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Regenerative Medicine

Cellular Supplementation Technologies for Painful Spine Disorders

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Abstract

Low back pain affects more than 80% of adults. A proportion of these adults develops chronic low back pain (CLBP) and becomes disabled by their condition. CLBP is expensive to diagnose and treat and in terms of associated loss of productivity in the work place setting by affected individuals. Although challenging, the source of CLBP can be identified. Contemporary literature contains several studies that have established prevalence estimates for various structural sources of CLBP. In young adults, the intervertebral disk is a common source of CLBP, once it incurs annular injury that heals incompletely. Effective treatment for painful disks currently is an unmet clinical need. In older adults, the facet and sacroiliac joints are more commonly responsible for CLBP. Although certain minimally invasive techniques do exist for these painful joints, an effective restorative intervention has yet to be established. Annular injury precipitates a physiologic response that can lead to a catabolic state within the disk that impairs disk restoration. Cell loss is a feature of this process as well as the pathophysiology associated with painful facet and sacroiliac joints. Cellular supplementation is an attractive treatment strategy to initiate the repair of an injured lumbosacral structure. The introduction of exogenous cells may lead to increased extracelluar matrix production and reduced pain and disability in diskogenic CLBP. Compelling data in animal studies have been produced, stimulating Food and Drug Administration–regulated trials in humans. Numerous questions remain regarding cell viability and sufficient native nutrients to support these cells. Clinical research protocols have focused predominantly on diskogenic CLBP, and very few have addressed painful facet and/or sacroiliac joints.

Introduction

Chronic low back pain (CLBP) and chronic neck pain are common and expensive clinical scenarios. It has been implied, for example, that CLBP cannot be diagnosed [1-3]. Yet, certain clinical features can help predict its etiology [4,5]. Accurately determining the source of symptoms is not a futile attempt. If the exact structural source of CLBP or chronic neck pain can be identified, then perhaps a definitive treatment can be directed at the appropriate structure. Understanding how and why such a structure becomes symptomatic then becomes critical in designing a sensible treatment. Similarly, reliable and predictive metrics for rendering this diagnosis are equally important if such measures can help predict a treatment response to the said intervention.

Numerous publications have reported prevalence estimates for various structural sources of CLBP [5,6]. The intervertebral disk is a common origin of CLBP and is estimated to affect 39%-43% of symptomatic adults [5,6]. CLBP pain typically arises from nonhealing annular fissures [5-8] and typically affects young and middle-aged adults [5]. Facet joint–mediated low back pain (LBP), followed by sacroiliac joint pain, become more prevalent in patients with CLBP who are closer to 60 years of age [5]. Clinical studies report the prevalence of facet joint pain is 32%, and sacroiliac joint pain is 18% of adults with CLBP [5,9,10].

The subspecialty of interventional spine care uses a structure-specific diagnostic approach to LBP. Such logic implies that an accurate diagnosis leads to effective treatment; however, optimal treatment for a common source of CLBP—persistently painful lumbar intervertebral disks—has not yet been developed. Spine fusion, artificial disk replacement, intradiskal heating, and intradiskal neurolytic agents have not consistently performed at acceptable levels. A reactionary approach is the common theme among these treatments rather than a reparative or regenerative concept. An alternate strategy of stimulating repair of an injured, painful disk is appealing for multiple reasons. Reducing pain and disability associated with CLBP would address more immediate needs. Yet, it is also reasonable to wonder

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whether the application of a reparative technology would help slow down or reduce onset of the degenerative cascade and hence curtail conditions as the spine ages such as spinal stenosis.

Determining how and when to intervene to introduce regenerative techniques requires understanding the balance among the interdynamics of disk biology and pathophysiology. Disk degeneration is complex but could be described as a consequence of the nonhealing of an annular fissure occurring after diskogenic injury. The features of disk degeneration include reduced nutrition and metabolic byproduct removal, altered biophysical context, cell loss, changes in matrix turnover, and altered biomechanics. Biologic regenerative treatments for painful intervertebral disks presumably must address each if not all of these factors; focusing on which of these factors is perplexing and accounting for the affected individual's genetic predisposition is a relative unknown.

The scope of this article will be restricted primarily to the current state of affairs regarding the intradiskal cellular supplementation platform. Such consideration requires an overview of the pathophysiology of the condition that indicates treatment with such technologies. Cell therapy approaches have not been explored in as much detail for painful lumbar facet and sacroiliac joints because these conditions are less prevalent and currently have reasonably effective treatments available.

Painful Intervertebral Disks

Pathophysiology

Annular fissures [7] (Figure 1) are the morphologic substrates of diskogenic CLBP and are a distinguishing feature of internal disk disruption (IDD). IDD is a condition in which derangement of substructures internal to the intervertebral disk result in pain while the external contour of the disk remains relatively unremarkable. In other words, IDD is a different condition than a herniated nucleus pulposus—the latter is defined partially by the volume of the herniated material external to the disk's external contour. Age-related changes in the disk, often times referred to as degeneration, are not necessarily indicative of a clinically painful intervertebral disk [7]. The medical spine community has come to understand that advanced imaging evidence of degenerative abnormalities is not absolutely diagnostic for IDD. Therefore, the degenerative cascade itself should not serve as the sole target of biologic treatments.

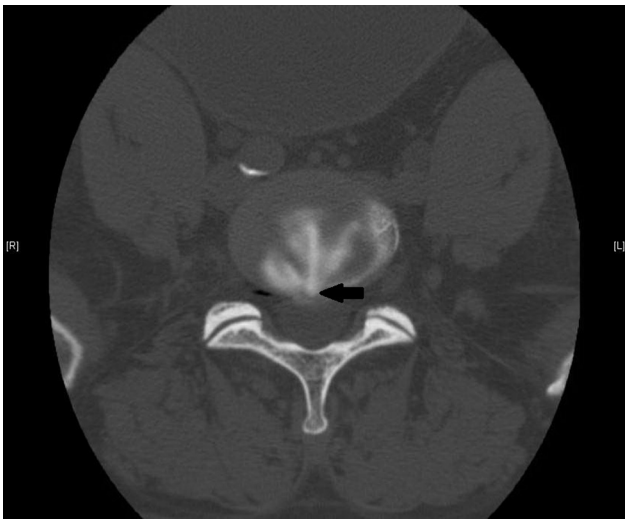

Figure 1. Postdiskography computed tomography axial cut demonstrating posterior, midline radial fissure (arrow) with circumferential outer annular extension.

Newly innervated and vascularized granulation tissue flanks these fissures that extend from the nucleus through the outer annulus [8,11-13]. In contrast, there is a paucity of innervated, vascularized granulation tissue in areas remote from these fissures within symptomatic disks and in degenerated but painless lumbar disks [8]. The innervated granulation tissue along these annular rents is a distinct histologic characteristic of IDD in patients with CLBP [8,11-13]. When performed by a technician by following stringent operational criteria, provocation lumbar diskography (Figure 2) can be used reliably to detect the annular fissures responsible for CLBP [7,14,15]. Anesthetizing these painful fissures after diskography reduces clinical LBP during provocative movements [16]. Evidence exists that supports the concept that these innervated annular fissures are a leading reason for diskogenic CLBP. Injury of the annulus catalyzes an attempt at repair typified by: inflammatory reaction [8], macrophage and mast cell invasion, and cytokine (interleukins-1, -6, and -8; tumor necrosis factor-α; proteoglycan-2) and growth factor (basic fibroblast growth factor, transforming growth factor-β) release. These changes culminate in a disk structure with altered mechanics and impairment of chondrocyte function [8,13,17-24].

Treatment Objectives

Either enhancing the accumulation of extracellular matrix or inhibiting its degradation theoretically reverses disk degeneration by rehydration. Specific chemical agents can be introduced into the disk by direct injection to: (1) stimulate proteoglycan production by protein growth factors or (2) inhibition of the cytokines that degrade/debase proteoglycans. A number of growth factors promote matrix accumulation, whereas certain cytokines impede matrix synthesis and accelerate its catabolism. Manipulation of gene expression, particularly transcription, rather than injecting preformed protein factors, is another method of regulating matrix turnover. Agents that protect against