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REVIEW ARTICLE

Genetic factors in intervertebral disc degeneration

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Abstract Low back pain (LBP) is a major cause of disability and imposes huge economic burdens on human society worldwide. Among many factors responsible for LBP, intervertebral disc degeneration (IDD) is the most common disorder and is a target for intervention. The etiology of IDD is complex and its mechanism is still not completely understood. Many factors such as aging, spine deformities and diseases, spine injuries, and genetic factors are involved in the pathogenesis of IDD. In this review, we will focus on the recent advances in studies on the most promising and extensively examined genetic factors associated with IDD in humans. A number of genetic defects have been correlated with structural and functional changes within the intervertebral disc (IVD), which may compromise the disc's mechanical properties and metabolic activities. These genetic and proteomic studies have begun to shed light on the molecular basis of IDD, suggesting that genetic factors are important contributors to the onset and progression of IDD. By continuing to improve our understanding of the molecular mechanisms of IDD, specific early diagnosis and more effective treatments for this disabling disease will be possible in the future.

Abbreviations: LBP, low back pain; IDD, intervertebral disc degeneration; IVD, intervertebral disc; NP, nucleus pulposus; AF, annulus fibrosus; EP, endplate; ECM, extracellular matrix; MRI, magnetic resonance imaging; SNP, single-nucleotide polymorphism; MMPs, matrix metalloproteinases; VDR, vitamin D receptor.

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Introduction

Low back pain (LBP) is a leading cause of disability worldwide and has tremendous effects on the economy and quality of life of the patients.[1–4] LBP imposes an economic burden similar to or even greater than that of coronary heart disease and other major health problems such as diabetes, Alzheimer's disease and kidney diseases.[5] As the second most common cause of doctor visits in the USA, LBP treatment costs $20–100 billion in direct care spending and contributes $100–200 billion each year in total economic burden, according to studies about the direct and indirect costs of LBP published in English from 1997 to 2007.[2,6–10]

Among many causes of LBP, intervertebral disc degeneration (IDD) is the most common diagnosis and target for intervention. IDD plays a critical role in LBP and correlates strongly with structural breakdown and dysfunction of the intervertebral disc (IVD).[11,12] The etiology of IDD is complex and multifactorial, in which aging, certain diseases and injuries, and genetic factors are involved. Since the mechanisms of IDD are still not completely understood, current treatment is largely limited to symptomatic relief using non-steroidal or steroidal anti-inflammatory medication and surgical intervention for late-stage IDD with severe neurological symptoms caused by herniation of IVD.[8] A better understanding of IDD will enable more targeted and less invasive therapies while keeping people mobile and functional.[3,8] This review article will focus on the recent advances in understanding the genetic mechanisms of IDD. The first section is a brief review of the basic structural and functional characteristics of IVD; the second section summarizes the recent studies on the most promising and extensively examined genetic factors associated with IDD in humans.

Structural and functional characteristics of IVD

The IVD is a fibrocartilaginous tissue connecting two adjacent vertebral bodies in the spine.[13] IVD is an elastic structure and functions as a weight-bearing cushion which plays a major role in maintaining flexibility and stability of the spine.[11] The IVD is composed of the external annulus fibrosus (AF) and the inner gel-like center, the nucleus pulposus (NP). The central NP consists of a water-based gel-like avascular substance rich in proteoglycans and a small amount of collagen type II and elastin fibers; the function of the elastic NP is to distribute hydraulic pressure in all directions within each disc under compressive loads.[7,11] The outer region AF encloses the NP with a type I collagen-based concentric lamellar structure.[8,11] Within each lamella, the collagen fibers are aligned approximately 30° with respect to the transverse plane of the vertebral endplates (EP). There are two thin EPs, which extend superiorly and inferiorly over the inner AF and NP and supply nutrients to discs by diffusion. The EPs consist of osseous and hyaline-cartilaginous layers and connect the intervertebral disc to the vertebral bodies. Only NP and the inner AF are covered by the cartilaginous endplates. The collagen fibers of the outer AF anchor directly into the bone of the apophyseal ring. There is no distinct border between the NP and the inner AF.[11]

There are different cell types located in various regions of the IVD. The cartilaginous EPs contain rounded chondrocytes, similar to the hyaline cartilage in other locations. The cells in the outer AF are elongated and fibroblast-like, whereas in the most inner zone of AF and the NP, the cells become more spheroidal and chondrocyte-like. The NP contains a relatively small number of fibroblasts and more numerous chondrocyte-like cells (Fig. 1A). The cell types of cartilaginous EP and AF remain relatively constant throughout their life. However, the NP goes through substantial cell type changes early in life.[7,14] Cells in NP at birth are largely of notochordal origin, but in most humans, the number of notochordal cells decreases rapidly after birth and eventually becomes undetectable at about 4–10 years of age.[15] At the same time, the NP is gradually populated with chondrocyte-like cells, probably originating and migrating from the cartilaginous EPs and the inner AF.[7] Although the detailed mechanism of this cell type transition is still unknown, it has been assumed that Fas, a member of the tumor necrosis factor receptor family, plays a role in this process. Apoptosis induced by an autocrine or paracrine Fas-mediated counterattack may be important in this transition.[14,16] Human notochordal cells gradually disappear with aging, which correlates with disc degeneration. These observations suggest that the notochordal cell population may be involved in maintenance and regeneration of IVD.[17] However, the transplantation of notochordal cells into IVD to reverse degeneration is not feasible clinically, because it relies on the removal of notochordal cells at an early age. The use of soluble factors produced by notochordal cells may be more practical than cell transplantation.[3,8,14]

The extracellular matrix (ECM) composition is very important for IVD structure and function because changes in ECM can eventually contribute to IDD.[3] Type I and II collagens are the main components of IVD. Peripheral AF ECM contains mostly type I collagen with relatively low proteoglycan and water content. ECM of the inner AF becomes higher in type II collagen and proteoglycans. In general, collagens account for approximately 60% of the AF dry weight whereas proteoglycans account for approximately 25%. Other collagen types, such as type XI and type IX collagens, which play a role in assembly of type II collagen fibers and formation of crosslinks between the adjacent collagen fibrils, comprise a small portion of ECM. In comparison with the AF, the ECM in NP contains more type II collagen and proteoglycans, the function of which is to maintain water content and to withstand conductive pressure. Aggrecan, the most common proteoglycan, constitutes up to 50% of NP dry weight and is responsible for osmotic properties and helps maintain disc height and ability to withstand compression.[3,9]

During the course of growth and skeletal maturation, under the influence of both intrinsic and extrinsic factors, the boundary between NP and AF becomes less obvious. The nucleus generally becomes more fibrotic and less gel-like, while the annular lamellae become irregular with disorganized collagen and elastin networks. During the progression of IDD, cleft formation with fissuring is usually seen within the disc, especially in the nucleus. Degeneration of the AF allows the NP to push out towards the outer AF causing disc bulge (Fig. 1B). Complete rupture of the AF allows the NP to protrude beyond the boundary of the disc