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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

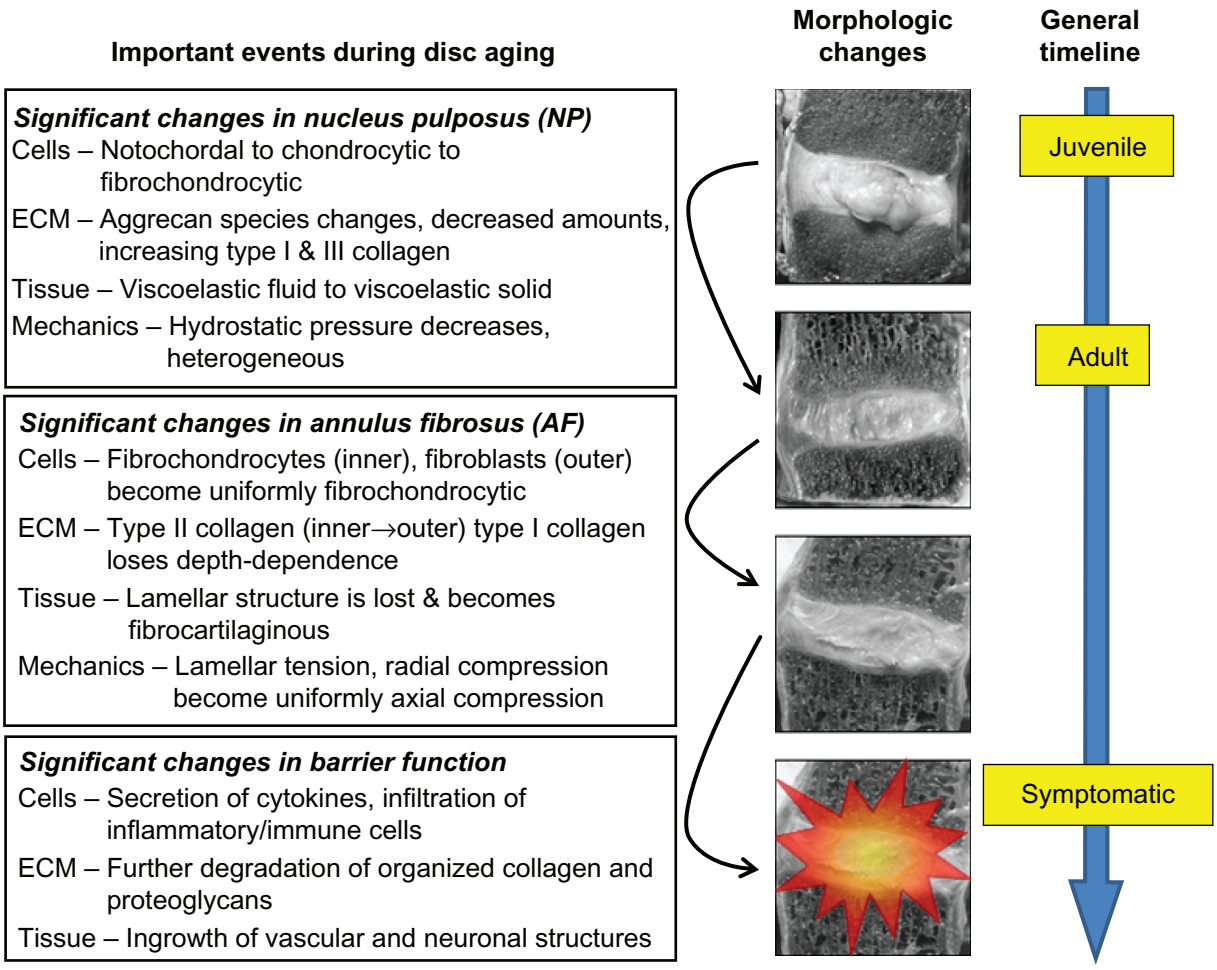

Figure 1 Highlights of the important cellular and cell-mediated processes (left column) associated with the traditional view of morphologic changes (middle) in the IVD during aging (right). It may be useful to consider the underpinnings of these changes as an overlapping series of progressive events, 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

The authors report no conflicts of interest in this work.

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