Review

Molecular Mechanisms and Targeted Therapeutic Strategies in Intervertebral Disc Degeneration

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ABSTRACT

Intervertebral disc degeneration (IVDD) is recognized as a predominant causative factor for chronic low back pain, representing a major clinical challenge in aging societies. The degenerative cascade involves complex interactions among multiple pathological mechanisms, encompassing cellular senescence, inflammatory amplification, oxidative damage, metabolic dysregulation, and aberrant biomechanical loading. This review comprehensively delineates the molecular network underlying IVDD pathogenesis, with particular emphasis on emerging mechanisms such as epigenetic modifications, mitochondrial dysfunction, and programmed cell death pathways. Furthermore, we critically evaluate cutting-edge therapeutic approaches targeting these pathological processes, including bioactive molecular interventions, CRISPR-based gene editing applications, and tissue-engineered regeneration strategies. The synthesized evidence provides a mechanistic framework for developing precision medicine interventions and highlights promising translational research directions in disc degeneration management.

INTRODUCTION

Intervertebral disc degeneration (IVDD), a classic pathological manifestation of spinal aging, is biologically characterized by the synergistic decline in tissue regenerative capacity and dysregulation of homeostatic maintenance mechanisms[1]. Currently, surgery remains the primary treatment for IVDD. However, studies suggest that depression and anxiety are risk factors for postoperative complications, chronic pain, and readmission after spinal surgery[2]. In this context, IVDD has become a major global public health burden. Epidemiological studies

confirm that a significant proportion of the general population experiences LBP, with 84% likely to suffer from

LBP during their lifetime [3]. The recurrence rate of LBP exceeds 80%[4] , accounting for over 40% of chronic pain cases and imposing immense socioeconomic costs worldwide[5, 6]. The urgency of addressing this issue is further highlighted by the U.S. National Institutes of Health's National Pain Strategy, which estimates the total direct and indirect economic costs of chronic pain in the U.S. to range between 560and560and630 billion annually[7].

At the molecular level, the senescence cascade of nucleus pulposus cells (NPCs) is a critical initiating factor in IVDD. Age-related accelerated telomere shortening leads to a significant age-dependent increase in p16INK4a-positive cells[8]. This senescent phenotype forms a vicious cycle with matrix degradation, manifested by elevated expression of senescence-associated secretory phenotype (SASP) factors such as IL-6 and MMP-13[9]. The intervertebral disc (IVD) exhibits a unique oxygen gradient, with oxygen partial pressure as low as 1% in the central nucleus pulposus (NP). Degenerated tissues show even lower oxygen levels than normal IVD tissues[10, 11]. This distinct microenvironment significantly regulates aging processes. Studies reveal a threefold higher mitochondrial DNA mutation rate and reduced autophagic flux in IVD tissues compared to other tissues. Such biomechanical-biochemical microenvironments limit the efficacy of traditional anti-osteoporosis drugs (e.g., bisphosphonates) in IVDD. Clinical data indicate that alendronate delays disc height loss by only 18% and fails to inhibit SASP[12].

Given the global annual incidence of 12 million new cases of IVDD-related LBP, surgical resection of degenerated discs compromises the stability of adjacent segments. Moreover, the probability of postoperative disc reherniation reaches 21.2%[12]. Elucidating senescence-specific mechanisms holds critical clinical significance. Recent studies reveal that NPCs mediate "inflammatory senescence" via the cGAS-STING pathway, a molecular mechanism distinct from osteocyte senescence, offering novel therapeutic targets[13]. This review synthesizes advances in senolytics (senescent cell-clearing agents), SASP inhibitors, and mitochondrial protectants. Combined with epidemiological features of Chinese populations (12% higher IVDD prevalence in individuals over 60 compared to Western cohorts), it constructs multidimensional intervention strategies based on senescence regulation, providing theoretical and practical guidance for addressing spinal degenerative diseases in aging societies.

PATHOGENESIS OF IVDD

Cellular Senescence

IVDD progression critically depends on the coordinated function of the annulus fibrosus (AF), nucleus pulposus (NP), and cartilaginous endplate (CEP), with NP extracellular matrix (ECM) homeostasis as the core. During IVDD, NPC senescence intensifies, marked by cell cycle arrest, overexpression of antiapoptotic and catabolic factors, and a robust SASP[14]. SASP factors, including IL-6 and MMP-3, directly degrade ECM components (e.g., aggrecan, type II collagen) and induce paracrine senescence in neighboring cells[15]. Molecularly, telomere shortening triggers the DNA damage response, activating the p53/p21 pathway[16]. Mitochondrial dysfunction exacerbates oxidative stress, accumulates mitochondrial DNA mutations, and impairs energy metabolism[17]. Additionally, impaired autophagy leads to the accumulation of damaged cellular components, accelerating senescence[18]. Degenerated discs exhibit a positive correlation between senescent NPC proportions and SASP factor expression, alongside significant downregulation of autophagy-related proteins, underscoring the central role of cellular senescence.

Inflammation and Oxidative Stress

Oxidative stress is a pivotal driver of IVDD. Chronic inflammation in the CEP originates from abnormal

mechanical stress, immune cell infiltration, and other factors, accelerating chondrocyte aging and impairing ECM maintenance. This process releases inflammatory cytokines, creating a vicious cycle[19]. Reactive oxygen species (ROS) imbalance plays a key role: excessive ROS damages nucleic acids, lipids, and proteins, inducing DNA breaks, membrane disruption, and protein dysfunction[20]. ROS activates the MAPK pathway to promote apoptosis while suppressing PI3K/AKT survival signaling. It also triggers NF-κB pathway activation, upregulating IL-1β and TNF-α expression, and stimulates the NLRP3 inflammasome, forming a "ROS-NLRP3-IL-1β" positive feedback loop. Mitochondrial fission and dysfunction further amplify oxidative stress, disrupting CEP structure[20]. Clinically, degenerated discs exhibit elevated ROS levels, reduced antioxidant enzyme activity, and upregulated inflammatory markers, confirming the centrality of inflammation and oxidative stress.

Metabolic Dysregulation

The hypoxic IVD microenvironment necessitates reliance on glycolysis for energy production[21]. In IVDD, dysregulated hypoxia-inducible factor-1α (HIF-1α) disrupts metabolic balance. Paradoxically, HIF-1α overexpression can reduce oxidant release and enhance antioxidant defenses, mitigating mitochondrial damage caused by excessive oxidative stress and delaying metabolic imbalance[22]. Experimental models show that hypoxia-induced HIF-1α activation enhances aggrecan and type II collagen expression while suppressing matrix metalloproteinase-13 (MMP13) and ADAMTS5 levels, restoring ECM metabolic equilibrium[23, 24]. Targeting metabolic dysregulation through HIF-1α and downstream pathways may correct glycolysis-oxidative phosphorylation imbalances and improve cellular metabolism.

Abnormal Mechanical Stress

Abnormal mechanical loading (e.g., chronic overloading, poor posture) activates profibrotic pathways, causing disorganized collagen alignment and structural rupture in the AF. Studies confirm that alterations in cell physiology and matrix catabolism directly correlate with non-physiological mechanical loading on discs. Maintaining typical disc function depends on physiological intradiscal pressure, whereas stress concentration caused by imbalanced stress distribution in degenerated discs exacerbates damage[25]. Mechanical overload elevates intracellular free Ca^{2+}, inducing ferroptosis[26]. This iron-dependent cell death results from iron metabolism dysregulation, reduced GPX4 activity, and lipid peroxidation accumulation, disrupting ECM synthesis. Degenerated discs exhibit aberrant expression of mechanosensitive signaling molecules and elevated ferroptosis markers, correlating with degeneration severity. Optimizing mechanical environments and blocking aberrant signaling represent promising therapeutic strategies.

TARGETED THERAPEUTIC STRATEGIES

Targeting Cellular Senescence

Therapies targeting NPC senescence focus on senescent cell clearance and senescence process modulation. Rapamycin (RA), an mTOR inhibitor, enhances autophagic flux, clears damaged components, suppresses SASP[14, 27], and restores ECM synthesis. RA treatment increases autophagy-related protein expression and reduces senescence markers. Senolytics (e.g., dasatinib + quercetin) selectively eliminate senescent NPCs, block SASP propagation, and improve disc histology and biomechanical properties[28]. Future therapies leveraging senescence-specific biomarkers may enable precision interventions.

Anti-Inflammatory and Antioxidant Therapies

TNF-α inhibitors, including infliximab and atsttrin, suppress inflammation and pain. Infliximab, an anti-TNF-α antibody, reduces pain to sham levels when injected into rat discs. Atsttrin, a synthetic protein containing three progranulin fragments, antagonizes TNF-α-mediated

inflammation by binding to TNF-α receptors[29, 30]. Exosomes (EXOs), extracellular vesicles secreted by cells, can be engineered for therapeutic purposes. For example, cartilage-affinity peptide (CAP)-modified exosomes carrying Nrf2 (CAP-Nrf2-Exos) target oxidative stress pathways, reducing ROS levels[31]. KEAP1-NRF2 pathway activators upregulate antioxidant proteins (e.g., HO-1, NQO1), ameliorating oxidative stress[20]. Future advances in nanocarrier-based drug delivery may enhance therapeutic efficacy.

Metabolic Reprogramming Interventions

Modulating HIF-1α and downstream metabolic pathways is critical. HIF-1α reduces oxidant release and enhances antioxidant defenses, protecting NPCs from oxidative stress-induced mitochondrial damage. Further studies reveal that HIF-1α's protective effects under oxidative stress involve PDK-1, a regulator of NPC glycolysis[32]. Mitochondria-targeted antioxidants (e.g., SOD and GSH-Px analogs) improve mitochondrial function and reduce ROS[33]. Single-cell metabolomics may identify novel targets for metabolic interventions.

Mechanotransduction-Targeted Interventions

Biomechanical interventions (e.g., exercise rehabilitation, bracing) optimize spinal load distribution and reduce disc pressure. Human AF tissues withstand circumferential tensile stresses up to 12.7 MPa[34]. Molecularly, integrin inhibitors block mechanotransduction signals, inhibiting AF fibrosis, while ferroptosis inhibitors (e.g., iron chelators, GPX4 upregulators) reduce cell death[19]. Preclinical studies demonstrate that combining biomechanical and molecular therapies improves disc morphology and function[35]. Integrating biomechanical monitoring with targeted therapies may revolutionize IVDD treatment.

KEY SIGNALING PATHWAY REGULATORY NETWORKS IN IVDD PROGRESSION

Senescence Regulatory Pathways

Senolytics target four classes of molecules in senescent cells: BCL-2 family proteins, HSP90 inhibitors, PI3K/AKT, and others[36-39]. PI3K/Akt regulates two downstream pathways to inhibit senescent cell apoptosis: (1) suppression of pro-apoptotic signals (e.g., Bax, Bad, FoxO)[40], and (2) modulation of mTOR and NF-κB pathways. mTOR, a central regulator of senescence and autophagy[41], and NF-κB, a key inflammatory mediator[42], are both PI3K/Akt-dependent. The BCL-2 family, characterized by BCL-2 homology (BH) domains, inhibits intrinsic apoptosis by blocking cytochrome c release[43]. Heat shock proteins (HSPs), induced under stress, stabilize DNA damage response (DDR) proteins. HSP90 activates Akt via phosphorylation and inhibits apoptosis in senescent cells. Radiation- or stress-induced DNA damage upregulates HSP90, stabilizing DDR proteins and promoting senescence[44, 45].

Inflammation-Oxidative Stress Axis

HIF-1α mitigates IVDD by reducing mitochondrial ROS production, suppressing inflammation, metabolic dysregulation, and apoptosis in NPCs[32]. Cortistatin knockout studies link it to mitochondrial ROS and NLRP3 inflammasome activation in IVDD, revealing novel therapeutic targets[46]. Honokiol activates SIRT3 via the AMPK-PGC-1α pathway, enhancing antioxidant capacity, mitochondrial dynamics, and mitophagy[47]. The NLRP3 inflammasome bridges oxidative stress and inflammation: mtROS induces NLRP3 oligomerization, recruiting ASC and caspase-1 to activate IL-1β[48]. Melatonin disrupts the IL-1β/NF-κB-NLRP3 feedback loop by inhibiting NF-κB and mtROS, reducing NLRP3, p20, and IL-1β levels in vitro and in vivo[49].

Metabolic Regulatory Pathways

Hypoxia-driven glycolysis in IVD depends on HIF-1α. HIF-1α binds ARNT, activating LDHA and PDK1 to promote glucose-to-lactate conversion. In IVDD, aberrant HIF-1α stabilization causes lactate accumulation, inhibiting SIRT1, downregulating PGC-1α, and disrupting

mitochondrial dynamics. Drp1 hyperphosphorylation (Ser616) induces mitochondrial fragmentation, reducing ATP production by 40% and increasing mtROS 2.5-fold[49]. Metabolic regulation occurs via enzyme expression changes, substrate availability, or post-translational modifications (PTMs). HIF-1α inhibitor 2ME2 reduces glycolysis by 35% and restores mitochondrial morphology, while PGC-1α agonist SSR180711 enhances mitochondrial DNA replication via TFAM upregulation[50].

Mechanotransduction Pathways

Abnormal mechanical stress activates Wnt/β-catenin signaling, promoting disc cell death and ECM degradation[51]. Wnt/β-catenin activation precedes NLRP3 inflammasome upregulation in IVDD mice, suggesting mechanical instability therapies may exacerbate cell death via Wnt signaling[52].

PATHWAY-SPECIFIC DRUG DELIVERY

Direct intradiscal or epidural drug injections risk CNS toxicity due to drug leakage. Nanoscale drug delivery systems (NDDS) enable localized, sustained release and targeted delivery, minimizing off-target effects[53, 54]. Nanoparticles, dendrimers, liposomes, micelles, and exosomes serve as nanocarriers for IVD repair, pain relief, and functional recovery[55, 56]. Studies suggest nanomedicines may offer safer, more reliable alternatives to surgery.

CONCLUSION

IVDD pathogenesis involves multifaceted interactions among senescence, inflammation, oxidative stress, and metabolic dysregulation. While targeted therapies (senolytics, metabolic modulators, biomechanical interventions) show promise, challenges persist in multi-mechanism integration, drug delivery optimization, and clinical translation. Future research should integrate multi-omics, biomechanics, and precision medicine to develop regenerative therapies, ultimately alleviating the global burden of IVDD-related disability.

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