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# Biologic Treatments in Intervertebral Disc Degeneration: Protein-Based and Cell-Based Therapies

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**Lumbar back pain is a clinical entity of global significance. Intervertebral disc degeneration (IDD) is a commonly attributed source of lumbar back pain that has a vast potential for treatment innovation. The current basis of treatments for IDD, both nonoperative and surgical, focuses largely on alleviating symptoms rather than restoring native anatomy, biology, and mechanics. Advances in the understanding of intervertebral disc (IVD) biology and IDD pathogenesis have given rise to the field of regenerative medicine including protein-based and cell-based therapies. The goal of biologic therapies in IDD is to cultivate molecular changes in the IVD toward repair. Protein-based therapies offer a way to manipulate the microenvironment of the diseased IVD with the goal of shifting the catabolic profile of IDD toward anabolism and matrix homeostasis. Cell-based therapies offer a way to repopulate the IVD with cells of a favorable phenotypic profile for disc matrix regeneration. Advances in the delivery of these therapies using biomaterial scaffolds have also provided an avenue for nucleus pulposus replacement. Although investigations for biologic treatments in IDD have largely been limited to in vitro and animal studies, this developing field has vast potential for future clinical application. This article reviews the native anatomy and biology of the IVD, the pathomechanisms and limitations of current treatments of IDD, and the status of emerging cell-based and biologic therapies including the challenges facing the field today.**
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## Introduction

Back pain encompasses a broad clinical entity that affects a growing percentage of the US population. Nearly 40% of the adult population is afflicted by back pain.[1] Back pain is an enormous cause of morbidity in the United States and is cited as one of the most common reasons for work days missed. The financial burden of back pain on the healthcare system is enormous, with estimates of its total cost exceeding 80 billion dollars annually.[2] The all-encompassing term "back pain" is poorly understood and often multifactorial. Intervertebral disc degeneration (IDD) has been implicated as one of the primary causes of back pain.[3] Some evidence points toward increased nociceptive nerve ingrowth occurring in the degenerated disc as a potential mechanism to explain the association between IDD and low back pain.[4] Therapies aimed to combat IDD range from nonoperative to minimally invasive and open surgical treatments. An area of rapid growth and development in the research realm is regenerative medicine and cell-based therapies to treat IDD. The goal of this article is to provide a brief insight into the anatomy and biology of the intervertebral disc (IVD),

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the pathomechanisms of IDD, and the status of current and emerging cell-based therapies to combat this condition.

## Anatomy

IVDs lie between vertebral bodies throughout the spine. The IVD provides many essential functions to the spine including load bearing, dispersion of forces, flexibility, and mobility[5] (Fig. 1).[6] The distinct anatomical components of the IVD each contribute to the biological and mechanical characteristics of the disc based upon their unique composition and characteristics. The nucleus pulposus (NP) is located centrally within the disc. The key function of the NP is to provide a cushioning effect to the IVD by absorbing axial compressive forces. The NP responds to compressive loads by absorbing and releasing water. It accomplishes this feat through the osmotic properties of the highly anionic proteoglycan aggregate composing of hyaluronic acid, link protein, and aggrecan interacting with glycosaminoglycan side chains. The primary cells within the NP are chondrocyte-like cells that synthesize key matrix components that form the structure of the NP including collagen (predominately type II), elastin, and proteoglycans (predominately aggrecan). Secondary cells are large and vacuolated appearing notochordal cells. Notochordal cells are proposed to play a protective role against disc degeneration as their disappearance coincides with the start of IDD progression.[7,8]

The annulus fibrosus (AF) comprises the remaining bulk of the IVD, encircling the centrally located NP. The AF can be further separated into the outer AF and inner AF, which have distinct function, composition, and morphology. The outer AF functions to resist hoop stresses at the edges of the IVD. The inner AF acts to contain the expanding NP and assists the NP in distributing compressive axial forces. The cells of the AF are elongated fibrochondrocytes residing within concentric lamellae composed of a collagen fiber and elastin matrix. The outer AF is fibrous in nature with fibroblastic cells that predominately produce collagen type I. The inner AF alternatively is more cartilaginous; inner AF cells are more spherical and chondroid in appearance and produce mostly collagen type II.[9]

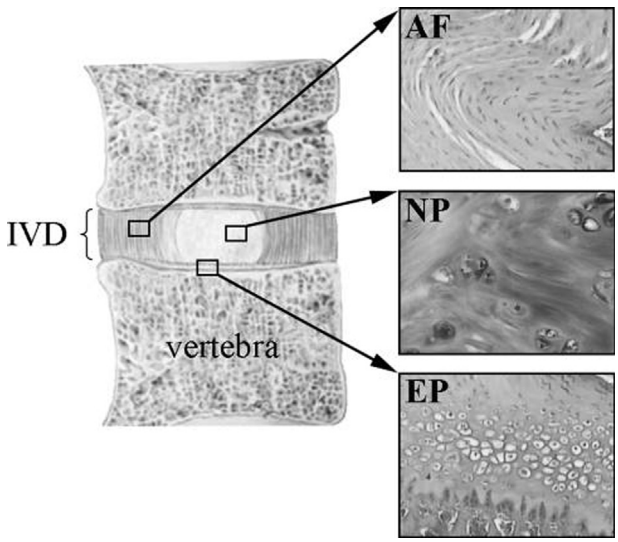


**Figure 1** The intervertebral disc (IVD) is composed of the following 3 components: the annulus fibrosus (AF) is a fibrocartilage organized with the fibroblast-like cells in dense concentric lamellae. The nucleus pulposus (NP) is a less structured gelatinous substance with chondrocyte-like cells. The IVD lies between cartilaginous end plates (EP). (Reprinted with permission from Mwale et al[6])

## Pathogenesis of IVD Degeneration

IDD is a term used to describe the cascade of biological and mechanical changes to the IVD resulting in abnormal changes in structure and function. In IDD, pathologic changes occur within the IVD from the molecular to the gross level. At the molecular level one of the major changes in IDD is the overall shift in homeostasis toward catabolism with slowed extracellular matrix (ECM) synthesis and increased breakdown.[10,11] The degeneration process is characterized by an upregulation of matrix metalloproteinases, nitric oxide, interleukins (IL), prostaglandins, or a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS).[12,13] As catabolic enzyme activity is increased, natural inhibitors such as tissue inhibitor of metalloproteinases (TIMP-1, -2, and -3) show suppressed function.[14] Generally, there is a slowing of the anabolic process with a decrease in growth factors; this results in decreased collagen and diminished proteoglycan synthesis.[12,15]

In IDD, the microenvironment of the disc is inundated by inflammatory cytokines such as IL-1, IL-6, IL-12, IL-17, tumor necrosis factor alpha (TNF-$\alpha$) and interferon gamma (IFN-$\gamma$).[14,16] Within this microenvironment, the IVD exhibits decreased capacity for tissue repair. The IVD has low baseline potential for repair and regeneration given its hypoxic, acidic, low nutrient environment and sparse cellularity.[17] The IVD is relatively avascular as it receives blood flow from the termination of the capillaries at the vertebral end plates. As the cartilaginous end plates ossify with the degeneration process it greatly diminishes the diffusion of the nutrient supply to the IVD, potentially contributing to cell death.[18] In IDD NP cells exhibit a phenotypic shift from type II to type I collagen expression and a decrease in aggrecan synthesis. This change leads to loss of matrix proteoglycan hydration, resulting in a fibrotic NP.[14] Within the layers of the AF, the dysregulation of ECM synthesis and breakdown results in a thickened, irregular framework of fiber bundles. As the disc loses structural integrity it loses its ability to withstand cyclic mechanical loading, furthering the cascade of disc degeneration.[19,20]

Conventional diagnostic tests such as x-ray and magnetic resonance imaging (MRI) are able to detect pathologic changes in IDD at the macroscopic level (Fig. 2).[21] Gross morphologic changes to the disc include reduced disc height or collapsed disc space, lack of distinction between boundaries of the AF and NP, loss of signal intensity on T2-weighted images, and lack of homogeneity of the NP.[21] Modern diagnostic modalities are far from perfect in diagnosing discogenic back pain, however, as frequently the appearance of disc degeneration on