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REVIEW

Update on the pathophysiology of degenerative disc disease and new developments in treatment strategies

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Abstract: Degenerative disc disease (DDD) continues to be a prevalent condition that afflicts populations on a global scale. The economic impact and decreased quality of life primarily stem from back pain and neurological deficits associated with intervertebral disc degeneration. Although much effort has been invested into understanding the etiology of DDD and its relationship to the onset of back pain, this endeavor is a work in progress. The purpose of this review is to provide focused discussion on several areas in which recent advances have been made. Specifically, we have categorized these advances into early, middle, and late phases of age-related or degenerative changes in the disc and into promising minimally invasive treatments, which aim to restore mechanical and biological functions to the disc.

Keywords: degenerative disc disease, quality of life, intervertebral, aging

Introduction

Understanding the pathophysiology of degenerative disc disease (DDD) remains an important research thrust, because age-related changes that occur in the intervertebral disc (IVD) are strongly associated with low back pain and other functional neurological deficits. In the United States, approximately 25% of individuals surveyed between 18–44 years of age during 2005 indicated that they experienced back pain within the past 3 months, and the percentage escalates to 31% and 33% for those aged 45–64 years and >65 years, respectively.[1] Including treatment and lost wages, the financial costs of low back pain have been estimated to exceed US $100 billion.[2] Costs are even higher for the substantial number of patients (~30%) whose outcomes are unfavorable, whether they subsequently choose conservative or operative treatment.[3,4]

Generally speaking, there are two strategies for engaging DDD, preventative and therapeutic. Our ability to prevent, or at least mitigate, degenerative biochemical and biomechanical changes in the disc hinges on elucidating the biological processes involved and the risk factors that instigate these processes. One can envision that such preventative strategies can be employed so long as the disc maintains the capability to produce and organize extracellular matrix (ECM) that supports its function. Therefore, this strategy is particularly relevant for healthy IVDs, juvenile or mature. Once the IVD has gone beyond a tenable state and/or becomes symptomatic, however, the aim transforms into a therapeutic one to restore quality of life. Protein- or cell-based biologics for stimulating production or inhibiting destruction of ECM material have been widely pursued, although these solutions may be limited to asymptomatic discs. For painful discs, there is a need to improve stabilization devices and our understanding of pain pathway(s).

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With these goals in mind, the objective of this review is to provide a synopsis of recent research findings and place them in the context of the pathophysiology of DDD and its treatment strategies. We have organized our discussions around the distinct issues that are relevant for the disc during aging and during disease, so as to serve as a guide for the development of respective preventative and treatment strategies in the future (Figure 1). To keep the review focused and concise, we were unable to include a comprehensive account of all disc-related research activities, and we apologize for any omissions.

Aging and degeneration of the IVD

Disc degeneration has often been described as an accelerated aging process. Therefore, a preventative strategy requires an understanding of the age-related biological events that may contribute to the pathophysiology of the disc. Although research has traditionally been focused on the mature IVD and on events that immediately precede the onset of symptoms, it is likely that the entire history of disc aging is important to its long-term health. As such, this section goes through what is known about IVD growth and aging, highlighting along the way new insight into the biology, physiology, and the risk factors that may contribute to degeneration.

Loss of notochord-derived cells in the nucleus pulposus

As detailed elsewhere,[5] the IVD has interesting developmental origins, consisting of three distinct lineages that comprise the nucleus pulposus (NP), the inner annulus fibrosus (AF), and the outer AF. The primary distinguishing characteristic of juvenile IVDs is the presence of notochord-derived cells in the NP.[6] Because this early notochordal-rich stage is transient, and the mature IVD remains functional in adulthood, the juvenile IVD has traditionally been neglected. However, recently, there have been efforts to understand

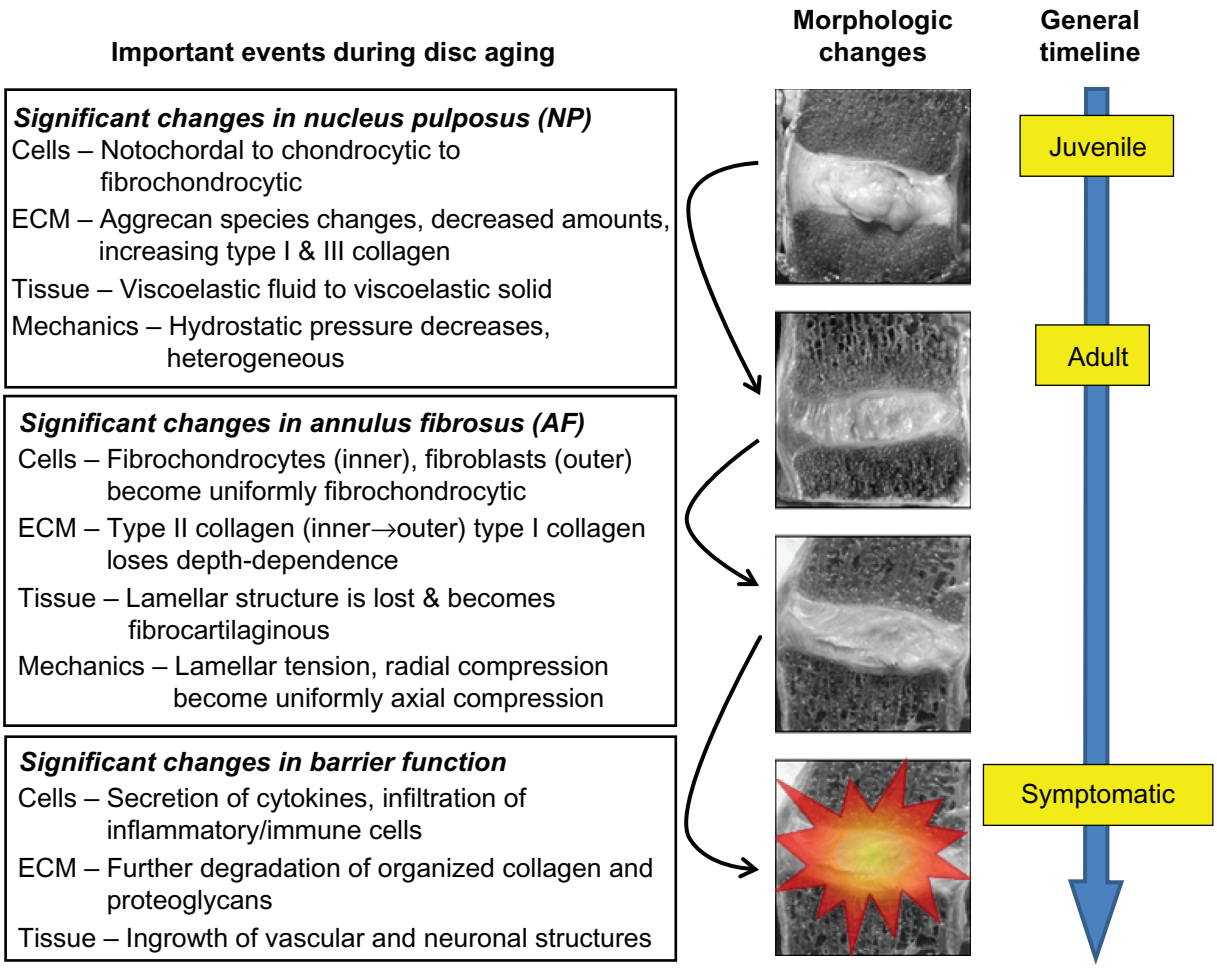

Figure 1 Highlights of the important cellular and cell-mediated processes (left column) associated with the traditional view of morphologic changes (middle) in the IVD during aging (right). It may be useful to consider the underpinnings of these changes as an overlapping series of progressive events, so that biologic interventions can be implemented to target specific phases of aging or degeneration.
Abbreviations: IVD, intervertebral disc; ECM, extracellular matrix.

notochord-derived cells and the juvenile NP because their unique biochemical or biomechanical characteristics may be significant to the long-term health of the IVD. Moreover, the biology and functional properties of the tissue can serve as a benchmark for regenerative strategies. Thus, although age-related changes in the juvenile IVD may be one step removed from those that occur at the symptomatic stages of DDD, their discussion is pertinent to the progression of events leading to morbidity.

One impetus for the increase in efforts toward understanding notochord-derived cells has been the broad observation that these cells persist in species that do not develop spinal complications, and these discs retain a healthy AF architecture.[7] Notably, it has been shown that chondrodystrophoid canine breeds do exhibit loss of notochord-derived cells, whereas other breeds do not.[7,8] Therefore, elucidating that cellular pathophysiology is important for prolonging disc health. Recent studies have demonstrated that these cells are particularly sensitive to their microenvironment in a complex manner. Specifically, it has been shown that notochord-derived cell function and viability are strongly influenced by the biochemical milieu, such as pH, osmotic environment, and nutrition, and these effects may also interact with monolayer and hydrogel culture effects.[9–11] Although the precise changes in the cellular microenvironment that occur in vivo are not well defined, these factors may contribute both to the differentiation of highly vacuolated cells into polygonal small chondrocyte-like cells[12] and to the signaling of neighboring chondrocytes or fibrochondrocytes.[13] The greater propensity for the small cells to propagate under certain conditions[9,11] and their greater resistance to low nutrient environments may lead to a population shift consistent with the more cartilaginous tissue phenotype observed in animal models of degeneration.[14,15]

Recent reports indicate that there may be remnants of this population in young adult human discs (although not in older ones).[16] Thus, although the notochord-derived cells are largely lost in the adult human disc, it may be possible to target these cells for regenerative approaches. This may be important because results from a number of studies suggest that coculture of certain cell populations with notochord-derived cells may have beneficial effects.[8,17–20] Towards a practical implementation of restoring notochord-derived cell to the NP, there has recently been an increased effort to identify genes that might confer an important specialized function or serve as "markers" for defining NP cell phenotype. These studies have taken a common approach of comparing notochordal and non-notochordal cells from the NP with cells from the AF and articular cartilage.[21–24] Although assessment techniques varied from small panels of genes using reverse transcriptase polymerase chain reaction to analysis of transcriptomes and proteomes, a finding common to most studies was that the expression of cytokeratins is higher in NP cells. Immunostaining techniques have demonstrated that the expression of cytokeratins is restricted to notochord-derived cells and becomes visually undetectable in human NP by 35–40 years of age.[21,23] On the transcriptional level, expression decreases approximately 10-fold in adulthood to levels similar to AF and cartilage cells, with further decreases with age and degeneration.[22,23] However, these population-based measures of expression are difficult to interpret because it is unclear what percentage of cells are expressing cytokeratins.

Disruption of the annular lamellae

Although the NP experiences marked changes during the early stages of aging, there are few indications of substantial effects in the AF until adulthood, typically characterized by mucoid degeneration, the presence of clefts and tears, and changes in collagen composition.[6,25] It has been traditionally hypothesized that the driving force behind the initiation of these changes is that the AF's structural function shifts from containment of the NP during loading to direct compression bearing as an axial strut.[15,26] However, this may be only part of the story. Recent studies of annular puncture injuries in animal models indicate that degenerative changes can occur even in the absence of significant external loading of the disc. A number of reports have confirmed that needle puncture of caudal discs can lead to morphologic changes,[14,27–30] and the puncture of nonloaded discs in organ culture also stimulates cell death.[31]

This mirrors the results observed with induction of spinal disc puncture injuries,[32–34] but in systems that are spared from loads generated by trunk muscle stabilizers. The NP, which is estimated to sustain a resting pressure of 100–200 kPa, places the AF in a state of residual tension stress. As alteration of disc mechanics caused by puncture appears to be necessary and sufficient for inducing degradative changes,[28,31] depressurization of the NP may be the primary contributing factor. In other scenarios, such as compressive loading, the loss of AF tension causes degeneration, whereas restoration of lost tension preserves annular morphology.[35] The dependence on needle injury size[28,36] suggests that the inflammation associated with injury may play only a minor role.

In addition to the lamellae, one aspect of the AF that had not drawn much attention previously, but which may be important in aging and degeneration, is the region of

tissue between lamellae. The interlamellar matrix of the adult disc is composed primarily of type I collagen fibrils, type IV collagen, elastin, aggrecan, and versican[37–40] and is populated by cells that appear to be distinct from lamellar fibroblasts and fibrochondrocytes.[41–43] Although the precise function of this tissue is not clear, the presence of lubricin in this region and the observed deformation of interlamellar tissue during annular tension suggest an important role in mediating shear stress between successive lamellae.[44,45] In healthy discs, the elastin content and colocalization with microfibrils increase from inner to outer AF,[40] mirroring the zonal increases in shear modulus and in-plane anisotropy.[46] During degeneration, there is a more dramatic increase in elastin content in the inner AF compared with the outer AF,[47] which would tend to diminish the zonal variation. Although no direct measurements have been reported, the trends are consistent with the notion that the AF, and indeed the IVD as a whole, becomes more uniform both biomechanically and biologically. Whether these shifts serve as contributory factors in the progression of DDD or represent a manifestation of the degenerative process is currently unclear.

Degradative changes and nerve ingrowth

A prominent gap in our understanding of DDD is its causal relationship to pain. Once the integrity of the aging or degenerative IVD is sufficiently compromised, complications such as disc herniations or spinal stenosis may develop, leading to pain or dysfunction. But with discogenic back pain, there is no physical impingement of the spinal cord or nerve root. Whether distinctions exist between the pathobiology of symptomatic and asymptomatic degenerative discs is currently unclear. Historically, numerous studies in herniated discs have highlighted contributions from inflammation and enhanced neovascularization around the extruded NP.[48–51] Taking a cue from these studies, recent efforts aimed at understanding the mechanisms of discogenic back pain have focused on similar factors. Thus far, the evidence is circumstantial but potentially important.

The processes leading up to the onset of discogenic back pain appear consistent with inflammation and involve a complex interplay among disc cells, immune cells, and inflammatory cytokines. Because of crosstalk, detangling the nature and implications of these interactions will likely be a significant challenge. Various cytokines have been found to be associated with degenerative discs, but tumor necrosis factor (TNF)-α and interleukin (IL)-1β have garnered the most scrutiny. Based on recent findings, it appears that these two cytokines may have both distinct and overlapping roles in discogenic back pain. TNF-α has long been suspected to be directly involved. In animal models, it had been shown that application of TNF-α to rat dorsal root ganglia (DRG) results in mechanical allodynia and nerve sensitization,[52–54] which can be exacerbated by DRG compression.[55] Disc herniation models support the potential for disc cell-secreted TNF-α to be involved in discogenic back pain. Blockade of TNF-α following the application of autologous NP to DRG has been demonstrated by several groups to improve behavior characteristics and allodynia in rats.[56–58] Notably, in mice, significantly less mechanical allodynia occurred using NP from TNF-knockout mice.[59]

Nerve ingrowth has been postulated as a mechanism that enables disc cell-secreted cytokines to generate pain in the absence of herniation. Painful discs have been found to have greater nerve penetration than nonpainful discs.[60–62] As reviewed by Freemont,[63] there may be a strong relationship between the ability for neuron or endothelial cells to migrate into the disc and both the cells and the ECM of the degenerative disc. It is possible that IL-1β and TNF-α may play important roles since they have been found to increase with age and degeneration in human disc tissues.[64–67] These inflammatory cytokines have recently been shown to upregulate neurotrophin expression,[68] promote vascular endothelial growth factor secretion,[69] sensitize disc cells for apoptosis,[70] further increase cytokine production,[71–73] and disrupt matrix homeostasis.[71,72,74–77]

Although the presence of elevated cytokine levels has been confirmed by several groups, the source of the cytokines remains unclear. It has been shown that disc cells are capable of producing various cytokines. In addition, CD68-positive cells have also been identified in degenerative discs, suggesting that monocytes or macrophages may infiltrate and constitute a secondary source of cytokines.[67,78] To complicate matters, there have also been reports that NP cells can exhibit a phagocytic phenotype possibly triggered by apoptosis,[79,80] but whether this has any short-term and/or long-term implications on cytokine production has not yet been examined. Thus, at this time, we must remain open to the possibility of complex interplay between cytokines that are secreted by disc cells to recruit immune cells and those produced by invading immune cells to stimulate disc cells.

Treatments for DDD

Current treatments of painful disc degeneration include approaches that range from noninvasive—such as "benign neglect," physical therapy, or symptom control with medication or injection—to outright surgical excision of the disc with or without fusion. These treatments are not

capable of improving the underlying degenerative changes, although they have proven to be effective for alleviating symptoms in some patients. The debate over best treatment option for discogenic back pain remains unresolved.[81] In a Norwegian randomized clinical trial, Brox et al[82] showed that it is possible for conservative treatments to yield results comparable to instrumented fusion surgery. By introducing a recently developed educational rehabilitation program based on cognitive-behavioral principles, they were able to achieve reduction in Oswestry Disability Index (ODI) v1 and its primary outcome measure from 43.0 to 29.7 and 42.0 to 26.4 in nonsurgical and surgical groups, respectively. This program also improved trunk musculature and muscle strength over the surgical group.[83] Conversely, there is also compelling evidence that surgical interventions can produce significantly better outcomes compared with "usual care" of physical therapy and/or anti-inflammatory drug administration. Notably, the recent Spine Patient Outcomes Research Trial (SPORT) randomized patients to surgical and nonsurgical treatment groups but allowed crossing over from their assigned groups.[84] Through 4 years of follow-up data, intent-to-treat analyses did not yield significant differences in primary outcomes (Short-Form-36, ODI) for degenerative spondylolisthesis and spinal stenosis. However, as-treated analyses indicate that surgical intervention yields significant improvements over conservative treatment.[85,86]

If a patient opts for surgery, the type of treatment intervention then becomes another consideration. Recent data suggest that discectomy with spinal fusion may be associated with disc degeneration in adjacent levels,[87–89] presumably due to altered biomechanics.[90] Motion-preserving modifications to rigid lumbar fusion, such as dynamic stabilization, have been used, but the questionable benefit and rates of observed failure have also drawn some attention, as reviewed by Kelly et al.[91] Total disc arthroplasty has become more widely used after US Food and Drug Administration (FDA) approval was granted for the CHARITÉ in 2004 and for the ProDisc in 2006. Randomized investigational device exemption trials reported to the FDA indicate that these devices generate no more complications than spinal fusion.[92,93] Moreover, range of motion appears to be better, and patient outcomes are at least in line with fusion.[94–97] Nevertheless, many consider that painful degenerative discs should, whenever possible, be treated with minimally invasive procedures, which preserve much of the IVD intact. The effectiveness of some such procedures, such as ablative techniques that use lasers or radiofrequency energy to decompress discs and alleviate pain, are not supported by the literature. As such, we will focus the discussion around updated developments in nucleus replacements and molecular therapy.

NP replacement

A number of so called "preformed" nucleus replacement technologies have been utilized and have been the subject of focused reviews.[98–100] These implants have defined shapes and often involve an insertion state that is smaller than its functional state caused either by swelling upon rehydration or by uncoiling. However, these implants typically require exposure of the IVD that is not insignificant, and biomechanical restoration of the disc and effects on adjacent levels using these technologies have not yet been investigated in great detail. Moreover, a number of recent studies using computational methods have shown that conformity of the NP-filling material to the nucleotomized space is important for transfer of axial stress into an annular circumferential hoop stress and improve stress distribution over the endplate,[101–103] confirming what had been postulated previously.[104]

As a way to address this limitation present in preformed nucleus implants, there have been several recent efforts to develop injectable materials for nucleus replacement. This area shares a common theme with tissue engineering in that the material must be biocompatible and mechanically robust. These materials could additionally overlap with tissue engineering strategies to support or, perhaps, promote regenerative biological processes, although current efforts have not yet focused on this potential aspect. A number of recent reports have described potential candidates for injectable polymers.[105–110] Thus far, focus has been primarily on materials' characterization to assess their biomechanical similarity with healthy NP tissues, but reports on their ability to restore gross mechanics of the motion segment have yet to be released. One pilot clinical study has been reported with good results.[111]

Molecular therapy

One of the major efforts in therapeutic strategies for disc degeneration is in the restoration of the disc's structural morphology. The main thesis has been that by restoring the disc matrix and reversing the appearance of disc degeneration, the symptoms of disc degeneration will be alleviated. Currently, tissue engineering is the most widely pursued area, but molecular therapy (growth factor therapy) is closer to actual clinical use. Some of the earliest research into molecular therapy included the study by Thompson et al[112] investigating the effects of insulin-like growth factor-1, epidermal growth factor, fibroblast growth factor, and transforming growth

factor on matrix synthesis and cell growth. The promitotic effect of growth factors and enhancement of disc matrix production were documented. However, cell mitosis may not be the most desirable characteristic, as the disc is nutritionally limited, and there is some evidence that there is an upper limit on cell density in disc matrix before which cells may not survive.[113] The most important parameter to consider may be the ability to increase disc matrix production to balance catabolism or outpace catabolism. Some of the molecules (bone morphogenic protein [BMP]-2, BMP-7, growth differentiation factor [GDF]-5, Lim Mineralization Protein-1, among others) promote a chondrogenic phenotype by disc cells, bone marrow-derived stem cells, and have proven to be highly effective in enhancing disc matrix production.[114–121] When compared with primarily mitogenic molecules, these molecules are more potent stimulators of matrix production on a per cell basis. More recent experiments have moved beyond proof of concept tissue culture experiments to show that molecular therapy can be effective in animal models of disc degeneration.[122–127] This has lead to two different FDA trials (BMP-7 and GDF-5) that are currently ongoing to test whether a single injection of therapeutic molecule can improve disc matrix appearance on magnetic resonance imaging and improve low back pain. Because there is no animal model of discogenic pain, these trials are the first "large animal" study of molecular therapy of disc degeneration. The thesis that disc matrix production will alleviate pain will be first tested in humans. If successful, these studies will be a major breakthrough in spinal care.

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Disclosure

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References

1. *Health, United States, 2007*. Hyattsville, MD: US DHHS, Center for Disease Control, National Center for Health Statistics; 2007.
2. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *J Bone Joint Surg Am*. 2006;88 Suppl 2:21–24.
3. Parker SL, Xu R, McGirt MJ, Witham TF, Long DM, Bydon A. Long-term back pain after a single-level discectomy for radiculopathy: incidence and health care cost analysis. *J Neurosurg Spine*. 2010;12(2):178–182.
4. Sherman J, Cauthen J, Schoenberg D, Burns M, Reaven NL, Griffith SL. Economic impact of improving outcomes of lumbar discectomy. *Spine J*. 2010;10(2):108–116.
5. Hsieh AH, Twomey JD. Cellular mechanobiology of the intervertebral disc: new directions and approaches. *J Biomech*. 2010;43(1):137–145.
6. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. *Spine (Phila Pa 1976)*. 2002;27(23):2631–2644.
7. Hunter CJ, Matyas JR, Duncan NA. Cytomorphology of notochordal and chondrocytic cells from the nucleus pulposus: a species comparison. *J Anat*. 2004;205(5):357–362.
8. Cappello R, Bird JL, Pfeiffer D, Bayliss MT, Dudhia J. Notochordal cell produce and assemble extracellular matrix in a distinct manner, which may be responsible for the maintenance of healthy nucleus pulposus. *Spine (Phila Pa 1976)*. 2006;31(8):873–882; discussion 883.
9. Guehring T, Wilde G, Sumner M, et al. Notochordal intervertebral disc cells: sensitivity to nutrient deprivation. *Arthritis Rheum*. 2009;60(4):1026–1034.
10. Hunter CJ, Bianchi S, Cheng P, Muldrew K. Osmoregulatory function of large vacuoles found in notochordal cells of the intervertebral disc running title: an osmoregulatory vacuole. *Mol Cell Biomech*. 2007;4(4):227–237.
11. Rastogi A, Thakore P, Leung A, et al. Environmental regulation of notochordal gene expression in nucleus pulposus cells. *J Cell Physiol*. 2009;220(3):698–705.
12. Kim JH, Deasy BM, Seo HY, et al. Differentiation of intervertebral notochordal cells through live automated cell imaging system in vitro. *Spine (Phila Pa 1976)*. 2009;34(23):2486–2493.
13. Kim KW, Ha KY, Lee JS, et al. Notochordal cells stimulate migration of cartilage end plate chondrocytes of the intervertebral disc in in vitro cell migration assays. *Spine J*. 2009;9(4):323–329.
14. Yang F, Leung VY, Luk KD, Chan D, Cheung KM. Injury-induced sequential transformation of notochordal nucleus pulposus to chondrogenic and fibrocartilaginous phenotype in the mouse. *J Pathol*. 2009;218(1):113–121.
15. Lotz JC, Colliou OK, Chin JR, Duncan NA, Liebenberg E. Compression-induced degeneration of the intervertebral disc: an in vivo mouse model and finite-element study. *Spine (Phila Pa 1976)*. 1998;23(23):2493–2506.
16. Weiler C, Nerlich AG, Schaaf R, Bachmeier BE, Wuertz K, Boos N. Immunohistochemical identification of notochordal markers in cells in the aging human lumbar intervertebral disc. *Eur Spine J*. 2010 Apr 7. epub
17. Aguiar DJ, Johnson SL, Oegema TR. Notochordal cells interact with nucleus pulposus cells: regulation of proteoglycan synthesis. *Exp Cell Res*. 1999;246(1):129–137.
18. Boyd LM, Chen J, Kraus VB, Setton LA. Conditioned medium differentially regulates matrix protein gene expression in cells of the intervertebral disc. *Spine (Phila Pa 1976)*. 2004;29(20):2217–2222.
19. Erwin WM, Ashman K, O'Donnel P, Inman RD. Nucleus pulposus notochord cells secrete connective tissue growth factor and up-regulate proteoglycan expression by intervertebral disc chondrocytes. *Arthritis Rheum*. 2006;54(12):3859–3867.
20. Erwin WM, Inman RD. Notochord cells regulate intervertebral disc chondrocyte proteoglycan production and cell proliferation. *Spine (Phila Pa 1976)*. 2006;31(10):1094–1099.
21. Gilson A, Dreger M, Urban JP. Differential expression levels of cytokeratin 8 in cells of the bovine nucleus pulposus complicates the search for specific intervertebral disc cell markers. *Arthritis Res Ther*. 2010;12(1):R24.
22. Minogue BM, Richardson SM, Zeef LA, Freemont AJ, Hoyland JA. Transcriptional profiling of bovine intervertebral disc cells: implications for identification of normal and degenerate human intervertebral disc cell phenotypes. *Arthritis Res Ther*. 2010;12(1):R22.

23. Rutges J, Creemers LB, Dhert W, et al. Variations in gene and protein expression in human nucleus pulposus in comparison with annulus fibrosus and cartilage cells: potential associations with aging and degeneration. *Osteoarthritis Cartilage*. 2010;18(3):416–423.
24. Chen J, Yan W, Setton LA. Molecular phenotypes of notochordal cells purified from immature nucleus pulposus. *Eur Spine J*. 2006;15 Suppl 15:303–311.
25. Nerlich AG, Boos N, Wiest I, Aebi M. Immunolocalization of major interstitial collagen types in human lumbar intervertebral discs of various ages. *Virchows Arch*. 1998;432(1):67–76.
26. Adams MA, McMillan DW, Green TP, Dolan P. Sustained loading generates stress concentrations in lumbar intervertebral discs. *Spine (Phila Pa 1976)*. 1996;21(4):434–438.
27. Han B, Zhu K, Li FC, et al. A simple disc degeneration model induced by percutaneous needle puncture in the rat tail. *Spine (Phila Pa 1976)*. 2008;33(18):1925–1934.
28. Hsieh AH, Hwang D, Ryan DA, Freeman AK, Kim H. Degenerative anular changes induced by puncture are associated with insufficiency of disc biomechanical function. *Spine (Phila Pa 1976)*. 2009;34(10):998–1005.
29. Zhang H, La Marca F, Hollister SJ, Goldstein SA, Lin CY. Developing consistently reproducible intervertebral disc degeneration at rat caudal spine by using needle puncture. *J Neurosurg Spine*. 2009;10(6):522–530.
30. Zhang KB, Zheng ZM, Liu H, Liu XG. The effects of punctured nucleus pulposus on lumbar radicular pain in rats: a behavioral and immunohistochemical study. *J Neurosurg Spine*. 2009;11(4):492–500.
31. Korecki CL, Costi JJ, Iatridis JC. Needle puncture injury affects intervertebral disc mechanics and biology in an organ culture model. *Spine (Phila Pa 1976)*. 2008;33(3):235–241.
32. Kim KS, Yoon ST, Li J, Park JS, Hutton WC. Disc degeneration in the rabbit: a biochemical and radiological comparison between four disc injury models. *Spine (Phila Pa 1976)*. 2005;30(1):33–37.
33. Masuda K, Aota Y, Muehleman C, et al. A novel rabbit model of mild, reproducible disc degeneration by an anulus needle puncture: correlation between the degree of disc injury and radiological and histological appearances of disc degeneration. *Spine (Phila Pa 1976)*. 2005;30(1):5–14.
34. Sobajima S, Kompel JF, Kim JS, et al. A slowly progressive and reproducible animal model of intervertebral disc degeneration characterized by MRI, X-ray, histology. *Spine (Phila Pa 1976)*. 2005;30(1):15–24.
35. Lotz JC, Hadi T, Bratton C, Reiser KM, Hsieh AH. Anulus fibrosus tension inhibits degenerative structural changes in lamellar collagen. *Eur Spine J*. 2008;17(9):1149–1159.
36. Elliott DM, Yerramalli CS, Beckstein JC, Boxberger JI, Johannessen W, Vresilovic EJ. The effect of relative needle diameter in puncture and sham injection animal models of degeneration. *Spine (Phila Pa 1976)*. 2008;33(6):588–596.
37. Melrose J, Smith SM, Appleyard RC, Little CB. Aggrecan, versican and type VI collagen are components of annular translamellar crossbridges in the intervertebral disc. *Eur Spine J*. 2008;17(2):314–324.
38. Ortolani F, Raspanti M, Franchi M, Marchini M. Localization of different alcian blue-proteoglycan particles in the intervertebral disc. *Basic Appl Histochem*. 1988;32(4):443–453.
39. Yu J. Elastic tissues of the intervertebral disc. *Biochem Soc Trans*. 2002;30(6):848–852.
40. Yu J, Tirlapur U, Fairbank J, et al. Microfibrils, elastin fibres and collagen fibres in the human intervertebral disc and bovine tail disc. *J Anat*. 2007;210(4):460–471.
41. Bruehlmann SB, Rattner JB, Matyas JR, Duncan NA. Regional variations in the cellular matrix of the annulus fibrosus of the intervertebral disc. *J Anat*. 2002;201(2):159–171.
42. Errington RJ, Puustjarvi K, White IR, Roberts S, Urban JP. Characterisation of cytoplasm-filled processes in cells of the intervertebral disc. *J Anat*. 1998;192(Pt 3):369–378.
43. Hastreiter D, Ozuna RM, Spector M. Regional variations in certain cellular characteristics in human lumbar intervertebral discs, including the presence of alpha- smooth muscle actin. *J Orthop Res*. 2001;19(4):597–604.
44. Pezowicz CA, Robertson PA, Broom ND. The structural basis of interlamellar cohesion in the intervertebral disc wall. *J Anat*. 2006;208(3):317–330.
45. Shine KM, Spector M. The presence and distribution of lubricin in the caprine intervertebral disc. *J Orthop Res*. 2008;26(10):1398–1406.
46. Fujita Y, Wagner DR, Biviji AA, Duncan NA, Lotz JC. Anisotropic shear behavior of the annulus fibrosus: effect of harvest site and tissue prestrain. *Med Eng Phys*. 2000;22(5):349–357.
47. Cloyd JM, Elliott DM. Elastin content correlates with human disc degeneration in the anulus fibrosus and nucleus pulposus. *Spine (Phila Pa 1976)*. 2007;32(17):1826–1831.
48. Carreon LY, Ito T, Yamada M, Uchiyama S, Takahashi HE. Neovascularization induced by anulus and its inhibition by cartilage endplate. Its role in disc absorption. *Spine (Phila Pa 1976)*. 1997;22(13):1429–1434; discussion 1446–1427.
49. Doita M, Kanatani T, Harada T, Mizuno K. Immunohistologic study of the ruptured intervertebral disc of the lumbar spine. *Spine (Phila Pa 1976)*. 1996;21(2):235–241.
50. Kawaguchi S, Yamashita T, Yokogushi K, Murakami T, Ohwada O, Sato N. Immunophenotypic analysis of the inflammatory infiltrates in herniated intervertebral discs. *Spine (Phila Pa 1976)*. 2001;26(11):1209–1214.
51. Koike Y, Uzuki M, Kokubun S, Sawai T. Angiogenesis and inflammatory cell infiltration in lumbar disc herniation. *Spine (Phila Pa 1976)*. 2003;28(17):1928–1933.
52. Ozaktay AC, Cavanaugh JM, Asik I, DeLeo JA, Weinstein JN. Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosis factor in rats. *Eur Spine J*. 2002;11(5):467–475.
53. Ozaktay AC, Kallakuri S, Takebayashi T, et al. Effects of interleukin-1 beta, interleukin-6, and tumor necrosis factor on sensitivity of dorsal root ganglion and peripheral receptive fields in rats. *Eur Spine J*. 2006;15(10):1529–1537.
54. Murata Y, Onda A, Rydevik B, Takahashi I, Takahashi K, Olmarker K. Changes in pain behavior and histologic changes caused by application of tumor necrosis factor-alpha to the dorsal root ganglion in rats. *Spine (Phila Pa 1976)*. 2006;31(5):530–535.
55. Liu B, Li H, Brull SJ, Zhang JM. Increased sensitivity of sensory neurons to tumor necrosis factor alpha in rats with chronic compression of the lumbar ganglia. *J Neurophysiol*. 2002;88(3):1393–1399.
56. Shamji MF, Allen KD, So S, et al. Gait abnormalities and inflammatory cytokines in an autologous nucleus pulposus model of radiculopathy. *Spine (Phila Pa 1976)*. 2009;34(7):648–654.
57. Norimoto M, Ohtori S, Yamashita M, et al. Direct application of the TNF-alpha inhibitor, etanercept, does not affect CGRP expression and phenotypic change of DRG neurons following application of nucleus pulposus onto injured sciatic nerves in rats. *Spine (Phila Pa 1976)*. 2008;33(22):2403–2408.
58. Olmarker K, Nutu M, Storkson R. Changes in spontaneous behavior in rats exposed to experimental disc herniation are blocked by selective TNF-alpha inhibition. *Spine (Phila Pa 1976)*. 2003;28(15):1635–1641; discussion 1642.
59. Yamashita M, Ohtori S, Koshi T, et al. Tumor necrosis factor-alpha in the nucleus pulposus mediates radicular pain, but not increase of inflammatory peptide, associated with nerve damage in mice. *Spine (Phila Pa 1976)*. 2008;33(17):1836–1842.
60. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet*. 1997;350(9072):178–181.
61. Peng B, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br*. 2005;87(1):62–67.

62. Coppes MH, Marani E, Thomeer RT, Groen GJ. Innervation of "painful" lumbar discs. *Spine (Phila Pa 1976)*. 1997;22(20):2342–2349; discussion 2349–2350.
63. Freemont AJ. The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. *Rheumatology (Oxford)* 2009; 48(1):5–10.
64. Le Maitre CL, Hoyland JA, Freemont AJ. Catabolic cytokine expression in degenerate and herniated human intervertebral discs: IL-1beta and TNFalpha expression profile. *Arthritis Res Ther*. 2007;9(4):R77.
65. Bachmeier BE, Nerlich AG, Weiler C, Paesold G, Jochum M, Boos N. Analysis of tissue distribution of TNF-alpha, TNF-alpha-receptors, the activating TNF-alpha-converting enzyme suggests activation of the TNF-alpha system in the aging intervertebral disc. *Ann N Y Acad Sci*. 2007;1096:44–54.
66. Lee S, Moon CS, Sul D, et al. Comparison of growth factor and cytokine expression in patients with degenerated disc disease and herniated nucleus pulposus. *Clin Biochem*. 2009;42(15):1504–1511.
67. Kokubo Y, Uchida K, Kobayashi S, et al. Herniated and spondylotic intervertebral discs of the human cervical spine: histological and immunohistological findings in 500 en bloc surgical samples. Laboratory investigation. *J Neurosurg Spine*. 2008;9(3):285–295.
68. Abe Y, Akeda K, An HS, et al. Proinflammatory cytokines stimulate the expression of nerve growth factor by human intervertebral disc cells. *Spine (Phila Pa 1976)*. 2007;32(6):635–642.
69. Ohba T, Haro H, Ando T, et al. TNF-alpha-induced NF-kappaB signaling reverses age-related declines in VEGF induction and angiogenic activity in intervertebral disc tissues. *J Orthop Res*. 2009;27(2): 229–235.
70. Zhao CQ, Liu D, Li H, Jiang LS, Dai LY. Interleukin-1beta enhances the effect of serum deprivation on rat annular cell apoptosis. *Apoptosis*. 2007;12(12):2155–2161.
71. Millward-Sadler SJ, Costello PW, Freemont AJ, Hoyland JA. Regulation of catabolic gene expression in normal and degenerate human intervertebral disc cells: implications for the pathogenesis of intervertebral disc degeneration. *Arthritis Res Ther*. 2009;11(3):R65.
72. Studer RK, Aboka AM, Gilbertson LG, et al. p38 MAPK inhibition in nucleus pulposus cells: a potential target for treating intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2007;32(25): 2827–2833.
73. Yoshida M, Nakamura T, Kikuchi T, Takagi K, Matsukawa A. Expression of monocyte chemoattractant protein-1 in primary cultures of rabbit intervertebral disc cells. *J Orthop Res*. 2002;20(6): 1298–1304.
74. Yoshida T, Park JS, Yokosuka K, et al. Up-regulation in receptor for advanced glycation end-products in inflammatory circumstances in bovine coccygeal intervertebral disc specimens in vitro. *Spine (Phila Pa 1976)*. 2009;34(15):1544–1548.
75. Seguin CA, Pilliar RM, Madri JA, Kandel RA. TNF-alpha induces MMP2 gelatinase activity and MT1-MMP expression in an in vitro model of nucleus pulposus tissue degeneration. *Spine (Phila Pa 1976)*. 2008;33(4):356–365.
76. Le Maitre CL, Pockert A, Buttle DJ, Freemont AJ, Hoyland JA. Matrix synthesis and degradation in human intervertebral disc degeneration. *Biochem Soc Trans*. 2007;35(Pt 4):652–655.
77. Le Maitre CL, Hoyland JA, Freemont AJ. Interleukin-1 receptor antagonist delivered directly and by gene therapy inhibits matrix degradation in the intact degenerate human intervertebral disc: an in situ zymographic and gene therapy study. *Arthritis Res Ther*. 2007;C9(4):R83.
78. Shamji MF, Setton LA, Jarvis W, et al. Pro-inflammatory cytokine expression profile in degenerative and herniated human intervertebral disc tissues. *Arthritis Rheum*. 2010;62(7):1974–982.
79. Nerlich AG, Weiler C, Zipperer J, Narozny M, Boos N. Immunolocalization of phagocytic cells in normal and degenerated intervertebral discs. *Spine (Phila Pa 1976)*. 2002;27(22):2484–2490.
80. Jones P, Gardner L, Menage J, Williams GT, Roberts S. Intervertebral disc cells as competent phagocytes in vitro: implications for cell death in disc degeneration. *Arthritis Res Ther*. 2008;10(4):R86.
81. Hanley EN Jr, Herkowitz HN, Kirkpatrick JS, Wang JC, Chen MN, Kang JD. Debating the value of spine surgery. *J Bone Joint Surg Am*. 2010;92(5):1293–1304.
82. Brox JI, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine (Phila Pa 1976)*. 2003;28(17):1913–1921.
83. Keller A, Brox JI, Gunderson R, Holm I, Friis A, Reikeras O. Trunk muscle strength, cross-sectional area, and density in patients with chronic low back pain randomized to lumbar fusion or cognitive intervention and exercises. *Spine (Phila Pa 1976)*. 2004;29(1):3–8.
84. Birkmeyer NJ, Weinstein JN, Tosteson AN, et al. Design of the Spine Patient outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)*. 2002;27(12):1361–1372.
85. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical compared with nonoperative treatment for lumbar degenerative spondylolisthesis. Four-year results in the Spine Patient Outcomes Research Trial (SPORT) randomized and observational cohorts. *J Bone Joint Surg Am*. 2009;91(6):1295–1304.
86. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonoperative treatment for lumbar spinal stenosis four-year results of the Spine Patient Outcomes Research Trial. *Spine (Phila Pa 1976)*. 35(14): 1329–1338.
87. Ekman P, Moller H, Shalabi A, Yu YX, Hedlund R. A prospective randomised study on the long-term effect of lumbar fusion on adjacent disc degeneration. *Eur Spine J*. 2009;18(8):1175–1186.
88. Kumar A, Beastall J, Hughes J, et al. Disc changes in the bridged and adjacent segments after Dynesys dynamic stabilization system after two years. *Spine (Phila Pa 1976)*. 2008;33(26):2909–2914.
89. Ghiselli G, Wang JC, Bhatia NN, Hsu WK, Dawson EG. Adjacent segment degeneration in the lumbar spine. *J Bone Joint Surg Am*. 2004;86-A(7):1497–1503.
90. Auerbach JD, Jones KJ, Milby AH, Anakwenze OA, Balderston RA. Segmental contribution toward total lumbar range of motion in disc replacement and fusions: a comparison of operative and adjacent levels. *Spine (Phila Pa 1976)* 2009;34(23):2510–2517.
91. Kelly MP, Mok JM, Berven S. Dynamic constructs for spinal fusion: an evidence-based review. *Orthop Clin North Am*. 2010;41(2): 203–215.
92. Synthes Spine. *Summary of safety and effectiveness data: ProDisc-L total disc replacement*. PMA# P050010. White Oak, MD: FDA; 2006.
93. Depuy Spine, Inc. Summary of safety and effectiveness data: CHARITÉ artificial disc. PMA# P040006. FDA, 2004.
94. Guyer RD, McAfee PC, Banco RJ, et al. Prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: five-year follow-up. *Spine J*. 2009; 9(5):374–386.
95. Fairbank J. Re: Zigler J, Delamarter R, Spivak J, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine 2007;32:1155–1162. *Spine (Phila Pa 1976)* 2007;32(25):2929–2930; author reply 2930–2931.
96. Zigler J, Delamarter R, Spivak JM, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. *Spine (Phila Pa 1976)*. 2007;32(11):1155–1162; discussion 1163.
97. Zigler JE. Lumbar spine arthroplasty using the ProDisc II. *Spine J*. 2004;4(6 Suppl):260S–267S.
98. Goins ML, Wimberley DW, Yuan PS, Fitzhenry LN, Vaccaro AR. Nucleus pulposus replacement: an emerging technology. *Spine J*. 2005;5(6 Suppl):317S–324S.
99. Di Martino A, Vaccaro AR, Lee JY, Denaro V, Lim MR. Nucleus pulposus replacement: basic science and indications for clinical use. *Spine (Phila Pa 1976)*. 2005;30(16 Suppl):S16–S22.

100. Carl A, Ledet E, Yuan H, Sharan A. New developments in nucleus pulposus replacement technology. *Spine J*. 2004;4 (6 Suppl):325S–329S.
101. Strange DG, Fisher ST, Boughton PC, Kishen TJ, Diwan AD. Restoration of compressive loading properties of lumbar discs with a nucleus implant-a finite element analysis study. *Spine J*. 2010;10(7): 602–609.
102. Dahl MC, Ahrens M, Sherman JE, Martz EO. The restoration of lumbar intervertebral disc load distribution: a comparison of three nucleus replacement technologies. *Spine (Phila Pa 1976)*. 2010;35(15): 1445–1453.
103. Rundell SA, Guerin HL, Auerbach JD, Kurtz SM. Effect of nucleus replacement device properties on lumbar spine mechanics. *Spine (Phila Pa 1976)*. 2009;34(19):2022–2032.
104. Meakin JR, Reid JE, Hukins DW. Replacing the nucleus pulposus of the intervertebral disc. *Clin Biomech (Bristol, Avon)*. 2001;16(7):560–565.
105. Vernengo J, Fussell GW, Smith NG, Lowman AM. Synthesis and characterization of injectable bioadhesive hydrogels for nucleus pulposus replacement and repair of the damaged intervertebral disc. *J Biomed Mater Res B Appl Biomater*. 2010;93(2):309–317.
106. Thomas JD, Fussell G, Sarkar S, Lowman AM, Marcolongo M. Synthesis and recovery characteristics of branched and grafted PNIPAAm-PEG hydrogels for the development of an injectable load-bearing nucleus pulposus replacement. *Acta Biomater*. 2010; 6(4):1319–1328.
107. Bron JL, Koenderink GH, Everts V, Smit TH. Rheological characterization of the nucleus pulposus and dense collagen scaffolds intended for functional replacement. *J Orthop Res*. 2009;27(5):620–626.
108. Leone G, Torricelli P, Chiumiento A, Facchini A, Barbucci R. Amidic alginate hydrogel for nucleus pulposus replacement. *J Biomed Mater Res A*. 2008;84(2):391–401.
109. Cloyd JM, Malhotra NR, Weng L, Chen W, Mauck RL, Elliott DM. Material properties in unconfined compression of human nucleus pulposus, injectable hyaluronic acid-based hydrogels and tissue engineering scaffolds. *Eur Spine J*. 2007;16(11):1892–1898.
110. Boelen EJ, Koole LH, van Rhijn LW, van Hooy-Corstjens CS. Towards a functional radiopaque hydrogel for nucleus pulposus replacement. *J Biomed Mater Res B Appl Biomater*. 2007;83(2):440–450.
111. Berlemann U, Schwarzenbach O. An injectable nucleus replacement as an adjunct to microdiscectomy: 2 year follow-up in a pilot clinical study. *Eur Spine J*. 2009;18(11):1706–1712.
112. Thompson JP, Oegema TR Jr, Bradford DS. Stimulation of mature canine intervertebral disc by growth factors. *Spine (Phila Pa 1976)*. 1991;16(3):253–260.
113. Horner HA, Urban JP. 2001 Volvo Award Winner in Basic Science Studies: effect of nutrient supply on the viability of cells from the nucleus pulposus of the intervertebral disc. *Spine (Phila Pa 1976)*. 2001;26(23):2543–2549.
114. Kim H, Lee JU, Moon SH, Kim HC, et al. Zonal responsiveness of the human intervertebral disc to bone morphogenetic protein-2. *Spine (Phila Pa 1976)*. 2009;34(17):1834–1838.
115. Kuh SU, Zhu Y, Li J, et al. Can TGF-beta1 and rhBMP-2 act in synergy to transform bone marrow stem cells to discogenic-type cells? *Acta Neurochir (Wien)*. 2008;150(10):1073–1079; discussion 1079.
116. Moon SH, Nishida K, Gilbertson LG, et al. Biologic response of human intervertebral disc cells to gene therapy cocktail. *Spine (Phila Pa 1976)*. 2008;33(17):1850–1855.
117. Kuh SU, Zhu Y, Li J, et al. The AdLMP-1 transfection in two different cells; AF cells, chondrocytes as potential cell therapy candidates for disc degeneration. *Acta Neurochir (Wien)* 2008;150(8):803–810.
118. Zhang Y, Phillips FM, Thonar EJ, et al. Cell therapy using articular chondrocytes overexpressing BMP-7 or BMP-10 in a rabbit disc organ culture model. *Spine (Phila Pa 1976)*. 2008;33(8):831–838.
119. Imai Y, Miyamoto K, An HS, Thonar EJ, Andersson GB, Masuda K. Recombinant human osteogenic protein-1 upregulates proteoglycan metabolism of human anulus fibrosus and nucleus pulposus cells. *Spine (Phila Pa 1976)*. 2007;32(12):1303–1309; discussion 1310.
120. Le Maitre CL, Freemont AJ, Hoyland JA. Expression of cartilage-derived morphogenetic protein in human intervertebral discs and its effect on matrix synthesis in degenerate human nucleus pulposus cells. *Arthritis Res Ther*. 2009;11(5):R137.
121. Cui M, Wan Y, Anderson DG, et al. Mouse growth and differentiation factor-5 protein and DNA therapy potentiates intervertebral disc cell aggregation and chondrogenic gene expression. *Spine J*. 2008; 8(2):287–295.
122. Huang KY, Yan JJ, Hsieh CC, Chang MS, Lin RM. The in vivo biological effects of intradiscal recombinant human bone morphogenetic protein-2 on the injured intervertebral disc: an animal experiment. *Spine (Phila Pa 1976)*. 2007;32(11):1174–1180.
123. Yoon ST, Park JS, Kim KS, et al. ISSLS prize winner: LMP-1 upregulates intervertebral disc cell production of proteoglycans and BMPs in vitro and in vivo. *Spine (Phila Pa 1976)*. 2004;29(23): 2603–2611.
124. Walsh AJ, Bradford DS, Lotz JC. In vivo growth factor treatment of degenerated intervertebral discs. *Spine (Phila Pa 1976)*. 2004;29(2):156–163.
125. Guehring T, Omlor GW, Lorenz H, et al. Stimulation of gene expression and loss of anular architecture caused by experimental disc degeneration – an in vivo animal study. *Spine (Phila Pa 1976)*. 2005; 30(22):2510–2515.
126. Masuda K, Imai Y, Okuma M, et al. Osteogenic protein-1 injection into a degenerated disc induces the restoration of disc height and structural changes in the rabbit anular puncture model. *Spine (Phila Pa 1976)*. 2006;31(7):742–754.
127. Kawakami M, Matsumoto T, Hashizume H, Kuribayashi K, Chubinskaya S, Yoshida M. Osteogenic protein-1 (osteogenic protein-1/bone morphogenetic protein-7) inhibits degeneration and pain-related behavior induced by chronically compressed nucleus pulposus in the rat. *Spine (Phila Pa 1976)*. 2005;30(17):1933–1939.