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Review Article

# The molecular basis of intervertebral disc degeneration

Christopher K. Kepler, MD, MBA[a,*], Ravi K. Ponnappan, MD[a], Chadi A. Tannoury, MD[b], Marakand V. Risbud, PhD[b], David G. Anderson, MD[a]

[a]*Department of Orthopaedic Surgery, Thomas Jefferson University & Rothman Institute, Philadelphia, PA 19107, USA*
[b]*Department of Orthopaedic Surgery, Thomas Jefferson University, Philadelphia, PA 19107, USA*

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**Abstract**

**BACKGROUND:** Intervertebral disc (IVD) degeneration remains a clinically important condition for which treatment is costly and relatively ineffective. The molecular basis of degenerative disc disease has been an intense focus of research recently, which has greatly increased our understanding of the biology underlying this process.

**PURPOSE:** To review the current understanding of the molecular basis of disc degeneration.

**STUDY DESIGN:** Review article.

**METHODS:** A literature review was performed to identify recent investigations and current knowledge regarding the molecular basis of IVD degeneration.

**RESULTS:** The unique structural requirements and biochemical properties of the disc contribute to its propensity toward degeneration. Mounting evidence suggests that genetic factors account for up to 75% of individual susceptibility to IVD degeneration, far more than the environmental factors such as occupational exposure or smoking that were previously suspected to figure prominently in this process. Decreased extracellular matrix production, increased production of degradative enzymes, and increased expression of inflammatory cytokines contribute to the loss of structural integrity and accelerate IVD degeneration. Neurovascular ingrowth occurs, in part, because of the changing degenerative phenotype.

**CONCLUSIONS:** A detailed understanding of the biology of IVD degeneration is essential to the design of therapeutic solutions to treat degenerative discs. Although significant advances have been made in explaining the biologic mediators of disc degeneration, the inhospitable biochemical environment of the IVD remains a challenging environment for biological therapies. 

*Keywords:* Disc degeneration; Biology of disc degeneration; Molecular basis of disc degeneration; Cytokine expression; Painful disc degeneration

## Introduction

Low back pain (LBP) is one of the most common musculoskeletal complaints, estimated to trigger between 2.8% [1] and 5% [2] of health-care visits in the United States and an even higher percentage in young patients with fewer chronic medical conditions. The overall cost of LBP exceeds $100 billion/year in the United States alone, when considering both direct costs and indirect costs, such as lost wages and productivity [3].

Although there are numerous potential pain generators in the lumbar spine, symptomatic disc degeneration is thought to be a significant contributor to LBP [4,5] and accounts for more than 25% of lumbar fusion surgery performed in the United States [2]. Lumbar spine disc degeneration begins earlier in life than degeneration of any other connective tissue in the human body, often by the second decade [6–9]. As degeneration progresses, the intervertebral disc (IVD) becomes less able to efficiently absorb physiological loads, resulting in load transfer to

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The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

* Corresponding author. Department of Orthopaedic Surgery, Thomas Jefferson University, 1015 Walnut St, Room 801, Philadelphia, PA 19107, USA. Tel.: (608) 209-2527; fax: (215) 955-9773.

*E-mail address*: chris.kepler@gmail.com (C.K. Kepler)

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adjacent vertebral bodies leading to end plate changes, osteophyte formation, and trabecular microfractures [10]. Increased loading is also borne by the facet complex [7] leading to arthrosis, hypertrophy, and possible neural impingement. Degenerative fissures in the lamellae of the annulus fibrosis (AF) coalesce [11], leading to a lack of structural integrity, which may allow herniation of the central nucleus pulposus (NP) material. This constellation of morphological changes often occur without associated symptoms as demonstrated by the high incidence of degenerative changes in the asymptomatic population [12] but may cause disc-related pain in some patients. Degenerative processes also likely contribute to susceptibility to disc herniation although the relationship between disc degeneration, discogenic pain, and disc herniation is incompletely understood from a clinical perspective. At present, other than ablative techniques that remove a symptomatic disc and reconstruct the segment through either a surgical fusion or disc arthroplasty, no treatments exist to restore or regenerate the damaged tissue. The clinical results of spinal fusion and disc arthroplasty remain suboptimal [13,14].

It is unclear whether disc degeneration can be reversed or halted once started. Puncture of the AF with a needle induces a seemingly minor injury but one that has been shown in numerous animal models to progress to obvious degenerative changes in quadruped animals that normally do not develop disc degeneration [15–19]. The inability of the disc to repair itself after such an injury has been capitalized on by scientists searching for a reproducible animal model of human disc degeneration [20]. Similarly, iatrogenic disc injury in humans after discography has been demonstrated to result in disc degeneration [21,22], a fact that raises questions regarding the feasibility of therapeutic intervention after the onset of symptomatic disc degeneration.

The molecular basis of degenerative disc disease has been an intense focus of research recently, which has greatly increased our understanding of the biology underlying this process. Alterations in IVD production of extracellular matrix (ECM), inflammatory cytokines, and degradative enzymes occur in a stepwise cascade leading to the end stage morphological changes evident on routine clinical imaging studies. The development of alternative biological treatment modalities for disc repair or regeneration will require a detailed understanding of these biological processes to reverse or halt the progression of degenerative changes within the native disc, if components of disc degeneration are found to directly contribute to associated symptoms. The objectives of this broad narrative review are to describe the biology of the normal IVD, potential explanations of the genetic basis for disc degeneration, and the characteristic molecular, structural, and cellular changes that occur during disc degeneration.

## Identification of articles

Relevant, recent research on the molecular basis of IVD pathobiology was identified via a search performed by the first author and reviewed by all coauthors using the Pubmed database. Included articles were limited to the English language. Search terms included the following: intervertebral disc degeneration, molecular basis of disc degeneration, ECM degradation, gene polymorphism, genetics of disc degeneration and combinations of these terms. Each term above was used with the word disk substituted for disc. Articles were reviewed to identify those that discussed genes postulated to play an important role in IVD degeneration and had a previously established role in normal or degenerative disc biology.

## Biology of normal IVD

The IVD is part of an anatomic unit that includes the NP located centrally, the AF located peripherally, and the cartilaginous end plates with their associated capillary beds both cranially and caudally. A summary of structural differences between AF and NP is found in Table 1. The healthy AF comprises concentric layers of predominantly type I collagen fibrils, which serve as a boundary containing the inner NP. The AF layers become less well-organized, incorporate an increasing proportion of type II collagen, and increase in water content moving from superficial layers inwards. The orientation of collagen fibers in the AF layers is not uniform; fibers are aligned at approximately 30° to the longitudinal axis of the spine alternating their direction with each concentric layer, a feature that provides optimal tensile strength for containment of the NP [23]. Although there is initially a distinct demarcation between the AF and NP, this distinction disappears early in life as IVD degeneration begins [10]. The NP, in contrast, is more isotropic than the AF with an amorphous arrangement of type II collagen. The

Table 1
Differences between normal AF and normal NP

| Feature | AF | NP |
|---|---|---|
| Cell shape | Elongated, fibroblast-like | Rounded, chondrocyte-like |
| Dominant collagen type | Collagen I | Collagen II |
| Proteoglycan content | Low (~25%) | High (~70%) |
| ECM water content | Low | High |
| Biomechanical role | Tensile force to contain NP | Resists axial compression |
| Primary form of degradation | Loses structural integrity | Loses proteoglycan and water content |

AF, annulus fibrosis; NP, nucleus pulposus.