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Review Paper

Molecular and Cellular Mechanisms of Intervertebral Disc Degeneration: A Narrative Mini-review

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ABSTRACT

Intervertebral disc degeneration (IVDD) is a major contributor to low back pain and spinal disorders, representing a significant global health burden. Once considered a consequence of aging and mechanical stress, IVDD is now recognized as a multifactorial process involving complex molecular and cellular mechanisms. This narrative mini-review summarizes current insights into the pathophysiology of IVDD, focusing on inflammatory signaling, extracellular matrix (ECM) degradation, oxidative stress, mitochondrial dysfunction, and cellular senescence. Understanding these interconnected pathways provides a foundation for developing targeted and regenerative therapeutic strategies.

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Introduction

Intervertebral disc degeneration (IVDD) is a leading cause of low back pain and disability worldwide, affecting millions of individuals and imposing a substantial socioeconomic burden. The intervertebral disc is a complex structure composed of the nucleus pulposus (NP), annulus fibrosus, and cartilage endplates, which together maintain spinal flexibility and load distribution. Under physiological conditions, disc homeostasis is maintained by balancing between extracellular matrix (ECM) synthesis and degradation. However, accumulating evidence indicates that IVDD is not merely a passive degenerative process but an active, cell-mediated disease involving inflammation, metabolic alterations, and biomechanical stress [1, 2].

A key feature of IVDD is the disruption of ECM integrity, particularly within the NP, where proteoglycans, such as aggrecan and type II collagen, are essential for maintaining hydration and mechanical resilience. During degeneration, there is a shift toward catabolic activity driven by increased expression of matrix-degrading enzymes, including matrix metalloproteinases and aggrecanases, such as a disintegrin and metalloproteinase with thrombospondin motifs4 (ADAMTS-4) and a disintegrin and metalloproteinase with thrombospondin motifs5 (ADAMTS-5) [3, 4]. This enzymatic degradation results in loss of disc height, reduced hydration, and compromised biomechanical function. The imbalance between anabolic and catabolic processes is largely mediated by pro-inflammatory cytokines, particularly interleukin-1β (IL-1β) and tumor necrosis factor-α, which are upregulated in degenerated discs [5, 6].

These cytokines activate key intracellular signaling pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to increased transcription of inflammatory mediators and catabolic enzymes [7]. This inflammatory microenvironment not only accelerates ECM breakdown but also inhibits matrix synthesis by disc cells. Furthermore, inflammation has been implicated in nociceptive signaling, linking molecular degeneration to clinical symptoms such as chronic low back pain [8-10].

Oxidative stress is another critical contributor to IVDD. Excessive production of reactive oxygen species (ROS) in disc cells leads to oxidative damage of DNA, proteins, and lipids, ultimately impairing cellular function [11]. Mitochondrial dysfunction further exacerbates ROS accumulation and disrupts energy metabolism, creating a detrimental feedback loop that accelerates degeneration. Studies have shown that oxidative stress also enhances inflammatory signaling pathways, reinforcing the interplay between these mechanisms [12, 13].

Cellular senescence and apoptosis are central to the progressive loss of functional disc cells. Senescent cells accumulate in degenerated discs and exhibit a senescence-associated secretory phenotype, characterized by the release of pro-inflammatory cytokines and matrix-degrading enzymes [14]. This phenotype contributes to chronic inflammation and perpetuates tissue degradation. In parallel, increased apoptosis of NP cells reduces the disc's regenerative capacity, further compromising its structural integrity [15, 16].

Recent advances in basic science have highlighted the role of epigenetic regulation, including microRNAs and long non-coding RNAs, in modulating gene expression during IVDD [17]. These regulatory molecules influence key pathways involved in inflammation, apoptosis, and ECM metabolism. In addition, extracellular vesicles, particularly exosomes, have emerged as important mediators of intercellular communication within the disc microenvironment and represent promising therapeutic tools for regenerative medicine [18, 19].

Mechanical loading and altered biomechanics also play a significant role in IVDD. Abnormal mechanical stress can disrupt disc cell metabolism and activate mechanotransduction pathways that promote catabolic responses [2]. The interplay between mechanical and molecular factors underscores the complexity of IVDD. It supports the concept of the spine as a dynamic system in which structural and biological changes are closely linked.

Taken together, IVDD is driven by a network of interrelated mechanisms involving inflammation, oxidative stress, cellular dysfunction, and biomechanical alterations. This integrated understanding has shifted the focus of research toward identifying disease-modifying therapies that target underlying molecular pathways rather than solely addressing symptoms.

Conclusion

IVDD is a multifactorial and biologically active process involving complex interactions among inflammatory, oxidative, and mechanical factors. Advances in basic science have provided critical insights into the molecular mechanisms driving disc degeneration and have identified potential targets for regenerative and disease-modifying therapies. Bridging these findings with clinical applications remains essential for improving patient outcomes in spinal disorders.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

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