress state in senescent cells can heighten their susceptibility to ferroptosis. On the other hand, key SASP components such as IL-1β, acting as an upstream signal that activates the NLRP3 inflammasome and triggers pyroptosis, establish a direct link between senescence and pyroptosis.

Therefore, therapeutic strategies targeting IVDD and associated pain should not be confined to a single cell death pathway.[53–55] Emerging classes of drugs such as Senolytics (selective elimination of senescent cells) and Senomorphics (inhibition of SASP secretion) offer new directions for simultaneously intervening in multiple pathological processes. By clearing these persistently inflammatory senescent cells or blocking their SASP signaling, it is possible to mitigate local inflammation, preserve the extracellular matrix, and indirectly modulate the activation of other cell death pathways. This approach could enable a more systematic and comprehensive intervention targeting the central axis of "cell death–neuroinflammation–pain sensitization". This SASP-driven inflammatory milieu interacts with and amplifies the more acutely destructive inflammatory cell death pathways collectively driving the progression of IVDD and pain, as detailed in the following section.[56]

The Emergence of Inflammatory Cell Death

As introduced above, apoptosis is a non-inflammatory process crucial for tissue homeostasis. In contrast, the novel programmed cell death pathways—pyroptosis, ferroptosis, and necroptosis—are collectively characterized as "inflammatory cell death" due to their lytic nature and the substantial release of pro-inflammatory mediators. While apoptosis involves orderly cellular condensation, fragmentation, and silent clearance by phagocytes without triggering inflammation, these emerging pathways lead to plasma membrane rupture. This rupture results in the uncontrolled spillage of

intracellular contents, including DAMPs, cytokines (eg, IL-1β, IL-18), and lipid peroxidation products, which actively recruit and activate immune cells, thereby fueling a self-perpetuating cycle of neuroinflammation and pain sensitization within the degenerative disc microenvironment. Therefore, targeting these inflammatory death modalities offers a distinct therapeutic strategy aimed not only at preserving cell numbers but, more importantly, at quenching the local inflammatory fire that directly drives discogenic pain.[35,57]

Pain Caused by Novel Programmed Cell Death

NPCs

The loss of NPCs facilitates aberrant innervation and vascular ingrowth into the disc. The death of NPCs leads to the secretion of various cytokines, which in turn promotes the breakdown of Aggrecan and Collagen II. This process ultimately compromises the stability of the extracellular matrix (ECM). Simultaneously, NGF fosters the ectopic extension of nerve fibers and blood vessels, and inflammation-related factors perpetuate local inflammatory responses and pain signaling, creating a self-sustaining cycle. Moreover, herniated nucleus pulposus tissue can directly compress nerve roots, exacerbating neuroinflammation and neural injury, which in turn initiates or amplifies low back pain. NPC death can be triggered by diverse factors through overlapping or distinct mechanisms. Therefore, mitigating NPC loss and inhibiting ECM degradation have emerged as pivotal therapeutic strategies for managing low back pain.[58]

Pyroptosis

Pyroptosis, which represents a major category of regulated cell death, occurs in multiple cell types during IVDD, including NPCs, AFCs, chondrocytes, macrophages, and neurons. This process is characterized by the substantial release of inflammatory cytokines, notably IL-1β, subsequently inducing the aberrant ingrowth of blood vessels and nerves into the disc. Inhibition of pyroptosis has been shown to alleviate the progression of IVDD and associated pain. Neurotrophic factors, including NGF and BDNF, which are secreted by blood vessels, function as key mediators that promote neuronal survival and pathological disc innervation, thereby acting as critical contributors to severe discogenic low back pain. Therefore, suppressing pyroptosis across various cell types in IVDD may help reduce pathological nerve ingrowth and pain; conversely, promoting pyroptosis in vascular endothelial cells could potentially exert beneficial effects in mitigating IVDD.[26]

Pyroptosis is characterized by the release of inflammatory cytokines. In IVDD, it contributes to disease pathogenesis through multiple molecular mechanisms. External stimuli such as lipopolysaccharide (LPS) and hydrogen peroxide can elevate intracellular ROS levels in NPCs, thereby activating the NLRP3 inflammasome and promoting caspase-1-mediated maturation of IL-1β and IL-18, which ultimately induces pyroptosis. Additionally, LPS suppresses microRNA-200c-3p expression, significantly leading to upregulation of inflammatory factors including TNFα and IL-6.[59] Conversely, human adipose-derived stem cell-derived exosomal miR-155-5p functions to mitigate NPC pyroptosis via direct targeting of TGFβR2, consequently slowing the advancement of IVDD.[60]

Inflammatory pathways are intricately linked with pyroptosis. Mechanistically, stromal cell-derived factor 1 (SDF1) enhances the expression of pyroptosis-related proteins, including NLRP3 and GSDMD, via activation of the CXCR4/NF-κB signaling axis. Duhuo Jisheng Decoction has been shown to inhibit this pathway, thereby reducing inflammation and cell death.[61] The NF-κB/NLRP3 pathway plays a central role in mediating neuropathic pain. Injection of NPCs into the dorsal root ganglion of rats significantly elevates the levels of NLRP3, caspase-1, and IL-1β/IL-18, thereby promoting central sensitization and pain.[62] IL-1β can trigger pyroptosis through the PI3K/AKT/NF-κB pathway, while Maltol and Notoginsenoside R1 alleviate pyroptosis and hyperalgesia by inhibiting this signaling axis.[63,64]

Mechanical stress also plays a significant role in pyroptosis. Abnormal mechanical loading promotes the accumulation of β-catenin by activating the Wnt/β-catenin signaling pathway, thereby mediating pyroptosis in NPCs and contributing to neuropathic pain. The mechanosensitive ion channel Piezo1 activates NLRP3 through the Ca^{2+}/NF-κB pathway, exacerbating inflammatory responses and cellular senescence. Additionally, the ROS-dependent TXNIP/NLRP3 axis is involved in regulating TBHP-induced pyroptosis in NPCs, and Verapamil alleviates this process by modulating the Nrf2/TXNIP/NLRP3 signaling pathway.[65]

The modulation of pyroptosis offers a novel therapeutic strategy. High-molecular-weight hyaluronic acid hydrogel reduces the expression of pain-associated factors such as IL-1R and NGF, thereby alleviating discogenic pain.[66] Autophagy inhibits pyroptosis through SQSTM1-mediated degradation of GSDMD. The autophagy inducer rapamycin delays the progression of IVDD, whereas the inhibitor 3-methyladenine augments the expression of pyroptosis-related proteins.[67] These results suggest that targeting pyroptosis-related signaling pathways may represent a potential therapeutic strategy for IVDD and lower back pain (Figure 2).

Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death that plays a critical role in the pathogenesis of IVDD and its associated pain.[68–70] The core mechanisms involve dysregulated iron metabolism, accumulation of lipid peroxidation products, and impaired antioxidant defense systems—particularly the dysfunction of glutathione peroxidase 4 (GPX4).[71,72] These processes ultimately lead to NPCs death, degradation of the extracellular matrix, and activation of neuroinflammatory responses.[73] In degenerated IVDs, the expression of GPX4 in NPCs is significantly reduced. Activating transcription factor 3 (ATF3) binds to solute carrier family 7 member 11 (SLC7A11), thereby inhibiting glutathione (GSH) synthesis, further diminishing GPX4 activity, exacerbating lipid peroxidation, and promoting ferroptosis.[74,75] The Xc^- system, a cystine/glutamate antiporter, has SLC7A11 as its key subunit. Nrf2 helps maintain

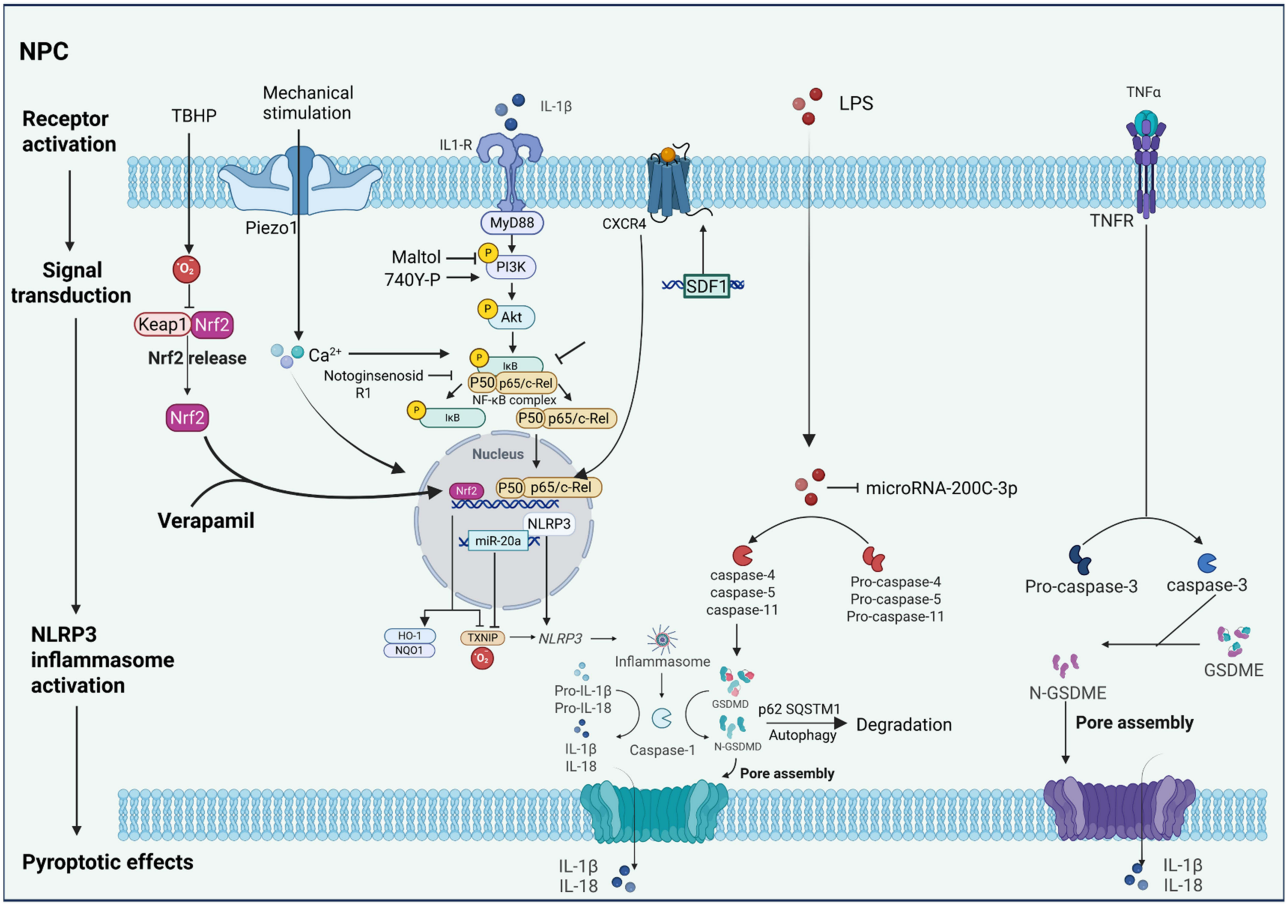

Figure 2 NPC pyroptosis pathways involved in the onset of pain in IVDD. The pyroptotic pathway involves sequential steps of NLRP3 inflammasome assembly and subsequent activation of caspase-1 or caspase-11/4/5. These activated caspases then cleave both GSDMD and the pro-forms of IL-1β/IL-18, ultimately leading to the maturation and release of these cytokines through pores formed by N-terminal GSDMD fragments. Autophagy may inhibit NPC pyroptosis through a P62/SQSTM1-mediated GSDMD-N degradation mechanism. The binding of TNFα to TNFR induces caspase-3 activation, leading to gasdermin E (GSDME) cleavage. The resulting N-terminal GSDME fragment forms membrane pores in a manner analogous to N-GSDMD. Meanwhile, IL-1β binding to IL-1R promotes NLRP3 inflammasome assembly via the PI3K/Akt pathway—a process that can be inhibited by Maltol and enhanced by Ca^{2+}, and the agonist 740Y-P. Separately, Piezo1, a mechanosensitive Ca^{2+} channel, activates NLRP3 inflammasomes through the Ca^{2+}/NF-κB signaling cascade. Additionally, ROS accelerate pyroptosis by suppressing the Nrf2/heme oxygenase-1 (HO-1) pathway, whereas Verapamil upregulates Nrf2 expression and modulates pyroptosis in nucleus pulposus cells via the Nrf2/TXNIP/NLRP3 axis.

redox homeostasis by regulating the GSH-GPX4 axis and the Xc^- system, making both GPX4 and Nrf2 important targets for intervening in ferroptosis. Specifically, Nrf2 can suppress ferroptosis by upregulating SLC7A11 and GPX4. Studies have shown that hesperidin can interact with Nrf2, enhance its expression, and inhibit the NF-κB pathway, thereby attenuating ferroptosis, protecting NPCs, and alleviating lower back pain.[67] Polydopamine nanoparticles can inhibit the ubiquitination-dependent degradation of GPX4, thereby alleviating oxidative stress and iron accumulation, and ultimately maintaining cellular homeostasis.[76] Furthermore, flavonoids inhibit ferroptosis in NPCs by activating the Nrf2/HO-1 signaling pathway, thereby reducing oxidative damage and matrix degradation.[77–79] Cynarin also suppresses the catabolism of NPCs in a dose-dependent manner, upregulates the expression of GPX4 and Nrf2, and reduces the levels of Fe^{2+}, lipid peroxides, and reactive oxygen species (ROS), thereby delaying the progression of IVDD in a rat model.[80]

On the other hand, iron metabolism also plays a central role in ferroptosis. Extracellular Fe^{3+} is reduced to Fe^{2+} by STEAP3 and transported into the cytosolic labile iron pool via the DMT1 transporter. Fe^{2+} can subsequently bind to ferritin for stable storage; however, excess free iron promotes the generation of phospholipid hydroperoxides through the Fenton reaction, thereby triggering ferroptosis. In a TBHP-induced IVDD model, the circular RNA Circ-STC2 was shown to upregulate transferrin receptor 2 (TFR2) by sponging miR-486-3p, which promotes ferroptosis in NPCs and inhibits cell viability.[71,79,81]

Necroptosis

Necroptosis is a regulated form of programmed necrotic cell death, the core mechanism of which relies on the cascade activation of RIPK1, RIPK3, and MLKL proteins. When cells are stimulated by factors such as TNF-α, interferon (IFN-γ), infection, drugs, or mechanical stress, and the apoptotic pathway is inhibited (eg, due to caspase-8 inactivation), RIPK1 interacts with RIPK3 via the RHIM domain to form the "necrosome".[82–84] Subsequently, RIPK3 phosphorylates MLKL, prompting its oligomerization and translocation to the cell membrane, where it disrupts membrane integrity. This ultimately leads to cell lysis and the release of DAMPs, triggering an inflammatory response.[85–87]

In IVD, the outer AF and adjacent structures rich in nociceptors, such as ligaments and the periosteum, are particularly susceptible to necroptosis. The inflammatory factors (eg, TNF-α, IL-1β, IL-6, NGF) and DAMPs released during this process can activate the TLR4/NF-κB signaling pathway in macrophages and nerve endings, directly leading to pain sensitization and inflammatory responses in nerve roots.

Studies have shown that in NPCs of degenerated IVDs, the expression of myeloid differentiation factor 88 (MyD88) is significantly upregulated and co-localizes with RIP3, suggesting that MyD88 signaling may be involved in regulating necroptosis in NPCs. Inhibition of MyD88 effectively reverses the decline in ATP levels, reduces ROS generation, and preserves mitochondrial function in NPCs treated with TLZ (TNF-α + LPS + z-VAD), thereby suppressing the occurrence of necroptosis[88] (Figure 3).

In terms of potential therapeutic strategies, Necrostatin-1 (Nec-1) and its derivatives (such as Nec1s and ZJU-37) can alleviate necroptosis in IVDD models by blocking RIPK1 phosphorylation and the formation of the RIP1-RIP3 complex.[89] Dabrafenib, a clinically approved B-Raf inhibitor, can also inhibit RIPK3 and attenuate its phosphorylation of MLKL, thereby disrupting the RIPK3/MLKL interaction, though its efficacy in IVDD remains to be investigated.[90] Additionally, Necrosulfonamide (NSA) targets the Cys86 residue of human MLKL protein, inhibiting cell membrane rupture and the release of inflammatory factors, thereby exerting a protective effect on NPCs.[91] (Figure 3)

Annulus Fibrosus Cell

Research indicates that AF rupture during IVDD results in collagen type I (COL1) overproduction, which establishes a microenvironment that promotes the aberrant ingrowth of sensory nerves and blood vessels and accelerates discogenic pain. This pathological process is further aggravated by the marked activation of programmed cell death, specifically pyroptosis and ferroptosis, in AFCs, intensifying local inflammation, oxidative stress, and tissue damage, thereby constituting a key mechanism in IVDD progression.[92]

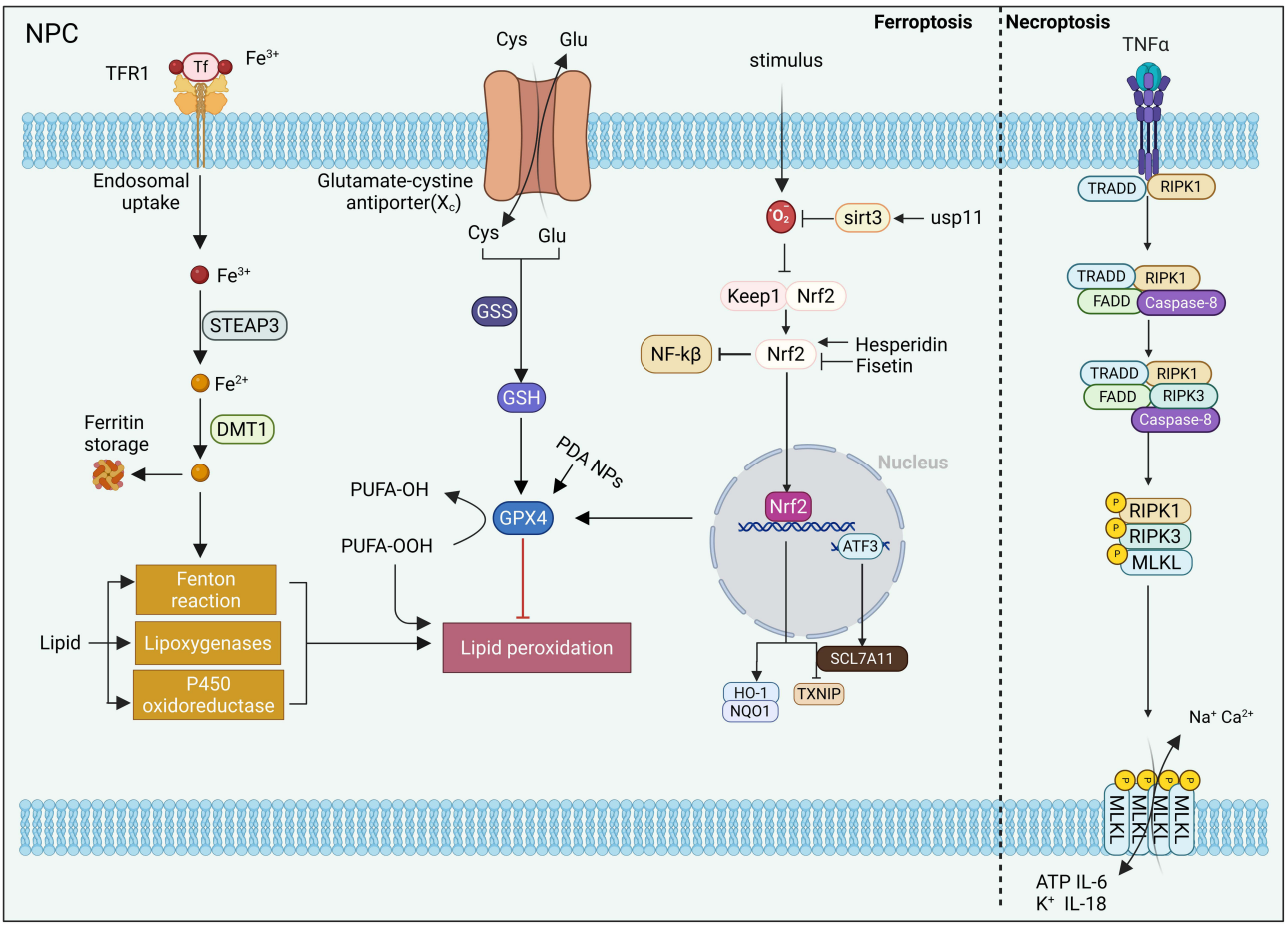

Figure 3 The pathogenesis of pain in IVDD involves metabolic pathways linked to NPC ferroptosis and necroptosis, together with interactions among their components and other cell death forms. As illustrated, the core regulatory network can be broadly divided into two segments: ferroptosis on the left and necroptosis on the right. The ferroptosis process encompasses iron metabolism—where extracellular iron enters via TFR1-mediated endocytosis—and antioxidant defense mechanisms, including the system Xc–/GSH/GPX4 axis and the Nrf2/NF-κB pathway. System Xc–, composed of SLC7A11 and SLC3A2, exports glutamate in exchange for extracellular cystine, while GPX4 utilizes GSH to reduce phospholipid hydroperoxides and limit ROS accumulation; disruption of GSH/GPX4 activity can induce ferroptosis. Furthermore, molecules such as USP11, hesperidin, polydopamine nanoparticles, and fisetin modulate ferroptosis by targeting specific pathway components. On the other hand, necroptosis is triggered by TNFα binding to TNFR, leading to phosphorylation of RIPK1, RIPK3, and MLKL through a signaling cascade involving TRADD, FADD, RIPK1, RIPK3, and caspase-8. Phosphorylated MLKL then oligomerizes to form plasma membrane pores, enabling Na^+ and Ca^{2+} influx and the release of ATP, K^+.

Pyroptosis

The pyroptosis of AFCs constitutes a key mechanism in IVDD, a process closely tied to ubiquitin modification and inflammasome activation. Evidence indicates that the deubiquitinating enzyme USP14 is positively correlated with the expression of NLRP3, caspase-1, IL-1β, and IL-18 in degenerated AFCs and is strongly implicated in triggering pyroptosis. The activation of the NLRP3 inflammasome in these cells not only elevates the pyroptosis rate but also potentially amplifies oxidative stress and NF-κB signaling. Experimental findings confirm that the NLRP3 inhibitor INF39 can effectively suppress pyroptosis induced by USP14 overexpression. Mechanistically, USP14 directly interacts with NLRP3 to regulate the NLRP3/Caspase-1/IL-1β/IL-18 axis, thereby promoting AFCs pyroptosis and accelerating IVDD pathology.[93,94]

Ferroptosis

The degeneration of AFCs also involves ferroptosis, driven primarily by disrupted iron metabolism and lipid peroxidation. A key regulator in this process is nuclear receptor coactivator 4 (NCOA4), which specifically mediates ferritinophagy to control intracellular iron homeostasis. In rat NPCs and AFCs, upregulation of NCOA4 facilitates its interaction with ferritin heavy chain 1 (FTH1), promoting ferritin degradation and elevating labile Fe^{2+}. The accumulated Fe^{2+} then

catalyzes excessive ROS generation through the Fenton reaction, inducing pronounced lipid peroxidation and membrane injury, and ultimately leading to ferroptotic cell death.[95–97]

Cartilaginous Endplate Cells

The cartilaginous endplate is a hyaline cartilage layer located on the superior and inferior surfaces of the vertebral bodies. As the IVD is avascular, nutrient exchange and metabolic waste removal are mediated exclusively through the cartilaginous endplate. Injury to the cartilaginous endplate not only contributes to the progression of IVDD but may also directly influence the development of discogenic pain.[98–100]

Studies have shown that patients with degenerated discs accompanied by physical microdamage to the endplate exhibit significantly higher pain and functional disability scores compared to those with degeneration but without endplate injury.[101] Cartilaginous endplate microdamage can be classified into six types: fissures, vascular mimicry, NP protrusion into the endplate, combined NP and bone tissue integration into the endplate, isolated bone tissue integration into the endplate, and traumatic nodules. The endplate is primarily composed of chondrocytes, and its extracellular matrix is rich in aggrecan. In vitro studies have demonstrated that aggrecan from human IVDs inhibits neurite outgrowth as well as the adhesion and migration of endothelial cells. Damage to the endplate facilitates the ingrowth of nerves and blood vessels into the disc through the endplate. The integrated structural and functional integrity of the cartilaginous endplate and AF is essential for preserving NP homeostasis and regulating internal disc pressure. Consequently, damage to either structure can compromise NP homeostasis, creating conditions that facilitate IVDD, aberrant innervation, and the onset of IVDD pain.[102–104]

Pyroptosis

The activation of pyroptosis in cartilaginous endplate cells is strongly linked to the development of lower back pain.[105] Compared to patients with vertebral burst fractures but without degeneration, individuals suffering from lower back pain exhibit significantly higher expression levels of caspase-1, IL-1β, and NLRP3 in their cartilaginous endplates. During the process of IVDD, elevated mechanical stress can promote the expression of NLRP3, caspase-1, and IL-1β within the cartilaginous endplate. Notably, NLRP3 is also highly expressed in areas of abnormal bone growth, suggesting that pyroptosis of cartilaginous endplate cells contributes to IVDD and acts as a driving factor in the development of lower back pain.[29,106,107]

Ferroptosis

Ferroptosis has also been implicated in the degeneration of endplate chondrocytes. In one study, intraperitoneal injection of iron dextran in mice and treatment of endplate chondrocytes with ferric ammonium citrate (FAC at 800 μM) were used to establish in vivo and in vitro iron overload models, respectively. The results demonstrated that iron overload downregulated the expression of key anti-ferroptotic proteins, GPX4 and SLC7A11, thereby inducing ferroptosis. In vivo experiments further revealed that iron overload promoted ferroptosis in a dose-dependent manner, as evidenced by decreased GPX4 levels and elevated levels of the lipid peroxidation product 4-HNE. Additionally, FAC treatment increased the expression of matrix metalloproteinases MMP3 and MMP13, while reducing the expression of chondrogenic markers SOX9 and type II collagen (COL II), leading to degeneration and functional impairment of endplate chondrocytes.[108–110]

Implications from Bone Tumor-Related Pain Models

The preceding discussion systematically elucidates the central roles of novel programmed cell death pathways—such as pyroptosis, ferroptosis, and necroptosis—in the development of IVDD and its associated pain. These mechanisms are not unique to IVDD but constitute a common pathological basis for various chronic pain disorders. Notably, emerging evidence has also revealed the critical contribution of these cell death pathways at the spinal level—involving both neurons and glial cells—in the highly destructive pain model of bone tumor-related pain. Investigating the commonalities of these mechanisms across different pain models can not only validate the universal therapeutic potential of targeting cell death pathways but also, through comparative studies, deepen our understanding of the core axis of "cell death–

neuroinflammation–pain sensitization". This will provide new perspectives and paradigms for mechanistic research and therapeutic translation in IVDD-related pain.

Numerous studies have indicated that inhibiting neuronal cell death and microglial activation in the spinal cord can alleviate bone tumor-related pain, while inducing programmed cell death in tumor cells may represent a novel therapeutic strategy for such pain. Bone tumors can cause significant osteolysis and persistent hyperalgesia, mechanisms that are closely associated with the loss of neurons in the spinal dorsal horn. Cancer cells and stromal cells within the tumor microenvironment release various cytokines that contribute to pain generation; these factors can also sensitize and abnormally activate peripheral nerves and nerve fibers, promoting aberrant innervation in bone tissues and thereby facilitating pain.[111–113] Furthermore, the growth of tumors within bone can directly damage nerve fibers, leading to neuropathic pain. Bone tumor-related pain severely adversely affects patients' quality of life, underscoring an urgent need to develop more effective analgesic strategies.[114–116]

Spinal Cord Neurons

Lipid peroxidation and oxidative stress have been demonstrated to contribute to the development of chronic pain. In a bone metastasis pain model established using luciferase-labeled mouse lung cancer cells, researchers observed a reduction in the number of GABAergic neurons in the spinal dorsal horn, accompanied by ferroptosis in spinal cord neurons, both of which contributed to pain-related behaviors. Oxidative stress may exacerbate bone tumor pain by inducing ferroptosis and loss of GABAergic neurons, which parallels the mechanism in IVDD pain where oxidative stress drives NP cell death and neural sensitization. The model animals also exhibited enhanced activation of ERK in the spinal cord, suggesting that elevated p-ERK levels may serve as a potential marker of ferroptosis. Cytokines and growth factors can stimulate the synthesis of COX-2, which is not only a key enzyme involved in pain and inflammation but is also considered a potential indicator of ferroptosis. Following treatment with the ferroptosis inhibitor Ferrostatin-1, the expression levels of both p-ERK and COX-2 were significantly reduced, indicating that ferroptosis in spinal neurons may contribute to bone cancer pain through the activation of the COX-2 and ERK pathways.[117–119]

In the rat model of chronic constriction injury (CCI) of the sciatic nerve, decreased levels of glutathione peroxidase 4 (GPX4) and increased expression of acyl-CoA synthetase long-chain family member 4 (ACSL4) in spinal cord tissue induce ferroptosis, which subsequently contributes to neuropathic pain, neuronal loss, and astrocyte activation. The ferroptosis inhibitor ferrostatin-1 significantly upregulates GPX4 expression, attenuates lipid peroxidation, and elevates mechanical and thermal pain thresholds.[120,121]

Spinal Microglia

As resident immune cells within the central nervous system, microglia can trigger neuroinflammation and fibrotic responses upon pyroptosis. Studies have shown that in the spinal dorsal horn of rats subjected to the spared nerve injury (SNI) model, the expression of SIRT2 and ferritin 1 (Ferritin1) in microglia is reduced. Intrathecal injection of a recombinant adenovirus overexpressing SIRT2 upregulates SIRT2 and ferritin 1, reduces microglial ferroptosis, and alleviates abnormal pain sensitivity in the model animals. These findings suggest that SIRT2 can alleviate neuropathic pain by inhibiting ferroptosis in microglia, indicating that modulating the death status of glial cells could serve as a potential therapeutic approach for various chronic pain conditions, including IVD-IVDDderived pain.[122] Furthermore, studies have demonstrated that intrathecal injection of the necroptosis inhibitor Necrostatin-1 can suppress neuropathic pain by modulating microglial activity and reducing the levels of pro-inflammatory cytokines.[123]

Promising Therapeutic Strategies

Recent studies have identified numerous natural compounds and traditional Chinese medicine (TCM) formulations that demonstrate considerable potential in regulating programmed cell death and alleviating pain. For instance, Qiangjin Zhuanggu Qufeng Mixture (QJZGQF) has been shown to exert anti-inflammatory, osteogenic, and immunomodulatory effects. It delays NPC pyroptosis and mitigates IVDD by inhibiting the NLRP3 inflammasome and maintaining extracellular matrix homeostasis;[124] Duhuo Jisheng Decoction alleviates discogenic pain by inhibiting the SDF-1/CXCR4/NF-κB/NLRP3 pathway, thereby reducing pyroptosis in NPCs;[61] Verapamil, a calcium channel blocker, not

only exerts cardiovascular effects but also inhibits ROS generation and pyroptosis via the Nrf2/TXNIP/NLRP3 axis, thereby alleviating pain;[65] Notoginsenoside R1 exhibits anti-inflammatory and antioxidant activities, inhibits pyroptosis through the NF-κB/NLRP3 pathway, and reduces mechanical and thermal hypersensitivity;[43] Maltol, a naturally occurring aromatic compound found in plants, demonstrates significant biological activities, particularly notable for its antioxidant, anti-inflammatory, and organ-protective effects. It inhibits pyroptosis and delays IVDD by modulating the PI3K/AKT/NF-κB signaling pathway.[63] Furthermore, studies have indicated that small-molecule drugs such as resveratrol, berberine, dexmedetomidine, and naringin can inhibit immune-inflammatory cascades, apoptosis, pyroptosis, and catabolic processes;[125] Melatonin, a compound primarily synthesized in the pineal gland and other tissues, alleviates IVD damage and reduces lower back pain by inhibiting ferroptosis in immune cells;[126] The deubiquitinating enzyme USP11 alleviates oxidative stress-associated ferroptosis by stabilizing SIRT3, thereby delaying IVDD and reducing pain;[71] Hesperidin protects NPCs from ferroptosis by upregulating Nrf2 and inhibiting NF-κB;[65] Hydroxytyrosol (HT) alleviates neuropathic pain by inhibiting the NF-κB, PI3K/AKT, and ERK pathways, thereby reducing apoptosis in disc cells and microglia-mediated neuroinflammation.[127]

A clinical study revealed that patients with more severe IVDD tend to exhibit a higher incidence of lumbar instability and apoptosis. In degenerated disc tissues, the expression of melatonin receptor 1 (but not receptor 2) was significantly upregulated, and its level was closely correlated with the extent of apoptosis, the severity of degeneration, and lower visual analog scale (VAS) scores for low back pain.[128] (Table 2)

Perspectives

Currently, clinical therapeutic strategies for pain associated with IVDD—including pharmacological and surgical interventions—are widely used in practice, yet they generally face limitations such as inconsistent efficacy, notable side effects, and an inability to fundamentally disrupt the mechanisms underlying pain generation. Current management largely relies on palliative non-steroidal anti-inflammatory drugs or surgical procedures that carry risks of chronic postoperative pain and adjacent segment disease, underscoring the urgent need to explore novel mechanisms. Unlike reviews that focus primarily on structural degeneration, this article systematically examines the roles of newly defined programmed cell death pathways—pyroptosis, ferroptosis, and necroptosis—from the perspective of pain initiation and maintenance. It should be noted that the field is advancing rapidly, and some recent significant studies as well as ongoing debates—for example, regarding the relative contributions of different cell death pathways at distinct pain stages or across clinical pain phenotypes, or how specific signals preferentially direct cell death toward pain sensitization—may not be exhaustively covered here. In particular, although recent work such as that by Chen et al[130] has comprehensively outlined various forms of programmed cell death in disc degeneration from a degenerative standpoint, the present review distinctly centers on discogenic pain as the core clinical issue. Furthermore, we have specifically summarized a range of small-molecule agents and natural compounds that modulate these death pathways, thereby providing insights for the translational development of targeted analgesics. In summary, existing evidence suggests that targeting these cell death pathways may open novel therapeutic avenues for pain relief by modulating neuro-immune inflammation, aberrant innervation, and nociceptive signaling.[131,132]

The application of single-cell omics and spatial transcriptomics will be instrumental in precisely resolving the sources and targets of cell-death-derived signals within pain-relevant key regions such as dorsal root ganglia and spinal dorsal horn. Defining how distinct death modalities govern the release of specific pain mediators (eg, IL-1β, HMGB1, ATP, lipid peroxides) and clarifying how these factors drive peripheral and central sensitization represent core objectives for future research. Meanwhile, developing highly selective interventions capable of discriminating anti-degenerative from analgesic effects—for instance, inhibitors targeting specific death pathways in neurons or glia—and evaluating their efficacy and safety in alleviating pain-related behaviors are critical for translational medicine. Additional important directions include optimizing targeted delivery systems for pain-conducting pathways, exploring combination strategies addressing multiple pain mechanisms, and identifying biomarkers correlated with pain scores.

Comparative pain-biology research across disease models holds particular value. By comparing the roles of these death pathways in different chronic-pain models—such as IVD-related pain, osteoarthritis pain, and bone-cancer pain—it will help distinguish universal pain-maintenance mechanisms from disease-specific drivers. For example, ferroptosis of

Table 2 IVDD Pain Treatments Targeting Novel Cell Death Modalities and Their Effects

Treatment	Cell	Animal Model	Experimental Models	Mechanism	Result	Ref
Verapamil	NPC	Rat	Puncture-induced rat models	Nrf2/TXNIP/NLRP3	Inhibit ROS overproduction and cellular pyroptosis	[65]
Duhuo Jisheng Decoction	NPC	Rat	LPS-induced models, Puncture-induced model	SDF-1/CXCR4/NF-κB/NLRP3	Inhibit pyroptosis and improve IVD pain manifestations	[124]
Melatonin	NPC	Mouse	LPS-induced macrophages conditional	ROS, cumulative iron	Reduces intracellular oxidative stress and iron accumulation, inhibits ferroptosis, induces the change of M1 to M2, down-regulates inflammation-associated factors, maintains the balance between synthesis and degradation of extracellular matrix, improves IVDD-associated low back pain	[126]
Hesperidin	NPC	Mouse	Puncture-induced model	Nrf2/NF-κB	Enhancement of Nrf2 expression and inhibition of NF-κB pathway to suppress oxidative stress-dependent ferroptosis	[67]
Levo-tetrahydropalmatine	Spinal cord microglial cells	Rat	Chronic compression injury model	Clec7a-MAPK/NF-κB-NLRP3	Attenuates NLRP3 inflammasome-mediated pyroptosis, reduce neuroinflammation and neuropathic pain	[129]

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spinal neurons in bone-cancer-pain models provides analogical clues for exploring central mechanisms in IVDD-related chronic pain and may reveal shared therapeutic targets.

Ultimately, translating these findings into clinical practice requires deep collaboration across disciplines including pain biology, degeneration research, and clinical analgesia. By systematically clarifying the roles of novel cell death pathways in the generation, transmission, and maintenance of discogenic pain signals, and prudently assessing their potential for alleviating patient pain and improving function, a solid foundation can be laid for developing precise therapies that truly alter the pain trajectory and enhance quality of life. This translational process will demand sustained, rigorous exploration and validation.[133–136]

Conclusion

In summary, this review consolidates a mechanistic framework for managing discogenic pain by targeting three key inflammatory cell death pathways: pyroptosis, ferroptosis, and necroptosis. We have delineated their cell-specific activation within disc tissues and linked their core molecular executors—the NLRP3 inflammasome/GSDMD axis for pyroptosis, the GPX4/iron metabolism axis for ferroptosis, and the RIPK1/RIPK3/MLKL cascade for necroptosis—to the generation of distinct clinical pain phenotypes, including nociceptive, neuropathic, and centrally sensitized pain.

The therapeutic implications of this framework reveal a dual strategic logic. Convergent strategies aim at shared upstream nodes, such as suppressing NF-κB signaling or mitigating oxidative stress, which broadly dampens the inflammatory milieu fueling all three pathways. In contrast, divergent strategies involve precision targeting of pathway-unique executors, exemplified by NLRP3 inhibitors for pyroptosis, iron chelators for ferroptosis, and RIPK1 inhibitors for necroptosis. Notably, many reviewed agents (eg, hesperidin, melatonin) exhibit pleiotropic modulation across these pathways, underscoring the therapeutic promise of targeting the integrated cell death network.

The scientific significance of this work lies in advancing the paradigm of discogenic pain from one centered on macroscopic structural failure to one focused on microscopic dysregulation of cellular fate. This shift identifies the programmed lytic death of disc cells and the consequent sustained release of damage signals as a critical driver of pain chronicity, providing a new pathophysiological model.

The translational value is substantial. By moving beyond symptomatic palliation to target these core pathological processes, future interventions hold the potential to become disease-modifying. Prioritizing research into the crosstalk between these death pathways and their interfaces with metabolic reprogramming and epigenetic regulation will be crucial. The ultimate goal is to stratify patients based on their predominant cell death signature and develop personalized therapies that not only alleviate pain but also modify the degenerative trajectory, thereby addressing a major unmet need in the clinical management of discogenic low back pain.

Abbreviations

IVDD, intervertebral disc degeneration; IVD, intervertebral disc; NPC, nucleus pulposus cell; IL-1β, interleukins 1β; TNF-α, tumor necrosis factor; MMPs, matrix metalloproteinases; COX-2, cyclooxygenase 2; NGF, nerve growth factor; LPS, lipopolysaccharide; SDF1, Stromal cell-derived factor 1; TXNIP, thioredoxin-interacting protein; GSDMD, gasdermin D; NLRP3, NOD-like receptor thermal protein domain associated protein 3; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; GSH, glutathione; USP, Ubiquitin-specific proteases; SIRT, Sirtuin.

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Disclosure

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