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Invited critical review

MMPs and ADAMTSs in intervertebral disc degeneration

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ABSTRACT

Intervertebral disc degeneration (IDD) is the most common diagnosis in patients with low back pain, a leading cause of musculoskeletal disability worldwide. The major components of extracellular matrix (ECM) within the discs are type II collagen (Col II) and aggrecan. Excessive destruction of ECM, especially loss of Col II and aggrecan, plays a critical role in promoting the occurrence and development of IDD. Matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTSs) are primary enzymes that degrade collagens and aggrecan. There is a large and growing body of evidence that many members of MMPs and ADAMTSs are highly expressed in degenerative IVD tissue and cells, and are closely involved in ECM breakdown and the process of disc degeneration. In contrast, targeting these enzymes has shown promise for promoting ECM repair and mitigating disc regeneration. In the current review, after a brief description regarding the biology of MMPs and ADAMTSs, we mainly focus on their expression profiles, roles and therapeutic potential in IDD. A greater understanding of the catabolic pathways involved in IDD will help to develop potential prophylactic or regenerative biological treatment for degenerative disc disease in the future.

Contents

Abbreviations: IVD, intervertebral disc; IDD, intervertebral disc degeneration; ECM, extracellular matrix; MMPs, matrix metalloproteinases; ADAMTSs, a disintegrin and metalloprotease with thrombospondin motifs; NP, nucleus pulposus; AF, annulus fibrosus; Col I, type I collagen; Col II, type II collagen; IL-1, interleukin-1; MAPK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; TIMP, tissue inhibitor of metalloproteinase; NGF, nerve growth factor; BMP, bone morphogenetic protein; TGF-β1, transforming growth factor-β1; SNPs, single nucleotide polymorphisms, miRNAs, microRNAs; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor κB; NO, nitric oxide; SDC4, syndecan-4; RSV, resveratrol; LfcinB, bovine lactoferricin; HO-1, heme oxygenase-1; MSCs, mesenchymal stem cells.

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1. Introduction

Low back pain is a chronic, expensive, common medical problem in the world. It is the most common cause of disability in people younger than 45 years of age. Over 80% of adults will experience low back pain during their lifetimes [1]. At present, low back pain has become the second most frequent cause for visits to the hospital. There is growing evidence that the majority of low back pain is associated with intervertebral disc (IVD) degeneration (IDD) [2]. IDD constitutes the pathological foundation of most musculoskeletal disorders of the spine, including spinal stenosis, instability, disc herniation, radiculopathy and myelopathy. Despite the pathogenesis of IDD has not been completely understood, the predominant changes to IDD are characterized by in active cell number reduction, extracellular matrix (ECM) degradation, altered phenotype of normal disc cells, and presence of inflammation [3,4]. Current treatment for IDD includes conservative management (bed rest, nonsteroidal anti-inflammatory drugs and physical therapy) and surgical procedures (laminectomy, corpectomy and fusion). If conservative treatment fails, then surgical fusion is commonly considered. All of these therapeutic methods are limited to treat the symptoms but do nothing to slow down or reverse the course of IDD. Thus, a greater understanding of IDD pathology is urgent to optimize treatment strategies and develop novel anti-IDD drugs.

The major ECM components within the discs are collagens and proteoglycans. In healthy discs, the rates of synthesis and breakdown of ECM are in equilibrium because of intricate regulation by growth factors and catabolic cytokines. When catabolism of ECM prevails over its anabolism, IDD often occurs. It is well established that loss of collagens and proteoglycans play a critical role in the development of disc degeneration [5]. Matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTSs) are primary enzymes that cleave collagens and proteoglycans. It has been already reported that many members of MMPs and ADAMTSs are highly expressed in degenerative IVD tissue and cells, and these enzymes are deeply implicated in ECM breakdown and IDD progression [6]. Moreover, inactivation or knockdown of MMPs and ADAMTSs has shown enormous potential in promoting ECM repair and retarding disc regeneration [7]. In this review, we summarize the expression patterns and roles of MMPs and ADAMTSs in IDD, and describe recent progress regarding their inhibition as a promising biological therapeutic approach for disc degeneration.

2. Structure and function of IVDs

The IVD is an important component of the spinal column and forms a shock absorber between each vertebra, allowing bending, flexion and torsion of the spine. Normal IVD is a complicated structure that contains three morphologically distinct regions: nucleus pulposus (NP), annulus fibrosus (AF) and cartilaginous end plates. The cartilaginous end plates are localized to the cranial and caudal aspects of each disc and contain the peripheral vasculature that nourishes the disc [8].

As a thick, dense structure, AF is divided into the outer and inner annuli. The outer annulus is made up of organized, collagenous concentric lamellae, which is primarily composed of fibroblast-like cells with elongated nuclei. The outer AF contains large amounts of type I collagen (Col I) together with collagen types III, V and VI. However, there is also a relatively low proteoglycan and water content within the outer annulus. In contrast to the outer annulus, the inner annulus is more fibrocartilaginous and is composed of both Col I and type II collagen (Col II), with a higher proteoglycan amount. Moreover, cells become more rounded and assume a chondrocyte-like phenotype. Taken together, collagen content in the AF comprises approximately 60% of dry weight, while proteoglycans account for approximately 25%. The biomechanical role of AF is to provide optimal tensile strength for containing NP [9].

NP locates in the central region of the IVD and is surrounded by the AF. The cell population in the NP varies with age. Cells in the NP at birth are predominantly composed of notochordal cells. However, with growth, these cells are converted to chondrocyte-like rounded cells, similar to those found in the inner annulus of AF [10]. As a gelatinous matrix, NP is rich in Col II and proteoglycans, and also includes small amounts of collagen types VI, IX and XI [11]. Among proteoglycans, aggrecan is the most common type and makes up as much as 50% of NP dry weight, which plays a critical role in absorbing water and contributes to the diffusion of nutrients from the periphery through maintenance of an osmotic gradient [12]. The hydrophilic nature of NP is responsible for a high swelling pressure. In a healthy IVD, the swelling pressure of NP and the tensile strength of AF keep balance and determine the intervertebral height, but allowing for the transformation of NP axial compression into AF hoop stresses [13]. A summary of structural and component differences between AF and NP is presented in Table 1.

3. Etiology of IDD

Although the exact pathophysiology of IDD has not been completely understood, the environmental and genetic factors are thought to be the main contributors to IDD. Occupational exposures such as vibration [14], mechanical influences including heavy lifting and weight [15], lifestyle factors such as lack of exercise [16], and the long use of non-Japanese cars [17] are known to promote IVD degeneration. Injuries associated with lifting or trauma [18,19] and tobacco use [20,21] have been also reported to be involved in the pathology of IDD. However, there is accumulating evidence that these environmental factors may explain only a small portion of IDD, and heredity is predominant and probably accounts for more than 70% of an individual's risk for degenerative disc disease [22]. Recently, Videman et al. have confirmed a close association of 25 structural, degradative, and inflammatory candidate genes with lumbar disc desiccation, bulging, and height narrowing, revealing disc degeneration as a polygenetic condition [23]. Another research has demonstrated the existence of familial predisposition to IDD with generally high heritabilities that range from 34% to 61% in different

Table 1
Structural and component differences between AF and NP.

Characteristics	AF	NP
Location	Surrounding of the NP	Central region of the IVD
Cell shape and type	Elongated, fibroblast-like	Rounded, chondrocyte-like
Primary collagen type	CI	CII
Collagen content	High, dry weight (60%)	Low, dry weight (20%)
Proteoglycan content	Low, dry weight (25%)	High, dry weight (65%)
Water content	Low	High
Biomechanical action	Tensile force to contain NP	Resists axial compression
Primary form of degradation	Destruction of structural integrity	Decreased proteoglycan and water contents