Articular Cartilage

Structure and Function
Articular cartilage is structurally well suited to support joint function: it provides a nearly frictionless interface between joint surfaces and protects underlying bones by redistributing loads. By bulk chemical analysis cartilage consists mainly of water (more than 70% of wet mass), proteoglycan (15% of wet mass), and collagen (15% of wet mass). More than 80% of the proteoglycan present is in the form of high-molecular-weight (more than 3.5 x 10^6 Da) aggregates of hyaluronic acid–linked aggrecan, a 250-kDa protein that is heavily populated with polyanionic sulfated glycosaminoglycans (keratan and chondroitin sulfate). In the matrix, aggrecan entrapment within a collagen fibril network results in densely packed negative charges, which are available to interact with water via hydrogen bonding. Electrostatic repulsion and a strong tendency to retain bound water enable cartilage to resist deformation under compression and to redistribute stresses by hydrostatic pressurization of the matrix.

Histologic analysis reveals depth-dependent variation in cartilage matrix structure; four distinct zones (superficial, transitional, radial, calcified) can be distinguished based on differences in cell morphology, matrix composition, and collagen fibril orientation. These depth-dependent variations result in marked anisotropy and, as a result, chondrocytes experience different stresses depending on their location in the depth of the matrix. The superficial zone is relatively low in proteoglycan content compared with the deeper zones and, in contrast to deeper zones where collagen fibrils run perpendicular or orthogonal to the surface, the collagen network runs parallel to the surface. Thus, this zone is specialized to resist tensile stresses. Superficial zone chondrocytes are also somewhat distinct from cells in other zones: they are comparatively flat in shape and less rigid due to the absence of vimentin filaments, which enhance the stiffness of the cytoskeleton. These features appear to be an adaptation to the relatively higher strains experienced by these cells compared with cells lodged in the deeper zones where proteoglycan is more abundant. Superficial chondrocytes also secrete a specialized glycoprotein called lubricin (also known as superficial zone protein, or PRG4), which coats cartilage surfaces and lowers surface friction. Intra-articular injection of recombinant lubricin prevented cartilage degeneration in a rat meniscal tear model of osteoarthritis (OA), indicating that friction plays a role in cartilage degeneration in OA.

The cartilage extracellular matrix (ECM) is thinly populated by chondrocytes, cells of mesenchymal lineage that are adapted for life in the demanding environment of the articular surface. Despite their low tissue density, articular chondrocytes exert a profound influence on cartilage matrix stability. Chondrocyte death is associated with aging and OA, and the prevention of chondrocyte death blocks matrix degeneration after cartilage injury. Chondrocytes maintain the ECM by actively synthesizing its components, but also contribute to matrix degradation by synthesizing matrix proteases. Disturbance in the balance between biosynthetic and degradative activities destabilizes the ECM and is a hallmark of OA.

Cartilage is avascular and nourished only by way of synovial fluid at its surface and through subchondral bone at its base. Intratissue oxygen saturation is predictably low (2% to 10%), but chondrocytes tolerate such mild hypoxic conditions, relying for the most part on glycolysis for adenosine triphosphate (ATP) production. Presumably, in normal cartilage ATP is generated in sufficient quantity to meet demands for maintenance-level biosynthesis of proteoglycans and collagens. However, very low oxygen levels (less than 1%) inhibit glycolytic activity via negative feedback by
Influence of Mechanical Stresses on Matrix Composition and Cellularity

In addition to lacking blood vessels, cartilage is deprived of the neural input that drives adaptation of bone and muscle to prevailing loading conditions. Yet, numerous examples of loading effects on cartilage would seem to indicate an intrinsic capacity for load adaptation. These observations have focused attention on chondrocyte mechanoresponses, which appear to mediate many of the effects of loading on cartilage. A wealth of in vitro studies indicate that chondrocytes are sensitive to frequency, rate, and magnitude of loading. In general, physiologic cyclic stress (1 to 5 MPa) applied at moderate frequencies (0.1 to 1 Hz) and rates (less than 1,000 MPa/s) stimulate matrix synthesis and inhibit chondrolytic activity, whereas excessive stress amplitudes (more than 5 MPa), static loading (less than 0.01 Hz), or stress rates in excess of 1,000 MPa/s suppress matrix synthesis and promote chondrolytic activity. The transduction of mechanical signals resulting in changes in gene expression has long been known to involve integrins and the cytoskeleton. However, more recent findings suggest that primary cilia may act as a mechanosensory organ in chondrocytes and osteoblasts. These studies show that intracellular calcium flux, a primary effect of mechanical strain, is mediated by single cilia that protrude into the pericellular matrix and are connected to stretch-activated channels in the cell membrane. The hypothesis that cilia play a role in cartilage homeostasis is supported by data from transgenic mice lacking functional cilia; signs of abnormal cartilage development and degeneration were apparent.

Evidence of load adaptation in cartilage was revealed by a study in which the effects of moderate running exercise (1 hour per day 5 days per week for 15 weeks) on the stifle joints of beagle dogs were determined. The authors found that running was associated with significant gains in cartilage thickness and increased proteoglycan content in femoral condyles and patellae. However, later studies showed that more strenuous long-distance running (up to 40 km per day for 40 weeks) resulted in cartilage thinning and proteoglycan loss, indicating that load tolerance and adaptive capabilities of canine cartilage are limited. The relevance of the canine models to humans is uncertain. There were no substantial differences in knee MRIs between elite athletes and nonathletes, suggesting that the capacity for human cartilage to add mass in response to increased loading is more limited than in dogs. However, another study showed substantial (14%) patellar cartilage thickening in weight lifters and bobsled sprinters compared to nonathletic control subjects. It remains to be seen whether human cartilage shows changes in matrix composition similar to those observed in the dog model. In a 2008 study, long-distance running effects in the human knee were tracked by serial radiography of patients over two decades (mean age = 58 years). Multivariate analysis revealed that runners (n = 45) showed no substantial increase in Kellgren-Lawrence scores compared to control subjects (n = 53), indicating that running was not associated with increased risk of OA.

Habitual strenuous loading is clearly harmful to cartilage, but some form of mechanical stimulation is required for cartilage health. Atrophy in response to unloading is well documented in both animals and humans. Joint immobilization models consistently show cartilage thinning, softening, and proteoglycan loss. Recent work in a rat model revealed increases in chondrocyte apoptosis, and increased hypoxia inducible factor-α (HIF-α), VEGF, matrix metalloproteinase-8 (MMP-8), and MMP-13 expression. This finding suggests that hypoxia may play a role in immobilization effects. MRI studies of human knees have shown progressive cartilage thinning within 2 years of spinal cord injury, indicating atrophy similar to that observed in joint immobilization models. The ability of cartilage to return to a trophic state when loading is resumed is also well established. Data from immobilization models have shown varying degrees of recovery of normal cartilage thickness, stiffness, and proteoglycan (PG) content. However, in most cases, extended immobilization results in permanent deficits of up to 25% in PG content and mechanical properties. The risk of such permanent effects on cartilage in patients with extended partial weight bearing is unclear due to uncertainties regarding the time course for immobilization-induced atrophy in humans; however, a study of patients recovering from ankle fracture showed significant losses of patellar cartilage thickness (-3%) and tibial cartilage thickness (-6%) after only 7 weeks of reduced loading.

Aging and Arthritis

The age-dependent incidence of OA supports the notion that age-related changes in articular cartilage are pathogenic. However, the connection of aging to OA remains unclear. Distinguishing normal age-related changes in cartilage, which do not progress to OA, from early changes that reliably progress to OA is still controversial. Therefore, longitudinal MRI studies may prove useful. In one example, MRI examination of patients with knee OA symptoms showed significant reductions in cartilage thickness over 1 year, indicating disease progression. Presumably, similar studies in age-matched patients without symptomatic OA would show less progressive thinning. This coupled with an
initial examination using MRI methods that are sensitive to cartilage matrix composition (delayed gadolinium-enhanced MRI of cartilage [dGEMRIC], T2, or T1ρ) could help to distinguish initial conditions that predispose patients to OA from those that do not.

Except in connection with injury, cell division is rare in mature articular cartilage, suggesting that most chondrocytes present at skeletal maturity are likely to remain in place for decades. Although their numbers remain relatively stable for most of adult life in normal cartilage, early OA is marked by increased apoptosis and, at later stages, by hypocellularity. Preventing apoptosis using caspase inhibitors ameliorates the development of OA in animal models and holds great promise for the treatment of some forms of OA in humans.

Although most chondrocytes may be long-lived, several in vitro tests document age-related declines in their performance, especially after the fourth decade of life when the risk of OA increases sharply. Losses in overall biosynthetic activity, particularly under growth factor stimulation, could contribute to the risk of OA by undermining matrix maintenance and repair. However, a pathogenic role for these relatively subtle cellular changes remains to be proved. Indeed, it is possible that age-related “loss” of matrix biosynthesis activity constitutes a successful metabolic adaptation to decreasing nutrition or other environmental changes, and that its association with OA is coincidental.

More obviously pertinent to OA are age-related changes in chondrocyte phenotype that lead to increased expression of catabolic cytokines and matrix proteases. Recent work suggests that dysregulation of the Wnt/β-catenin pathway, which regulates multiple genes involved in cartilage development, is strongly associated with OA. Wnt-induced signaling protein 1 (WISP-1) was found to upregulate matrix protease expression in chondrocytes. Inactivating mutations in the gene encoding frizzled-related protein-3, a key negative regulator of the Wnt pathway, were found to predispose patients to OA. Moreover, transgenic mice overexpressing β-catenin, a key positive regulator of the Wnt pathway, develop osteoarthritic changes. Interestingly, β-catenin activation is regulated by mechanical stresses in chondrocytes, suggesting a role for the Wnt pathway in integrin-mediated mechanoresponses.

The cause of age-related changes in the Wnt pathway or other alterations in phenotype is uncertain. Some evidence suggests that the age-dependent accumulation of epigenetic changes alters the pattern of chondrocyte gene expression. This involves altered activity of DNA methyltransferases and/or histone acetylases/deacetylases, which inappropriately silences or activates gene expression by modifying cis-acting sequences that control gene transcription. For example, the expression of the aggrecanase encoding gene a disintegrin and metalloproteinase with thrombospondin motif-4 (ADAMTS-4) in normal and osteoarthritic cartilage was analyzed, and the enzyme was found to be upregulated in superficial zone chondrocytes in OA. Further analysis revealed that increased expression in OA was related to loss of cytosine methylation at critical CpG islands in the ADAMTS-4 gene promoter. Loss of DNA methylation in a patient with developmental dysplasia of the hip was associated with increased expression of MMP-13, MMP-9, and MMP-3, all of which contribute to ECM degradation. The availability of drugs targeting methylation and histone modification for cancer therapy has stirred discussion of their use in the treatment of OA.

Cell senescence, a phenomenon underlying many degenerative diseases, also occurs in articular cartilage. Senescence is defined as permanent growth arrest, but the term is also often used in connection with profound alterations in gene expression. Senescent cells can be long-lived, which might not be problematic except that they are not entirely quiescent and show abnormalities in matrix metabolism that actively disrupt tissue function. Chronic oxidative damage has been shown to induce senescence in human chondrocytes and senescent cells accumulate in articular cartilage with aging. Chondrocytes generate oxidants in response to mechanical stress, suggesting a connection between mechanical factors, oxidative damage, and senescence. Thus, it appears that aging changes might be slowed by avoiding stresses that result in deleterious oxidant release.

In most of the studies described above it is implicitly assumed that aging affects all cells in cartilage in the same way. However, it is increasingly apparent that cartilage harbors progenitor cells, which are distinct from normal chondrocytes in that they are highly migratory, pluripotent, and clonogenic. Progenitor cells have been identified in late-stage osteoarthritic cartilage, and may participate in the repair of damaged matrix. Thus, age-related declines in this subpopulation could have a disproportionate effect on matrix stability.

### Injury and Repair

**Biologic Responses to Mechanical Injury**

Physical injury to articular cartilage surfaces can occur under a variety of circumstances, including articular fracture, ACL rupture, or simple strains. High loading rates (>1,000 MPa/s) and high peak stress amplitudes (>20 MPa) initiate focal damage that can spread to involve even larger areas of the joint surface, leading to posttraumatic OA. Biologic responses act to repair or limit the damage inflicted by injurious stress, but progressive degeneration is a common sequela to injury, particularly in middle-aged and elderly patients. At the high loading rates characteristic of impact injuries, overall cartilage strain and water loss are minimal. However, local strains in the superficial zone during impact injuries can exceed 40%, and matrix fissuring and chondrocyte death are evident postimpact. These changes have been shown to lead to the development of OA in a rabbit model of single blunt-impact injury.

### Strategies to Promote Healing or Regeneration

Superficial zone chondrocyte death is strongly associated with physical injury to articular cartilage. Most of the available evidence indicates that the resulting devitalization of the cartilage matrix is permanent and de-
stabilizing; thus, injury-induced cell death is among the earliest pathogenic events in posttraumatic OA. Preventing cell death in the immediate aftermath of injury has become a major target of therapy for posttraumatic OA as it has for stroke and heart attack. Interestingly, neuronal death after stroke and chondrocyte death after cartilage injury both appear to involve oxidative damage associated with free radical release.

Both apoptosis and necrosis have been observed at sites of high-energy impact injury. Impact-induced chondrocyte apoptosis is a caspase-dependent process. Caspase inhibitors reduce the severity of OA in vivo. Caspase inhibitors and the surfactant P-188 were also shown to prevent nearly 50% of the chondrocyte death that occurred in human ankle cartilage subjected to a single impact. P-188 is thought to prevent necrosis by restoring cell membrane integrity, which is compromised by injury. In addition, BMP-7 applied intrarticularly within 3 weeks after an experimental impact injury in the sheep stifle joint prevented apoptosis and ameliorated progressive degenerative changes in the cartilage matrix.

Evidence of mitochondrial involvement in injury-induced apoptosis comes from a cartilage explant injury model, in which it was shown that a wave of calcium was released from the endoplasmic reticulum following blunt impact injury. An increase in calcium level induced permeability transition pore (PTP) formation in the inner mitochondrial membrane. The resulting depolarization was associated with cytochrome C release, Bcl-2 degradation, and caspase-dependent apoptosis. Chondrocyte apoptosis was inhibited by blocking the increase in cytoplasmic calcium or by blocking PTP formation. These results show the central role of calcium in chondrocyte responses to mechanical trauma and provide evidence that mitochondria-dependent apoptosis is a significant consequence of the disruption of calcium homeostasis.

Recent work in a bovine explant model showed that impact-induced chondrocyte death was significantly reduced by treatment with the intermediate free-radical scavenger N-acetyl cysteine (NAC), and similar effects have been shown using a superoxide dismutase (SOD) mimetic. NAC applied within 2 hours of impact spared more than 75% of cells that would have otherwise died within 72 hours of injury. Moreover, impact-related decline in PG content 7 days after injury was blocked by early postimpact NAC treatment. Additional studies established that superoxide radicals are released from mitochondria in response to impact injury; blocking mitochondrial electron transport at complex I using rotenone ablated superoxide release had chondrocyte-sparing effects similar to those of NAC (Figure 1).

These studies demonstrate the central role of oxidative stress and mitochondrial dysfunction in acute chondrocyte death induced by articular injury. It is known that cell death under these conditions is preventable and that preserving cellularity improves tissue function and short-term matrix stability. However, the ability of such acute cytotherapies to prevent OA is not yet clear. Relieving contact stresses in injured joints via distraction offers considerable promise. This strategy,
which involves external fixation and separation joint surfaces, has been applied to patients with OA of the ankle. In one study conducted 30 months after frame removal, 21 patients (91%) experienced significant improvement; only 2 of these patients had arthrodensis. The mechanisms of distraction effects on articular cartilage repair and stability are still largely unknown.

Noninvasive Assessment of Cartilage Health

Novel MRI-Based Approaches

The exquisite soft-tissue contrast of MRI and the multiplicity of contrast mechanisms available in a single examination have established MRI as the method of choice for imaging articular cartilage. A typical MRI protocol will acquire proton density, T1, T2, and fat-suppressed images, which give a comprehensive picture of the morphologic changes associated with injury and subsequent degenerative processes. Ultimately, however, it is the biomechanical properties of cartilage that determine its functional state. Biomechanical properties of cartilage may in turn be assessed based on related biochemical composition of the ECM, especially in terms of PG and collagen content, the primary components responsible for the mechanical strength of healthy cartilage. Thus, the development of a noninvasive and quantitative assessment of cartilage PG content would greatly enhance the evaluation of acute injury and treatment efficacy in the clinical setting. MRI is presently the only imaging modality capable of generating this information, with four distinct techniques available to generate PG-sensitive images for interpretation and quantification. These include sodium (23Na) imaging, T2 mapping, dGEMRIC, and T1p imaging. Sodium nuclear magnetic resonance spectroscopy has long been applied to investigate PG depletion in cartilage. The basis for this method is that PG loss yields a reduction of fixed charge density and a loss of sodium ions (as well as a change in sodium relaxation parameters). These changes can be seen and quantified from sodium-based MRI as well and present a very direct correlation to PG loss. However, sodium MRI requires specialized hardware, and has relatively poor resolution and signal-to-noise ratio, and is unlikely to translate to standard clinical imagers. At the other end of the spectrum, T2-based MRI is a widely used and mature technique, and T2-weighted images are routinely acquired as part of musculoskeletal MRI protocols. Quantification of T2 relaxation times is also a readily available technique on most clinical scanners. Several studies have shown significant changes in T2 relaxation times in areas of cartilage degeneration, and these changes may be seen in subjects with OA in the absence of volume and thickness changes, suggesting sensitivity to biochemical changes in early OA. These changes in T2 relaxation time are relatively small, and may result from multiple mechanisms such as PG loss, water content, and collagen concentration and orientation. Thus, although T2 changes in cartilage are seen in degenerative processes and may often be diagnostically valuable, it can be unclear which of these mechanisms is the predominant cause, potentially limiting the sensitivity and specificity to PG loss.

The dGEMRIC protocol is currently the most widely used of the methods for in vivo characterization of PG loss. The principle of dGEMRIC is based on the fact that glycosaminoglycans (GAGs), which are linked to core proteins to form PGs, are negatively charged. If a negatively charged MRI contrast agent such as Gd(DTPA)2 is introduced, the distribution of this agent will be in inverse proportion to the GAG concentration. Further, the Gd(DTPA)2 concentration can be measured through measurement of T1 relaxation time through standard imaging and processing techniques, yielding a marker of GAG concentration and PG loss. Numerous in vivo and in vitro studies suggest dGEMRIC is the most specific for GAG concentrations among the described methods, demonstrating direct correlations between dGEMRIC measurements and GAG and even mechanical properties. This specificity comes at a cost of high complexity in implementing the examination. Subjects receive an intravenous injection of contrast agent, followed by a period of mild exercise to distribute the agent. Imaging then takes place 1 to 2 hours after injection. In many cases, a precontrast examination is also desirable for robust measurement of relaxation changes. Thus, while dGEMRIC shows strong abilities for accurate measurements of PG depletion, the rigors of the examination may prevent its use in clinical settings. T1p MRI represents a promising “middle ground” between T2 mapping and dGEMRIC. T1p MRI is a completely noninvasive method for quantifying cartilage PG content without the need for special hardware, contrast agents, exercise, or extended timing considerations while generating information very similar to dGEMRIC.

The relaxation processes measured with T1p depend primarily on the exchange of protons between water and macromolecules, but are also influenced by interactions caused by collagen fibril orientation. The T1p technique generates images with a standard spin-echo-based pulse sequence attached to the beginning with a group of magnetization preparation pulses to set up varying amounts of T1p contrast, and can therefore be implemented on any clinical scanner. The image analysis required to quantify T1p is very similar to that required for T2 measurements. The close ties between PG content and cartilage function make T1p MRI a much more direct and valuable indicator of cartilage health and treatment efficacy than purely anatomic imaging. Because of the dependence on proton exchange between water and PGs, quantifying PG depletion associated with early OA development with T1p is a more discriminatory cartilage assessment than T2 sequences. Thus, T1p MRI pulse sequences may be able to detect cartilage compromise occurring after catastrophic ACL ruptures. Although this dependence may not be as exclusively based on PG content as dGEMRIC, both in vitro and in vivo studies suggest that the relationship is sufficiently strong and sensitive that it may be preferred in many cases because of the considerably simpler logistical requirements. The development and validation of T1p MRI as an objective and quantitative measurement standard of cartilage condi-
Biomarkers
Numerous biomarkers related to cartilage matrix metabolism have been tested for their power to predict the progression of primary arthritis. The crosslinked C-telopeptide of type II collagen (CTX-II) generated in articular cartilage by noncollagenase proteinases is a reliable urinary marker of cartilage degeneration in primary OA. Collagen type II neoepitopes resulting from collagenase activity (Col2-3/4 long, Col2-3/4 short) have also been extensively used as degenerative markers as has the aggrecan neoepitope (VDIPEN) generated by MMPs. Markers of cartilage matrix biosynthesis include the C-terminal propeptide of type II collagen (PI-ICP) and chondroitin sulfate epitopes of aggrecan (for example, 3B3). In addition to cartilage matrix markers, urinary glucosyl galactosyl pyridinoline (Glc-Gal-PYD) levels have been used to assess synovial degeneration, which is evident in OA.

In general, the cartilage biomarker studies show that the levels of individual markers do not predict OA consistently, perhaps due in part to the influence of factors including age, sex, and body mass index. However, combinations of markers appear to give better results. One study found that levels of CTX-II in urine correlated with multiple indices of joint degeneration in patients with hip or knee OA. High CTX-II levels and low collagen propeptide levels (PIINP) were found to be related to the rate of progression of knee OA. However, the ratio between CTX and PIINP was more strongly predictive of arthritis breakdown than either marker alone. Based on these findings, it is suggested that the calculated ratio represents disturbances in the equilibrium between collagen degradation and synthesis in osteoarthritic cartilage. The ratio of COL2-3/4 short to COL2-3/4 long was also shown to be more predictive of OA progression than the individual markers. Urinary levels of the synovium-specific carbohydrate marker Glc-Gal-PYD also effectively predicted OA progression and correlated with pain and other symptoms better than cartilage matrix markers.

### Section 1: Principles of Orthopaedics

#### Intervertebral Disk

**Structure and Function**

The intervertebral disk is a fibrocartilaginous structure that resides between adjacent vertebral bodies of the spine collectively called a motion segment (Figure 2). The three principal regions of the intervertebral disk, the nucleus pulposus, anulus fibrosus, and the end plates, form this specialized structure that maintains an optimal biomechanical environment in the spine. The nucleus pulposus, the central element of the intervertebral disk, has a fluidic matrix primarily composed of aggrecan and type II collagen. The cells that reside in the nucleus pulposus are originally derived from the notochord and may contain large vacuoles and prominent cytoskeletal elements in situ. Based on their biosynthetic profile and response to mechanical stimuli, nucleus pulposus cells are distinct from other cell populations in the intervertebral disk. The anulus fibrosus is composed of concentric lamellae of collagen type I fibers that circumferentially confine the fluidic nucleus pulposus. Cells of the anulus fibrosus have an ellipsoidal morphology, reside within lamellae of the anulus fibrosus, and produce both type I and type II collagen. Cells within the innermost annular regions are more rounded and sparsely distributed. By early adulthood in the human, however, the nucleus pulposus becomes populated by chondrocyte-like cells that may migrate from the adjacent end plate or inner regions of the anulus fibrosus. The vertebral bodies are separated from

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the nucleus pulposus superiorly and inferiorly by cartilaginous end plates.

A normal adult intervertebral disk consists of a large amount of ECM and very few viable cells (approximately 1% of total disk volume). Despite very low numbers, the resident cells are necessary for maintaining disk health, producing matrix components, and controlling matrix turnover by regulating the activation and production of extracellular and intracellular proteases. Inactive forms of growth factors such as basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-β), and insulin-like growth factor (IGF) are normally bound by cartilage intermediate layer protein to the ECM. When chondrocytes secrete MMPs, matrix is degraded to make room for newly synthesized matrix products. Matrix-bound growth factors are released during this event that in turn stimulate the resident cells to produce more matrix, and inhibit the production of MMPs. The other factors that play important roles in maintaining tissue turnover are tissue inhibitors of metalloproteinases (TIMPs), interleukin-1 (IL-1), interferon (IFN), and tumor necrosis factor-α (TNF-α).

Due to its lack of vascularity, the intervertebral disk is deficient in nutrient supply and exchange of metabolic waste products. This deficit in solute transporte manifests itself in the form of steep gradients in oxygen tension and glucose and lactic acid concentrations, which play roles in maintaining the phenotype of disk cells.

Development and Maturation

The development of the spinal column begins at the embryonic stage with the nucleus pulposus derived from the central notochord (endoderm) with the rest of the structure (vertebral bodies, cartilage, and anulus fibrosus) from the surrounding mesenchyme (mesoderm). In the embryonic disk, there is a distinct structural and compositional demarcation between the fluid-like nucleus pulposus (rich in notochordal cells and PG) and the fibrous anulus fibrosus (fibroblast-like cells and collagen). Above and below the newly forming embryonic disks, the notochord disappears and is replaced by mesenchymal cells, giving rise to the bone and cartilaginous end plates of the vertebrae. Changes in the composition of the embryonic disk begin right after birth. In the nucleus pulposus, notochordal cells are slowly replaced by chondrocyte-like cells. Complete replacement of notochordal cells occurs by 10 years after birth, leading to compositional changes and making the nucleus pulposus resemble the inner anulus fibrosus. Concurrently, the vertebral end plates decrease in thickness and diameter due to endochondral ossification. In a mature intervertebral disk, cell density is significantly low compared to its earlier stages of development, providing the rationale of decreased repair capability of a mature disk. Lack of vascularization and immune compromise limits removal of cell remnants and cellular organelles. A recent study showed that nucleus pulposus cells are capable of phagocytosis and this event may be important in maintaining tissue structure and function during major cell loss. Although a mature disk is inhabited by cells of similar origin (mesenchymal), they express very distinct phenotypes depending on their location and matrix composition.

Normal Aging Compared With Degeneration

Aging causes progressive changes in disk matrix composition that resemble those of other aging collagenous tissues such as the articular cartilage. One of the earliest age-related phenomena is the fragmentation of the PGs in the nucleus. There is also a concurrent increase in collagen content (especially type I) rendering the nucleus pulposus more fibrous. Fragmented PGs degrade further and leach out of the nucleus pulposus, decreasing its capacity to imbibe water. The decrease in fluid retention results in inadequate hydrostatic pressure, a major biomechanical deficit. Because of limited repair capability, low cell density, and decreased matrix turnover, the intervertebral disk fails to recover, leading to further biologic and structural deterioration. In addition, increased crosslinking among collagen fibers and nonenzymatic glycation further inhibits matrix turnover. With exception to localized proliferation after injury, cell density and cellular function decrease with age, resulting in reduced matrix turnover. Phenotypic changes in cell populations are observed with changes in matrix composition and local stress distribution. The loss of hydrostatic pressure in the nucleus pulposus results in the anulus fibrosus sharing most of the compressive loads. These changes transform the intervertebral disk from a structure that is strong, hydrated, and flexible to one that is very stiff, desiccated, and weak. At this juncture, “normal” biomechanical forces become excessive, and lead to structural damage such as delamination and tears of the anulus fibrosus, disk prolapse, herniation, and end plate fractures. Narrowing of the disk space and radial bulging also occur because of loss of fluid pressure and end plate fractures. Age-related changes peak and signs of discogenic pain are observed as early as the third decade of life.

Degeneration and aging have similar biochemical and structural changes. However, the distinction can be made by the magnitude and mechanisms that lead to the changes in the intervertebral disk. Age-related changes that involve structural disruptions are fewer and smaller, whereas degenerative changes exhibit major structural disruptions. Aging is an inevitable process that starts soon after birth and changes are unrelated to pain in the disk, whereas degeneration is correlated to discogenic pain. Age-related changes also are common to all disks of the spine, whereas macroscopic degenerative changes occur only at levels L4-S1. Although age-related changes render the disk susceptible to further degenerative changes, intervertebral disk degeneration can be defined as a condition of structural failure and irreversible loss of biomechanical function through physical and biologic mechanisms. A degenerated disk can have accelerated and advanced signs of aging along with a possibility of pain generation. Hence, multiple factors may, in combination, incrementally predispose the intervertebral disk to degenerative disk disease.
Nutritional Deficiency
As mentioned previously, the intervertebral disk is avascular with blood vessels restricted to the outer anulus fibrosus. Most metabolite transport occurs through diffusion across end plates. Aging causes decreased metabolite transport, whereas degenerative changes and end plate disruption increase solute transport affecting intervertebral disk homeostasis. The porosity of the end plate is significantly reduced due to calcification. Periannular solute transport is minimal and occurs through microtubes, with diffusivity decreasing from the inner anulus fibrosus to its outer rings. Low oxygen tension in the center of a disk leads to anaerobic metabolism, resulting in a high concentration of lactic acid and low pH. In vitro experiments show that a chronic lack of oxygen causes nucleus pulposus cells to become quiescent, whereas a chronic lack of glucose can cause cell death. Interestingly, mature nucleus pulposus cells are more tolerant to hypoxia when compared to notochordal cells, indicating that end plate porosity plays a role in regulating the phenotype of nucleus pulposus cells. Deficiencies in metabolite transport appear to limit both the density and metabolic activity of disk cells. As a result, disks have only a limited ability to recover from any mechanical or chemical injury. Computational models developed to study solute transport in normal and degenerated disks suggest that aging, end plate calcification/disruption, and mechanical loads influence solute concentrations, affecting cell viability and activity.

Nutritional deficiencies are a by-product of aging and it is unclear if improving metabolite transport would save the intervertebral disk from degenerative changes. However, there is evidence to suggest that accelerated degenerative signs may occur due to pathologic and/or environmental factors (for example, diabetes and smoking, respectively) that can affect vascular health and in turn render the metabolic status out of balance before natural aging could take its course. Tools for early detection and intervention may be beneficial to slow the process of degeneration.

Soluble Factors
The process of degeneration is manifested by a chronic imbalance in matrix turnover, with increased expression of catabolic cytokines and decreased anabolic activity. The stromelysin family of enzymes (MMPs) and ADAMTS collection are involved in matrix catabolism during intervertebral disk degeneration. MMP-1,-3, -7, -9, -10, and -13 have been shown to be involved in degenerative activities in various studies. The ADAMTS family is composed of aggrecans that have been shown to be highly active in degenerated disks. In particular, ADAMTS-1,-4,-5,-15 are upregulated in degenerated intervertebral disks whereas endogenous TIMP-3 expression is low, affecting matrix homeostasis. TNF-α and IL-1α and β are proinflammatory cytokines that have been studied extensively in the context of their regulation of MMPs. TNF-α has also been shown to induce sensory nerve in growth in the intervertebral disk, indicating their possible role in pain induction in degenerative disks. Upregulation of the IL-1 system is shown to induce MMPs, ADAMTS, and proteinase-activated receptor-2 (PAR-2). Cytokines also suppress synthesis of matrix components such as collagen type II, which is largely replaced with collagen type I in the nucleus pulposus. Cytokines mediate catabolic responses to advanced glycation end products via the advanced glycation and end products receptor (RAGE) complex. Furthermore, angiogenesis, neurogenesis and apoptosis of intervertebral disk cells depend to some extent on cytokines. The receptor antagonist of IL-1 system (IL-1Ra), which inhibits IL-1 signaling, is not upregulated in degenerated disks. Gene expression profiling of degenerated human disks suggests that TNF-α may be an early response mediator of degeneration, whereas IL-1β may be the key mediator that sustains the upregulation of matrix-degrading molecules.

Recently, the presence of nerve growth factor, brain-derived neurotrophic factor (and associated receptors) and the pain-associated neuropeptide substance P were identified in human nucleus pulposus tissue along with upregulation of IL-1β, suggesting that proinflammatory cytokines can stimulate nociception and initiate pain response via nerve ingrowth. Although implicated in regulating cell proliferation, apoptosis, and senescence, elevated expression of stress proteins such as Hsp-27 and Hsp-72 in degenerated disks suggests their possible role in the degenerative catabolic process. Local expression of Fas ligand (FasL) was found to be decreased in degenerated human nucleus pulposus, supporting the hypothesis that FasL may be involved in inhibiting pathologic neovascularization. Increased expression of connective tissue growth factor in degenerated disks is associated with angiogenesis in intervertebral disk degeneration. Angiogenesis may also be driven by overproduction of hypoxia inducible factor-1 α, which is coexpressed with VEGF in the nucleus pulposus. Caveolin-1 has been shown to be increased in the nucleus pulposus of degenerated disks but not in aged normal disks, indicating its role in degenerative rather than age-induced changes in the nucleus pulposus. In the same study, a positive correlation with the expression of cyclin-dependent kinase inhibitor p16INK4a shows that caveolin-1 may be linked to the senescent phenotype in the intervertebral disk caused by a phenomenon known as stress-induced premature senescence. These findings also support the senescence-related increased SA-βGal expression in degenerated disk. The pathogenic role of reactive oxygen species and reactive nitrogen species in OA suggests they may also play a role in intervertebral disk degeneration. The presence of nitrosylation products in the degenerated nucleus pulposus and stimulation of IL expression (-1β, -6, and -8) by peroxynitrite supports this hypothesis. Moreover, mechanically induced reactive oxygen species production is a phenomenon described in articular cartilage, and could also contribute to stress-induced premature senescence in cells of the intervertebral disk.
It is unclear what initiates the imbalance in cytokine profiles in intervertebral disk, but there is evidence to suggest the involvement of mechanical loading and genetic factors.

Genetic Influences
Heritable factors are linked to the risk for intervertebral disk degeneration. Based largely on studies of twins, the variance in genetic predisposition to disk degeneration has been estimated at 29% to 74%. These studies strongly implicate polymorphisms of vitamin D receptor and collagen IX to increased risk for degeneration. Other candidate degeneration-linked genes include collagen type I, IL-6, aggrecan, MMP-3, thrombospondin, TIMP-1 and cyclo-oxygenase (COX-2), cartilage intermediate layer protein, and IL-1 family members. In a recent study that involved 588 subjects, aggrecan, collagen types (COL-9A1, -9A2, -1A1, -3A1 and -11A1), and ILs (IL-1A,-18R1, and -18RAP) were found to be associated with cardinal signs of degeneration such as disk bulging and desiccation. Significant correlation between genetic influence and range of motion (in particular, flexion) was observed in patients with degeneration with an attributable variance of 64%. Asporin, also known as periodontal ligament-associated protein 1, is a member of the family of small leucine-rich PG family. It is identified as a susceptibility gene in OA and was also found to be locally expressed in the outer anulus of degenerated disks among Asian and caucasian subjects.

Although genetic factors associated with degeneration are significant, their mechanistic effect on the degenerative cascade in the intervertebral disk is still largely unknown. Functional analysis of genetic polymorphisms in the context of molecular pathology of intervertebral disk degeneration warrants investigation.

Mechanical Influences
Computational models and in vitro biomechanical studies have previously shown that the incidence of disk degeneration and discogenic pain may be directly related to increased mechanical demands of the lumbar spine. There is increasing evidence that mechanical loads regulate solute transport and there is a physiologic range of micromechanical stimuli that may promote maximum biosynthesis, maintain cellular phenotype and cell-mediated repair. Excessive spinal loading caused by environmental factors (such as heavy lifting and increased body weight), significant traumatic injury, annular injury, and scoliosis can lead to the development of the radiologic and biochemical features of degeneration. Once initiated, degeneration is expected to alter the local mechanical environment furthering degeneration, via further mechanical overload, structural damage, vascularization, and altered cell and matrix biology. Concerted efforts are under way to understand the role of mechanical stimuli on intervertebral disk biology at the cellular level. Recently, in vivo and in vitro studies have re-emphasized existing hypotheses that dynamic loading is more tissue-friendly than static loading. There is also current evidence that the effect of degradative enzymes can be inhibited by mechanical stimulation, providing new insights to the subject of forestalling degeneration. Disk cells are responsive to mechanical loads depending on the type, magnitude, duration, and also anatomic zone of origin.

Although cellular responses to mechanical stimuli are documented, little is known of the mechanisms that regulate these cellular changes, nor is much known regarding the precise mechanical stimuli experienced by cells during loading. Advances in the field of computational biomechanics and intervertebral disk biology may provide new insights into intervertebral disk mechanobiology. Guidelines for tissue engineering and regeneration, better management of low back health, and prevention of intervertebral disk degeneration are a few goals that are currently envisioned.

Summary
Several recent developments inspire renewed confidence that cartilage degeneration in OA may be subject to interventions that delay or even reverse its progression. This optimism is based on a more comprehensive understanding of the molecular and biomechanical mechanisms driving degeneration, which provide a wealth of potential targets for pharmacologic intervention. In that regard, BMP-7, Wnt pathway modulators, antioxidants, and caspase inhibitors all show considerable promise as disease modulators. Moreover, the further development of strategies such as joint distraction aimed at modifying mechanical conditions in vivo can only be enhanced by recent advances in understanding the mechanobiology of cartilage. The ability to quantify the effects of such treatments in vivo using MRI and molecular biomarkers provides an enormous opportunity to further accelerate progress in treatment development.

The intervertebral disk is a highly specialized tissue with a heterogeneous structure and composition. The cells residing inside the intervertebral disk are influenced by their microenvironments and exhibit unique phenotypes depending on their regional location. Based on studies to date, the cause of intervertebral disk degeneration is multifactorial. However, it is also evident that there may be a salient factor(s) that may outweigh the others during the initiation and progression of the disease. Genetic inheritance may increase predisposition to intervertebral disk degeneration. However, disk degeneration does not occur until the fourth decade of life and affects only the lower lumbar spine, indicating that environmental factors may play a greater role and genetic predisposition may only be an additive risk factor. Nutritional deficit is one of earliest changes that occurs in the intervertebral disk during maturation, with the nucleus pulposus being the most affected. However, aging changes may be the primary cause of nutritional changes and the cells seem to adapt to the environments accordingly by altering their phenotype. Numerous molecular factors have been shown to be al-
tered in degeneration. Although of potential therapeutic value, all soluble factors identified to date are also involved in adaptive remodeling and growth. Also, cytokines and growth factor imbalance are only effects of a “cause” and not necessarily the underlying factor of degeneration. Current understanding suggests that the mechanical influence on intervertebral disk degeneration may have a greater bearing on initiation and progress of disk degeneration. Animal studies have shown that cell-mediated changes always occur following structural failure due to mechanical trauma. Hence, mechanically induced structural damage may outweigh all other factors in initiating an irreversible cell-mediated cascade leading to further degradation. Aging, genetic inheritance, nutritional deficit, and soluble factors may only predispose the disk to degeneration by weakening the structure. The role of reactive oxygen species in intervertebral disk degeneration has not received much attention in intervertebral disk biology. As in the articular cartilage, intervertebral disk may undergo similar age- and trauma-related increases in oxidative stress, weakening the tissue’s metabolic system and inducing premature senescence and even cell death. There is immense therapeutic value in understanding the role of pro-oxidants in intervertebral disk degeneration and further studies are warranted. Advances in the field of intervertebral disk mechanobiology may also provide new insights in to disk pathology, facilitating development of novel interventions to prevent the initiation or forestall the progression of this debilitating disease.

Annotated References


A recombinant form of lubricin (LUB1) was delivered intra-articularly one to three times per week for 4 weeks after induction of OA in a rat meniscal tear model. Compared to saline controls LUB1 treatment significantly reduced cartilage degeneration and structural damage.


Hypoxia inducible factor-1α expression induced by hypoxia in inflamed arthritic joints activates VEGF expression by chondrocytes, leading to neovascularization of cartilage. VEGF is also thought to promote the expression of catabolic factors that contribute to cartilage degeneration. This suggests that hypoxia and VEGF contribute significantly to the pathogenesis of OA.


Articular chondrocytes sense and respond to the strains imposed on cartilage via nonmotile single cilia protruding into the pericellular matrix, which act as switches that trigger calcium release upon cartilage compression. Calcium release in turn activates intracellular signaling that results in altered gene expression, which helps cartilage to adapt to changing mechanical conditions. Moreover, the chondrocyte cilium with its Indian hedgehog-activated Smo receptor is a key player along with PTHrP in endochondral bone formation.


Wild-type mice and mice bearing mutations in the ciliary proteins Bbs1, Bbs2, and Bbs6 were evaluated with respect to histologic and biochemical differences in chondrocytes from articular cartilage and xiphoid processes. The fraction of ciliated chondrocytes in cultures from mutant mice was significantly lower than in the wild-type cultures (P < 0.05). Bbs mutant mice showed significantly thinner articular cartilage (P < 0.05) and lower PG content (P < 0.05) than wild-type mice.


Cartilage measurements at 1.5 or 3 Tesla are technically accurate, reproducible, and sensitive to change. The authors suggest that MRI of articular tissues represents a potent tool in experimental, epidemiologic, and pharmacologic intervention studies.


Fourteen professional athletes (seven weight lifters and seven bobsled sprinters) were examined and compared with 14 nonathletic volunteers who had never performed strength training. Cartilage morphology was assessed with MRI. Patellar cartilage was 14% thicker in athletes than in nonathletes, but there were no significant differences in thickness in other areas of the knee.

10. Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF: Long distance running and knee osteoarthritis:

The knees of 45 long-distance runners and 53 control subjects with a mean age of 58 years in 1984 were imaged by serial radiography through 2002. Radiographic scores showed little initial OA (6.7% of runners and 0 control subjects) and by the end of the study runners did not have more prevalent OA than did control subjects (*P* = 0.25). In contrast, higher initial body mass index and initial radiographic damage were associated with worse radiographic OA at the final assessment.


Immobilization effects on cartilage morphology and on the expression of hypoxia inducible factor-1α, VEGF, and the antiangiogenic factor, chondromodulin-I (ChM-1), were studied in ankle joints of 12-week-old rats. Significant thinning of the articular cartilage was noted in immobilized joints and vascular channels were found between calcified cartilage and subchondral bone. Hypoxia inducible factor-1α and VEGF expression increased and ChM-1 expression declined with immobilization.


3T MRI was used to study articular cartilage thinning over 1 year in 79 women and 77 men (mean age 60.9 years) with symptomatic and radiographic knee OA. The greatest rate of cartilage loss (1.9% per year) was observed in the weight-bearing medial femoral condyle. There was a trend toward higher thinning rates in obese participants, but this was not statistically significant.


Preliminary studies suggest that caspase inhibition, which prevents chondrocyte apoptosis, might slow OA progression. Because of the potential for unwanted systemic side effects from such agents, caspase treatments will likely need to be delivered intra-articularly. Additional interventions will be needed to reverse catabolic-anabolic imbalance in surviving cells.


Aging is the foremost risk factor for OA. This might be attributed to mechanical wear and tear, or the accumulation of time-related modifications of the matrix, or the loss of viable cells over time. However, recent findings support the hypothesis that stressful conditions might promote chondrocyte senescence, which might be of particular importance for the progression of OA. Senescence might someday be targeted for therapeutic intervention.


Wnt-induced signaling protein 1 (WISP-1) expression was strongly increased in the synovium and cartilage of mice with experimental OA. Wnt-16 and Wnt-2B were also markedly upregulated during the course of disease. Interestingly, increased WISP-1 expression was also found in human OA cartilage and synovium. Stimulation of macrophages and chondrocytes with recombinant WISP-1 resulted in IL-1-independent induction of several MMPs and aggrecanase and overexpression of WISP-1 in murine knee joints induced cartilage damage.


Epigenetic features were characterized in hip articular cartilage from patients with primary age-related OA and from a 23-year-old patient with secondary OA due to developmental hip dysplasia. MMP-3, MMP-9, MMP-13, and ADAMTS-4 were immuno-localized and the methylation status of specific promoter CpG sites was determined. Both primary and secondary OA were characterized by loss of aggrecan, formation of clones, and abnormal expression of the proteases that correlated with epigenetic DNA demethylation.


ADAMTS-4, one of the major aggrecanases involved in OA, was nearly absent in control cartilage, but was expressed by numerous chondrocytes in OA cartilage and increased with disease severity. DNA methylation was lost at specific CpG sites in the ADAMTS-4 promoter in OA chondrocytes, suggesting that ADAMTS-4 is epigenetically regulated and plays a role in aggrecan degradation in human OA.


Articular chondrocytes exhibit an age-related decline in proliferative and synthetic capacity while maintaining the ability to produce proinflammatory mediators and matrix degrading enzymes. These findings are characteristic of the senescent secretory phenotype and are most likely a consequence of extrinsic stress-induced senescence driven by oxidative stress rather than intrinsic replicative senescence.

Bovine osteochondral explants subjected to a single impact load and treated thereafter with N-acetylcysteine, or a pan-caspase inhibitor, or P-188 surfactant. N-acetylcysteine doubled the number of viable chondrocytes assayed 48 hours after impact, and this effect was significantly greater than that caspase inhibitor or P-188. Moreover, N-acetylcysteine treatment significantly improved PG content at the impact sites at both 6 and 14 days after injury.


In this preview, the authors cite Moinge and colleagues (Koelling et al, 2009) who reported that migratory progenitor cells occupy degenerating OA tissue but that this population is not present in healthy cartilage. Better understanding of this system will enable the manipulation of chondrogenic progenitor cells to fully commit to the chondrogenic phenotype and drive the process of repair and regeneration.


The fascinating discovery of tissue-resident adult stem/progenitor cells in recent years led to an explosion of interest in the development of novel stem cell-based therapies for improving the regenerative capacity of these endogenous immature cells or transplanted cells for the repair of damaged and diseased tissues. This review discusses therapeutic strategies for treating premature aging and age-related disorders including hematopoietic and immune disorders, heart failure and cardiovascular diseases, neurodegenerative, muscular, and gastrointestinal diseases, atherosclerosis, and aggressive and lethal cancers.


A single high-energy impact blow to the medial femoral condyles of young rabbits resulted in histologic signs of articular cartilage degeneration (chondrocyte and PG depletion) at 3 and 6 months postinjury. In situ hybridization revealed that type II collagen and BMP-2 mRNA declined at injury sites at 3 months, suggesting impact-related impairment of anabolic activity.


Histologic analysis showed that a single impact delivered to human ankle cartilage resulted in chondrocyte death, cartilage degeneration, and spread of apoptosis to areas around the impact site. Inhibitors of caspase-3 and -9 reduced death in the impact site only at early time points, but were ineffective in the area around the site, whereas P-188 prevented cell death in both the impact site and adjacent cartilage.


Impact injuries in sheep stifle joints were treated by two intra-articular injections of BMP-7 (OP-1) at varying times after injury and effects were evaluated after at least 97 days postinjury. Treatment within the first 21 days significantly reduced OA progression, but delaying treatment until 90 days was ineffective. Chondroprotective effects were thought to be due to enhanced chondrocyte survival.


Transient mitochondrial depolarization was observed in equine cartilage explants subjected to impact. This leads to activation of caspase-9 and apoptosis. Blocking intracellular calcium release from the endoplasmic reticulum, or blocking activation of calcium-dependent kinase or calcium-dependent proteases, inhibited both depolarization and apoptosis.


This is a retrospective review of 25 patients who underwent ankle distraction from 1999 to 2006. SF-36 scores showed modest improvement in all components. Only two of the patients in the study underwent fusion after ankle distraction. Total ankle motion was maintained in all patients, with improvement in the functional arc of motion in five patients who started with mild equinus contractures.


MRI parameters, T2-weighted, T1rho-weighted, and dGEMRIC, enable clinicians to see OA as a regional and responsive (reversible) disease and may lead to new paradigms for developing and applying lifestyle, medical, and surgical therapeutic interventions.


This study (n = 2,483 patients) showed that urinary levels of CTX-II decreased with risedronate in patients with knee OA and levels reached after 6 months were associated with radiologic progression at 24 months.


Bovine intervertebral disc cells were competent phagocytes and worked as efficiently as dedicated phagocytes such as monocytes and macrophages in an in vitro model.


Glucose availability has implications to intervertebral tissue recovery state for loaded disks to catch up with diffusion in unloaded disks.


Effects of sustained mechanical loading on transport of small solutes was investigated in vivo on normal human lumbar intervertebral disks using serial postcontrast MRI. The results suggested that supine creep loading (50% body weight) for 4.5 hours retards transport of small solutes into the center of human intervertebral disk, and it required 3 hours of accelerated diffusion to reestablish matrix production within the time frame studied.


In vitro analysis of cells isolated from human IVDs indicated that TNF-α may be an important initiating factor in matrix degeneration, IL-1β plays a greater role in established pathologic degradation.


Proteinase-activated receptor-2 (PAR-2) is a G protein-coupled receptor identified in human intervertebral disk tissues. The expression of PAR-2 is regulated by IL-1β stimulation. PAR-2 activation accelerates the expression of matrix-degrading enzymes. PAR-2 may play an important role in the cytokine-mediated catabolic cascade and consequently may be involved in intervertebral disk degeneration.


Employing a bovine coccygeal intervertebral disc model, the authors demonstrate that advanced glycation end products (AGEs) and receptors of AGE were localized within the bovine intervertebral disks. AGEs significantly decreased the aggrecan expression in bovine intervertebral disk as in human intervertebral disk, and the effect was enhanced further with the presence of IL-1β.


Based on increased expression of heat shock proteins hsp-27 and -72 in clustered cells of herniated disks, the authors suppose that clustered cells may be mounting a protective response to abnormal environmental factors associated with disk degeneration.


Human nucleus pulposus cells showed strong positive staining for FasL with a significant decrease in FasL expression in the degenerated group compared with the nondegenerated group indicating a potential mechanism of protection of the intervertebral disk against degeneration.


Connective tissue growth factor plays a pivotal role in angiogenesis. Increased expression of connective tissue growth factor–degenerated disks within areas of neovascularization may suggest their role in angiogenesis in the human degenerated intervertebral disk.

Immunohistochemistry showed that human intervertebral disk cells express glucose transporters GLUT-1, -3 and -9 in both the nucleus pulposus and anulus fibrosus with hypoxia inducible factor-1α co-expression only in the nucleus pulposus. GLUT expression also changed as degeneration progressed, suggesting metabolic changes with disease pathology.


45. Gruber HE, Ingram JA, Davis DE, Hanley EN Jr: Increased cell senescence is associated with decreased cell proliferation in vivo in the degenerating human anulus. *Spine* 2009;34(11):1127-1133. Asporin, also known as periodontal ligament-associated protein 1 (PLAP1), reported to have a genetic association with OA. Its D14 allele has recently been found to be associated with lumbar disk degeneration in patients of Asian descent. Immunohistochemical localization of asporin in the disk of Caucasian subjects and the sand rat showed that asporin was present in the outer anulus fibrosus, but not in the nucleus pulposus. Increased expression was observed in degenerated disks when compared to normal disks.

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