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Basic Science

Behavioral signs of axial low back pain and motor impairment correlate with the severity of intervertebral disc degeneration in a mouse model

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Abstract

BACKGROUND CONTEXT: Chronic low back pain is debilitating and difficult to treat. Depending on the etiology, responses to treatments vary widely. Although chronic low back pain is frequently related to intervertebral disc degeneration, the relationship between disc degeneration severity and clinical symptoms are still poorly understood.

In humans, studies investigating the relationship between disc degeneration severity and low back pain are limited by the difficulty of obtaining disc samples from well-characterized patients and pain-free controls. We have previously described the secreted protein, acidic, rich in cysteine (*SPARC*)-null mouse model of chronic low back pain. SPARC is a matricellular protein involved in regulating the assembly and composition of extracellular matrix. The SPARC-null mice develop age-dependent disc degeneration of increasing severity accompanied by behavioral signs suggestive of axial low back pain, radiating leg pain, and motor impairment. The existence of this model allows for examination of the relationships between clinical symptoms *in vivo* and pathological signs of disc degeneration ex vivo.

PURPOSE: The goal of this study was to explore the relationship between behavioral signs of pain and the severity of lumbar disc degeneration using the SPARC-null mouse model of disc degeneration-related low back pain.

STUDY DESIGN: This study used a cross-sectional, multiple-cohort behavioral and histological study of disc degeneration and behavioral symptoms in a mouse model of low back pain associated with disc degeneration.

FDA device/drug status: Not applicable.

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METHODS: SPARC-null and wild-type control mice ranging from 6 to 78 weeks of age were used in this study. The severity of disc degeneration was determined by *ex vivo* analysis of the lumbar spine using colorimetric histological staining and a scoring system adapted from the Pfirrmann scale. Behavioral signs of axial low back pain, radiating leg pain, and motor impairment were quantified as tolerance to axial stretching in the grip force assay, hypersensitivity to cold or mechanical stimuli on the hindpaw (acetone and von Frey tests), and latency to fall in the rotarod assay, respectively.
RESULTS: The SPARC-null mice exhibited decreased tolerance to axial stretching, hindpaw cold hypersensitivity, and motor impairment compared with age-matched control mice. The severity of disc degeneration increased with age in both SPARC-null and control mice and by 78 weeks of age, the same proportion of lumbar discs were abnormal in SPARC-null and control mice. However, the degree of degeneration was more severe in the SPARC-null mice. In both SPARC-null and control mice, tolerance to axial stretching but not hindpaw cold sensitivity correlated with disc degeneration severity. Motor impairment correlated with degeneration severity in the SPARC-null mice only.
CONCLUSIONS: These data suggest that internal disc disruption contributes to axial low back pain and motor impairment but not to radiating leg pain. These results have implications for the optimization of mechanism-based treatments strategies.

Keywords: Animal model; Correlation; Degenerative disc disease; Histology; Intervertebral disc; Low back pain; SPARC

Introduction

Low back pain (LBP) affects 12%–35% of the global population and *intervertebral discs* (IVDs) are estimated to be primary contributors in 40%–45% of the cases [1,2]. Other underlying tissue sources include facet joints, muscles, and ligaments, and frequently a physical source cannot be identified [1,3–5]. Depending on the underlying mechanisms, responses to treatments vary widely. It is therefore critical that we deepen our understanding of the underlying causes of LBP.

Intervertebral disc degeneration and low back pain

Although degeneration of the IVDs is associated with an increased incidence of LBP, the relationship between disc health and LBP is complex. Disc degeneration is not always painful: Magnetic resonance imaging (MRI) of individuals with no previous history of low back pain, sciatica, or neurogenic claudication revealed that 20% of subjects below the age of 60 years have substantial IVD abnormalities (including herniation and spinal stenosis), and after 60 years of age the proportion of asymptomatic subjects increased to 57% [6]. However, although disc degeneration is frequently asymptomatic, it is more prevalent in individuals with LBP [7]. Furthermore, in some cases, restoring disc height reverses back pain [8] and removing herniation alleviates sciatica [9], arguing for the direct participation of disc degeneration in a subpopulation of LBP patients.

Assessment of disc degeneration severity

The first attempt to assess disc degeneration severity in living humans was done in 1922 [10] with myelography, which assessed the severity of dorsal bulging, and multiple scales have been developed to quantify disc degeneration based on the methods available at the time. The first scale was based on the shape of the *nucleus pulposus* (NP) during an injection of contrasting material into the disc [11]. The five-point (I–V) Thompson scale was developed with cadaveric samples and grades gross morphological changes, taking into account the shape of the NP, *annulus fibrosus* (AF), end plate, and vertebral body [12]. Given its basis in *ex vivo* morphology, its clinical utility is limited. In 2011, Pfirrmann et al. developed a five-point scale (I–V) based on T2 MRI images in which disc height, water content, and compartmentalization were considered [13]. In T2 MRI images, the signal intensity of the IVD correlates with water and proteoglycan content [14,15]. In the Pfirrmann scale, abnormal discs range from grades 2 (slight change in white signal from NP, normal disc height) to 5 (black disc with no distinction between NP and AF, narrow disc height). Although all these scales describe the severity of internal disc degeneration, they do not include bulging or herniation as grading criteria.

The secreted protein, acidic, rich in cysteine (SPARC)-null mouse model

We have previously characterized a mouse model of LBP associated with IVD degeneration [16–20]. The SPARC-null mice presented with progressive age-dependent disc degeneration and pathological disc innervation. The SPARC is involved in extracellular matrix remodeling through numerous actions including collagen binding, modulation of growth factors, and regulation of matrix metalloproteinases [21]. The SPARC-null mice have defects in other connective tissues including dermis, adipose, periodontal ligaments, and bone [22,23]. Interestingly, neither our preliminary investigations nor published studies report signs of osteoarthritis, which would have been a confounding factor for the present study.

Behaviorally, the SPARC-null mice display signs of axial LBP as measured in the grip, tail suspension, or FlexMaze assays, and localized signs of cold but not mechanical or heat hypersensitivity in the hindpaw [16,18–20]. Because hypersensitivity to cutaneous stimuli does not generalize across