Low Back Pain: Pathophysiology and Management

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Abstract

Basic research is advancing the understanding of the pathogenesis and management of low back pain at the molecular and genetic levels. Frequently, low back pain is caused by disorders of the intervertebral disk. Cytokines such as matrix metalloproteinases, phospholipase A_2, nitric oxide, and tumor necrosis factor-α are thought to contribute to the development of low back pain. Drugs are being developed to modulate these chemical mediators. Recent research using growth factors to promote chondrocyte regeneration appears to be promising. Advances in gene therapy to both prevent disk degeneration and regenerate the disk eventually may have clinical application.

J Am Acad Orthop Surg 2004;12:106-115

Between 70% and 85% of the population suffer from low back pain at some time in their lives. The annual incidence of back pain in adults is 15%; its point prevalence is approximately 30%.[1] Low back pain is the primary cause of disability in individuals younger than 50 years. Potential sources of low back pain include the intervertebral disks, facet joints, vertebrae, neural structures, muscles, ligaments, and fascia. Research on the pathophysiology of low back pain and radiculopathy is integral to developing new management strategies. Current advances in basic research eventually may translate into treatment.

Intervertebral Disk Structure

Composed of fibrocartilaginous tissue, the intervertebral disk absorbs and dissipates the loads on the spinal column and allows smooth movement of the spine. The disk has a unique structure composed of an inner gelatinous nucleus pulposus surrounded by an outer anulus fibrosus (Fig. 1). Hydraulic and ion transport properties, as well as the mechanical behavior of the collagen-aggrecan solid matrix, influence the deformational characteristics of the nucleus pulposus. The anulus fibrosus is composed of sheets of interlacing lamellae of collagen and contains a relatively homogeneous population of chondrocyte-like cells that synthesize a matrix rich in collagen and poor in proteoglycans.

Types I and II collagen are the predominant forms of collagen in the disk material (Fig. 2). Type I collagen is present in the highest concentration in the anulus fibrosus and type II collagen, in the nucleus pulposus. Types V and XI are present in small concentrations in the anulus and the nucleus pulposus, respectively. Certain nonfibrillar, short-helix collagens, such as VI and IX, are present in both the anulus and nucleus, whereas type XII is present in the anulus fibrosus only.

In the healthy intervertebral disk, vascular and neural elements are limited to the peripheral fibers of the anulus fibrosus. Above and below the disk are sheets of hyaline cartilage called end plates that have pores that provide channels for diffusion, the main mechanism of nutrition for the disk.[2] Cells are sparse in the intervertebral disk, composing only 1% to 5% of the tissue volume. Chondrocytes are the predominant cell types in the nucleus, and the number of cells decreases rapidly across the disk from the end plate to the nucleus.

The collagen network within the anulus fibrosus provides tensile strength and limits the expansion of proteoglycan aggrecan molecules within the nucleus. These molecules provide compressive stiffness and enable the tissue to undergo reversible deformation. The nucleus is rich in proteoglycans and normally has 70% to 80% water content, which helps maintain disk height and dissipate loads. This viscoelastic property of the nucleus and inner anulus is biphasic and is associated with volumetric changes that occur because of extrusion and

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None of the following authors or the departments with which they are affiliated has received anything of value from or owns stock in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Biyani and Dr. Andersson.

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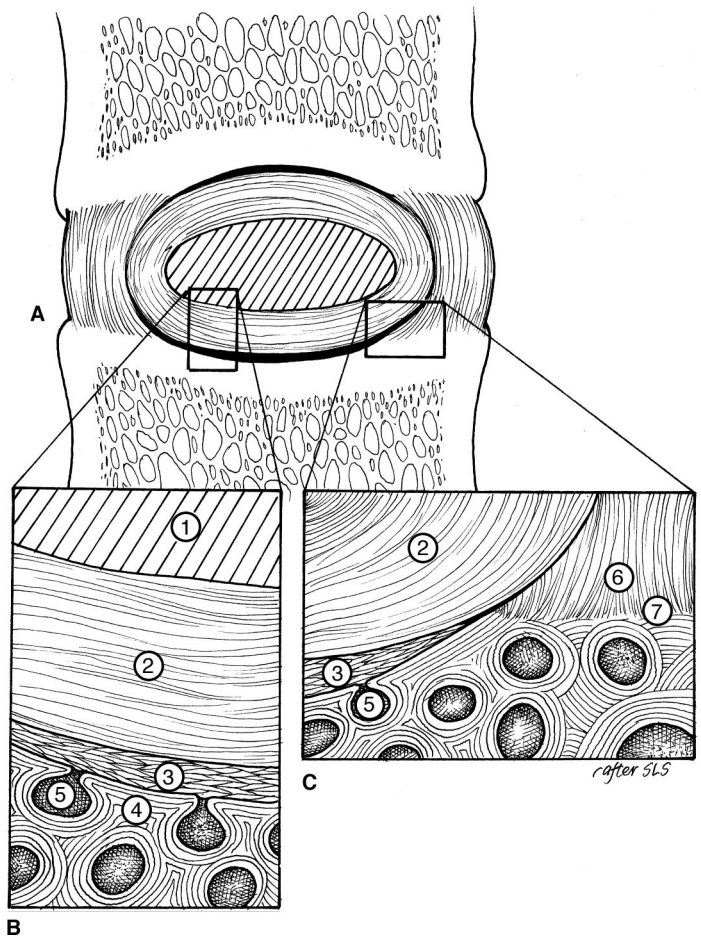

Figure 1 Arrangement of the fibrocartilaginous fibers of the anulus fibrosus. **A,** Fibers are arranged in a concentric lamellar fashion. **B,** Magnified view of the central part of the disk. 1 = nucleus pulposus, 2 = anulus fibrosus, 3 = horizontal disposition of the collagen fibers of the cartilaginous end plate, 4 = bony end plate, 5 = vascular channel in direct contact with the cartilaginous end plate. **C,** Fiber arrangement of the peripheral part of the disk. 6 = outer fibers of the anulus fibrosus, 7 = anchoring of the fibers to the bony end plate (Sharpey-type fibers). (Adapted with permission from Dupuis PR: The anatomy of the lumbosacral spine, in Kirkaldy-Willis WH, Burton CV [eds]: *Managing Low Back Pain*, ed 3. New York, NY: Churchill Livingstone, 1992, pp 10-27.)

imbibition of interstitial fluid. Bending and compression of the vertebra-disk-vertebra motion segments cause disk bulging, end-plate deformation, and volumetric changes. By contrast, torque distorts the shape of the anulus fibrosus without volumetric changes.

The functional properties of the intervertebral disk depend on the composition and integrity of the extracellular matrix. A complex activator-inhibitor system seems to regulate the normal processes in the intervertebral disk that, when deregulated, lead to degeneration. Loss of homeostasis between catabolism and synthesis in the matrix may lead to biochemical and microstructural changes in the disk that precede gross morphologic alterations.

Changes in the Disk Structure With Aging and Degeneration

Changes in disk volume and shape occur almost universally with aging. In as many as 90% of individuals, the lumbar disks may develop degenerative changes by age 50 years.[3] Beginning in the third decade of life, the nucleus pulposus gradually becomes less hydrated, and the number of viable cells and the concentration of proteoglycans decline. The size of the outer anulus fibrosus remains the same, but the fibrocartilaginous inner layers of the anulus expand as the nucleus pulposus becomes turgid and less hydrated. Further changes develop within the disk tissue in the elderly, as the inner layers of the anulus and the nucleus pulposus become indistinguishable and change into a stiff, desiccated fibrocartilaginous material.

Trivalent pyridinoline cross-links are present in highest concentration in the collagen within a healthy nucleus pulposus; their main function in the human intervertebral disk is to maintain tissue cohesiveness. Pentosidine is a pentose-mediated cross-link between lysine and arginine and is a marker of advanced glycosylation. With aging, levels of pyridinoline cross-links decrease and levels of pentosidine increase in lumbar intervertebral disks.[4] With age-related degeneration, protein glycosylation products, such as pentosidine, accumulate and alter the biochemistry of the matrix. The exact reasons for and effects of these biochemical changes are not clear.

In the early stages, degeneration affects the nucleus pulposus and the end plate more than it does the anulus fibrosus. Both anabolic and catabolic processes are upregulated during the early stages of intervertebral disk degeneration. With time, the rate of catabolism outstrips that of anabolism and the matrix degenerates. The exact mechanism of intervertebral disk degeneration is not clear, but several factors may be responsible for the process (Table 1). The concentration of viable cells decreases because of the loss of aggregating proteoglycans, degradative enzyme activity,

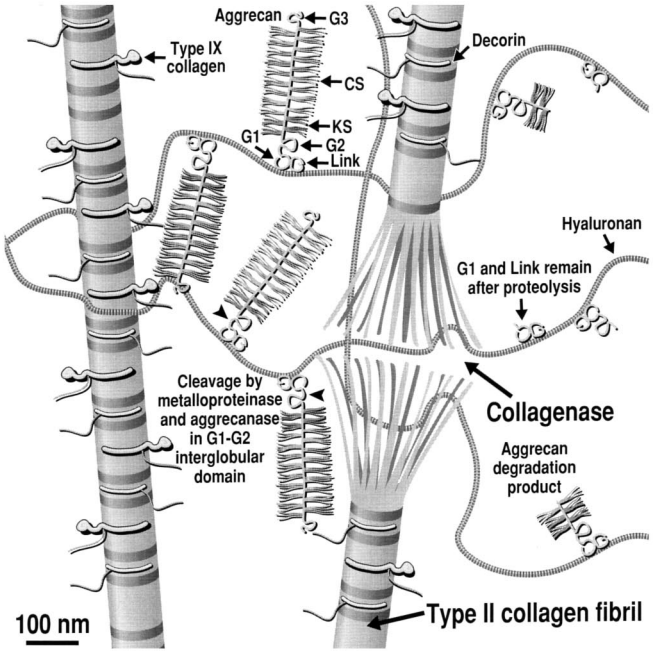

Figure 2 Structure of collagen and the proteoglycan aggrecan. Sites of attack by collagenase and other proteinases (arrowheads). CS = chondroitin sulfate, G1–G3 = globular domains, KS = keratin sulfate. (Adapted with permission from Recklies AD, Poole AR, Banerjee S, et al: Pathophysiologic aspects of inflammation in diarthrodial joints, in Buckwalter JA, Einhorn TA, Simon SR [eds]: *Orthopaedic Basic Science: Biology and Biomechanics of the Musculoskeletal System*, ed 2. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2000, pp 489-530.)

cell senescence, and apoptosis (programmed cell death). Comorbid conditions, such as diabetes, vascular diseases, and smoking, may accelerate the degenerative process.

As degeneration progresses, the number of arterioles supplying the periphery of the disk is markedly diminished, and the remaining blood vessels may be obliterated by calcification of the cartilaginous end plates. Loss of end-plate vascularity and porosity reduces the transport of nutrients and waste products. The lactate level rises locally within the hypovascular tissues because of increased production of lactate and its decreased rate of removal. Cell apoptosis ensues because of decreased pH caused by elevated lactate levels.[5] (Apoptosis plays an important role in the development of and homeostasis in healthy tissues, as well as in the pathophysiology of several diseases, including disk degeneration.)

Other biochemical processes, such as posttranslational protein modification, increased collagen cross-linking through nonenzymatic glycation, and lipid peroxidation, also may contribute to degeneration with aging.[5] Diffusion of nutrients and assembly of newly synthesized molecules also may be affected. Loss of proteoglycan from the extracellular matrix and accumulation of degraded matrix macromolecules may alter the mechanical and metabolic behavior of the degenerated intervertebral disk.

Cell senescence also may contribute to the degenerative process as the cells lose their biochemical and synthetic capabilities. Alterations in gene expression and transcription factors are thought to be responsible for cell senescence. This diminishes the ability of the disk to recover from deformation and renders the matrix more vulnerable to failure from progressive fatigue.

Thinning or microfracture of the end plate may alter its hydraulic properties. Increased permeability may allow rapid exudation of fluid from the cartilage end plate upon loading, thereby rendering the hydrostatic pressure mechanisms involved in load transference less effective and nonuniform. Focal rise in shear stresses at the disk level may further compromise the disk structure and damage the anulus fibrosus.

Clearly, intervertebral disk degeneration involves structural disruption as well as cell-mediated changes in the disk composition. Whether the degenerative process is initiated by biomechanical factors or biochemical changes is not known. One possibility is that mechanical disruption may initiate a biochemical process that, in turn, further weakens the disk structure. Minor compression of a middle-aged lumbar vertebra, creating a 1% loss of height, may be sufficient to significantly alter the end plate and induce progressive changes in the distribution of internal stress in adjacent intervertebral disks.[6] Subsequent cyclic loading of the anulus fibrosus may allow disruption of the annular fibers and migration of the nucleus pulposus. Alternatively, slow loss of proteoglycans and biochemical alterations may predispose the intervertebral disk to injury by mechanical forces.

Fissures and cracks usually develop between the lamellae and may establish channels of communication between the peripheral layers of the anulus and the nucleus. Disk tissue can herniate through these cracks. In contrast with the normal disk, the herniated disk has markedly higher degradative activity against type I collagen and elastin and very little activity against type II collagen. This also may account for a weakened anulus fibrosus in the herniated disk.[7] The most common site of annular disruption that leads to a symptomatic

Table 1
Pathophysiology of Intervertebral Disk Aging and Degeneration

Process	Effects
Diminished cellular responses	Senescence (alteration in gene expression and transcription factors) Apoptosis (programmed cell death)
Biochemical processes	Imbalance between catabolic and anabolic activity: Posttranslational protein modification Increased collagen cross-linking through nonenzymatic glycation, lipid peroxidation Loss of proteoglycans Altered diffusion of nutrients Impaired assembly of newly synthesized molecules
End-plate changes	Diminished vascularity and decreased porosity because of end-plate calcification ↓ Elevated lactate levels and reduced pH ↓ Cell apoptosis Thinning or microfracture of the end plate ↓ Increased permeability and altered hydraulic property ↓ Nonuniform load transference and increased focal shear stresses ↓ Disk degeneration and annular damage

disk herniation is at the insertion of the outer anulus into the vertebral body. A weakened anulus fibrosus that has a full-thickness defect may allow complete herniation of the nucleus pulposus material, particularly when the disk is loaded in flexion and torsion.

Pathophysiology of Low Back Pain

The relationship between intervertebral disk degeneration and low back pain is not clearly understood. It appears that alteration in biomechanical properties of the disk structure, sensitization of nerve endings by release of chemical mediators, and neurovascular ingrowth into the degenerated disks all may contribute to the development of pain. Degenerated disks may have notable ingrowth of nerve fibers and blood vessels within the inner anulus fibrosus and nucleus pulposus.[8] The loss of disk structure also alters the loading response and alignment of the rest of the spinal column, including that of the facet joints, ligaments, and paraspinal muscles, which eventually may become additional pain generators.

Back and radicular pain can be present even in the absence of distinct morphologic changes; conversely, many patients report no pain, even in the presence of marked degeneration.[9] Autologous nucleus pulposus has been shown to produce inflammatory and degenerative changes consistent with damage to the nerve root without mechanical compression.[10-12] Recently, the concept of local chemical mediation of pain by the injured tissue has gained favor. Several cytokines have been identified that may be responsible for chemical mediation of pain (Table 2). Similarly, endogenous inhibitors of these cytokines have been isolated.

The presence of nitric oxide has been detected in the granulation tissue around the extruded intervertebral disk by histochemical techniques and in situ hybridization.[13,14] Some investigators[14-16] have implicated phospholipase A_2, derived from the herniated nucleus pulposus, in the production of pain by irritating nerve roots, but others[17] deny its role in causing pain. Allograft and autograft intervertebral disk tissues have been shown to produce hyperalgesia in the rat. From their animal experiments, Kawakami and colleagues[14,18] concluded that autologous nucleus pulposus implanted on the lumbar nerve roots produces mechanical hyperalgesia, and anulus fibrosus provokes thermal hyperalgesia. Mechanical hyperalgesia is probably mediated by activation of phospholipase A_2 because mepacrine, which is a relatively selective inhibitor of phospholipase A_2, abolishes mechanical hyperalgesia produced by the nucleus pulposus. Thermal hyperalgesia produced by autologous anulus fibrosus may be induced by direct effects of nitric oxide at the level of the dorsal root ganglion. Kawakami et al[18] speculated that nitric oxide paradoxically may inhibit mechanical hyperalgesia and produce thermal hyperalgesia, depending on the amount of nitric acid produced after the disk material is applied.

Matrix metalloproteinases (MMPs) belong to a family of zinc-dependent enzymes capable of degrading extracellular and basement membrane components. MMPs are responsible for normal extracellular matrix remodeling in connective tissues. Active forms and inactive proforms of MMP-2 and MMP-9 have been found to be elevated in degenerated intervertebral disk specimens,[13] and

Table 2
Common Chemical Substances and Their Functions

Chemical Substance	Function
Phospholipase A_2	Mediates mechanical hyperalgesia
Nitric oxide	Inhibits mechanical hyperalgesia and produces thermal hyperalgesia
MMP-2 (gelatinase A) and MMP-9 (gelatinase)	Degrade gelatin (denatured fibrillar collagens) and other matrix molecules Act synergistically with MMP-1
MMP-1 (collagenase-1) MMP-3 (stromelysin-1)	MMP-1 degrades collagen Both MMP-1 and MMP-2 may play a role in spontaneous regression of the herniated disk
IL-1, TNF-α, prostaglandin E_2	Promote matrix degradation Enhance production of MMPs
CGRP, glutamate, substance P (neurotransmitters)	Modulate dorsal root ganglion responses
IL-6	Induces synthesis of TIMP-1
TIMP-1	Inhibits MMPs
TGF-β superfamily	Blocks synthesis of MMPs
IGF-1, PDGF	Have an antiapoptotic effect

CGRP = calcitonin gene−related peptide; IGF = insulin-like growth factor; IL = interleukin; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; TGF = transforming growth factor; TIMP = tissue inhibitor of metalloproteinase

MMP-1 (collagenase-1) and MMP-3 (stromelysin-1) have been implicated in the pathogenesis of disk herniation.[19] MMP activity also is thought to be more prevalent in intervertebral disk herniation than in other intervertebral disk disorders.[19] Kang et al[13] noted increased in vivo production of MMP in herniated lumbar disks from patients undergoing diskectomy compared with diskectomy specimens from patients undergoing anterior surgery for scoliosis and traumatic burst fractures.

Extrusion of nucleus pulposus into the epidural space evokes an autoimmune response and inflammatory cell infiltration. These inflammatory cells, in turn, secrete chemotactic cytokines, which further recruit the macrophages. Cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), are believed to enhance production of MMP.[19-21] Takahashi et al[22] performed a biochemical and immunohistochemical analysis of disk tissues in 77 patients with herniated intervertebral disks and noted increased production of prostaglandin E_2 as well as the presence of IL-1, IL-6, and TNF-α. MMP is produced by invading blood vessels, perivascular tissues, and locally present disk cells. The presence of capillary invasion and fibrous tissue has been well documented in surgically removed sequestered or extruded disk specimens.[23]

Expression of MMP-1 and MMP-3 has been noted to be higher in the granulation tissue, chondrocytes, macrophages, and fibroblasts from transligamentous extrusion and sequestered specimens than from protruded intervertebral disks. This finding suggests that inflammatory tissue rich in these proteinases causes degradation of the disk material and the collagen contained within the posterior longitudinal ligament (PLL), leading to weakening and eventual rupture of the PLL. An alternative scenario would be an increase in the production of MMP after the PLL has ruptured. A more likely explanation is a synergistic effect in which increased granulation tissue forms when the PLL is torn, and vice versa.[24]

It appears that proforms of MMPs, such as prostromelysin, are secreted by intervertebral disk cells and that these proforms subsequently may become activated by cytokines.[13] Sedowofia et al[25] reported that a latent form of collagenase is 3.5 times more abundant than the active form in the nucleus pulposus. They also reported that the quantity of latent collagenase is 1.5 times greater than the active form in the anulus fibrosus.

Endogenous tissue inhibitors of MMPs also have been identified. The tissue inhibitor of metalloproteinase-2 (TIMP-2) is expressed at low levels in all tissues, whereas TIMP-1 expression is increased in diseased intervertebral disk material.[26] An imbalance between MMPs and endogenous TIMP may play an important role in the degenerative process by inducing disk resorption.[21,27] Doita et al[21] demonstrated that, when stimulated by IL-1α, IL-1β, and TNF-α, cells isolated from extruded disk material produced greater amounts of MMP-1 and MMP-3 in vitro than did cells from protruded disk material. The MMP-3:TIMP ratio was higher in the extruded disk material than in the control group.[21] IL-6 is believed to increase the production of TIMP-1.[19,20]

MMPs also may play a role in the natural history of intervertebral disk herniation. The spontaneous regression primarily of large herniated disks versus protruded disks over time[24] is thought to be related to the increased synthesis of the MMPs. Although the precise mechanism of intervertebral disk resorption remains unclear, neovascularization, macrophage infiltration, and inflammatory cytokines are believed to be integral to this resorptive process. Inflammatory cytokines such as IL-1, IL-6, and TNF-α induce and en-

hance the expression of MMPs, leading to regression of a herniated intervertebral disk. Fibroblast growth factors also may regulate the proteolytic activity in herniated disk material.[26]

Brown et al[28] speculated that there is proliferation of vascularity and sensory nerves containing calcitonin gene–related peptide in the end-plate region and vertebral body adjacent to the degenerate disk. The increase in the density of sensory nerves and the presence of cartilage plate defects suggest a potential role of end plates and vertebral bodies as pain generators in patients with degenerated intervertebral disks.

Dorsal Root Ganglia

Dorsal root ganglia (DRG) are thought to be instrumental in modulating low back pain. DRG have abundant blood supply without a blood-brain barrier and provide a link between the intrathecal spinal nerve and extrathecal peripheral nerve. Nervi nervorum and mechanically sensitive nociceptors located on the DRG are thought to form several neuropeptides, including calcitonin gene–related peptide and substance P.[29] Harrington et al[30] suggested that the severity of pain caused by a herniated intervertebral disk is worse the closer the disk is to the DRG. DRG have a high density of glutamate receptors, which are closely associated with the nociceptors within the DRG. Proteoglycan breakdown may be accelerated in herniated intervertebral disks, which have a high concentration of glutamate neurotransmitters. Degradation of herniated intervertebral disk material by endogenous enzymes then could be a source of free glutamate that would potentiate pain signals by acting on glutamate receptors of the DRG neurons.

Based on animal studies, Yabuki et al[31] suggested that intervertebral disk herniation without nerve root compression sometimes may be painful because of an increase in the endoneurial fluid pressure and a decrease in the blood flow to the DRG when exposed to nucleus pulposus tissue. Ohtori et al[32] found that the dorsal portions of the lumbar intervertebral disks in rats receive segmental sensory innervation from the upper DRG via the sympathetic trunk and from the lower DRG via the sinuvertebral nerve (SVN). Thus DRG may play a central role in mediating low back pain from intervertebral disk–related disorders.

Sinuvertebral Nerve and Nociceptors

The SVN arises from the ventral root and gray rami communicantes near the distal pole of DRG. The SVN innervates structures within the vertebral canal (Fig. 3) as well as the PLL, ventral dura, posterior anulus fibrosus, and blood vessels. It has an ascending branch that innervates the PLL and a smaller descending branch that supplies the PLL and the anulus fibrosus. The ascending branch courses along the lateral border of the PLL, reaches the intervertebral disk above, and overlaps the innervation of the cephalad SVN. The anterior longitudinal ligament is supplied by branches of the gray rami communicantes or the sympathetic trunk.[33]

Medial branches of the dorsal primary rami course around the base of the superior articular facet and innervate the lumbar facet joint capsule at the same level. The medial descending branch travels caudally and innervates the muscles, ligaments, and facet joint below. Each facet joint thus receives innervation from at least two spinal nerves.

Nociceptors are peripheral terminal nerve endings of sensory neurons that respond selectively to painful stimuli.[29] The mechanosensitive afferent fibers from the lumbar posterior longitudinal ligament have a principally nociceptive function.[34] Nakamura et al,[35] who treated 33 patients with a selective L2 nerve root block with good relief of back pain, hypothesized that main afferent pathways of pain from lower intervertebral disks in patients with discogenic back pain are sympathetic in nature and are mediated through the L2 nerve root via the SVN.

The precise pathophysiologic mechanism by which chemical mediators within the intervertebral disk produce hyperalgesia is not clear. Weinstein et al[36] investigated the pain reproduced by diskography and concluded that various neurochemical changes within the disk are expressed by sensitized annular nociceptors. Kawakami et al[14] hypothesized that these chemicals may be transported into the axons of a nerve root and initiate production of inflammatory

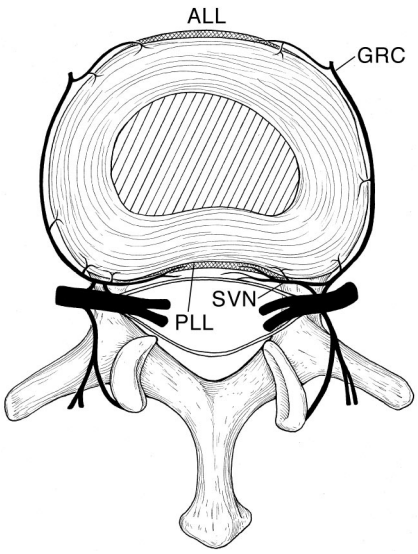

Figure 3 Transverse view of the lumbar intervertebral disk showing nerve supply. Branches of the gray rami communicantes (GRC) and the sinuvertebral nerves (SVN) are shown entering the disk and the anterior and posterior longitudinal ligaments (ALL, PLL). Branches from the SVN also supply the anterior aspect of the dural sac and dural sleeve. (Adapted with permission from Bogduk N: *Clinical Anatomy of the Lumbar Spine and Sacrum*, ed 3. New York, NY: Churchill Livingstone, 1997, p 142.)

agents, such as prostaglandins, which may lead to radicular pain. Byröd et al[37] demonstrated a direct transport route to the axons of the spinal nerve roots and suggested that the chemical produced in the epidural space may be able to alter the excitability of C fibers.

Table 3
Future Treatment Strategies for Low Back Pain

Approach	Treatment Strategies
Cellular	Decrease apoptosis Chondrocyte transplantation Stem cell transplant
Enhance anabolism	Gene therapy Growth factors
Decrease catabolism	Inhibition of chemical mediation of pain: TIMP TNF-α inhibition

TIMP = tissue inhibitor of metalloproteinase; TNF = tumor necrosis factor

Management Strategies in Development

Biologic and Biochemical Approaches

Recently, basic research into the pathophysiology of low back pain has focused on the development of biologic repair strategies and pharmacologic approaches to intercept and modulate the degenerative cascade (Table 3). Attempts also are being made to identify an ideal culture system to facilitate basic research into the metabolism of the entire intervertebral disk. The response of intact disks and experimental models of degenerated intervertebral disks then can be monitored after various therapeutic manipulations, allowing new avenues for biologic and biochemical treatment of low back pain to be explored. Newer disk culture techniques, such as the alginate tissue culture system, may promote greater proteoglycan synthesis within the nucleus pulposus and anulus fibrosus as well as maintain a higher content of extracellular matrix components.[38] Similarly, development of three-dimensional disk culture techniques may allow intervertebral disks to be used as an active carrier matrix.

In a recent study, Hutton et al[39] showed that autologous intervertebral disk chondrocyte cells transplanted into dogs remained viable, produced matrix, and achieved a normalized distribution within the disk space. Nishimura et al[40] created a model of degenerative intervertebral disk disease in rats and noted delayed degeneration of the remaining nucleus pulposus, anulus fibrosus, and end plate upon percutaneous reinsertion of autogenous fresh or cryopreserved nucleus pulposus. Coculture of nucleus pulposus and anulus fibrosus cells has been shown to invigorate the growth of anulus fibrosus cells, and in vivo disk degeneration is substantially delayed when nucleus pulposus cells are activated by coculture with anulus fibrosus cells.[41] Nomura et al[42] showed in rabbits that injection of an intact allogeneic nucleus pulposus is more effective than injection of nucleus pulposus cells alone. These authors hypothesized that the extracellular matrix might play an important role in slowing intervertebral disk degeneration.

Therapeutic strategies being actively investigated include gene therapy, growth factor therapy, and inhibition of chemical mediators of pain. These approaches, however, are still in the early stages of development and may not be universally applicable to the management of low back pain or even intervertebral disk degeneration. Biologic therapy of intervertebral disk degeneration may not be suitable for patients with severe changes because end-plate sclerosis impairs local tissue nutrition, with the result that the local environment may become too hostile for repair. Similarly, biologic repair may not be a viable option when the stability of a motion segment is significantly compromised because of continued stress on the disk tissue.

Gene Therapy

The role of gene therapy in the treatment of low back pain has been extensively evaluated to prevent degenerative disk disease, regenerate degenerated intervertebral disks, and promote spinal fusion. Genes regulate the synthesis of specific RNA and protein molecules, and their manipulation by gene therapy is an attractive tool for inducing expression of growth factors. Gene therapy involves transfer of a particular gene into a cell by means of a vector, which leads to transcription of the gene into mRNA. Ribosomes then translate the mRNA into specific proteins.

The delivery of genes may be accomplished by means of viral and nonviral vectors. Liposomes, gene guns, and gene-activated matrices are nonviral vectors that induce gene transfer by transfection. They are easier to produce than viral vectors and are chemically more stable, but they have limited ability to transfect cells. Gene expression over extended periods may not be possible.[43]

Genes can be transferred to the cell genome by ex vivo or in vivo techniques. Ex vivo therapy is considered to be safer because the vector is not introduced directly into the patient,

and the manipulated gene may be evaluated in the laboratory for its safety before it is transferred to live subjects. Retroviruses are small RNA viruses commonly used for ex vivo gene transfer. They infect only actively replicating cells at the time of transduction. An exogenous gene is integrated into the cell genome, thus transmitting the transgene to the daughter cells. The ex vivo technique of gene transfer is a useful adjunct to cell-based therapy and tissue engineering. In vivo techniques use direct transfer of the gene within the cells with the help of adenoviruses, which infect both dividing and quiescent cells. Unlike retroviral ex vivo transduction, integration of DNA into the cell genome does not occur with adenoviral in vivo techniques.

Gene delivery is considered to be beneficial for tissue engineering and repair. There are several advantages in delivering genes to the tissues rather than administering gene products. Gene delivery allows local production of sustainable high concentrations of the gene product for extended periods. Targeted delivery of gene product is possible, which maximizes therapeutic potential while minimizing side effects. In addition, endogenously produced proteins may have greater biologic activity than exogenously administered recombinant proteins do.[44] However, transgene expression commonly declines over time.

The choice of a viral vector depends on several factors, including the duration of the gene expression required, cell type to be transduced, and immunogenicity of the host tissue environment. The appropriate timing depends on the reason for gene expression. A long-term gene expression clearly would be beneficial for preventing disk degeneration. Markers for prolonged gene expression, such as lacZ and luciferase, have been identified in rabbit intervertebral disks. A shorter time for expression may be appropriate for regeneration of a degenerated intervertebral disk.[45]

A potential strategy to prevent or treat disk degeneration may be to modify the intervertebral disk genetically so that the proteoglycan content is not diminished within the nucleus. Nishida et al[46] noted a marked increase in proteoglycan synthesis after gene transfer in their animal experiments. Gene therapy may alter the course of the degenerative process. Any attempts to delay intervertebral disk degeneration by gene therapy also must address the issue of delaying natural disk degeneration that might result in increased low back pain later in life.[45]

The intervertebral disk is largely avascular and composed of poorly characterized, slowly dividing cells in an immunoprotected environment. Relatively encapsulated, avascular tissue would maintain injected viral vectors for long periods. In vivo gene transfer with adenoviral vectors therefore may be more appropriate for the nucleus pulposus, particularly to prevent disk degeneration. Ex vivo methods of gene therapy, with the help of a bioreactor or tissue scaffold, may be preferable for disk regeneration. However, the virus may leak through annular fissures in the degenerated intervertebral disk and evoke an immune response. An ideal treatment program for degenerative disk disease, however, must allow repeated injections of gene therapy at the same or different disk levels.[45]

Growth Factors

Recent advances in molecular biology have led to cloning and characterization of bone morphogenetic proteins (BMPs), including BMP-2, BMP-7, and BMP-like molecules, such as cartilage-derived morphogenic proteins. BMP-7, also known as osteogenic protein-1 (OP-1), is a member of the transforming growth factor-beta (TGF-β) superfamily that promotes differentiation of mesenchymal stem cells along the chondrogenic and osteogenic pathways. BMPs have shown promising results in promoting spinal fusion in several animal studies[47,48] and in early clinical trials.[49] Studies also are being conducted to evaluate whether, under the influence of growth factors such as OP-1, metabolically impaired cells in an intervertebral disk that exhibits degenerative or age-related changes can repair their own matrix and the disk structure. OP-1 appears to have an anabolic effect on proteoglycan and collagen synthesis. This stimulatory effect appears to be more pronounced on nucleus pulposus cells than on anulus fibrosus cells.

Inhibition of Chemical Mediators of Pain

A better understanding of the biochemical mediators of pain may facilitate development of pharmacologic approaches to inhibit them. The role of MMPs in the pathophysiology of back pain has been well established, and the inhibition of enzyme activity or inhibition of enzyme synthesis are two principal ways to decrease MMP levels. TGF-β appears to suppress MMP synthesis by suppressing transcription. IL-1 receptor antagonists also may block the IL-1–induced synthesis of MMPs and may have a potential role in treatment. $Alpha_2$ macroglobulins and exogenous TIMP have been found to be inapplicable or ineffective. An alternative and more attractive option may be to increase local production of TIMP with agents that upregulate TIMP expression.

Early clinical trials with monoclonal humanized chimeric antibodies against TNF-α have been undertaken recently, and early results are promising.[50] Other cytokines also may be beneficial, such as insulin-like growth factor-1 and platelet-derived growth factor, which reduce cell apoptosis in human disk cells in vitro[51] by some as-yet unknown mechanism.

Summary

The last decade has seen a better understanding of the pathophysiology of low back pain and new management possibilities with modalities such as gene therapy, the inhibition of chemical mediators of pain, and growth factors that promote spinal fusion and regeneration of disk material. New pharmacologic approaches for abolishing low back pain with agents such as platelet-derived growth factor and monoclonal chimeric antibodies against TNF-α are being tested clinically. Future gene therapy research likely will focus on proper selection of the gene and delivery method so that a sufficient amount of gene is expressed within the target tissue for an appropriate time.

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