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ORIGINAL ARTICLE

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A potential role for cell-based therapeutics in the treatment of intervertebral disc herniation

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Abstract Lower back pain and disc degeneration negatively affect quality of life and impose an enormous financial burden. An extensive body of scientific work has evolved that characterizes the disc, demonstrating spinal anatomy and morphology that contribute to risk and likely promote failure. Ultimately, matrix failure is responsible for mechanical failure, which in turn results in spinal compromise anatomically and subsequent pain. One intervening approach to breaking this sequence has been to repopulate the anatomy with autologous disc chondrocytes – cells capable of restoring the matrix and retaining the mechanical balance by which the disc functions. This strategy has been implemented both in patients and in animal models, and early results, although preliminary, support the premise as a positive approach.

Keywords Spine · Intervertebral disc · Intervertebral disc degeneration · Cell-based therapeutics · Tissue engineering

Introduction

The structure of the spine has been conserved in basic design across several classes of living organisms. Although inter-species variation accounts for a differing number of individual vertebrae, the metameric nature of spine has evolved to permit continued axial growth. Humans' uniqueness in upright posture accommodates an opportunity for unparalleled forelimb dexterity, but comes at the price of spine instability.

Spine degeneration and low back pain affects the adult population to a sufficient extent that personal risk should be considered only an ancillary basis of the etiology. This is not to discount previous studies validating genetic predisposition [1, 12, 20, 23] or disc nutrition [22] as factors in the degenerative process, but to suggest that the high prevalence reflects a myriad of yet-unidentified risks that effect similar symptoms. Over the course of a lifetime, the human disc undergoes marked changes in shape, volume, and composition – all factors that affect performance and mechanical function. Even in asymptomatic patients, 93% of individuals older than 60 years demonstrate evidence of degenerative change [4]. In another retrospective analysis of cadaver material, a comparable prevalence indicates degenerative anatomical change as a progressive, age-dependent phenomenon that is present in 97% of individuals who are 50 years old [15]. Ultimately, it is a loss of correct anatomical structure that potentiates disc herniation and leads to pain and the subsequent need for surgical intervention.

Numerous scientific studies have provided observations that lend to understanding the biochemistry and biomechanics of the disc itself, offering insights into structure-function relationships that attribute inclusive cause-effect relationships [5]. General agreement has it that intervertebral discs lose water over time, and in doing so reduce the functional capacity to resist axial loading [3]. What remains challenging is to intercept the water loss as a function of matrix binding, addressing composition and decomposition in terms of binding capacity, and ultimately to examine loading as an incendiary to shifting metabolic capacity. Knowing that intervertebral disc degeneration leads to slow but insidious desiccation and

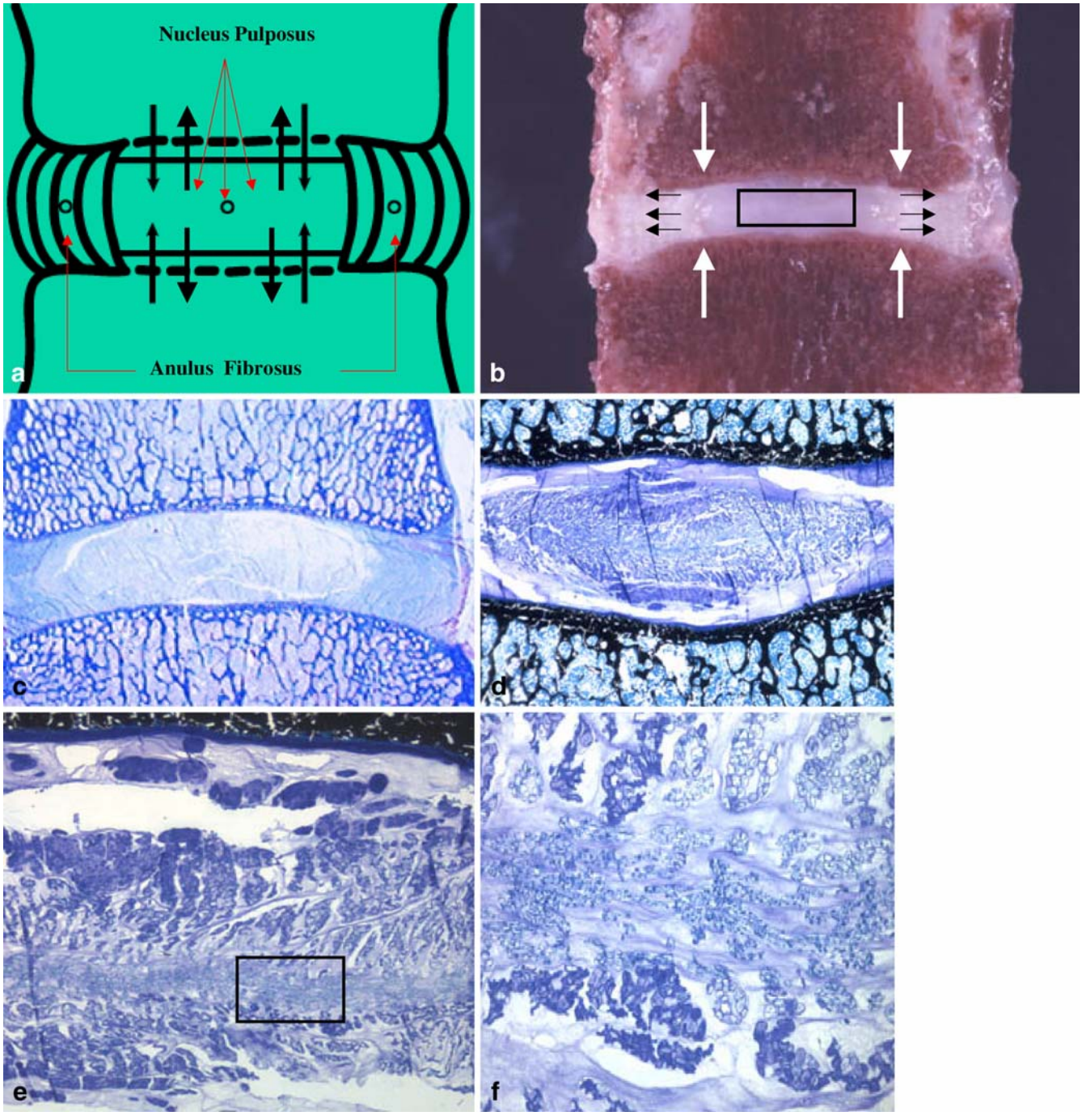

Fig. 1 **A** The intervertebral disc consists of two basic components: a central proteoglycan-rich nucleus pulposus and an outer series of concentric lamellae known collectively as the anulus fibrosis. The anular fibers insert directly into adjacent vertebral endplates, thereby constraining the central region of the intervertebral disc. **B** A cut section of the spine is represented. The *white arrows* indicate axial compression loads that the human spine would be subjected to. The *black lines* represent the lateral deforming direction of the nucleus and its central constraint within the anulus fibers. **C** Histology of the normal motion segment demonstrates the subchondral margins of adjacent vertebrae and the axial confinement imposed by a non-deformable vertebral body. **D** At higher magnification, variations in cell morphology within the nucleus can be seen (4×, MacNeal's Toluidine Blue). **E** Further magnification reveals different cell lines, and different morphologies within the nucleus (10×, MacNeal's Toluidine Blue). **F** The *area outlined in **E*** represents a central repository of nucleus cells which proliferate and reorient themselves in the direction of the axial load. These cells are capable of high matrix production, as indicated by the intense staining, and are also proliferative as clonal expansions within the nucleus material

eventual loss of morphology associated with the disc itself, the inherent challenge in seeking a remedy will be to recognize aspects of the causal condition and redress changes that will relieve symptoms and effect conditions that will maintain functional morphology. Although cells form only 1% of the adult disc tissue by volume, their role in balancing constitutive expression of matrix synthesis and metabolic turnover is vital. Most assessments of intervertebral disc failure have focused on degenerative change – changes in morphology that affect the biomechanical performance of the motion segment. In this consideration, mechanical failure is little more than a corollary of matrix structure, which in turn depends on balanced cell metabolism for efficient maintenance of the disc matrix. Given the value of cells to the metabolic health of the disc, one therapeutic strategy would be to either replace, regenerate, or in some other manner augment the intervertebral disc cell complement, with a goal of correcting matrix insufficiencies and restoring normal segment biomechanics. Understanding the basis for structure in the context of degeneration is critical to appreciating the potential value of cells as a means of therapy.

Intervertebral disc gross structure

It is impossible to discuss an intervertebral disc without defining the integral unit of a motion segment. The term "motion segment" was coined to denote two vertebrae and the disc connecting them. Within the motion segment, each intervertebral disc is composed of two parts: a central, deformable nucleus pulposus, and an outer ring of connective tissue described as the anulus fibrosis (Fig. 1). Together the two components function to dissipate axial loading by using the tensile properties of collagen, the principal component of the anulus fibrosis. In balance the force exchange is efficient, coupling progressive recruitment of collagenous fibers radially in response to central deforming action of the nucleus. Within the context of the two components lies a more subtle balance, with anatomical differences between the two components – more a spectrum than an interface. Separate from these two main components lies the vertebral endplate of each vertebra, which itself has distinctions along its entire margin.

Anulus fibrosis

The anatomy of the disc is often described from its central structures to its peripheral components. While such descriptions respect the ontogeny of the development process, they fail to fully explain the basis of action or how imbalance results in tissue failure. The anulus fibrosis is characterized in the literature as a series of concentric laminae connecting two intervertebral discs [5]. The anulus inserts into the periphery of the superior and inferior vertebrae, isolating a central disc of the endplate that resembles articular cartilage in many regards. In almost every respect the anulus fibrosis is a ligament – connective tissue in composition connecting two bones in function. Ligaments insert into bone as series of distinct laminations, themselves varying in both collagen and mineral content as a continuum in transition [6].

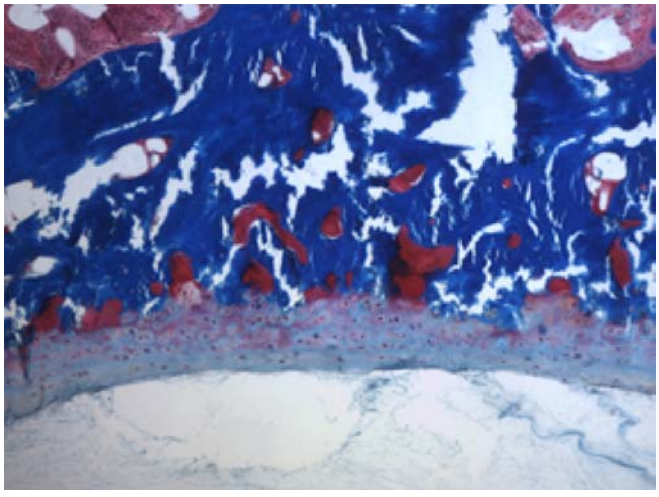

Fig. 2 The central subchondral interface and the hyaline cartilage covered endplate directly interface with the central nucleus pulposus (100×, Goldner tri-chrome)

The central disc of cartilage underlying the nucleus pulposus resembles in every respect articular cartilage at the end of long bones (Fig. 2). This central cartilage demonstrates an interface with the subchondral base different from that of the areas where the anulus fibers insert. As more an articular than a fibrous cartilage, a key difference of the central plate is that it has a lower density of types I and III collagen, instead featuring type II, a nonfibrillar cartilage [8, 17]. Being more an articular component (biomechanical buffer) than an interface for tendon insertion, the central region is less calcified and has a thinner subchondral plate. These variations are important in the context of the intervertebral disc, and the nucleus in particular, because of its metabolic demands and its structural morphology.

Nucleus pulposus

The nucleus pulposus is the central component of the intervertebral disc, demonstrating a high matrix to cell ratio as the most striking feature. This central area exists without blood supply, innervation, or lymph drainage in the adult spine, although during development it has both. Chondrocytes make a matrix that is highly charged due to its proteoglycan content, thereby creating a tissue capable of structuring water. This biochemical formulation offers the central matrix a unique capacity, in essence creating a

hydraulic space of fixed volume and alterable dimension. When this sphere is loaded axially, it carries with it the capacity to deform the anulus on account of the axial force, progressively recruiting additional fiber in an attempt to retain water. When the loading history of the spine matches the force, the mechanical function is elastic, restoring and retaining previous morphometric and biochemical balances.

Unfortunately, it is not always possible either for the human body as a whole, or for the intervertebral disc, to maintain the ideal hydration-force balance. When forces exceed the balance of tissue design, then either water is extruded, or tissue fails. Several reports have confirmed the differences in disc height that accompany enhanced or prolonged loading [10, 11, 13]. During sustained imbalance over an extended period of time, force imbalance results in a slow ebbing of water content, focal increases of charge within the extracellular matrix, and reduced metabolic production. These long-term sustained imbalances result in a loss of disc height, and a change in the basic paradigm of structure-function efficiency. Short-term variations in metabolic process are correctable, in many cases full disc height recovers overnight [14].

Sustained loss of water, however, changes the height of the disc, and results in not only a loss of matrix, but of the nucleus cells responsible for making the matrix. As the peripheral anulus fibers are capable of holding less water than the central proteoglycan matrix of the nucleus, water flows centrally from the periphery in addition to flowing across the subchondral endplate directly into the nucleus. Articular cartilage is extremely functional as an aqueous sieve, thereby precipitating a lake of calcium that accompanies relative levels of hydration.

In a somewhat destructive cycle, exaggerated loading first distends and then pushes water peripherally. If not replenished, the imbalance of water alters the compression-extension balance, and peripheral anulus fibers that developed with a load history to accommodate tension are placed into a physical condition of axial compression. Previous studies show that tension promotes homeostasis in tendons and ligaments, and that a reduction in tension or a condition of slack promotes collagenase expression [16]. The outcome of the imbalance then has repercussions separate from the mere loss of water, effecting morphology changes that in turn change metabolic properties.

Vertebral endplate thickening has been suggested to be part and party to nutritional imbalance, reducing water flow into the intervertebral disc and thereby contributing to a "nutritional desert" [21]. Considering the basic chemistry of diffusion and osmosis, water tends to flow from areas of higher concentration to areas of lower concentration, diluting ions to equilibrium. In that consideration, water should flow into the nucleus and the anulus and the subchondral vertebral plate should thin to effect more rapid transport of water. The reduction in water flowing into the disc and the accompanying thickening of bone instead supports the hypothesis that the reduction in water content in the anulus and the nucleus functionally shifts the interstitial precipitation point of calcium, leaving a lake of mineral in the wake of receding water concentration. Tide marks and changing tidemarks are always found more adjacent to the subchondral bone than near the surface of hyaline cartilage.

As the subchondral base thickens, the ability for water to be differentially shed through the endplate changes, and water moving from the nucleus to the anulus as a means of force dissipation occurs in a more constrained environment. Respecting the fact that the ligamentous anulus is a strong fibrous material, it will yield to focused peripheral force before the mineralized endplate will fail in shear. Basing anulus response on known outcomes in ligaments in other areas of the body, the anulus fibrosis would be predictably weaker, less stiff, more compliant and less viscous, resulting in elongation and potentiating ligament failure [7].

This model accounts for herniation of the nucleus peripherally, rather than a pushing of the nucleus through the endplate. Extrusion of the nucleus through the endplate does occur and is defined by the morphology and pathology of the Schmorl node, a condition prevalent but masked by the lack of nerve receptors in the central cartilaginous disc. Separate from the topic in this discussion, these perforations of the endplate have been noted in 46% of patients seen at autopsy [25]. Few were symptomatic, and although all nodes were detectable by radiographic study, such screening would be an unacceptable procedure for unsymptomatic individuals.

In the early stages of mechanical force, particularly in intervertebral discs with limited degeneration, the weakest component is the subchondral plate. Under sustained imbalance, anulus degeneration accompanied by subchondral thickening shifts the most susceptible anatomy to the anular fibers. The perceptible difference to the patient is immediate, with the nerve roots anything but a benign interface for the bulging anulus. Nuclear herniation through the anulus is generally posterolateral, and the juncture of nerve and nucleus results in pain. This important distinction of functional anatomy is critical to formulating attempts to reconstitute the anatomy, remove pain, and restore function to the spinal motion segment.

Nucleus replacement (cell-based therapeutics)

Failure of the disc results from overloading, and the type of failure is closely correlated with the nature of the force. Chronic forces will result in slow but sure desiccation, in many cases paralleled by "pains of aging" rather than sudden and disabling lower back problems. In incidences of acute overload [cartilage is velocity dependent (viscoelastic)], the force (nucleus extrusion) will be neutralized either through the plate or through the peripheral anulus

fibers. Knowing that the hydraulic has a limited capacity for compression, tissues with lesser water content will yield before the more hydraulic tissue deforms.

Understanding the basis for disc failure, the goal must be two-fold: first to regain disc height to reduce the axial nerve compression and restore the tissue dynamics of the anulus, and second, to reconstitute the central nucleus with a matrix that can hold water and effect a different balance of nutritional flow. One technology that has emerged in this context is the hydrogel implant, or prosthetic disc nucleus (PDN). The PDN was designed to restore disc height, and to fluctuate in diurnal flow, conceptually the same as the human disc. It is composed of a hydrogel within a biologically inert jacket, and is surgically implanted in pairs. With rigid dimensions, it does not fully simulate the plasticity of the original disc in terms of its deformability, and its size requires a fairly invasive procedure. Instead of restoring height with an amorphic prosthetic, a second goal and consideration has been to engender the nucleus with a complement of its original cells, and to allow these cells to reconstitute a matrix that will change the metabolic balance as well as restore disc kinematics.

Autologous disc chondrocyte transplantation (ADCT)

Disc chondrocyte cultivation has been approved as a therapeutic drug in Germany since 1997. German law permits physicians to address clinical projects from the purview of their own experience, and regulates therapy-controlled studies rather than requiring prospective clinical trials. Such a regulatory architecture permits promising technologies to be implemented at a faster pace, and offers a current basis for the most advanced interpretation to date. Applications that show clinical promise continue under carefully controlled clinical parameters so that they will meet standards of acceptable practice for worldwide clinical treatment. The procedure for ADCT is straightforward when surgical discectomy is indicated for the treatment of disc herniation and spinal cord or nerve root compression. Instead of fixing the tissue in formalin, sectioning, identifying, and storing the information, the material recovered in surgery is sent for tissue culturing, and returned at a later date for percutaneous transplantation. As one might suspect, it is impossible to differentiate the tissue recovered in surgery into either all nucleus or all anulus (Fig. 3). It is clear from published studies that co-culture actually enhances the matrix production and accelerates the proliferation rate of nucleus pulposus cells [19]. The standard interval between discectomy and transplantation has yet to be optimized, but it is important to affirm anulus healing prior to transplanting cells. Our experience has determined that a time interval of 8–12 weeks has been acceptable to the outcome.

Cells are carefully cultured under conditions of good manufacturing practices, ensuring that autologous cells

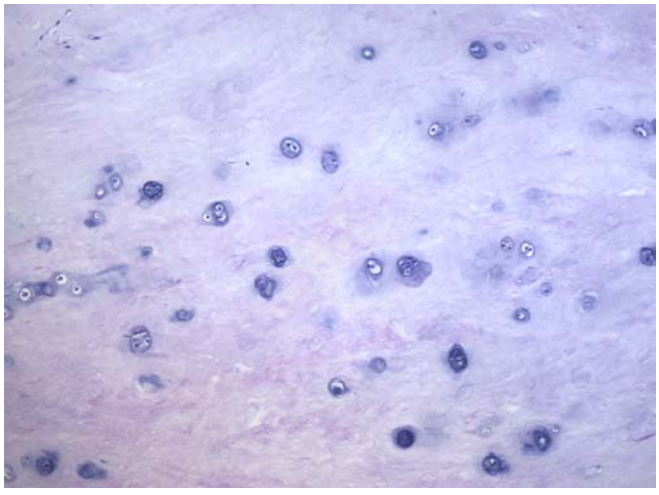

Fig. 3 Tissue removed during discectomy has cells that resemble both nucleus and anulus within its matrix (250×, H&E)

are returned to the patient and that process validation is accountable from harvest to return. This is a critical aspect of the cell process, ensuring correct receipt and optimal conditions for cell growth and phenotypic maintenance.

The first studies to look at the feasibility of the procedure have been performed in Switzerland and Germany. Patients participating in the studies were carefully selected to reflect acute traumatic herniation, in effect to still have active and viable nuclear morphology, albeit it displaced posteriorly as a herniated disc. Although the groups are small, patients from the Swiss group have responded in a positive fashion, remaining asymptomatic several years following transplantation. Magnetic resonance (MR) images of two of the patients demonstrates a restructuring of the spine and a lack of Modic changes at the subchondral plate (Fig. 4). Signal intensity associated with substantial matrix enhancement is not apparent, but considering the extent of damage that accompanies surgical dissection, the repair and conformation of the signal is acceptable. A lack of pain and functional recovery are the chief measures of clinical efficacy, and were demonstrated by all patients participating.

A second study was instituted and performed at the Bergmannstrost Clinic in Halle, Germany, by one of the authors (H.J.M.). Similar to the first study, the goal of this project was to develop confidence that the technology was sound in principle, and could achieve symptomatic relief and functional recovery. Patients in this study were evaluated clinically and also by MRI, demonstrating anatomical recovery in some cases with heightened nuclear signal. Moreover, prior to the cells being transplanted, the internal pressure of the disc was evaluated (Fig. 5). An in-line pressure gauge was developed specifically for this study, to provide an assurance that the cells would be placed into a fixed space, and not leak through another

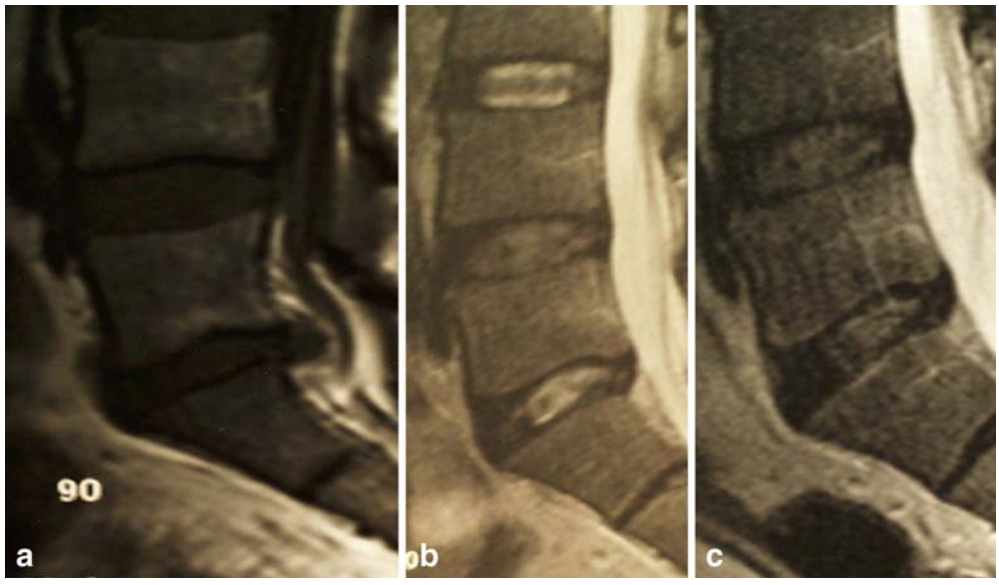

Fig. 4A-C **A** 38-year-old woman undergoing discectomy. **A** At presentation, **B** 15 months after transplantation, and **C** 30 months after transplantation

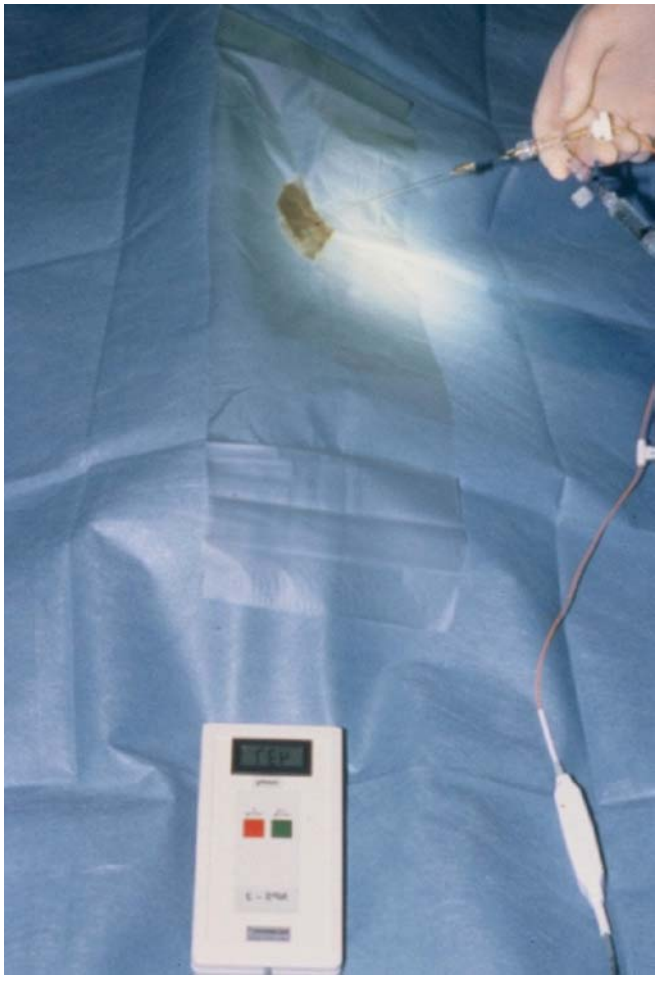

Fig. 5 Pressure was measured prior to inserting the cells to ensure that cells would not leak. Normal saline was injected to a pressure of 600 mm Hg for 3 min, and if no decay of pressure occurred, the saline was withdrawn and the cells were transplanted

fissure in another area of the anulus under mechanical load. Pressure was held for 3 min, and only after an assurance that no pressure decay had occurred were the cells transplanted.

What remains encouraging from both of these studies is the sustained symptomatic relief that the patients have attained from this procedure. Encouraged by the results in these clinical treatments, additional studies were designed to look more closely at the biological mechanism underlying the apparent surgical success. Studies were performed in canine models to examine biological healing by radiography, histology, and MRI along a 1-year time course, and using labeled cells to demonstrate the cells responsible for the activity.

Canine study

A study was designed to directly show the effect of the cells, contrasting a degeneration model with an area in the same dog that had been treated by chondrocyte transplantation. All transplantations were done during a single 2-day session. In all animals vertebrae L1–L4 served as the experimental site, with disc levels L1-L2 and L3-L4 serving as biopsy sites and L2-L3 acting as the control level. Cells were transplanted into L3-L4, but not into L1-L2, to demonstrate the effects of cell transplantation over spontaneous healing.

Several variables in this study provided a strong basis for accepting the results as positive. It was impossible to standardize the debridement of the tissue during the sampling for the biopsy. Individual dogs demonstrated different growth curves for their chondrocytes in culture and differences in the number of cells that were transplanted, both in indexed number and in fluid volume that could be injected. Additionally, some dogs received their trans-

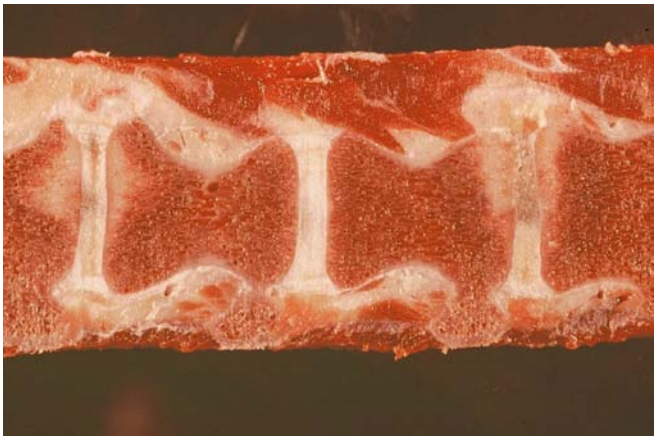

Fig. 6 Appearance of tissue grossly 3 months after transplantation. From *left to right* L4–L1. Note the marked difference in level L3-L4, which received cells, compared to the changes in tissue at the level that did not receive the cells

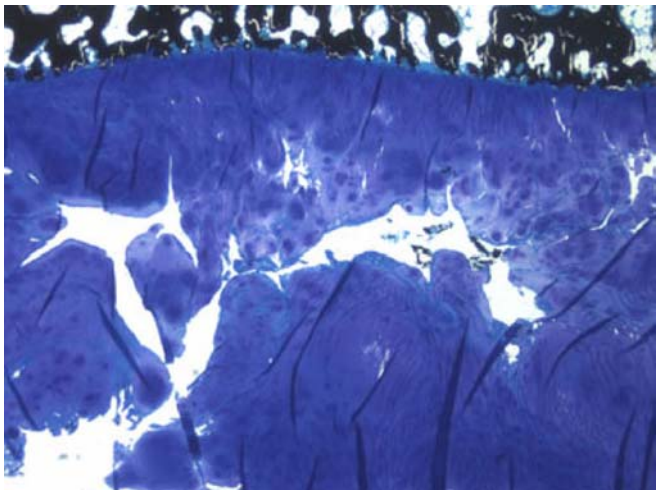

Fig. 7 Cells that had been transplanted at 12 months demonstrated abundant matrix formation, although the morphology was not directly comparable to normal nucleus pulposus (40×, MacNeil's Toluidine Blue)

plantation at 5 weeks, while others received cell therapy at 12 weeks. The goal was to better understand the interval in setting a time to surgery and the value of anular healing in the success of the cell therapy. Several conclusions could be drawn from this study, but the positive change in tissue morphology with time was the most encouraging aspect.

At the 3-month timepoint, much of the matrix was still in flux from the biopsy procedure. This was true whether cells were transplanted at 5 weeks or held until 12 weeks, as was the case for all the autologous cell transplantations (Fig. 6). The biopsy procedure was particularly aggressive, and resulted in a model that related more to damage than to degeneration. However, in this model the presence of cells positively affected the development of a clear subchondral margin.

The surgical biopsy was a causal factor in osteophyte formation, and was present in all animals on the lateral aspect of the vertebral articulation and therefore considered a response to periosteal inflammation. Differences in the amount of bone formation varied with the level that had received the cells. Intervertebral discs receiving cells displayed less osteophyte formation.

During the remodelling process of the vertebral endplate, marrow fibrosis was a common occurrence. This was not unexpected, as both bone remodelling and inflammatory responses to surgical injury are known to increase tissue and matrix permeability. Intervertebral disc levels that had received cells showed a tendency for less scarring, evident as a deep-yellow color grossly in intervertebral discs that had not received cells. Histology supporting chondrocyte transplantation offered evidence that nucleus pulposus-like cells were within the region of the injection, were surrounded by matrix, and exhibited phenotypic characteristics consistent with normal cell morphology (Fig. 7).

Disc height varied considerably, from obvious collapse in some animals that had not received cells, to a slight diminution despite the addition of transplanted chondrocytes. In some cases, thicker intervertebral discs actually displayed poorer morphology, but at some point function and form must mediate mechanical and morphometric balance in active locomotion. Disc height could be shown to have a positive trend associated with cell transplantation, but the larger the number of variables, including cell number injected, the more difficult it became to see the positive trend. The longer the dogs were examined (clinical durability), the greater the healing and the stronger the differences between the level transplanted and that left to degenerate.

All of the dogs gained a separation of the subchondral plate and clear delineation of the separate morphologies. In no cases was a morphotypic "nucleus pulposus" generated, but in every case cells comparable to and appropriate for consideration as chondrons could be found. These cells displayed characteristic territorial matrix surrounding each group of cells. No evidence of necrotic change was present. The lack of active vascularization, formation of bone in the intervertebral space, and the general "normal" gain of the matrix suggests that active remodeling is guided by some innate patterning principle capable of effecting an anatomical basis separate from either cell- or matrix-directed regenerative change.

Progressive changes in regenerative potential could be seen through changes over time in the various aspects of the healing process, e.g. marrow vascularity, sclerotic changes in bone, disc height, inflammatory cellularity. At the 3-month time point, much of the matrix was still undergoing changes in response to the original biopsy procedure and the on-going mechanical demands (and chang-

ing demands at that). This was true whether cells were transplanted at 5 weeks or held until 12 weeks. With the exception of a single dog, no gross instability was evident. It seems that subchondral resolution was the primary positive change that was positively associated with time. Accompanying the formation and clear margins of the subchondral bone, marrow fibrosis seen at early analysis time points no longer factored in the potential for vascularizing and fusing the disc. Unfortunately, osteophyte formation was also associated with increasing time following transplantation. Even though osteophytes were stimulated by aggressive debriding of tissue, they did not interfere with matrix deposition or in the basic pathology of the disc. Over time, it would be expected that lateral bridging would impart a bias to mechanical loading, which in turn will precipitate biochemical changes, that will likely affect both matrix composition and matrix performance.

What appears to be the ultimate driver is the initial damage sustained in taking the biopsy. Second most important is the time over which the animal and spinal level in particular has to heal. Finally, no evidence could be found that would indicate that time to transplant could be positively correlated with outcome.

Models of cell transplantation

Other considerations of nucleus replacement have taken into account the interdependence and potential importance of anulus cells in stimulating nucleus cells in culture [19]. Using a rabbit model, and measuring cell proliferation as a function of DNA synthesis, Okuma and co-workers reported that co-culturing stimulated cell proliferation, inhibited degeneration, and enhanced the synthesis of type-II collagen in the matrix. Additionally, they were able to show that increases in type-II collagen were coupled with BrdU incorporation of the transplanted cells. They cautiously interpret these findings as showing that the positive results of cell proliferation in the presence of disc degeneration do not always indicate regeneration. Their results differ slightly from those of Wang et al., who concluded that nucleus pulposus cells are insensitive to culture conditions [24].

Cell culture in alginate, three-dimensional matrix is engaging for several reasons, not the least of which is the limitations the cross-linked matrix imposes on cell proliferation. Achieving a tissue in phenotype consistent with the in situ nature of the cells is attractive for obvious reasons, most critically the ability of cells in alginate to reflect collagen and proteoglycan synthesis that mirrors gene expression in disc tissue [2]. While placement continues to be an issue needing resolution, it does appear that transplanted cells can retain a phenotypic appearance and attain cellular capacity in vivo.

Other studies have demonstrated the sand rat as an effective model of spontaneous disc degeneration and have shown histochemical and morphologic changes to support cell transplantation [9] and maintenance of disc height and significant differences in matrix expression. The propensity for spontaneous degeneration and the general poor health of this animal relative to its kidney function and water transport axis offers two sentiments for consideration. The first, of course, is the challenge in demonstrating active regeneration in an animal model that has been shown to have active endocrine bias (diabetes) and poor kidney and water shunting. Being able to demonstrate active recovery against a gradient of failure offers strong assurances of potential success in other systems.

The second point, and a critical one, is the fact that small rodents actively grow throughout their lives, maintain an active apophyseal architecture at the end of each spine, and, as such, have inner dampening through the vertebral body growth plate. This anatomy changes the dynamic of axial loading compared to the humans', and imparts some bias in considering the results. Still, this and other studies in rats and lagomorphs [18] demonstrate the capacity of cell transplantation to stave off further degeneration, where that in itself may be a mediator of a protective advantage in the timeframe of effective remedy.

All of the cell studies demonstrate a capacity to buffer degeneration, those cells placed with attendant matrix demonstrating a greater capacity. Cells appear to be viable, retain a capacity for proliferation, and demonstrate an ability to make appropriate matrix, to undergo gene expression consistent with the phenotypic demands of the anatomy, and, in our hands at least, to facilitate clinical durability.

A capacity for improvement will be the hallmark of the acceptability of this technology as a clinical therapeutic. At the current time, autologous transplant in controlled conditions presents the least challenging option to the clinic. It complies with the standard of least manipulation of a cell line, imposes little chance of immune rejection, and, as a terminally differentiated lineage, also puts an emphasis on cells and intention. Still to be proven is whether the tissue morphology over time will retain the new form and to what extent cells could be given as a prophylactic to reduce vertebral compromise before it becomes symptomatic. The human spine is most unusual, and the scientific desire for remedy strong. Under these conditions, the potential for regenerative repair of the motion segment will become a contending option for stabilization procedures, which today offer fusion as an option to unstable and painful motion.

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