OSTEOARTHRITIS

Joint Anatomy, Physiology, and Pathobiology

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Osteoarthritis is not a single disease but a syndrome characterized by pathologic change of the synovial or diarthrodial joint accompanied by clinical signs of pain and disability. The condition is confined to the joint, although disability associated with joint abnormality may have an impact on the patient as a whole. It is a complex condition with a multitude of interacting biochemical and biomechanical factors (Fig. 1). Despite the prevalence of the condition and the impressive body of literature addressing the topic, the specific etiopathogenesis of osteoarthritis remains unknown, and a curative treatment has not been identified. Osteoarthritis has been estimated to affect as much as 20% of the canine population over 1 year of age (Pfizer Animal Health proprietary market research; survey of 200 veterinarians, 1996).

Osteoarthritis can be defined as a disorder of movable joints characterized by deterioration of articular cartilage; osteophyte formation and bone remodeling; changes in periarticular tissues; and a low-grade, nonpurulent inflammation of variable degree. The presence or absence of inflammation has generated controversy regarding appropriate terminology. The terms degenerative joint disease and osteoarthrosis have also been used to describe this condition, usually by individuals wishing to place less of an emphasis on an inflammatory component of the condition. Although considerable debate can occur regarding the appropriate appellation, it is recognized that any of these terms allows communication of a clinical syndrome that is distinguished from inflammatory arthritis. Inflammatory arthritis is typically associated with an influx

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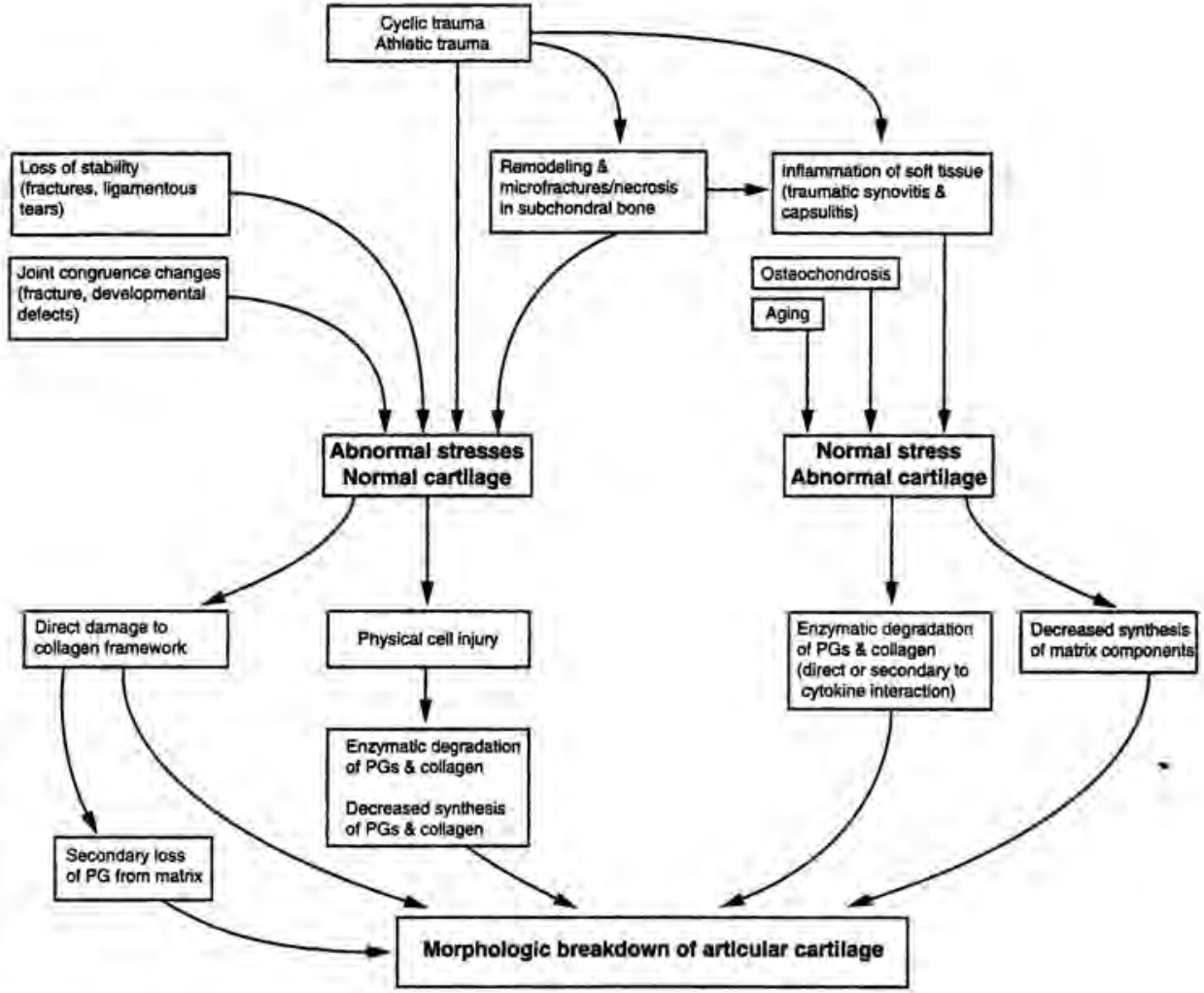

Figure 1. Factors involved in articular cartilage degradation in osteoarthritis. PG = proteoglycan. (*From* McIlwraith CW: General pathobiology of the joint and response to injury. *In* McIlwraith CW, Trotter GW (eds): Joint Disease in the Horse. Philadelphia, WB Saunders, 1996, p 42.)

of inflammatory cells and is most appropriately associated with conditions having immune-mediated or infectious etiologies. Rheumatoid arthritis is the classic example of a primary immune-mediated systemic condition that is associated with immune cell invasion of periarticular tissues, destruction of bone, and erosive change of articular cartilage. Although many of the same mediators, including the cytokines, prostaglandins, leukotrienes, degradative enzymes, and inflammatory cells, are common to both osteoarthritis and rheumatoid arthritis, they are considered to have a much greater role as primary etiologic agents in rheumatoid arthritis as compared with osteoarthritis. Despite the fact that some cases of canine elbow, hip, and stifle osteoarthritis can severely limit normal function and may even result in shortening of an animal's life span, rheumatoid arthritis is considered to be a much more severe, progressive, and debilitating condition than is osteoarthritis.

Osteoarthritis is typically a slowly progressive, degenerative condition that most frequently involves the highly movable, or diarthrodial, joints. Although the etiology of osteoarthritis can be difficult to determine, in animals, it is usually secondary to some type of trauma. This includes an abnormal force on a normal joint (exogenous trauma, typified by articular fracture or joint luxation) or a normal force on an abnormal joint (occurring secondarily to a developmental condition such as osteochondrosis or hip dysplasia) (see Fig. 1). Interestingly, there is little evidence that moderate or even prolonged and vigorous use of normal joints results in osteoarthritis, although similar use of an abnormal joint can hasten the development of osteoarthritis.[11,42] Other sources of osteoarthritis recognized in man but not commonly recognized in dogs and cats include metabolic, endocrine, and genetic disorders.[74] Despite the varying causes, there appears to be a final molecular and cellular common pathway leading to terminal disruption of articular cartilage, subchondral bone, synovium, and joint capsule.[28] Treatment of this condition requires an understanding of the anatomy, physiology, and pathology involved.

NORMAL CARTILAGE

Hyaline cartilage is an avascular, aneural, and alymphatic tissue found at the end of long bones. It is a smooth, resilient, and wear-resistant tissue that allows nearly frictionless motion and also provides a method by which compressive load and shearing force is transmitted to subchondral bone.[78]

Chondrocytes

Cartilage is composed of chondrocytes and extracellular matrix. Chondrocytes are relatively few in number, making up less than 5% of the tissue volume.[78] Chondrocytes are metabolically active cells and are

responsible for producing and maintaining the extracellular matrix and their immediate pericellular microenvironment. The chondrocyte is enclosed within a pericellular capsule, and the combination of chondrocyte, capsule, and pericellular matrix makes up a structural and functional entity called the "chondron."[79] The chondrocyte and its extracellular matrix may be a continuum because some molecules in the extracellular matrix may be bound to the plasmalemma.[3] The chondron is thought to be able to respond to changing properties of the surrounding matrix.[78]

Extracellular Matrix

The extracellular matrix is comprised primarily of collagen, proteoglycans, and water. The combination of collagen fibril orientation, proteoglycans, and water functions together to form a matrix that effectively distributes force over the underlying subchondral bone and provides a smooth, nearly frictionless surface that allows movement of the joint. When a disturbance occurs in the normal distribution of these components, the function of articular cartilage is altered, leading to the changes typically associated with osteoarthritis.

Collagen

Collagen fibrils provide a structural support for the cartilage matrix. There are 19 different types of collagen.[51] Collagen fibrils are made of monomers of the protein stacked in a quarter-stagger array.[99] Each monomer is composed of three polypeptide chains (each polypeptide chain is called an α chain) arranged in a triple helix. Differences between the many types of collagen are due to varying combinations and modifications of the different α chains within the triple helix. Associated with these differences, some collagens form fibrils (types I, II, III, V, XI), although others do not.[99] Despite considerable knowledge of the molecular structure of collagen, the relationship of this structure with how each type of collagen meets the physiologic demands placed upon it is largely unknown.

Collagen type II is the predominant form of collagen in articular cartilage. Small amounts of collagen types VI, IX, X, and V/XI are also found in normal cartilage. Type VI collagen is found in the pericellular region of the chondrocyte and is thought to help bind the cell surface to matrix collagen and proteoglycans.[80] Type IX collagen is thought to link collagen type II fibrils together and limit their separation by proteoglycan swelling, to limit fibril diameter, and also possibly to bind proteoglycan molecules to collagen type II.[21, 22, 49, 51] Mice deficient in type IX collagen develop articular cartilage change typical of osteoarthritis.[24] Type X collagen is found in hypertrophic cartilage during development and in the deep, calcified zone of adult articular cartilage.[51, 52] Its function is undetermined. Type V and XI collagens are no longer considered to be distinct types but instead a single type.[25, 51] The function of type V/

XI collagen is currently unknown, but type XI collagen is found at the core of the same collagen fibrils as type II collagen.[52]

Proteoglycans

Proteoglycans comprise most of the extracellular matrix that is not collagen and make up 22% to 38% of the dry weight of adult articular cartilage.[48] A proteoglycan monomer is made up of a core protein to which one or more types of glycosaminoglycan chains are attached (Fig. 2*C*). The common glycosaminoglycans of articular cartilage are chondroitin sulfate, keratan sulfate, and dermatan sulfate. The glycosaminoglycans are chains of variable length made up of repeating disaccharide subunits. Examples of the repeating disaccharide subunits are N-acetyl galactosamine and glucuronic acid for chondroitin sulfate (Fig. 2*D*) and N-acetyl glucosamine and galactose for keratan sulfate. Due to carboxyl and sulfate groups associated with the various subunits, the glycosaminoglycans are negatively charged. This negative charge causes the glycosaminoglycans to remain separated when attached to the core protein, resulting in the molecule occupying a large area. The combination of the polyanionic nature of the glycosaminoglycans and excess of molecules in cartilage matrix compared with external solution results in an osmotic gradient that contributes to the hydrophilic properties of proteoglycan.[94] Retention of water by proteoglycan within the extracellular matrix creates a swelling pressure and turgidity that is integral to normal articular cartilage function (Fig. 2*B*).

The nomenclature of proteoglycans can be confusing. Proteoglycans are grouped as aggregating or nonaggregating, determined by the proteoglycan monomer's ability to aggregate with hyaluronan. Hyaluronan is a glycosaminoglycan, although it is not sulfated and does not bind to a core protein like chondroitin and keratan sulfate. Hyaluronan is found in the extracellular matrix, where it forms a chain with which the proteoglycan monomers interact noncovalently (see Fig. 2*C*). The term aggrecan has been given to the proteoglycan monomer that aggregates with hyaluronan and is found in articular cartilage (Fig. 2). Aggrecan is the major proteoglycan (by mass) of articular cartilage. The core protein of aggregan has various domains (see Fig. 2*C*), including the hyaluronan binding region on the amino terminal end (also known as the G1 domain), a second (G2) domain that is followed by a glycosaminoglycan binding region, and a terminal (G3) domain on the carboxy-terminal end. The glycosaminoglycans making up this aggrecan monomer are chondroitin and keratan sulfate. Many aggrecan monomers attach to a hyaluronic acid chain to form an aggrecan aggregate (see Fig. 2*B*). This attachment occurs through the hyaluronan binding region (G1 domain) of the proteoglycan monomer and is stabilized by a link protein. An aggrecan aggregate from articular cartilage may contain over 100 aggrecan monomers.[87] Aggregan aggregates are of various lengths, depending on the condition and location of the cartilage. Other proteoglycan monomers do not aggregate. Examples include the small

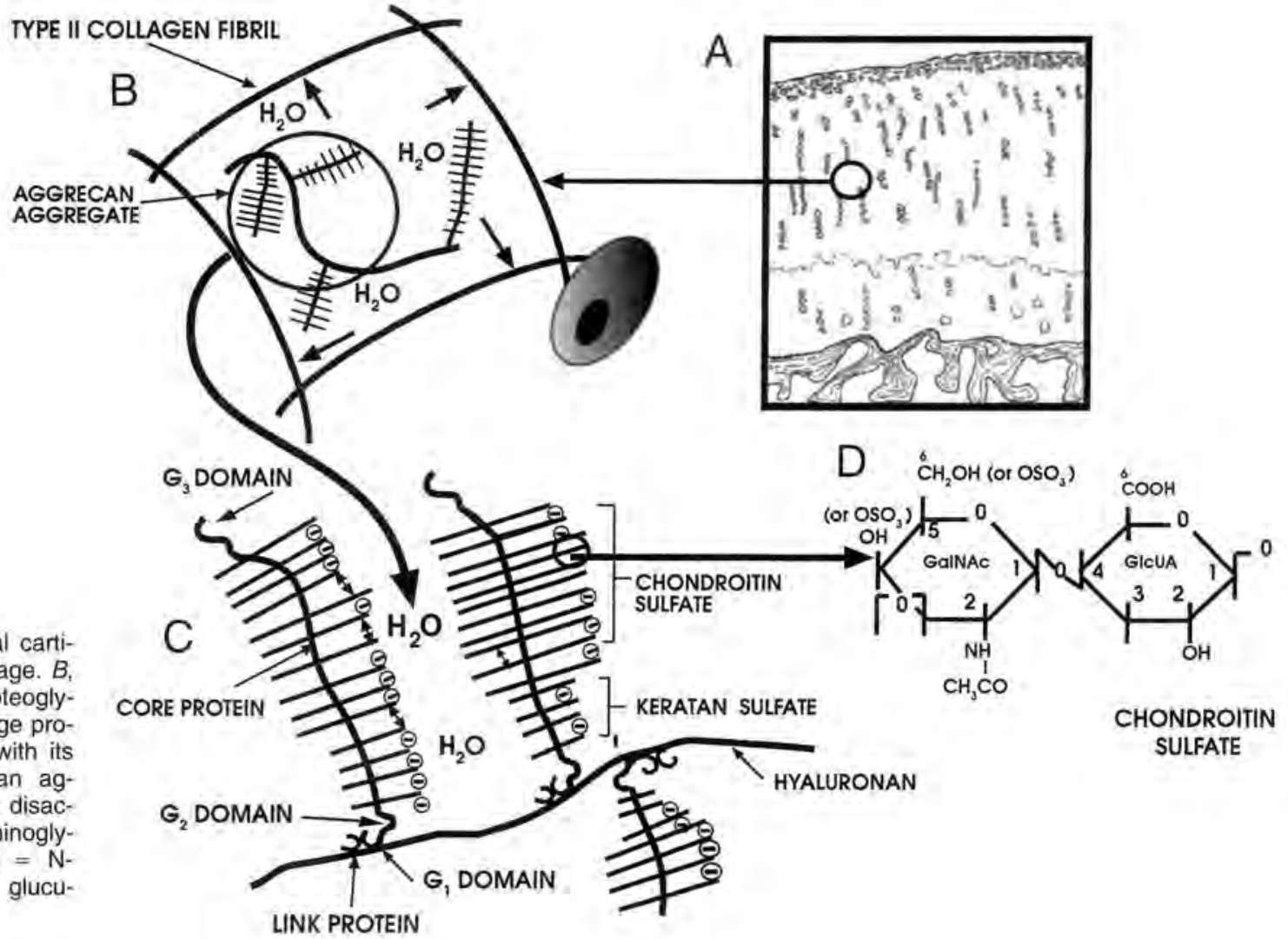

Figure 2. Components of normal cartilage. *A*, Diagram of normal cartilage. *B*, Interaction of collagen fibrils, proteoglycans, and water in normal cartilage provides normal articular cartilage with its resiliency. *C*, Components of an aggrecan aggregate. *D*, Repeating disaccharide subunit of the glycosaminoglycan chondroitin sulfate. GalNAc = N-acetyl galactosamine, GlcUA = glucuronic acid.

proteoglycans decorin and biglycan, which are proteoglycans made up of chondroitin sulfate and dermatan sulfate.[70] The functions of decorin and biglycan are not entirely known, although decorin is thought to be involved with collagen fibrillogenesis.[70]

Hyaluronan is an important component of both the articular cartilage matrix and synovial fluid. Hyaluronan found in the extracellular matrix is produced by chondrocytes, whereas hyaluronan found in synovial fluid is produced by type B synoviocytes.[61] Synovial fluid hyaluronan functions as a lubricant and a molecular barrier.[4] Hyaluronan functions as a barrier due to the steric configuration that the hydrated molecule forms. The configuration allows hyaluronan to act as a molecular sieve, and this allows hyaluronan to exclude macromolecules from the domain it occupies.[4, 29, 94] Hyaluronan penetrates only the surface layer of articular cartilage but is also found in the synovial lining layer and in intra-articular ligaments.[4, 95] Hyaluronan is a boundary lubricant for soft tissues but apparently has no role in cartilage-on-cartilage lubrication.[49, 94]

Articular Cartilage Morphology

Description of articular cartilage morphology has classically employed a zonal pattern to describe this tissue. The zonal pattern is based on chondrocyte organization, collagen fiber orientation, and proteoglycan distribution (Fig. 3*A*).[78] Zone 1 is the superficial layer and is characterized by sparse cellularity, little proteoglycan content, and collagen fibrils oriented tangentially to the articular surface. Zone 2 includes a major portion of the matrix volume, is more cellular, and has increased proteoglycan content as compared with zone 1. Collagen fibrils are obliquely oriented. Zone 3, along with zone 2, is a major portion of the cartilage matrix. Chondrocyte density and proteoglycan content increase further in this zone, and cells tend to be arranged in vertical columns. Collagen fibrils are radially aligned. Zone 4 is the calcified cartilage layer and is distinguished by the tidemark, which is its upper limit. This zone contains radially oriented collagen fibrils but little proteoglycan. The calcified cartilage layer is adjacent to and separated from the subchondral bone by a cement line at the osteochondral junction. This convoluted interface helps to maintain adhesion of the cartilage to the subchondral bone.[78]

Interaction of Collagen and Proteoglycan

The orientation of collagen fibrils in extracellular matrix is necessary so that cartilage may function well as a whole. The tangentially oriented collagen fibrils of the superficial zone, along with relatively low proteoglycan content, have the greatest ability to withstand high tensile stresses, thereby resisting deformation and distributing load more evenly

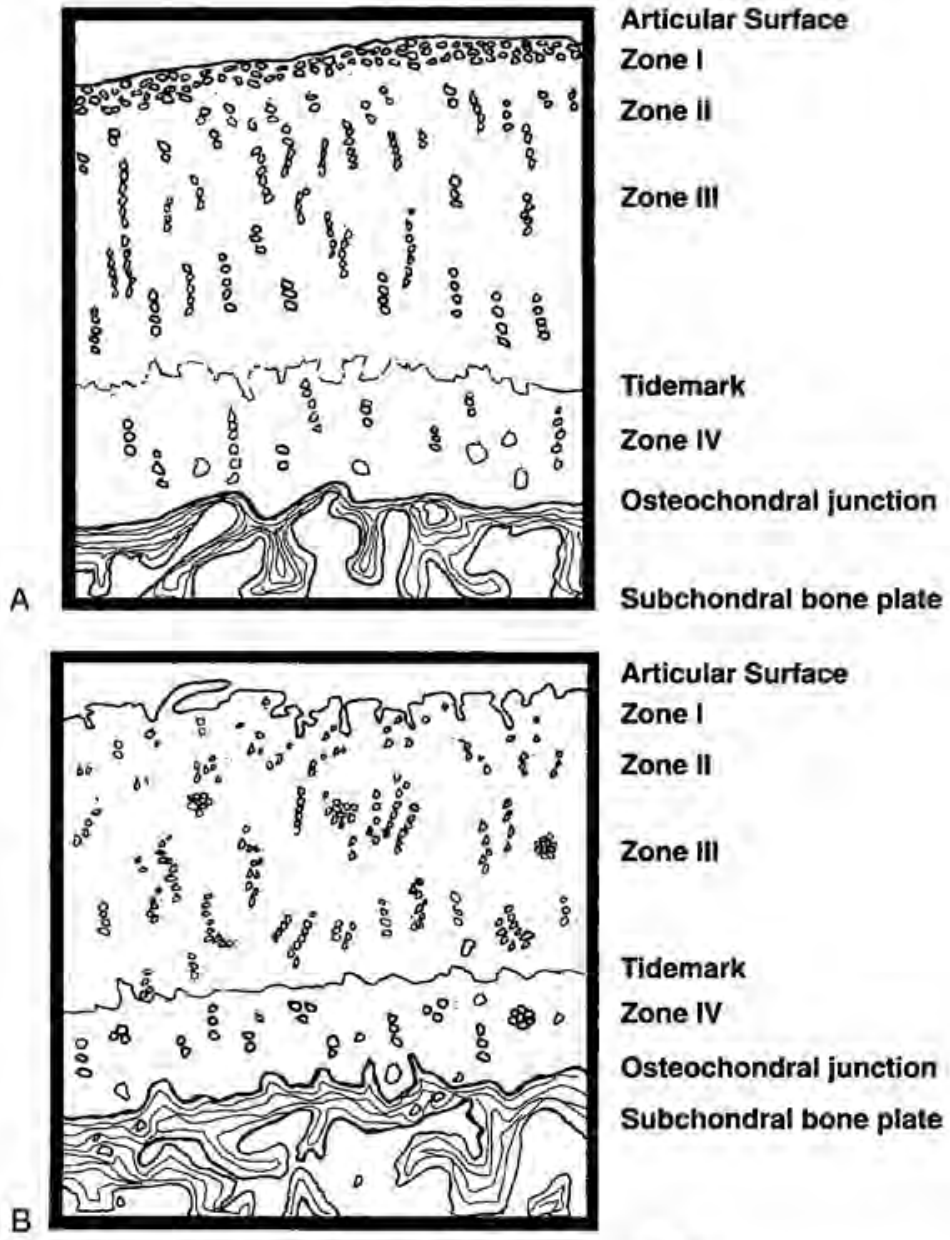

Figure 3. *See legend on opposite page*

over the surface of the joint.[3] They also allow this layer to act as a "skin" to resist the swelling pressure exerted by proteoglycans of the deeper zones.[3] Loss of this superficial layer, as occurs in the early stages of cartilage fibrillation (roughening of the articular surface) associated with osteoarthritis, alters the biomechanical properties of articular cartilage.[89] The high concentration of proteoglycan in zones II and III allows this tissue to better withstand compressive loads. The continuation of collagen fibrils from zone III through the tidemark provides a transition from the more compliant, nonmineralized cartilage to the stiffer, calcified

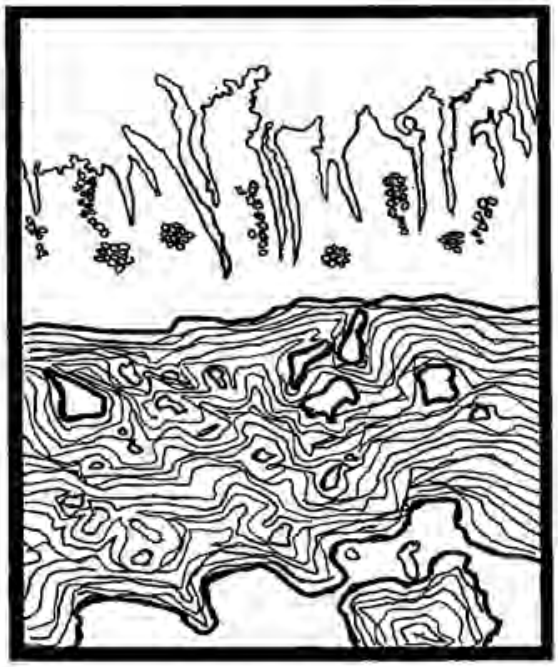

Figure 3. Cross section of normal articular cartilage and changes typical of osteoarthritis. *A*, Normal cartilage. See text for description. *B*, Mild osteoarthritis. Note fibrillation of articular surface, loss of superficial chondrocytes, and some clustering of other chondrocytes. *C*, Deep fissuring occurs in severe osteoarthritis, and there is loss of cartilage matrix. Chondrocytes are sparse and found in clusters. There is thickening of the subchondral bone.

cartilage.[3] Although collagen fibrils do not cross the cement line into the subchondral bone, the mineralized cartilage is held in place by the undulating, interdigitating contours found at this boundary.[82] The undulating nature of this junction allows shear stresses to be converted into potentially less damaging compressive forces on the subchondral bone.[82]

Proteoglycans have a great affinity for water and can occupy a volume up to 50 times their dry weight volume when hydrated.[41] Proteoglycans are normally contained within a meshwork formed by collagen fibrils (see Fig. 2*B*). The collagen framework limits the ability of the proteoglycans to expand and retains the individual proteoglycan to within 20% of its potential volume.[41] This swelling pressure keeps the cartilage turgid, helping to resist deformation when a compressive load is applied. Fluid can move within this meshwork, although movement is slow due to the density of the collagen fibrils and the steric configuration of the proteoglycans within the collagen meshwork. The unique ability of articular cartilage to resist compression is due to the spatial relationship between collagen and proteoglycan and to the hydrophilic nature of proteoglycan. When cartilage experiences a compressive load, water moves slowly within the cartilage matrix. Fluid flow through the extracellular matrix is dependent on the density of collagen meshwork and the pore size created by the proteoglycan molecules.[94] Some water

is forced out of the cartilage until an equilibrium is reached between the osmotic force generated by the proteoglycans and the compressive force applied. This movement of water results in weeping of fluid onto the articular surface, allowing lubrication (designated as weeping or hydrostatic lubrication) of the joint. When load is applied rapidly to the articular surface, cartilage acts as a stiff material, because water distributes slowly.[71] When load is applied slowly, articular cartilage acts as a more compliant material.[71]

The combination of collagen fibrils and proteoglycan forms a fiber-reinforced composite material which is necessary to allow articular cartilage to withstand the various forces it experiences (see Fig. 2*B*). Collagen fibrils alone cannot sustain compressive forces without collapse but tolerate tensile force well, and hydrated proteoglycan complexes are weak in shear but resist compressive force.[10] When integrated, however, the result is a dynamic tissue able to tolerate high compressive and shear loads without damage which allows transmission of these forces to underlying structures. The ability to tolerate these high loads is dependent on the interconnecting nature of the collagen fibrils.[10, 101] If these connections are broken, propagation of fissures in articular cartilage will occur, leading to the morphologic changes characteristic of arthritis (Fig. 3*B* and *C*).[81]

Articular cartilage seems to adapt to the predominant stress level it experiences.[96] In areas of high stress, cartilage is stiffer and has increased proteoglycan content; softer cartilage is found in areas of low stress.[37, 96] Excessive stress in areas of soft cartilage may result in matrix damage and subsequent osteoarthritis. Although mechanical stress can modulate the metabolic activity of chondrocytes, the specific mechanism of signal transduction is unknown. It has been speculated that cellular deformation occurs with mechanical stress and that this may be the source of signal transduction that leads to cartilage adaptation. Under normal loading conditions, alterations in chondrocyte height and volume have been found to range between 17% and 26%, depending on chondrocyte location within the matrix.[33]

Subchondral Bone

The subchondral region consists of a thin plate of bone that is in direct contact with the calcified layer of cartilage and the cancellous bone supporting this bony plate (see Fig. 3). The cancellous bone forms a lattice-like meshwork in the epiphyseal end of the bone. This region has been found to be approximately 10 times more deformable than cortical bone.[83] This deformability has an important role in force distribution. At rest, joints have slightly incongruent surfaces. When load is applied, there is compliance of the joint so that maximal contact occurs between the two articular surfaces. This large contact area allows load distribution, and compliance of subchondral bone helps to reduce peak load, thereby potentially decreasing cartilage damage.[81] In the example

of a ball-and-socket joint, it has been speculated that the convex surface is more compliant than the concave surface.[93] Study of the canine shoulder has demonstrated that the subchondral plate of the glenoid fossa is five to six times thicker than the humeral head and that the humerus is six times more compliant than the scapula.[93]

Stiffening of the subchondral bone is associated with the development of osteoarthritis. Unfortunately, the time course during which this occurs has not been defined. Intuitively, it has been speculated that degradation of cartilage matrix, as occurs in osteoarthritis, causes a loss of cushioning ability by the articular cartilage layer and thus exposure of subchondral bone to excessive force. This would lead to thickening of the subchondral layer and less deformability. Articular cartilage has been demonstrated to be an ineffective shock absorber but nevertheless is most important for transmitting and distributing load to the underlying subchondral bone.[81, 83] An alternative theory is that repetitive trauma causes microfracture and stiffening of the subchondral bone. Once subchondral bone density increases, the cartilage cannot deform normally, resulting in the chondrocytes and matrix being exposed to, and damaged by, applied forces and thereby initiating the pathologic cycle associated with osteoarthritis.[82] Therefore, the question is raised as to whether subchondral bone change is an initiating or subsequent event in the development of osteoarthritis.

A study of the association of subchondral bone changes and cartilage alterations in osteoarthritis resulting from canine hip dysplasia demonstrated a connection between these two processes but failed to define a causal relationship.[95] As anticipated, the most pronounced changes in both subchondral bone and cartilage were found in the major weight-bearing areas of the femoral head, suggesting that mechanical stress has an important role in the development of osteoarthritis. Study of changes associated with the development of osteoarthritis in the canine cranial cruciate ligament transection model of osteoarthritis also confirmed the development of subchondral bone changes.[19] Three months after ligament transection in this model, there was decreased subchondral plate thickness and decreased thickness of trabecular bone. Although stiffness was not measured directly, these changes should allow greater compliance of subchondral bone. Nevertheless, articular cartilage changes consistent with osteoarthritis were noted in this model as early as 3 months after ligament transection. Increased thickness of the subchondral plate, particularly of the medial aspect of the tibial plateau and of the medial femoral condyle, was noted at 54 months compared with 3 months.[8, 19] Because articular cartilage change was noted prior to subchondral bone thickening, it was concluded that increased subchondral bone stiffness is not necessary for the development of osteoarthritis.[6, 19]

Based on the available information, it is likely that changes in subchondral bone and articular cartilage matrix occur concurrently. The role of subchondral bone or cartilage matrix alteration as a primary initiating event is likely to be variable and dependent upon the nature

of the inciting cause in the individual joint. Although increased subchondral bone stiffness may not be necessary for the development of osteoarthritis, it may certainly have an important role in the progression of the disease.[6] If osteoarthritis is viewed as a syndrome instead of a disease, this explanation is consistent with the clinical course of the condition.

Osteophytes

Osteophytes are frequently associated with the development of osteoarthritis. They are composed of a central core of bone that blends in with the subchondral bone, are covered by hyaline and fibrocartilage, and are formed by a process similar to enchondral ossification.[54, 58] Osteophytes tend to occur at the joint periphery, most frequently at the junction of the synovium, perichondrium, and periosteum, although they may occur centrally in the joint.[17, 58] Osteophytes are distinguished from enthesophytes, which are bony proliferations found at the insertion of ligaments, tendons, and capsule to bone.[17, 55, 86]

The role of osteophytes in osteoarthritis is not clear. It has been speculated that they increase joint stability by increasing surface area. They may also cause pain by distending the periosteum and periarticular tissues or altering the normal motion between articular surfaces or between cartilage and the synovium.

The specific etiologic mechanism of osteophyte development is not known. Mechanical instability is widely believed to be a predisposing factor, although osteophytes have been recognized to develop in the presence of inflammation without instability, suggesting that synovial membrane inflammation may have a role.[18, 56] Altered vascularity due to invasion of blood vessels or venous congestion has been suggested as a possible etiology.[48]

Osteophytes can form quickly after the induction of injury. Although most frequently thought to form over a period of weeks to months,[54] various experimental models have demonstrated initial osteophyte formation as early as 3 days to 1 week after the creation of instability.[31, 58]

Joint Capsule and Synovium

The joint cavity is defined by a joint capsule that invests the entire joint. The joint capsule can be divided into three layers: the synovial lining layer (also called the synovial intima or synovial membrane), a subsynovial (subintimal) layer, and the fibrous joint capsule. Nomenclature varies for this region, and frequently, the term synovium is used to refer to the synovial lining and subsynovial layers and the term joint capsule refers to the fibrous joint capsule.[98] The innermost layer is the synovial lining layer. This layer is normally quite thin, often only one to two cell layers thick. Two types of synoviocytes are found in this layer.

Type A synoviocytes are macrophage-like cells that have a role in removing debris from joints and processing antigen.[62] Type B synoviocytes are fibroblast-like cells that are responsible for production of hyaluronan. Type B cells are also able to produce degradative enzymes.[62] Both types of synoviocytes produce cytokines and other mediators.[62] The function of the lining layer is the production of synovial fluid and providing a low-friction lining to the joint. The synovial lining does not extend onto the articular surface but instead extends from the margin of the articular surface and is then reflected at the insertion of the joint capsule.[49] The second layer of the joint capsule is the subsynovial layer. It is found between the synovial lining layer and the fibrous joint capsule. Fibroblasts are found within this layer, and the stroma may be organized into loose, areolar connective tissue or a more fibrous tissue, depending on location. The subsynovial layer is vascular, contains free nerve endings, and serves to allow motion between the synovial membrane and fibrous joint capsule.[49] The third layer of the joint capsule is the tough fibrous layer that contributes to the physical stability of the joint. During normal range of motion of the feline carpus, the fibrous joint capsule contributes approximately 47% to total elastic stiffness.[35] This layer attaches to the bone close to the articulating surface by a fibrocartilagenous insertion.[85] Ligaments are frequently incorporated in or attached to the fibrous capsule and help to decrease the load the capsule actually experiences. The fibrous layer is vascular and well innervated.

Menisci are considered to be extensions of the joint capsule that have undergone modification to form fibrocartilage.[85] Menisci are not covered by the synovial lining layer. They are stabilized by attachment to the joint capsule or ligaments, as occurs in the canine stifle joint. The function of the meniscus, when present, is to aid in stabilizing the joint.

Synovium Function

Under normal conditions, the synovium selectively prevents large molecules like proteins from entering the joint cavity. Synovial fluid contains electrolytes and small molecules (such as glucose, lactate, oxygen) in similar proportions as in plasma; therefore, synovial fluid is frequently referred to as a dialysate of plasma. There is a normal ingress and egress of fluid across the synovial lining layer, thereby allowing the replenishing of small molecules within the synovial fluid pool. The interstitial space between synovial lining cells has an important role in controlling transsynovial exchange of small molecules.[91] Release of inflammatory mediators such as prostaglandins and cytokines, as occurs with injury to synovium or chondrocytes, results in increased permeability of the synovial vasculature. This results in an increase in the protein content of the synovial fluid, disturbing the normal oncotic balance that helps to control synovial fluid volume.

Increased production of synovial fluid frequently occurs in response to injury or inflammation. When intrasynovial volume increases, the

exchange of small molecules across the synovial membrane increases. This is speculated to occur due to the combination of thinning of the synovial membrane that occurs as the joint cavity is distended and the increased synovial blood flow that occurs with synovitis.[91] Protein, however, is cleared by lymphatic drainage from the joint.[92] Protein clearance from the stifle of dogs with surgically transected cranial cruciate ligaments increased approximately three times over that of the contralateral normal limb.[64] This finding has implications when measurement of plasma or synovial fluid levels of cartilage breakdown products such as glycosaminoglycan or collagen fragments is considered to be a marker of joint disease. The increased rate of removal of these molecules, along with variable rates of release from cartilage, results in the inability to use these markers as indicators of disease severity.[1, 7, 43, 65]

Joint Capsule Change in Osteoarthritis

During the course of osteoarthritis, the joint capsule becomes thickened and vascularity increases. Synoviocytes are an important source of cytokines and leukotrienes, which contribute further to change by attracting inflammatory cells and the release of prostaglandins and other inflammatory mediators. Study of the joint capsule obtained at the time of cruciate ligament surgery in dogs with naturally occurring disease shows that some dogs have distinct lymphocytic/plasmacytic nodules, although others have a diffuse infiltration of mononuclear cells.[27] All populations have hypertrophy of the villous synovium and an increase in the mature and immature collagen in the subsynovial tissues.[27] Fibrosis of the synovium may be influenced by cytokine stimulation of fibroblasts, leading to increased collagen production.[40, 74] Joint capsule fibrosis and thickening result in a decreased range of motion and pain; they also contribute to the stiffness typically associated with clinical signs in the osteoarthritic patient.

Progressive alteration of the synovium has been demonstrated in naturally occurring canine hip dysplasia.[47] Initial changes include thickening of the synovial intima from one to two cell layers thick to three to four cell layers thick, the development of synovial villi that eventually involve 100% of the intima surface, and increased vascularity and infiltration of the subsynovial stroma by lymphocytes. In the most severely affected specimens, the subsynovial stroma and fibrous joint capsule demonstrated fibroplasia. It was concluded that changes in the synovium preceded changes in the articular cartilage.[47] Changes in the synovial lining layer, subsynovial tissue, and fibrous joint capsule have also been studied in the canine cranial cruciate ligament transection model. Initial changes, noted as early as 1 week following ligament transection, include increased cellularity of the synovial lining layer and infiltration of the subsynovial layer by mononuclear cells.[44, 54] Increased vascularity of the subsynovial layer and fibrous joint capsule is noted at that time as well as the development of synovial villi. Fibrosis of the joint capsule,

most pronounced on the medial aspect of the joint, is noted at 3 to 4 weeks following ligament transection.

The changes in the synovium are believed to result from phagocytosis of proteoglycan and collagen fragments in synovial fluid by synovial lining macrophages.[74] This, in turn, may stimulate synoviocytes to produce cytokines and metalloproteinase, which cause further degeneration of cartilage and perpetuation of this cycle.[75] Synovial tissue has also been demonstrated to be a rich source of proinflammatory mediators such as prostaglandin E_2, leukotriene B_4, and leukotriene C_4.[100] The question of whether synovitis occurs first and contributes to cartilage degeneration or in response to phagocytosis of cartilage degradation products has not been completely resolved.[13] Studies by Walker et al[97] suggest that synovial inflammation is not a primary event for osteoarthritis but contributes to the progression of the disease when associated with mechanical damage to the cartilage matrix. In severe, "end-stage" osteoarthritis, shards of articular cartilage from the fibrillated articular surface are frequently found in the synovium, but these shards are not found during early stages of osteoarthritis.[66]

Joint Lubrication

Joint lubrication has long been one of the great marvels of nature. The coefficient of friction that exists between two cartilage surfaces in the normal articulating joint is extremely low. Although the study of joint lubrication is extremely complex and over 30 theories on joint lubrication have been proposed,[26] the clinician can consider lubrication in two forms. These are known as hydrostatic (or weeping) lubrication and boundary lubrication.

Hydrostatic lubrication occurs under relatively high loads. When cartilage is compressed, as occurs during loading, water is squeezed from the viscoelastic gel in the cartilage matrix. This fluid accumulates in the small depressions on the articular surface. As greater load is applied and the cartilage is compressed, more fluid is present between the two surfaces. Release of this fluid also allows a leading edge of fluid to provide lubrication for the advancing contact site of the two cartilage surfaces. When the compressive force is relieved, this fluid returns to the cartilage matrix. This type of lubrication is not dependent on hyaluronate concentration.

Weeping lubrication does not explain lubrication when a compressive force does not exist. A second type of lubrication is necessary to decrease friction between noncompressed (non-load-bearing motion) cartilaginous surfaces and between the synovial lining layer and cartilage. The glycoprotein lubricin is thought to adhere to each surface to act as a lubricant.[91] Recent work suggests that a surface-active phospholipid is the active agent in boundary lubrication, and it is speculated that lubricin is the carrier protein for this agent.[34] Hyaluronan may function as a boundary lubricant for the periarticular tissues but appar-

ently has little role in boundary lubrication for cartilage-on-cartilage contact.[49]

In arthritis, the elasticity and viscosity of synovial fluid may be decreased due to the presence of hyaluronan molecules of lower molecular weight and to a dilution effect caused by fluid exudation into the joint cavity.[4, 63, 73] This decreases the viscoelasticity and lubricating ability of hyaluronan. Because friction associated with movement between the synovial membrane and articular surface is much higher than cartilage-to-cartilage contact, the decreased quality of synovial fluid that occurs with release of degradative enzymes associated with osteoarthritis can lead to joint stiffness and pain.

NOCICEPTION

Pain is a dominant sign associated with osteoarthritis.[102] The normal joint is rich with neural receptors, including those that provide for the sensation of pain (nociceptors) and those that allow recognition of the position and load applied to the joint (mechanoreceptors). Nociceptors are associated with thinly myelinated Aδ or unmyelinated C fibers, and mechanoreceptors are associated with myelinated Aβ fibers. The fibrous joint capsule is the most richly innervated layer of the joint capsule and contains all types of receptors, although only C fibers are present in the synovial lining layer. C fibers are also associated with vasculature in the subsynovial layer.[98] Other tissues containing nociceptors include the tendons, ligaments, and subchondral bone.[20, 39]

The normal pathway for nociception occurs with stimulation of the local nociceptor. This can occur due to a chemical or mechanical stimulus. Stimulation of the nociceptor results in an impulse that travels to the dorsal spinal horn. The impulse then synapses on a second-order neuron and ascends the spinal cord to the brain, or a reflex arc occurs with an efferent impulse being transmitted via the dorsal root to the effector organs, typically the muscles surrounding the joint. This reflex activity can cause a state of muscle hypertonus or spasm, contributing greatly to the pain associated with osteoarthritis.[102]

Chemical mediators for nociception include prostaglandins, leukotrienes, substance P, bradykinin, and cytokines.[23] Prostaglandins are products of the cyclooxygenase pathway of arachidonic acid metabolism, and leukotrienes are products of the lipoxygenase pathway. Both are recognized as proinflammatory mediators and have been demonstrated to be increased in the synovial fluid of osteoarthritic joints.[100] Leukotrienes are potent chemotactic agents. Prostaglandins sensitize nociceptors to algesic (pain-producing) substances such as bradykinin and histamine as well as decrease the pain threshold to both chemical and mechanical stimulation. Lowering of the nociceptive threshold is a key component of pain associated with osteoarthritis as this results in a painful response to normally innocuous stimuli such as stretching, motion, or pressure.

Neuropeptides are neurosecretory products of afferent nerves that are released antidromally (in the opposite direction of nerve impulse transmission) in response to nociceptor stimulation. Many neuropeptides exist, but two, substance P and calcitonin gene-related peptide, have been most frequently associated with rheumatoid arthritis and osteoarthritis.[38, 39, 46, 98] Both neuropeptides are associated with vasodilation and inflammation, and substance P is associated with hyperalgesia. Substance P stimulates the release of prostaglandin E_2 and collagenase from fibroblasts and synoviocytes and the release of cytokines from monocytes.[39] The release of substance P into the joint has been associated with more severe osteoarthritis.[39, 102] Substance P has been found to be elevated in the synovial fluid of horses with degenerative joint disease.[16]

Ligaments are strong, relatively avascular structures that have a nerve supply.[20] Muscle weakness or abnormal joint function can cause excessive stress on ligaments, resulting in pain perception.[57] The loss of ligamentous support, as occurs with cruciate ligament rupture, can place stress on other ligaments as well as on the joint capsule. Stimulation of nociceptors located within these tissues results in pain perception.

Pain from subchondral bone is thought to be due to stimulation of the nociceptors in this region following damage to the articular cartilage. Increased intraosseous pressure, hypoxia, and increased lactate concentration have been reported in the femoral head of humans with hip osteoarthritis.[36] Increased intraosseous pressure is thought to be due to venous stasis secondary to soft tissue compression and to femoral head deformity associated with degenerative change.[36] Alleviating intraosseous pressure by drilling a hole in the bone has been reported to relieve pain.[2]

Pain and disability can be a vicious cycle in the arthritic patient. Joint pain results in decreased exercise, which leads to muscle atrophy. Diminished muscular support of the joint leads to increased stress on the joint capsule, ligaments, and articular cartilage. Damage to articular cartilage results in the release of inflammatory mediators, causing a decrease in the nociceptive threshold and hyperalgesia. Minimal stimuli of the periarticular tissues cause pain, resulting in decreased use of the painful joint, thereby further contributing to muscle weakness. Interrupting this cycle is integral to the treatment of osteoarthritis.

ETIOPATHOGENESIS OF OSTEOARTHRITIS

Changes associated with osteoarthritis typically involve all joint tissues, including the joint capsule, subchondral bone, ligaments, and muscle. The changes in the articular surface attract the most attention, however, and have been well documented histopathologically and biochemically. The initial change recognized microscopically is fibrillation of the superficial cartilage layer (see Fig. 3*B*).[32] This results in microscopic roughening of the articular surface. Fibrillation tends to occur in a manner that suggests flaking of the superficial cartilage layers, because

separation tends to occur between collagen fibrils that course parallel to the joint surface.[3] Once fibrillation of the superficial layer progresses sufficiently to result in loss of the integrity of this stiff outer layer, the underlying cartilage experiences abnormal stresses, and subsequently, fissures develop in deeper layers (see Fig. 3*C*).[3] Fissures tend to develop in a vertical plane due to the orientation of the collagen fibrils in deeper regions. These fissures can extend to the subchondral bone.

Alterations in chondrocyte morphology are also part of degenerative change. Chondrocytes initially become larger and are found in clusters instead of in the distribution found in normal cartilage (see Fig. 3*B*, and *C*). In areas of pressure, there is thinning of the cartilage and in areas of indirect contact, the articular surface may actually increase in thickness, although the normal architecture is greatly altered. Ultimately, these changes can progress to complete loss of cartilage, with exposure of subchondral bone. The release of free cartilage fragments occurs concurrently with cartilage degradation. These free fragments can initiate an inflammatory response in the synovium as they are phagocytized by type A synoviocytes.[5, 30] The release of inflammatory mediators such as cytokines and prostaglandins follows, thereby initiating an inflammatory response of varying severity.

Depletion of proteoglycan from articular cartilage matrix is considered to be one of the defining features of osteoarthritis. Proteoglycan loss initially occurs from the more superficial regions of cartilage, despite a hypertrophic response by individual chondrocytes.[60] The proteoglycans synthesized by osteoarthritic cartilage are abnormal.[14, 53] Despite increased synthesis, proteoglycan breakdown is also enhanced, and the rate of catabolism usually exceeds the anabolic rate. The changes in proteoglycan content and quality can occur even before there is any grossly visible damage to the cartilage surface.[53]

In addition to proteoglycan alterations, one of the earliest changes that occurs in osteoarthritic cartilage is an increase in water content. This is thought to occur due to damage to the collagen fibrils, resulting in abnormal hydration of the proteoglycans present.[48] Collagen breakdown is suspected to be due to degradative proteases released from damaged chondrocytes. Loss of collagen cross-links allows greater separation of the collagen fibrils by the hydrated proteoglycans, thereby increasing the thickness of articular cartilage.[12] Collagen fibrils become radially aligned instead of forming an interlocking meshwork, thereby decreasing the ability to retain proteoglycans and resist compressive force.[9] Proteoglycans are lost into the synovial fluid. Articular cartilage undergoing this type of change is grossly noted to be softer than normal cartilage and is more susceptible to mechanical injury.

Degradative enzymes are normally found within chondrocytes. The normal joint maintains a delicate homeostasis between the anabolic and catabolic activities associated with normal turnover of matrix. There is continuous synthetic activity by chondrocytes, with removal of existing matrix by degradative enzymes. These enzymes include various proteases. These proteases can be grouped according to their active site.

The major categories are the serine proteases, cysteine proteases, and metalloproteinases. Many of these proteases are found within chondrocytes but may also be produced by synoviocytes, and some are produced by inflammatory cells.[69] The metalloproteinase family is generally regarded as having a major role in the breakdown of articular cartilage. There are at least 11 different molecules in the metalloproteinase family.[68] The collagenases and stromelysins, and perhaps the gelatinases, are considered to be important in osteoarthritis.[74] Most of the proteases can act on multiple substrates. Collagenases act on collagen fibrils to break down the structural framework of cartilage. Stromelysin cleaves aggrecan between the G1 and G2 domains, leading to loss of proteoglycan from the extracellular matrix. Stromelysin also acts on some types of collagen. In healthy cartilage, the activity of these enzymes is controlled by physiologic inhibitors known as tissue inhibitors of metalloproteinase. In osteoarthritic cartilage, there is an imbalance between active metalloproteinase levels and tissue inhibitors of metalloproteinase, resulting in cartilage catabolism.[50] Evidence of the involvement of the serine and cysteine proteases in osteoarthritis is less clear, although these enzymes do have a role in the development of rheumatoid arthritis.[74]

Changes in chondrocytes and cartilage matrix do not occur in an isolated manner. Concurrent with or perhaps prior to the release of proteases, chondrocyte damage initiates a biochemical response. Cytokines are the chemical messengers that allow communication within the joint and serve to translate diverse etiologic factors into pathogenic forces and maintain the chronic phase of inflammation and tissue destruction.[45] Most cytokines are not normally expressed or are maintained at low levels during homeostasis and are only produced in response to injury.[45] The cytokines believed to be of greatest importance in osteoarthritis include interleukin-1, interleukin-6 and tumor necrosis factor α. Among other functions, cytokines further stimulate chondrocytes and synoviocytes to produce and release more degradative enzymes. In the presence of cytokines, increased production of metalloproteinases occurs, although the synthesis of proteoglycans is altered and that of type II collagen is inhibited.[45] Interleukin-1 stimulates fibroblasts to produce collagen types I and III, and this may contribute to fibrosis of the joint capsule in the osteoarthritic joint.[45, 74] Other cytokines, including insulin-derived growth factor-1 and transforming growth factor-β, are synthesized by chondrocytes and associated with an anabolic function. Both insulin-derived growth factor-1 and transforming growth factor-β can stimulate proteoglycan and collagen synthesis.[74, 77] The interaction between cytokines is complex. Ultimately, however, catabolic activities exceed anabolic activities, resulting in articular cartilage degradation.

Cytokines such as IL-1 exert their effect by interacting with cell surface receptors. The most studied of these in osteoarthritis is the IL-1 receptor, which requires only a low level of occupancy to stimulate cytokine action.[76] An exciting area of research activity is studying the effect of blockage of cytokine activity through the production of IL-1

receptor antagonist (IL-1ra). IL-1ra is a naturally occurring cytokine. Intra-articular administration of IL-1ra to dogs undergoing cranial cruciate ligament transection resulted in protection against the development of cartilage lesions.[15] The role of IL-1ra in the treatment of osteoarthritis remains to be determined.

It is unclear whether chondrocytes or synoviocytes are the most important source of protease production within the arthritic joint. It is generally believed that chondrocytes are the most active source of degradative protease production but that this production is stimulated primarily by cytokines and leukotrienes produced by the synovium. Nevertheless, doubt exists as to the ability of synovitis alone to result in the progressive change of osteoarthritis.[12] It has been proposed that substructural disruption (alteration in collagen-collagen bonds or collagen-proteoglycan interactions) due to impulsive (high loading rate) loading of either a single supraphysiologic load or small repetitive impulsive loads is the initiating event and is necessary for the development of osteoarthritis.[84] It has been noted that immobilization of the stifle joint following experimental cranial cruciate ligament transection prevents the development of osteoarthritic changes, supporting an integral role of mechanical disruption in the pathogenesis of osteoarthritis.[72] Alternatively, strict hemostasis (and thus less inflammatory stimulus) during cranial cruciate ligament transection is associated with a lesser degree of synovitis and slower development of degenerative articular change, suggesting that synovitis influences the development of osteoarthritic change.[67]

The interaction of collagen, proteoglycans, and water is integral to the maintenance of articular cartilage.[59] The turgidity of articular cartilage is maintained by the interaction of the osmotic swelling pressure generated by proteoglycans and water as well as the restraint to swelling provided by the collagen network. Disruption of the collagen fibrils due to mechanical or chemical insult diminishes intrinsic tensile stiffness of articular cartilage, and loss or alteration of proteoglycan content reduces compressive stiffness. Water content of cartilage increases with collagen disruption, leading to cartilage swelling. Changes in the material properties lead to compromise of the lubricating and load-carrying capacity of articular cartilage.[88, 90] These changes tend to be progressive and correlate with the degree of degeneration present.[59]

SUMMARY

Normal cartilage is a complex material consisting of a solid matrix composed primarily of collagen and proteoglycan, which is saturated with water. It is not a homogenous material. The interaction of the physical and biochemical structures of cartilage is necessary to allow the normal function of providing nearly frictionless motion, wear resistance, joint congruence, and transmission of load to subchondral bone. Chondrocytes are responsible for synthesizing and maintaining this material.

Osteoarthritis occurs when there is disruption of normal cartilage structure and homeostasis.

Osteoarthritis results from a complex interaction of biochemical and biomechanical factors that occur concurrently and serve to perpetuate degradative change. The progressive pathologic change that occurs in osteoarthritis has been characterized, not only for articular cartilage but also for periarticular tissues. The occurrence of mechanical and biochemical changes is well established, but the role of each in the etiopathogenesis of osteoarthritis is not rigidly defined. It is likely that there are multiple etiologies sharing common pathways of physical and chemical disruption (see Fig. 1).

The changes associated with osteoarthritis ultimately have an impact on the patient through decreased ability to use the joint or the production of pain, or both. Unfortunately, once these changes are severe enough to be recognized clinically, they are likely to be irreversible with current treatments. Nevertheless, understanding the basic mechanisms involved in the development and progression of osteoarthritis provides a basis for establishing a reasonable expectation for the patient and a rational plan for medical and surgical treatment of this condition.

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