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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.

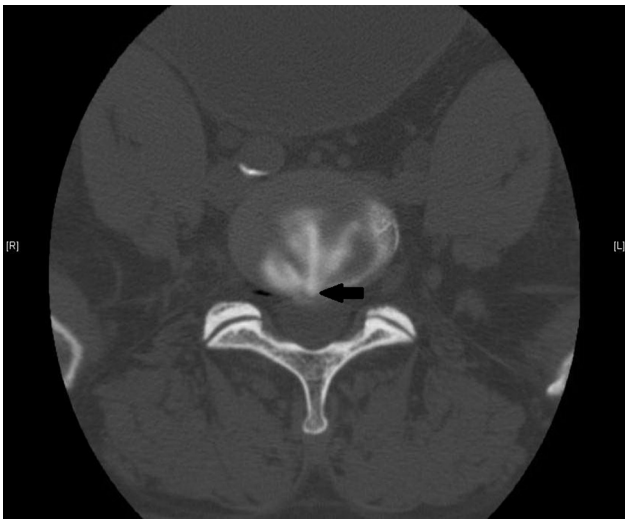

Figure 1. Postdiskography computed tomography axial cut demonstrating posterior, midline radial fissure (arrow) with circumferential outer annular extension.

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

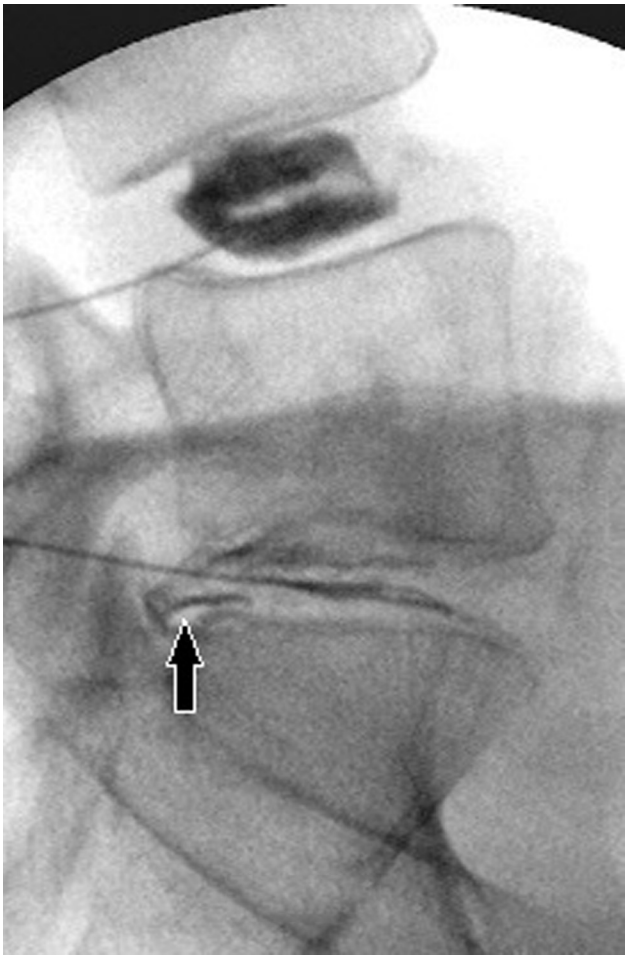

Figure 2. Intraoperative, fluoroscopic image of disk stimulation of L4-5 and L5-S1. The vertical arrow depicts filling of the annular fissure by contrast material.

cell death or promote mitosis may hold value in disk regeneration, given the relative avascularity of the disk. Structural repair of the annular fissure may be more successful if disk degeneration is arrested and/or reversed.

Intradiskal biologic treatments for painful intervertebral disks should address the catabolic state inherent in these disks as well as counter or reverse the degenerative changes. Yet, a defining feature of successful biologic treatments will likely include healing the annular tear itself as well as the degradation initiated by the annular tear. Characteristics of painful disks such as reduced oxygen tension, acidic pH, modic endplate changes, and desiccation will influence the likelihood of any injected therapeutic agent's ability to produce positive results. For example, reduced oxygen tension and pH may reduce the longevity of an injected biologic agent. Endplate changes and disk desiccation could impede the nutrient supply needed to support newly injected biologic agents. Our current understanding of these interdynamics is still evolving. Although different intradiskal biologic strategies (growth factors, tissue scaffolding) are being pursued, cellular supplementation is the one strategy with compelling contemporary human data.

Cellular Supplementation

Cellular attrition is a consequence of degeneration, and these native cells may be less responsive to exogenous growth factors [25]. Hence, the introduction of cells capable of regenerating disk tissue may potentially halt or reverse the degeneration associated with IDD. Anabolic and anticatabolic effects and the depth of in vitro and animal data are advantages of the cellular supplementation strategy. Yet, the viability of these new cells in the setting of limited cellular nutrition and differentiation signals, and concern whether the extracellular matrix produced by these is similar to native matrix, are acknowledged disadvantages.

Nonetheless, cells from a variety of sources have been explored. Autologous (ie, from the patient) sources include native disk cells and mesenchymal stem cells (MSCs) accumulated from bone marrow. Intuitively, the cells collected from the patient's own degenerated disks are less attractive because they would likely be inherently abnormal and poorly suited to act as an agent of repair. The premise for autologous disk cell transplantation has been established with the use of rat [26] and canine [27,28] models. Autologous human disk cells gathered during therapeutic diskectomy have been evaluated, and results from a 2-year prospective, controlled, randomized, multicenter study are promising [28-30]. Obtaining pure nucleus pulposus cells free of other cells (eg, fibroblasts and macrophages), however, is challenging [29,30]. The batches of autologous stem cells obtained from the patient's own bone marrow through density centrifugation and adherence to plastic probably do not contain a high concentration of pure homogenous mesenchymal cells with defined characteristics. Human adipose-derived MSCs are abundant and easy to harvest and have become a focus of interest for application to diskogenic CLBP [31]. Commercially available techniques currently are under development [32].

Therefore, the use of autologous progenitor cells, regardless of their source, calls for an ex vivo expansion of the cells after being immunoselected in preparation for implantation—an expensive process [33]. Cell expansion, however, currently is not approved for clinical use outside of the Food and Drug Administration—regulated premarket studies of new technologies. The use of allogeneic (ie, obtained from same species subjects other than the patient) MSCs may be more cost-effective. MSCs are self-renewing, undifferentiated, pluripotent cells with the capacity to differentiate into osteoblasts, chondroblasts, and adipocytes [34-38]. MSCs assume an intervertebral disk-like phenotype after induction by transforming growth

factor-β, dexamethasone, and ascorbate [39], allowing the creation of a universal donor line of these cells. Bone marrow [40-42] stromal cells have been the studied most extensively among the available sources of such cells. In animal models, autologous bone marrow MSCs have been shown to survive and replicate 8-48 weeks after transplantation [42-44]. A single injection of MSCs into the degenerate ovine disk nucleus pulposus restored proteoglycan content and disk height 6 months after injection [45]. On the basis of these animal data, a Food and Drug Administration–regulated, phase 2 safety and effectiveness study of a single intradiskal injection of allografted MSCs is underway in humans [46].

This phase 2, randomized, controlled study of allogeneic MSCs injected into a single, mildly degenerate lumbar intervertebral disk has produced preliminary data [47]. At 12 months after injection, 69% (95% confidence interval [95% CI] 53%-86%) of patients treated with MSCs experienced ≥50% reduction in LBP. Conversely, 33% (95% CI 19%-48%) of control patients achieved this end point. Similarly, a greater proportion of patients who received MSCs experienced minimal residual LBP at 12 months compared with controls. Fifty-two percent of the treatment patients (95% CI 34%-70%) and 18% (95% CI 6%-30%) of the control subjects reported low-intensity LBP (≤2/10) at 12 months after injection. Hence, on statistical grounds the MSC-treated group fared better regarding meaningful reduction of LBP. A large, pivotal phase 3 follow-up study is under development.

Articular chondrocytes are phenotypically similar to disk cells [48]. Juvenile chondrocytes (JCs) maintain an increased capacity to synthesize extra cellular matrix compared with adult cells [49]. Furthermore, JCs lack cell surface markers that trigger immune responses [49]. Thus, culture-expanded JCs may survive transplantation in unrelated recipients.

A 15-subject pilot study of a single intradiskal injection of JCs into diskography proven painful lumbar disks has yielded promising results [49]. At 1 year after injection, the mean numerical pain score and Oswestry Disability Index both decreased significantly. Although primarily only group data were published, 87% (95% CI 78%-96%) of treated subjects experienced a 30% reduction in Oswestry Disability Index scores [49]. On the basis of these early findings, a larger randomized, controlled trial has been launched [24,50].

Allogeneic adult chondrocytes are now being harvested and expanded in the laboratory after immunoselection. Intervertebral disk tissue is procured from adult human donors, which undergoes a multistep process to select, expand, and enrich progenitor cells. These cells are multipotent for mesenchymal lineages capable of exogenous production of proteoglycan and collagen II. Although untested in human subjects, this emerging cell therapy technology has safely improved disk height and proteoglycan and collagen content in animal models [47]. A phase 1 human clinical trial is being developed.

The survival of the transplanted cells for a sufficient period of time for them to accomplish their intended objective is of peak interest. As discussed, a degenerated disk's interior is acidic, hypoxic, and lacks nutrients. Transplanted cells may need to be prepared to survive within this environment after intradiskal injection, possibly by genetic manipulation, to restore extracellular matrix under these suboptimal conditions.

Painful Facet and Sacroiliac Joints

Pathophysiology

The lumbar facet joint (FJ) is a diarthrodial synovial joint encased by an inner synovial membrane and outer joint capsule containing articular and subchondral cartilage, an intra-articular meniscus, and rheological synovial fluid. Nociceptive C-type fibers have been confirmed on both the synovial membrane and joint capsule, and group III high-threshold, slow-conducting mechanosensitive, somatosensory units are present in both the articular and subchondral cartilage [51-54]. It seems sensible therefore that the synovial membrane, joint capsule, and articular and subchondral cartilage can transmit pain.

The progression of the lumbar spine degenerative cascade results in disk desiccation and loss of disk height. Consequently, an escalating compressive load is shifted onto the posterior elements [55], leading to degeneration and increased excitability of the synovial membrane nociceptive nerve fibers, joint capsule, and articular and subchondral cartilage [51-53,56]. In experimental models of osteoarthritis, these articular nerves become hyperalgesic, spontaneously discharge, and are sensitive to non-noxious joint movements [56]. Arthritic lumbar FJs can become symptomatic, leading to pain and disability [5]. A hallmark of osteoarthritis is the imbalance of cartilage and matrix degradation and their synthesis resulting in a catabolic state. Components of the extracellular matrix include proteoglycans comprising glycosaminoglycans attached to a backbone of hyaluronic acid (HA) [57], which provides the viscoelastic quality of synovial fluid affording lubricant and shock absorber functions [58]. The viscoelasticity of the synovial fluid is reduced as the concentration and the molecular weight of intra-articular HA decrease as a result of the arthritic state. As these lubricant properties decrease, destruction of cartilage and bone ensues. Because of its viscoelastic properties, HA protects cells and anatomic structures against mechanical overloading [58,59].

The sacroiliac joint is the largest axial joint in the body and on average has a surface area equal to 17.5 cm^2 [60]. A shear force can contribute to altered

mechanics of the articulating components of the sacroiliac joint [61]. Anatomical studies in cadavers have detected nociceptors within both the joint capsule and in the surrounding ligaments [62]. Furthermore, clinical studies have documented evoking of LBP upon capsular distension performed in asymptomatic volunteers [63-66]. Therefore, the sacroiliac joint is exposed to injurious events and contains nociceptive fibers capable of transmitting pain.

Treatment

A paucity of work has been completed in which authors have investigated the role of biologic treatments for lumbar facet and sacroiliac joints. Exogenous HA enhances the synthesis of matrix proteins, glycosaminoglycan, and proteoglycans; alters inflammatory mediators [59]; and reduces apoptosis of chondrocytes [67], all of which collectively may promote or spare intra-articular cartilage [59] in painful FJ arthropathy. Exogenous HA may be able to balance the spectrum away from cartilage degradation back towards its synthesis [59].

Successive intra-articular injections of exogenous HA (hylan G-F 20) into painfully arthritic lumbar FJs can reduce LBP, disability, and improve sitting tolerance up to 6 months after treatment. Patient satisfaction improved and oral analgesics reduced similarly during the first 6 months but not during the second 6 months after treatment. The lack of a durable treatment effect could be indicate that the injected exogenous HA achieved some analgesic effect via modulation of the nociceptors within the joint. Although speculative, injecting a smaller volume (0.5 mL) per injection and completing more injections per joint may more successfully reduce LBP over time by stimulation of matrix proteins and chondrocyte proliferation. These pilot data support the pursuit of follow-up, rigorous controlled trials to better determine the effectiveness and safety of viscosupplementation for FJ—mediated LBP. Although this strategy does not involve cellular supplementation, the act of introducing exogenous HA into an arthritic FJ may promote native chondrocyte activity.

Although yet to be tested, the direct injection of stem cells into painful lumbar FJs is supported by the current promising findings of similar techniques for painful arthritic knee joints [68,69] which, similar to FJs, contain cartilage and synovium.

Conclusion

The most common structural source of adult CLBP is the intervertebral disk. Painful disks suffer from nonhealing annular fissures. Emerging intradiskal biologic treatment technologies should address both the annular tear and associated degeneration. Effective intradiskal biologic treatments will need to also improve the biomechanical performance of the injured intervertebral disk. Otherwise, cells supplemented into this inhospitable environment may not survive over time because of a lack of adequate nutrients and harmful intradiskal pressures. Ultimately, a multipronged approached may prove optimal by combining different technologies, such as tissue scaffolding for 3-dimensional proliferation and lamellar cross-linking; cellular supplementation to produce matrix and reduce inflammation; and growth factors to stimulate the inserted cells. However, given the current state of regulatory constraints, the process for commercializing a product of multiple biologic technologies may be too prohibitive.

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Disclosure

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