The Intervertebral Disc and Its Role in Spinal Disorders

a report by

Simon Stephan,[1] **Audrey Gilson**,[2] **Olga Boubriak**,[2] **Sally Roberts**[1] *and* **Jill Urban**[2]

1. Centre for Spinal Studies, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, and Institute of Science and Technology in Medicine, Keele University; 2. Department of Physiology, Anatomy and Genetics, Oxford University

Intervertebral Disc Structure

The intervertebral discs are the joints of the spinal column and lie between the vertebral bodies. They allow movement and transmission of loads within the spine. The disc has a complex organised structure (see *Figure 1a*) and is composed of a central nucleus pulposus that is rich in type II collagen and the proteoglycan aggrecan, which is responsible for maintaining a water content of around 80%. The nucleus is surrounded by the annulus fibrosus, which is composed of collagenous concentric lamellae. Since collagen and proteoglycan content are essential to the load-bearing properties of the disc, any parameter that decreases proteoglycan concentration or weakens the collagen network will be detrimental to disc function.[1] Healthy disc tissue is avascular with a relatively low cell density.

Intervertebral disc cells normally operate in an environment that would be inhospitable to most other cells, with low oxygen levels, high mechanical load and high osmolality. These environmental conditions influence the activity of the cells and their ability to survive.[2]

The disc cells have the essential function of synthesising matrix components and proteases, which allow matrix remodelling. Disc structure and function are dependent on a balance between synthesis and degradation. An imbalance, with decreased synthesis and increased breakdown, leads to an alteration of matrix composition and loss of both water content and organisation. It is commonly believed that this process is a precursor to the onset of disc degeneration.

Changes in Disc Morphology with Age and Degeneration

At birth and in infancy the boundary between the jelly-like nucleus pulposus and the annulus fibrosus is clearly discernible, but it becomes less so throughout adolescence. By 20 years of age, many intervertebral discs already show some signs of degeneration, although the molecular mechanisms involved remain poorly understood. Ageing and degeneration are accompanied by progressive changes in composition; there is an increase in collagen fibre density in the central portion of the disc as well as a loss of aggrecan and a fall in water content.[3] These biochemical changes lead to further disorganisation of the fibrocartilage in the annulus. Dehydration and loss of proteoglycan from the disc result in a decrease in height, which is observed as a loss of disc space on magnetic resonance imaging (MRI) or X-ray. The flexibility and elasticity of the spine are consequently reduced and the disc's load-bearing ability is compromised.

The disorganised morphology of the disc commonly leads to macroscopic alterations including nuclear clefts and annular tears.[4] Prolonged degeneration is characterised by an invasion of blood vessels and nerves into the disc. Changes in morphology of the disc during the process of disc degeneration are shown in *Figure 1b*.

Disorders of the Intervertebral Disc

Spinal disorders – including disc herniation and sciatica, deformation (scoliosis), stenosis and spondylolisthesis – are pathological conditions associated with compromised disc integrity.

Degenerative Disc Disease and Back Pain

Degeneration of the intervertebral disc is usually most severe in the lower lumbar segments of the spine and, although it is highly associated with low-back pain, sciatica and other spinal disorders,[5] in many instances disc degeneration remains asymptomatic.[6] Nevertheless, at least 50% of the population will experience some degree of low-back pain or sciatica during their lifetime. Low-back pain thus represents one of the most common causes of disability in the Western industrialised world,[7] placing a huge economic burden on society.[8] In addition to disc degeneration contributing to back pain, it is believed to precede some other clinical conditions such as disc herniation and spinal stenosis.

Disc Herniation

Disruption of the annulus in degenerate discs followed by expulsion of disc tissue into the spinal canal is known as disc herniation or prolapse. In some cases it can compress the nearby spinal nerve roots. Compression alone is asymptomatic in many cases, but herniation coupled with inflammation is now thought to cause sciatica, and can also lead to back pain.

Spinal Stenosis

Spinal stenosis refers to a diminution of the diameter of the lumbar

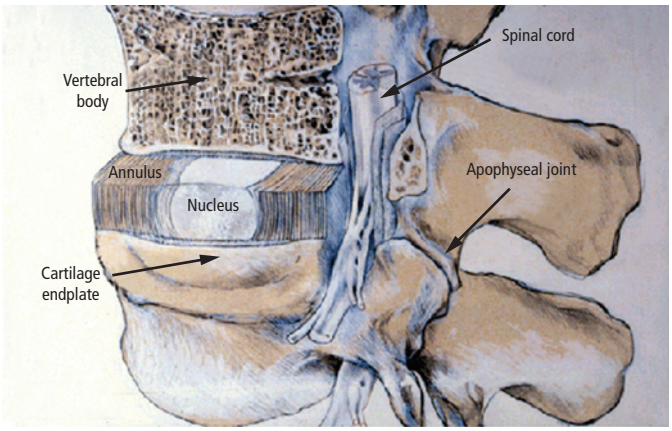
Sally Roberts is Director of Spinal Research at the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry. Her research interests lie in the aetiopathogenesis of intervertebral disc degeneration and spinal deformities and tissue engineering of cartilage. She obtained her PhD from Birmingham University in 1984.

E: Sally.Roberts@rjah.nhs.uk

Jill Urban is a Senior Arthritis Research Fellow in the Physiology, Anatomy and Genetics Department at Oxford University. Her research interests lie in the physiology of articular cartilage and intervertebral discs and the effect of the environment on cell metabolism. She obtained her PhD from Imperial College, London, in 1977.

E: jpgu@physiol.ox.ac.uk

Figure 1a: Location of the Intervertebral Disc (Annulus and Nucleus) Within the Spine



spinal canal. This narrowing can be congenital, but it occurs predominantly from loss of turgidity and height of degenerated discs, which then bulge into the spinal canal, together with increased calcification of tissues adjacent to the spinal cord or nerves. It is one of the most common spinal disorders in elderly patients, causing neurogenic claudication, paraesthesia and back pain.

Scoliosis

Scoliosis is a spinal deformity resulting in abnormal lateral curvature of the spine, in which the intervertebral discs are asymmetrical and 'wedged'. Some cases of scoliosis are congenital (e.g. with hemi-vertebrae) or are a consequence of neuromuscular diseases, but about 75–80% of cases are idiopathic.

Spondylolisthesis

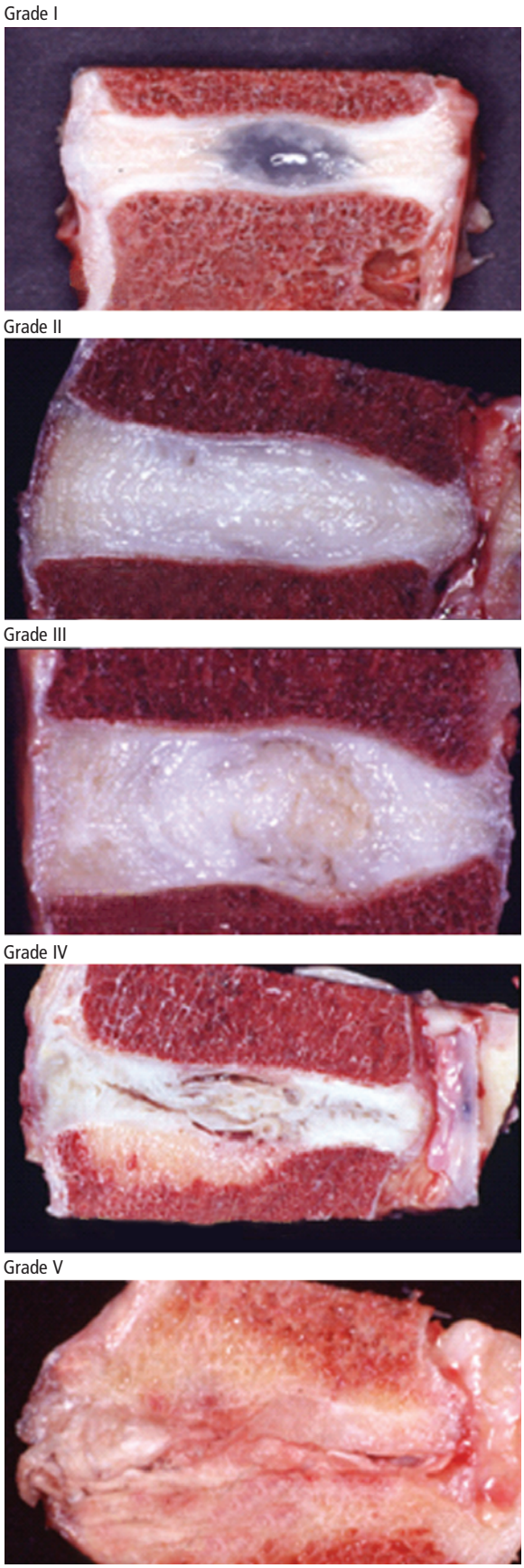
Spondylolisthesis is another spinal disorder affecting the intervertebral disc, where there is horizontal displacement of one vertebral body relative to the adjacent one. Depending on the degree of slippage, the symptoms greatly differ among patients. Though spondylolisthesis can be present without any symptoms, altered pressure on spinal nerves can lead to pain and disability.

Why Do Discs Degenerate?

The causes of disc degeneration are not known, but have long been of interest because of the strong association between disc degeneration and spinal disorders discussed above. For many decades, mechanical factors including lifting heavy loads, torsional stresses and long-term exposure to vibration (due to motor vehicle driving), as well as smoking, were thought to be the major risk factors.[9] However, over the past 15 years studies have shown that the contribution of these risk factors to the development of disc degeneration is low and that genetics plays a more significant role.

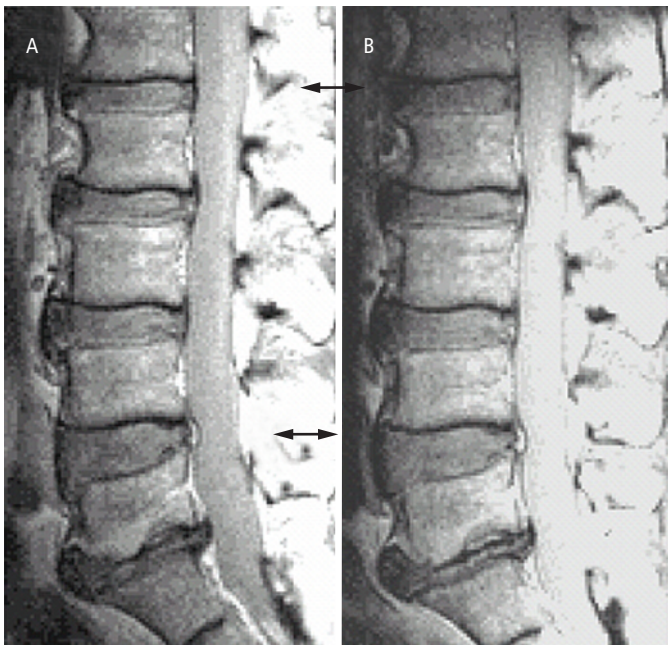
The importance of genetics in disc degeneration is indicated by family studies showing, for instance, that the risk of lumbar disc herniation before 21 years of age is five times higher in patients with a positive family history.[9] However, the most compelling evidence for the role of genetics comes from twin studies. Studies conducted on monozygotic male twin pairs from the Finnish population demonstrated substantial familial aggregation in the degree and location of disc degeneration (see *Figure 2*), with significantly greater similarities between co-twins than would be expected

Figure 1b: Discs at Various Stages of Degeneration



Sagittal sections through human spinal segments show discs at various stages of degeneration together with part of the adjacent vertebral bodies. Grade I discs are young and healthy and still show signs of an infantile morphology. Grade II discs have a lower water content in the nucleus than grade I discs, but show no other degenerative changes. Grade III discs show some desiccation in the nucleus and separation between nucleus and annulus. Grade IV discs show presence of severe fissures and desiccation, changes in the endplate, loss of disc height and changes in surrounding vertebral bodies and ligaments. Grade V discs are grossly degenerate and deformed, with almost total loss of disc material. Adapted from Boos et al., 2002.[31]

Figure 2: Magnetic Resonance Imaging Scans from Identical Twins



A typical set of magnetic resonance imaging (MRI) scans showing very similar degenerative patterns between identical twins (A and B) differentially exposed to environmental risk factors such as long-term heavy loading. Note, in particular, the similar abnormalities at the disc levels marked by arrows. Adapted from Battie et al., 1995.[10]

by chance.[10] In contrast, occupational and leisure time physical loading, driving and smoking had very modest effects.[11] Another twin study[12] found that, using an overall degenerative score, high heritability was shown for both the lumbar spine (74%) and the cervical spine (73%).

Within the last decade a number of studies have attempted to identify genes associated with disc degeneration. Most studies have examined associations with genes of the extracellular matrix (ECM), particularly collagen IX, aggrecan and the vitamin D receptor. However, at present the results are confusing. Collagen IX, for instance, is present in all areas of the disc (nucleus, annulus and adjacent cartilaginous vertebral endplates) and is thought to help stabilise collagen organisation. Specific sequence variants have been found to increase the risk of sciatica and lumbar disc degeneration by up to three-fold in a Finnish population[13] and also in a Chinese population, but had no discernable effect on disc degeneration in a Greek population.[14] CILP, a protein found in the matrix, has been associated with disc degeneration in a Japanese[15] but not a Finnish or Chinese population.[16] Vitamin D receptor polymorphism associations, first identified in Finland,[17] appear more robust, having also been reported in Australian, Chinese and Japanese populations;[15] however, the function of the receptor in the disc is unclear.

It seems likely that disc degeneration is complex and multifactorial, arising from the interplay between a number of different genes, all with only moderate contributions towards its development. Further genetic studies will undoubtedly uncover more genes associated with this process. However, this work is only in its initial stages and it will be many years before genetic pathways leading to failure of the disc are understood and the information gathered can be used to develop diagnostic or treatment strategies.

Treatment Measures – Present and Future

Diagnosis and treatment of degenerative disc disease remains a difficult and controversial topic, often with no clear consensus on optimal methods of treatment. There are few objective criteria for diagnosis and currently no early diagnostic tests to allow preventative interactions. Indeed, even identifying the source of pain in these patients can be extremely difficult.

Current therapeutic strategies to combat disc degeneration and pain include conservative therapy and surgical intervention. Conservative therapy often consists of controlled physical activity, sometimes linked to manipulations. This may be coupled with the use of oral medications such as anti-inflammatory drugs, analgaesics and muscle relaxants or tranquillisers. Pain may also be countered by administration of an epidural (cortisone) injection, but this often offers only transient pain relief.[18]

Surgical intervention may be used in some cases of disc herniation or spinal stenosis to decompress the spinal cord, or to fuse and so immobilise two adjacent vertebral bodies to relieve pain and stabilise the degenerate disc. However, patient spinal mobility is restricted using this latter method and often discs above or below the fixated region begin to degenerate. Recently, artificial disc replacements that preserve spinal mobility to some extent have replaced fusion in some clinical centres. Although there is currently a great deal of interest in this area, disc replacement surgery is technically very difficult and involves major risks to the patient because of the invasive nature of the surgery and the potential problems of revision surgery if the implant fails.[19]

Future Strategies

While conservative and surgical therapies attempt to reduce pain and prevent further disc deterioration, they do not generally enhance the ability of the disc to regain its original architecture and function. There is thus now considerable effort in the development of potential biological therapeutic strategies for restoring the degenerate disc. This includes introducing recombinant or natural proteins or their genes into the disc. Researchers are also investigating how to introduce new cells into the disc so that they can produce and maintain a healthy disc matrix and restore its function.

It seems likely that disc degeneration is complex and multifactorial, arising from the interplay between a number of different genes, all with only moderate contributions towards its development.

Genetic Engineering

Since disc degeneration is a chronic and progressive disorder occurring over many years, it is likely that therapeutic agents such as recombinant proteins will need to be present in the disc for extended periods of time to stimulate regeneration. The

intra-disc injection of these agents alone may not fulfil this prerequisite; rather, the delivery of genes that encode the proteins or growth factors in question may be required to provide a prolonged stimulus. It has been demonstrated that disc cells can be genetically modified *in situ*.[20] However, intervention using gene therapy approaches often raises ethical concerns regarding induction of inflammatory responses, ectopic expression of the transgene, tumour formation or even inadvertently influencing germline gene expression.

Tissue Engineering

Tissue engineering is currently used clinically as a technique to repair other cartilaginous tissues, for example articular cartilage,[21–23] and is being employed in at least one centre for the intervertebral disc.[24] This is based on the hypothesis that implantation of cells into a damaged disc may boost its capacity to recover structure and function. Stem cells are possible candidates for this purpose since numerous studies have indicated that they have the ability to differentiate into various cell types.[25,26] These can be sourced from various tissue types including adipose tissue[27] and bone marrow;[28,29] the cell population can be expanded *in vitro* and then induced into a chondrogenic phenotype[30] in appropriate culture conditions. However, it remains uncertain whether the 'induced' cell is close enough to a disc cell to offer regenerative potential for damaged discs, or even whether cells introduced into damaged disc would remain alive and fully functional for significant periods of time.

Conclusions

It is clear that new approaches to combat disc degeneration and back pain are required by an increasingly aged population. Further advances in gene therapy and/or tissue engineering may unveil potential new therapies that will both alleviate low-back pain and restore spinal function. However, progress in researching mechanisms of disc degeneration and back pain (and therefore developing appropriate new therapies) would be improved if better diagnosis were possible. ■

Acknowledgements

Simon Stephan and Audrey Gilson are supported by funding from the Biotechnology and Biological Sciences Research Council (BBRSC). Jill Urban is supported by the Arthritis Research Council.

Editor's Recommendation

'Rumours of my death may have been greatly exaggerated': a brief review of cell death in human intervertebral disc disease and implications for cell transplantation therapy.

Johnson WE, Roberts S, *Biochem Soc Trans*, 2007:35(Pt 4):680–82.

The avascular nature of the human intervertebral disc is thought to reduce the ability of resident disc cells to maintain their extracellular matrix, rendering the tissue susceptible to degeneration. It has also been suggested that the lack of a blood supply may result in disc cell death via nutrient deprivation. Therefore, transplanting new cells into the disc to promote tissue regeneration would be akin to 'putting cells in a coffin' and doomed to failure. This review considers the available evidence for cell death in the human intervertebral disc, describing briefly the methods used to assay such death, and concludes that further analysis is required to ascertain whether extensive cell death truly is a marked feature of human intervertebral discs and whether it bears any relationship to disc degeneration and, hence, regenerative strategies. ■

1. Adams MA, Roughley PJ, What is intervertebral disc degeneration and what causes it, *Spine*, 2006;31(18):2151–61.
2. Bibby SRS, Urban JPG, Effect of nutrient deprivation on the viability of intervertebral disc cells, *Eur Spine J*, 2004;13(8): 695–701.
3. Lyons G, Eisenstein SM, Sweet MB, Biochemical changes in intervertebral disc degeneration, *Biochim Biophys Acta*, 1981;673(4):443–53.
4. Haefeli M, Kalberer F, Saegesser D, et al., The course of macroscopic degeneration in the human lumbar intervertebral disc, *Spine*, 2006;31(14):1522–31.
5. Luoma K, Riihimaki H, Luukkonen R, et al., Low back pain in relation to lumbar disc degeneration, *Spine*, 2000;25(4):487–92.
6. Boden SD, Davis DO, Dina TS, et al., Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation, *J Bone Joint Surg Am*, 1990;72(3): 403–8.
7. Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S, The health and productivity cost burden of the 'top 10' physical and mental health conditions affecting six large US employers in 1999, *J Occup Environ Med*, 2003;45:5–14.
8. Waddell G, Aylward M, Sawney P, *Back pain, incapacity for work and social security benefits: an international literature review and analysis*, London: The Royal Society of Medicine Press, 2002.
9. Varlotta GP, Brown MD, Kelsey JL, Golden AL, Familial predisposition for herniation of a lumbar disc in patients who are less than twenty-one years old, *J Bone Joint Surg Am*, 1991;73:124–8.
10. Battie MC, Haynor DR, Fisher LD, et al., Similarities in degenerative findings on magnetic resonance images of the lumbar spines of identical twins, *J Bone Joint Surg Am*, 1995;77:1662–70.
11. Battie MC, Videman T, Parent E, Lumbar disc degeneration: epidemiology and genetic influences, *Spine*, 2004;29:2679–90.
12. Sambrook PN, MacGregor AJ, Spector TD, Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins, *Arthritis Rheum*, 1999;42:366–72.
13. Ala-Kokko L, Genetic risk factors for lumbar disc disease, *Ann Med*, 2002;34:42–7.
14. Chan D, Song Y, Sham P, Cheung KM, Genetics of disc degeneration, *Eur Spine J*, 2006, e-pub ahead of print.
15. Seki S, Kawaguchi Y, Chiba K et al., A functional SNP in CILP, encoding cartilage intermediate layer protein, is associated with susceptibility to lumbar disc disease, *Nat Genet*, 2005;37: 607–12.
16. Virtanen IM, Song YQ, Cheung KM, et al., Phenotypic and population differences in the association between CILP and lumbar disc disease, *J Med Genet*, 2007, e-pub ahead of print.
17. Videman T, Leppavuori J, Kaprio J, et al., 1998 Volvo Award winner in basic science studies – Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration, *Spine*, 1998;23:2477–85.
18. Arden NK, Price C, Reading I et al., A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: the WEST study, *Rheumatol*, 2005;44:1399–1406.
19. Wagner WH, Regan JJ, Leary SP et al., Access strategies for revision or explantation of the charite lumbar artificial disc replacement, *J Vasc Surg*, 2006;44:1266–72.
20. Wallach CJ, Kim JS, Sobajima S, et al., Safety assessment of intradiscal gene transfer: a pilot study, *Spine J*, 2006;6:107–12.
21. Brittberg M, Lindahl A, Nilsson A, et al., Treatment of Deep Cartilage Defects in the knee with Autologous Chondrocyte Transplantation, *N Engl J Med*, 1994;331:889–95.
22. Peterson L, Minas T, Brittberg M, et al., Two- to 9-Year Outcome After Autologous Chondrocyte Transplantation of the Knee, *Clin Orthopaed Relat Res*, 2000;374:212–34.
23. Roberts S, Caterson B, Menage J, et al., Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc, *Spine*, 2000;25(23):3005–13.
24. Ganey TM, Meisel HJ, A potential role for cell-based therapeutics in the treatment of intervertebral disc herniation, *Eur Spine J*, 2002;11:S206–14.
25. Pittenger MF, Mackay AM, Beck SC, et al., Multilineage potential of human mesenchymal stem cells, *Science*, 1999;284:143–7.
26. Khademhosseini A, Zandstra PW, Enginering the *In Vitro* Cellular Microenvironment for the control and Manipulation of Adult Stem Cell Responses. In: Turksen K (ed.), *Adult Stem Cells*, Totowa, NJ: Humana Press, 2004;289–314.
27. Zuk PA, Zhu M, Ashjian P, et al., Human adipose tissue is a source of multipotent stem cells, *Mol Biol Cell*, 2002;13: 4279–95.
28. Im G, Shin Y-W, Lee K-B, Do adipose tissue derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow derived cells, *Osteoarth Cartilage*, 2005;13:845–53.
29. Steck E, Bertram H, Abel R et al., Induction of intervertebral disc like cells from mesenchymal stem cells, *Stem Cells*, 2005;23:403–11.
30. Lin Y, Luo E, Chen X, et al., Molecular and cellular characterisation during chondrogenic differentiation of adipose tissue derived stromal cells *in vitro* and cartilage formation *in vivo*, *J Cell Mol Med*, 2005;9:929–39.
31. Boos N, Weissbach S, Rohrbach H, et al., Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science, *Spine*, 2002;27:2631–44.