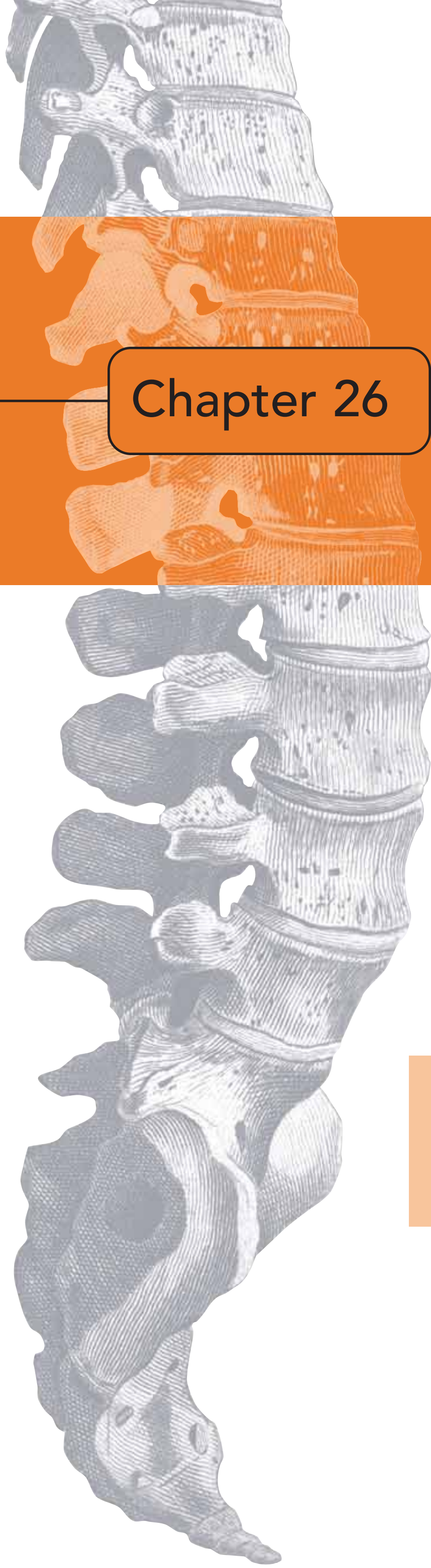

Chapter 26 Biologics and Nucleus Arthroplasty™ Technology Applications

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THE INTERVERTEBRAL DISC IS A COMPLEX BIOLOGICAL STRUCTURE CONFERRING MANY OF THE DYNAMIC AND BIOMECHANICAL CHARACTERISTICS TO THE HUMAN SPINE.

KEY POINTS

- Alterations in the biochemical composition and properties of the intervertebral disc result in changes in the disc's biomechanical properties and subsequent clinical manifestations.
- Animal models of intervertebral disc degeneration have been validated and provide the opportunity to assess the potential of novel biologic treatment strategies, such as growth factor delivery, gene therapy, and cell transplantation.
- At this time, evaluations of biological strategies in human clinical trials are pending.
- The use of biological strategies in conjunction with nucleus replacement technologies may provide a stepping stone until a suitable stand-alone biological solution is available.

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INTRODUCTION

The intervertebral disc is a complex biological structure conferring many of the dynamic and biomechanical characteristics to the human spine. The disc's broad range of function is a result of the interrelation and variation in the properties of each of its anatomic components.

The outer annulus fibrosus imparts significant tensile strength to the intervertebral disc, due to the highly organized structure of its collagen fibers. The orientation of the lamellae provides resistance to the axial and torsion loads experienced between adjacent vertebral bodies during physiologic range of motion. The inner nucleus pulposus is less organized and composed primarily of a few notochordal cells dispersed within a heterogeneous extracellular matrix. This matrix consists largely of proteoglycans that are highly hydrophilic and enable the nucleus pulposus to retain large quantities of water.

In a healthy disc, the nucleus pulposus is a gelatinous core that serves as a hydrostatic load-bearing structure functioning in conjunction with the annulus fibrosus to effectively distribute loads in the spine. The differing properties of these two components contribute substantially to spinal stability.

Intervertebral disc degeneration disrupts the balance of these properties and, subsequently, their biomechanical capacities. As the nucleus pulposus degenerates, it gradually loses proteoglycans and corresponding aqueous content such that it can no longer effectively sustain physiologic loads. Experimental models have shown that the removal of the nucleus pulposus dramatically increases spinal mobility, as the disc's ability to resist compression is lost.[1-3]

Studies have also demonstrated that removal of the nucleus pulposus can initiate disc collapse, causing the fibers of the annulus fibrosus to respond or deform differently based on their anatomic location. During loading of a collapsed disc, the peripheral fibers of the annulus protrude outwardly, while the inner fibers protrude into the vacant center.[4-6] This response places additional stress on the remaining annular fibers resulting in an increase in annular disruption, tears and disc prolapse. Such injury to the annulus negatively impacts its structural integrity and function, altering stresses within the intervertebral disc.[4, 7, 8] As the components of the intervertebral disc begin to fail, radiographic and clinical manifestations develop, such as loss of disc height, compression of the neural structures, and disruption of spinal stability.

Unfortunately, the lack of direct arterial supply or proximity to nutrient rich synovial fluid mandates that the biologically active components within the intervertebral disc receive their nutrition via diffusion from the adjacent vessels in the vertebral endplate. This avascular nature of the intervertebral disc provides little capacity to slow disc degeneration, undergo significant repair, or potentially regenerate.

To date, traditional conservative and surgical treatment options have targeted the clinical manifestations of intervertebral disc degeneration such as pain and instability, as opposed to treating its underlying cause. While lumbar fusion has shown success in treating intervertebral disc degeneration, it is not without significant potential morbidity and cost. Similarly, though the initial enthusiasm for lumbar intervertebral disc arthroplasty has waned, clinical improvement in an appropriately selected patient group may be expected as well.

Presently, a number of novel treatment strategies are being pursued that seek to target the actual etiology of disc degeneration in the hope of slowing the degenerative process and potentially inducing regeneration. Several promising *in vitro* studies have attempted to maintain the aqueous composition of the nucleus pulposus by increasing production of the highly hydrophilic proteoglycans, or by decreasing the rate of their degradation.[9, 10] Additionally, *in vivo* studies in non-degenerated intervertebral

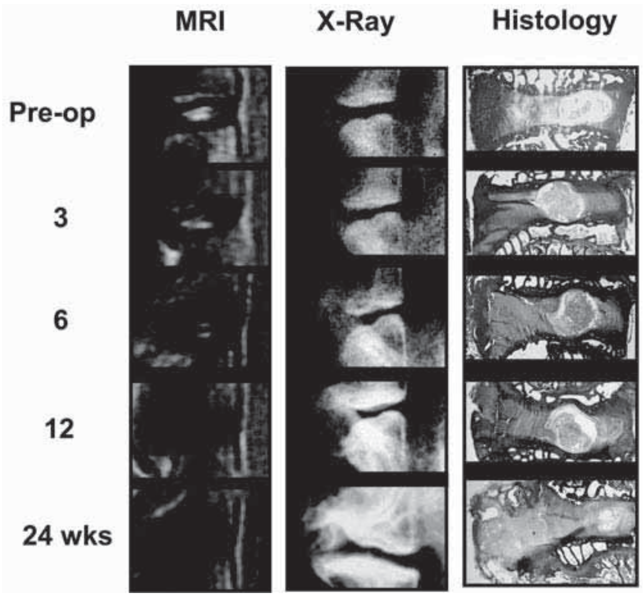

Figure 1: Animal model of disc degeneration showing reproducible changes in magnetic resonance imaging, radiographs, and histology, consistent with intervertebral disc degeneration.

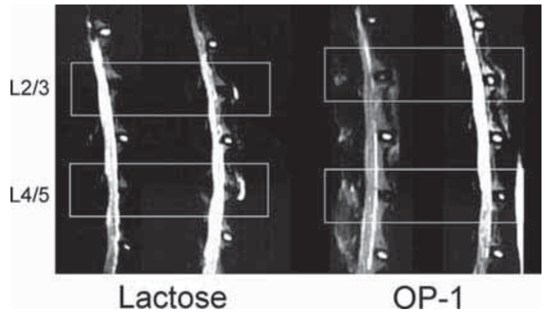

Figure 2: *In vivo* injection of the factor OP-1 to a degenerative intervertebral disc results in increased signal intensity on T2 weighted images, consistent with increased aqueous content.

discs have demonstrated that the delivery of growth factors, either directly or with the assistance of gene therapy, can favorably modulate biological activity with improved production of proteoglycans and radiological evidence of increased water retention.[11, 12]

While promising, these studies were performed in relatively "healthy" intervertebral discs. Additional studies are required to determine if cells within a degenerated intervertebral disc demonstrated the same capacities. As such, the development of a valid and reproducible animal model for intervertebral disc degeneration is of critical importance to accurately assess whether these novel treatment strategies can favorably alter the biologic activity within degenerated discs.

Recently, such an animal model was successfully established by creating an annular defect of defined depth with a hypodermic needle.[13, 14] This "injury" model reliably demonstrated radiographic evidence of disc degeneration on conventional x-rays and serial magnetic resonance imaging. In addition, the resulting histological changes were consistent with degeneration (Figure 1). With this tool, researchers can now assess a wide array of potential treatments to evaluate their capacity to alter both the biological and radiographic indicators of disc degeneration.

INJECTION OF OSTEOGENIC PROTEIN-1 (OP-1) INTO DEGENERATIVE INTERVERTEBRAL DISCS HAS BEEN SHOWN TO INCREASE SIGNAL INTENSITY OF THE INTERVERTEBRAL DISC ON T2-WEIGHTED IMAGES.

Several different methods to deliver biologic factors have been suggested including direct injection and stimulation of local production via gene or cell-based therapies. Proponents of gene therapy have argued that direct delivery of growth factors would likely have minimal effect on the biological composition of the intervertebral disc due to their relatively short half-life; however, recent studies suggest that this in fact may not be true.

Injection of Osteogenic protein-1 (OP-1) into degenerative intervertebral discs has been shown to increase signal intensity of the intervertebral disc on T2-weighted images, consistent with an increase in water composition.[15] Biochemical analysis of the treated cells also showed a significant increase in proteoglycan concentrations suggesting that, despite the relatively short half-life of this factor, sustained radiographic and biochemical changes can be induced with a single direct delivery approach (Figure 2). Based on these findings, clinical trials are now underway to evaluate the potential for such treatments to alleviate the symptoms of intervertebral disc degeneration.

THE CONCEPT BEHIND CELL-BASED THERAPY IS THAT STEM CELLS COULD THEORETICALLY BE DIRECTED TO DEVELOP INTO CELLS SIMILAR TO THE NUCLEUS PULPOSUS, AND THEREFORE BE USED TO REPOPULATE THE DISC ITSELF.

The application of gene therapy techniques in the established degenerative animal model is also ongoing, with similar results.[16] Though sustained production of growth factors within the degenerative disc has obvious benefits, one of the major criticisms associated with using gene therapy is the inability to adequately control or stop the production of the gene of interest, as excess production may have deleterious effects. To address this issue, regulatory systems have now been developed that enable the investigator to turn the expression of the transduced gene "on" or "off." Recent studies have demonstrated the ability to adequately regulate protein expression in transduced nucleus pulposus cells using an *in vitro* model;[17] however, similar findings have yet to be adequately documented *in vivo*.

Another option for the biologic treatment of degenerative disc disorders is the use of cell-based therapies. The concept behind cell-based therapy is that stem cells could theoretically be directed to develop into cells similar to the nucleus pulposus, and therefore be used to repopulate the disc itself. This is important as the success of any biological therapy requires that an adequate number of "healthy" cells are available to populate the degenerative intervertebral disc.

Studies have shown that the *in vitro* development of phenotypically similar cells is feasible, with gene expression similar to that of the native nucleus pulposus cells.[18] In theory, the ability to repopulate the nucleus pulposus would re-establish the native biochemical composition and corresponding biomechanical properties, potentially restoring disc height, retensioning the annulus fibrosus, and slowing disc degeneration. Experimental degenerative models using allograft replacement of the nucleus pulposus have reinforced this concept showing success in their ability to slow subsequent disc degeneration.[19] While these early studies are promising, much work remains before this technology can be applied in a clinical setting.

Finally, one concept that may hold promise is the ability to couple technologies to address disc degeneration. Specifically, the use of a biological therapy in conjunction with nucleus arthroplasty or other replacement technologies may be an ideal solution until a suitable stand-alone biological approach is available.

The use of a coupled approach offers the distinct advantage of providing additional mechanical support to assist in load distribution during early regeneration. In addition, depending on the device design, the implant may also serve as a carrier to ensure proper delivery and/or placement of the biological treatment, while providing a suitable environment or scaffold during initial regenerative activities.

THE APPLICATION OF BIOLOGICAL SOLUTIONS SUCH AS GENE THERAPY AND STEM CELL REPLACEMENT TO THE TREATMENT OF DISC DEGENERATION REPRESENTS AN EXCITING NEW FRONTIER.

The application of biological solutions such as gene therapy and stem cell replacement to the treatment of disc degeneration represents an exciting new frontier. While clinical application of such treatments as stand-alone technologies is not yet within reach, the studies discussed in this chapter have demonstrated that the concept is certainly feasible. As an interim approach, the use of a hybrid treatment that seeks to address both the etiology and clinical aspects of disc degeneration may bear further investigation.

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DEPENDING ON THE DEVICE DESIGN, THE IMPLANT MAY ALSO SERVE AS A CARRIER TO ENSURE PROPER DELIVERY AND/OR PLACEMENT OF THE BIOLOGICAL TREATMENT, WHILE PROVIDING A SUITABLE ENVIRONMENT OR SCAFFOLD DURING INITIAL REGENERATIVE ACTIVITIES.