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Articular Cartilage and Osteoarthritis

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Abstract

Articular cartilage, which makes possible the painless, low-friction movement of synovial joints, consists of a sparsely distributed population of highly specialized cells called chondrocytes that are embedded within a matrix and provide articular cartilage with remarkable mechanical properties. Chondrocytes form the tissue matrix macromolecular framework from three classes of molecules: collagens, proteoglycans, and noncollagenous proteins. The matrix protects the cells from injury resulting from normal joint use, determines the types and concentrations of molecules that reach the cells, acts as a mechanical signal transducer for the cells, and helps maintain the chondrocyte phenotype. Throughout life, articular cartilage undergoes internal remodeling as the cells replace matrix macromolecules lost through degradation. Aging decreases the ability of chondrocytes to maintain and restore articular cartilage and thereby increases the risk of degeneration of the articular cartilage surface. Progressive degeneration of articular cartilage leads to joint pain and dysfunction that is clinically identified as osteoarthritis. Investigation regarding the pathogenesis of posttraumatic osteoarthritis, the form of osteoarthritis that develops following joint injury, is helping to explain the development and progression of joint degeneration.

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Synovial joints make normal, pain-free movement possible. These complex structures, formed from multiple distinct tissues including joint capsule, ligaments, menisci, subchondral bone, synovium, and hyaline articular cartilage, have been progressively refined over hundreds of millions of years.[1] Walt Whitman recognized the beauty of the design of synovial joints when he observed that "the narrowest hinge in my hand puts to scorn all machinery."[2] Despite the remarkable advances in joint arthroplasty, synovial joints still put to scorn all machinery; no currently available prosthesis comes close to duplicating the function and durability of synovial joints.

The tissue that contributes the most to these extraordinary functional capacities is the articular cartilage that forms the bearing surfaces of all synovial joints.[3,4] It responds to alterations in use, and allows pain-free movement with a level of friction less than that of any prosthetic joint surface. It varies in thickness, cell density, matrix composition, and mechanical properties within the same joint, among joints, and among species.[5] Nonetheless, in all synovial joints it consists of the same components, has the same general structure, and performs the same functions. Although at most only a few millimeters thick, it has surprising stiffness to compression and resilience and excep-

tional ability to distribute loads, thereby minimizing peak stresses on subchondral bone.[6,7] Perhaps most importantly, it has great durability—in many people it provides normal joint function for 80 years or longer.

Unfortunately, articular cartilage has a limited ability to maintain and repair itself, and with age these capacities decline. As a result, the risk of progressive degeneration of the tissue increases with time in individuals older than 40 years.[8] The degeneration of articular cartilage and associated changes in subchondral bone result in the joint pain and dysfunction that characterize osteoarthritis.[8]

For orthopaedic surgeons to understand how joint degeneration develops and progresses, it is important to be familiar with the current understanding of articular cartilage design (the cell and matrix composition and structure that make possible the normal function of articular cartilage), the interactions between chondrocytes and their matrix that maintain the tissue, the biomechanics of the matrix, and the tissue degeneration that leads to osteoarthritis.[9,10]

Articular Cartilage Composition

Upon gross and microscopic examination, adult articular cartilage appears to be a simple inert tissue. Opening a normal synovial joint exposes the smooth, slick, firm articular cartilage surfaces that resist
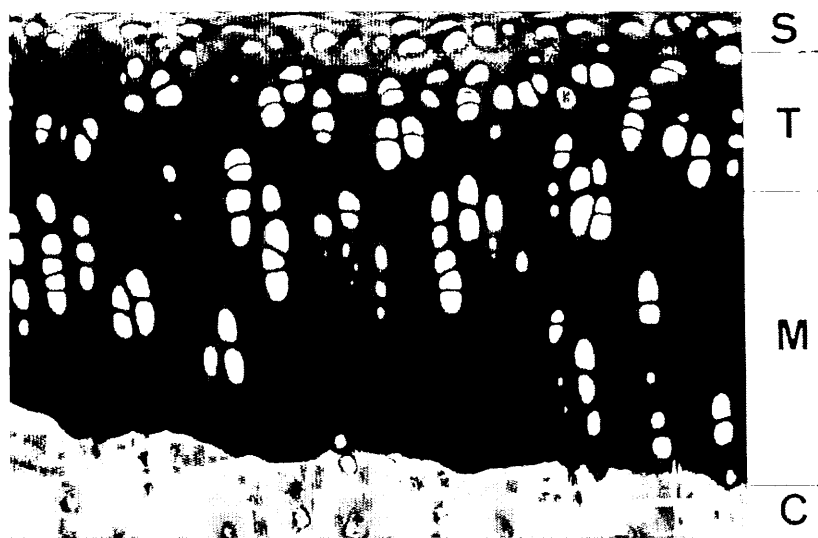
Figure 1 Articular cartilage from the medial femoral condyle of an 8-month-old rabbit. The tissue is organized into four layers or zones: the superficial zone (S), the transitional zone (T), the middle (radial or deep) zone (M), and the calcified cartilage zone (C). Bar = 50 nm. (Reproduced from Buckwalter JA, Hunziker EB, Rosenberg LC, et al: Articular cartilage: Composition and structure, in Woo SL, Buckwalter JA (eds): *Injury and Repair of the Musculoskeletal Soft Tissues.* Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1988, pp 405-425.)

deformation when probed. Light microscopic examination shows that articular cartilage consists primarily of extracellular matrix with a sparse population of cells and that it lacks blood vessels, lymphatic vessels, and nerves (Figures 1 and 2). Compared with tissues such as muscle and bone, articular cartilage has a low level of metabolic activity; unlike these other tissues, its responses to loading or injury can only be detected by microscopy or metabolic studies. Despite its unimpressive appearance and low level of metabolic activity, study of the morphology and biology of adult articular cartilage shows that it has an elaborate, highly ordered structure and that complex interactions between the chondrocytes and the matrix maintain the tissue.

Chondrocytes

Only one type of cell, the highly specialized chondrocyte, exists within normal articular cartilage[2] (Figure 2). Chondrocytes make up only about 1% of the volume of adult human articular cartilage (in other species, especially small animals such as mice, rats, and rabbits with thin articular cartilages, the cell density is many times greater than in humans).[11,12] Chondrocytes from different cartilage zones differ in size, shape, and probably metabolic activity,[13,14] but all of these cells contain the organelles necessary for matrix synthesis, including endoplasmic reticulum and Golgi membranes. Also, they frequently contain intracytoplasmic filaments, lipid, glycogen, and secretory vesicles. Chondrocytes surround themselves with their extracellular matrix and do not form cell-to-cell contacts. A spheroidal shape, synthesis of type II collagen, large aggregating proteoglycans, and specific noncollagenous proteins distinguish mature chondrocytes from other cells.

At first glance, chondrocytes seem to be observers rather than participants in the function of mature articular cartilage. They appear to remain unchanged in

size, location, appearance, and activity for decades. The unique mechanical properties of articular cartilage depend on the matrix (the types of macromolecules that form the framework of the matrix and the concentrations of water and macromolecules).[3,4,6] However, a matrix formed by mixing appropriate concentrations of water and cartilage macromolecules (collagens, proteoglycans, and noncollagenous proteins) will not duplicate the properties of articular cartilage. To produce tissue that can provide normal synovial joint function, the chondrocytes must first synthesize appropriate types and amounts of macromolecules and then assemble and organize them into a highly ordered macromolecular framework. Maintenance of the articular surface requires turnover of the matrix macromolecules (continual replacement of degraded matrix components) and probably alteration in the matrix macromolecular framework in response to joint use. To accomplish these activities, the cells must sense changes in the matrix composition resulting from the degradation of macromolecules and the mechanical demands placed on the articular surface, and then respond by synthesizing appropriate types and amounts of macromolecules.

Aging profoundly alters chondrocyte function. With aging, the capacity of the cells to synthesize some types of proteoglycans, their proliferative capacity, and their response to anabolic stimuli including growth factors decreases.[15-24] These changes may limit the ability of the cells to maintain and restore the tissue and thereby contribute to the development and progression of articular cartilage degeneration.[19-23]

Extracellular Matrix

The articular cartilage extracellular matrix consists of two components: tissue fluid and the framework of structural macromolecules that give the tissue its form and stability. The interaction of the

tissue fluid and the macromolecular framework give the tissue its mechanical properties of stiffness and resilience.[6,25]

Tissue Fluid Water contributes up to 80% of the wet weight of articular cartilage, and the interaction of water with the matrix macromolecules significantly influences the mechanical properties of the tissue.[4,6,26-29] This tissue fluid contains gases, small proteins, metabolites, and a high concentration of cations to balance the negatively charged proteoglycans. At least some of the water can move freely in and out of the tissue. Its volume, concentration, and behavior within the tissue depends primarily on its interaction with the structural macromolecules, particularly the large aggregating proteoglycans that help maintain the fluid within the matrix and fluid electrolyte concentrations. Because these macromolecules have a large number of negative charges that attract positively charged ions and repel negatively charged ions, they increase the concentration of positive ions such as sodium and decrease the concentration of negative ions such as chloride. The increase in total inorganic ion concentration increases the tissue osmolarity (creating a Donnan effect). The collagen network resists the Donnan osmotic pressure caused by the inorganic ions associated with the proteoglycans.[6,25]

Structural Macromolecules The structural macromolecules of the articular cartilage (collagens, proteoglycans, and noncollagenous proteins and glycoproteins) make up 20% to 40% of its wet weight.[4] The three classes of macromolecules differ in their concentrations within the articular cartilage and in their contributions to its properties. Collagens contribute about 60% of the dry weight of articular cartilage, proteoglycans contribute 25% to 35%, and the noncollagenous proteins and glycoproteins contribute 15% to 20%. Collagens are distributed relatively uniformly throughout the depth of the cartilage, except in the collagen-rich superficial zone. The

collagen fibrillar meshwork gives cartilage its form and tensile strength.[25] Proteoglycans and noncollagenous proteins bind to the collagenous meshwork or become mechanically entrapped within it, and water fills this molecular framework. Some noncollagenous proteins help organize and stabilize the matrix macromolecular framework, whereas others help chondrocytes bind to the macromolecules of the matrix.

Articular cartilage, like most tissues, contains multiple genetically distinct collagen types, specifically, collagen types II, VI, IX, X, and XI.[30-32] Collagen types II, IX, and XI form the cross-banded fibrils seen on electron microscopy (Figure 3). The organization of these fibrils into a tight meshwork that extends throughout the tissue provides the tensile stiffness and strength of articular cartilage and contributes to the cohesiveness of the tissue by mechanically entrapping the large proteoglycans. Collagen type II accounts for 90% to 95% of the articular cartilage collagen and forms the primary component of the cross-banded fibrils. Type IX collagen molecules bind covalently to the superficial layers of the cross-banded fibrils and project into the matrix, where they also can bind covalently to other type IX collagen molecules. Type XI collagen molecules bind covalently to type II collagen molecules and probably form part of the interior structure of the cross-banded fibrils. The functions of type IX and type XI collagens remain uncertain; however, it is thought that they help form and stabilize the collagen fibrils assembled primarily from type II collagen. The projecting portions of type IX collagen molecules may also help bind together the collagen fibril meshwork and connect the collagen meshwork with proteoglycans.[31-35] Type VI collagen appears to form an important part of the matrix immediately surrounding the chondrocytes and helps chondrocytes attach to the matrix.[36,37] The presence of type X collagen only near the cells of the calci-
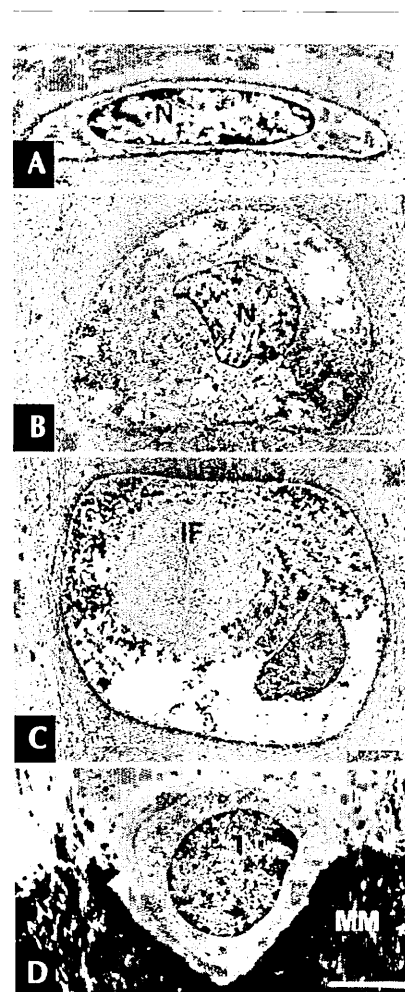

Figure 2 Electron micrographs showing the superficial zone (A), transitional zone (B), middle (radial or deep) zone (C), and calcified cartilage zone (D) of mature articular cartilage chondrocytes from the medial femoral condyle of a rabbit. N = nucleus, G = glycogen, IF = intermediate filaments, MM = mineralized matrix, UN = unmineralized matrix, bar = 3 nm. (Reproduced from Buckwalter JA, Hunziker EB, Rosenberg LC, et al: Articular cartilage: Composition and structure, in Woo SL, Buckwalter JA (eds): *Injury and Repair of the Musculoskeletal Soft Tissues*. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1988, pp 405-425.)

fied cartilage zone of articular cartilage and the hypertrophic zone of growth plate (where the longitudinal cartilage septa begin to mineralize) suggests that it has a role in cartilage mineralization.

Figure 3 Electron micrographs showing the superficial zone (A), transitional zone (B), upper portion of the middle (radial or deep) zone (C), and lower portion of the middle zone (D) of the articular cartilage interterritorial matrix from the medial femoral condyle of an 8-month-old rabbit. Arrows indicate proteoglycans precipitated with ruthenium hexamine trichloride. Bar = 0.5 nm. (Reproduced from Buckwalter JA, Hunziker EB, Rosenberg LC, et al: Articular cartilage: Composition and structure, in Woo SL, Buckwalter JA (eds): *Injury and Repair of the Musculoskeletal Soft Tissues.* Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1988, pp 405-425.)
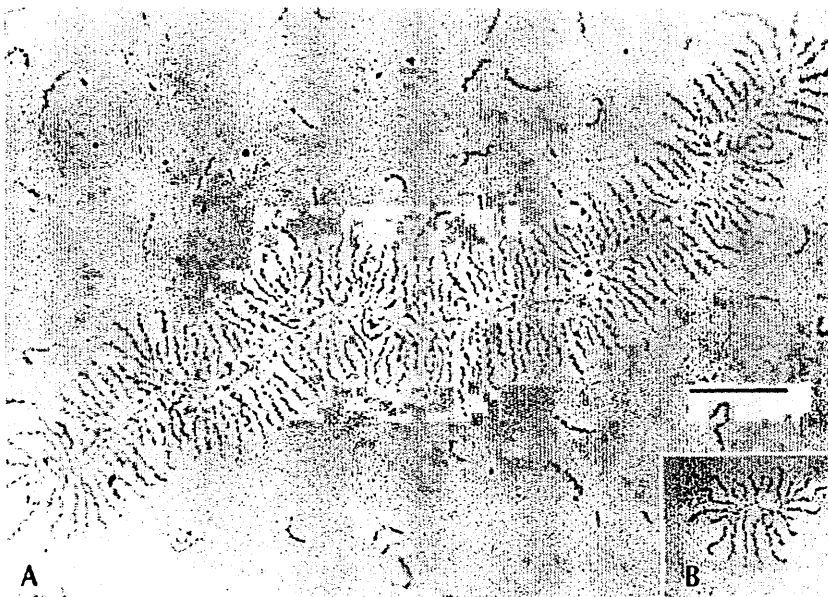

Figure 4 Transmission electron micrographs showing bovine articular cartilage proteoglycan aggregates from a calf (A) and steer (B) consisting of central hyaluronan filaments and multiple attached aggrecans. Aggregates from older animals have shorter hyaluronan filaments and fewer aggrecans. In addition, the aggrecans are shorter and vary more in length. Bar = 500 nm. (Reproduced with permission from Buckwalter JA, Kuettner KE, Thonar EJ-M: Age-related changes in articular cartilage proteoglycans: Electron microscopic studies. *J Orthop Res* 1985;3:251-257.)

Proteoglycans consist of a protein core and one or more glycosaminoglycan chains (long unbranched polysaccharide chains consisting of repeating disaccharides that contain an amino sugar).[35,38-40] Each disaccharide unit has at least one negatively charged carboxylate or sulfate group so the glycosaminoglycans form long strings of negative charges that repel one another and other negatively charged molecules and attract cations. Glycosaminoglycans found in cartilage include hyaluronic acid, chondroitin sulfate, keratan sulfate, and dermatan sulfate. The concentration of these molecules varies among sites within articular cartilage and also with patient age, cartilage injury, and disease.

Articular cartilage contains two major classes of proteoglycans: large aggregating molecules or aggrecans (Figure 4) and smaller proteoglycans including dEcoRIn, biglycan, and fibromodulin.[35,38-45] Because it may have a glycosaminoglycan component, type IX collagen is also considered a proteoglycan.[35] Aggrecans have large numbers of chondroitin sulfate and keratan sulfate chains attached to a protein core filament (Figure 5). Cartilage also contains large nonaggregating proteoglycans that resemble aggrecans in structure and composition and may represent degraded aggrecans.[17,38] DEcoRIn has one dermatan sulfate chain, biglycan has two dermatan sulfate chains, and fibromodulin has several keratan sulfate chains.[35] The tissue probably also contains other small proteoglycans that have not been identified. Aggrecan molecules fill most of the interfibrillar space of the cartilage matrix. They contribute about 90% of the total cartilage matrix proteoglycan mass, whereas large nonaggregating proteoglycans contribute 10% or less and small nonaggregating proteoglycans contribute about 3%. Although the small proteoglycans contribute relatively little to the total mass of proteoglycans compared with the aggrecans, they may be present in equal

or higher molar amounts because of their small size.

In the articular cartilage matrix, most aggrecans (Figure 5) noncovalently associate with hyaluronic acid (hyaluronan) and link proteins (small noncollagenous proteins) to form proteoglycan aggregates[44-46] (Figure 4). These large molecules have a central hyaluronan backbone that can vary in length from several hundred to more than 10,000 nm.[44,45] Large aggregates may have more than 300 associated aggrecan molecules.[45] Link proteins stabilize the association between monomers and hyaluronic acid and appear to have a role in directing the assembly of aggregates.[47,48] Aggregate formation helps anchor proteoglycans within the matrix, preventing their displacement during deformation of the tissue, and helps organize and stabilize the relationship between proteoglycans and the collagen meshwork.

The small nonaggregating proteoglycans have shorter protein cores than aggrecan molecules; unlike aggrecans, they do not fill a large volume of the tissue or contribute directly to its mechanical behavior. Instead, they bind to other macromolecules and probably influence cell function. DEcoRIn and fibromodulin bind with type II collagen and may have a role in organizing and stabilizing the type II collagen meshwork.[35,49-51] Biglycan is concentrated in the pericellular matrix and may interact with type VI collagen.[35] The small proteoglycans also can bind transforming growth factor-β (TGF-β) and may influence the activity of this cytokine in cartilage.[52]

Although a wide variety of noncollagenous proteins and glycoproteins exist within normal articular cartilage, only a few of them have been studied thus far. In general, they consist primarily of protein and a few attached monosaccharides and oligosaccharides.[53,54] At least some of these molecules appear to help organize and maintain the macromolecular structure of the matrix. Anchorin CII, a colla-
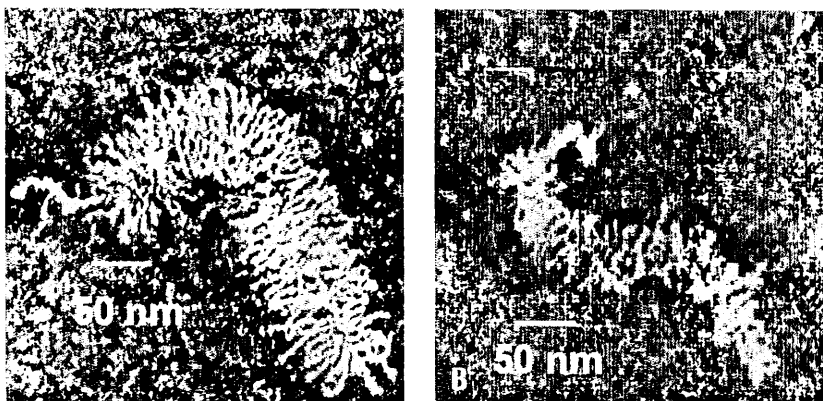

Figure 5 A, Atomic force image of aggrecan from fetal bovine epiphyseal cartilage. Note that glycosaminoglycan chains project from the central protein filament of the aggrecan molecule. B, Atomic force image of aggrecan from mature bovine nasal cartilage. Note that the aggrecan molecule from a skeletally mature animal is shorter and has shorter glycosaminoglycan chains. (Reproduced with permission from Ng L, Grodzinsky AJ, Sandy JD, et al: Structure and conformation of individual aggrecan molecules and the constituent GAG chains via atomic force microscopy. J Struct Biol 2003;143:242-257.)

gen-binding chondrocyte surface protein, may help anchor chondrocytes to the matrix collagen fibrils.[55,56] Cartilage oligomeric protein, an acidic protein, is concentrated primarily within the chondrocyte territorial matrix and appears to be present only within cartilage and have the capacity to bind to chondrocytes.[57,58] This molecule may have value as a marker of cartilage turnover and of the progression of cartilage degeneration in patients with osteoarthritis.[59-61] Fibronectin and tenascin, noncollagenous matrix proteins found in a variety of tissues, have also been identified within cartilage.[62-68] Their functions in articular cartilage remain poorly understood, but they may have roles in matrix organization, cell matrix interactions, and in the responses of the tissue in inflammatory arthritis and osteoarthritis.[62,68,69]

Articular Cartilage Structure

To form articular cartilage, chondrocytes organize the collagens, proteoglycans, and noncollagenous proteins and glycoproteins into a unique, highly ordered structure.[4] The composition, organization, and mechanical properties of the

matrix, cell morphology, and probably cell function vary with the depth from the articular surface (Figures 1 through 3). Matrix composition, organization, and function also vary with the distance from the cell (Figure 6).

Zones

The morphologic changes in chondrocytes and matrix from the articular surface to the subchondral bone make it possible to identify four zones or layers: the superficial zone, the transitional zone, the middle (radial or deep) zone, and the calcified cartilage zone (Figure 1).[3] The relative size and appearance of these zones vary among species and among joints within the same species; although each zone has different morphologic features, the boundaries between zones cannot be sharply defined. Nonetheless, recent biologic and mechanical studies have shown that the zonal organization has functional significance. The matrices differ in water, proteoglycan, and collagen concentrations and in the size of the aggregates.[4] Cells in different zones not only differ in shape, size, and orientation relative to the articular surface (Figure 2),
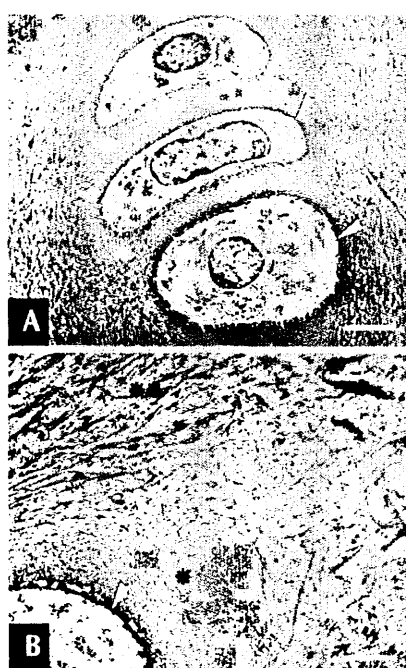
Figure 6 A, Electron micrograph showing the articular cartilage matrix compartments of the medial femoral condyle of an 8-month-old rabbit. Arrows indicate pericellular matrix, * indicates territorial matrix, and ** indicates interterritorial matrix. Bar = 3 nm. **B,** A higher magnification electron micrograph of the same showing the matrix compartments and the relationship between the cell membrane and the pericellular matrix. Bar = 1 nm. Notice the short-cell processes that extend through the pericellular matrix. (Reproduced from Buckwalter JA, Hunziker EB, Rosenberg LC, et al: Articular cartilage: Composition and structure, in Woo SL, Buckwalter JA (eds): *Injury and Repair of the Musculoskeletal Soft Tissues.* Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1988, pp 405-425.)

but they also appear to differ in metabolic activity.[13] They may respond differently to mechanical loading, suggesting that development and maintenance of normal articular cartilage depend in part on differentiation of phenotypically distinct populations of chondrocytes.

Superficial Zone The unique structure and composition of the thinnest articular cartilage zone, the superficial zone, give it specialized mechanical and possibly biologic properties. It typically consists of two layers. A sheet of fine fibrils with little polysaccharide and no cells covers the joint surface. This portion of the superficial zone presumably corresponds to the clear film, often identified as the lamina splendens, which can be stripped from the articular surface in some regions. Deep to this acellular sheet of fine fibrils, flattened ellipsoid-shaped chondrocytes arrange themselves so that their major axes are parallel to the articular surface (Figure 2). They synthesize a matrix that has a high collagen concentration and a low proteoglycan concentration relative to the other cartilage zones, and examination of superficial zone cells in culture solution shows that they degrade proteoglycans more rapidly and synthesize less collagen and proteoglycans than cells from the deeper zones.[13] Fibronectin and water concentrations are also highest in this zone.

The dense mat of collagen fibrils lying parallel to the joint surface in the superficial zone (Figure 3) helps determine the mechanical properties of the tissue and affects the movement of molecules in and out of cartilage. It gives this cartilage zone greater tensile stiffness and strength than the deeper zones, and it may resist shear forces generated during joint use.[3,6,70] In vitro experiments show that the superficial zone also makes an important contribution to the compressive behavior of articular cartilage.[71] Removal of this zone increases tissue permeability and probably increases loading of the macromolecular framework during compression; disruption or remodeling of the dense collagenous matrix of the superficial zone is one of the first detectable structural changes in experimentally induced articular cartilage degeneration, suggesting that alterations in this zone may contribute to the development of osteoarthritis by altering the mechanical behavior of the tissue.[72] The densely packed collagen fibrils of the superficial zone also create a "skin" for the articular cartilage that may limit ingress of large molecules (such as antibodies or other proteins) and the egress of large cartilage molecules. By acting as a barrier to passage of large molecules between the synovial fluid and the cartilage, the superficial zone may effectively isolate cartilage from the immune system. Thus, disruption of the superficial zone may not only alter the structure and mechanical properties of articular cartilage, it may also release cartilage molecules that stimulate an immune or inflammatory response.

Transitional Zone As the name implies, the morphology and matrix composition of the transitional zone is intermediate between the superficial zone and the middle (radial or deep) zone. It usually has several times the volume of the superficial zone. The cells have a higher concentration of synthetic organelles, endoplasmic reticulum, and Golgi membranes than superficial zone cells (Figure 2). Transitional zone cells assume a spheroidal shape and synthesize a matrix that has larger diameter collagen fibrils, a higher proteoglycan concentration, but lower concentrations of water and collagen than the superficial zone matrix.

Middle Zone The chondrocytes in the middle zone are spheroidal in shape, and they tend to align themselves in columns perpendicular to the joint surface (Figures 1 and 2). This zone contains the largest diameter collagen fibrils, the highest concentration of proteoglycans, and the lowest concentration of water. The collagen fibers of this zone pass into the tidemark, a thin basophilic line seen on light microscopic sections of decalcified articular cartilage that roughly corresponds to the boundary between calcified and uncalcified cartilage. The nature of the tidemark remains uncertain.[73] It may result from concentration of basophilic calcified material at the interface between calcified and uncalcified matrix, possibly accentuated by the tissue processing, and thus represent a "high water mark" for

calcification. One study identified a band of fine fibrils corresponding to the tidemark, alternatively suggesting that it represents a well-defined matrix structure.[74]

Calcified Cartilage Zone A thin zone of calcified cartilage separates the middle zone (uncalcified cartilage) and the subchondral bone. The cells of the calcified cartilage zone have a smaller volume than the cells of the middle zone and contain only small amounts of endoplasmic reticulum and Golgi membranes (Figure 2). In some regions, these cells appear to be completely surrounded by calcified cartilage and buried in individual calcific sepulchers. This appearance suggests that they have an extremely low level of metabolic activity. However, recent work suggests that they may have a role in the development and progression of osteoarthritis.[73]

Matrix Regions

Variations in the matrix within zones distinguish three regions or compartments: the pericellular matrix, territorial matrix, and interterritorial matrix[4] (Figure 6). The pericellular and territorial regions appear to serve the needs of chondrocytes by binding the cell membranes to the matrix macromolecules and protecting the cells from damage during loading and deformation of the tissue. They may also help transmit mechanical signals to the chondrocytes when the matrix deforms during joint loading. The primary function of the interterritorial matrix (Figures 3 and 6) is to provide the mechanical properties of the tissue.

Pericellular Matrix Chondrocyte cell membranes appear to attach to the thin rim of the pericellular matrix that covers the cell surface (Figure 6). This matrix region is rich in proteoglycans and also contains noncollagenous matrix proteins, including the cell membrane associated molecule anchorin CII,[55,56] and nonfibrillar collagens, including type VI collagen.[36,37] It has little or no fibrillar collagen.

Territorial Matrix An envelope of territorial matrix surrounds the pericellular matrix of individual chondrocytes and, in some locations, pairs or clusters of chondrocytes and their pericellular matrices (Figure 6). In the middle zone, a territorial matrix surrounds each chondrocyte column. The thin collagen fibrils of the territorial matrix nearest to the cell appear to adhere to the pericellular matrix. At a distance from the cell they decussate and intersect at various angles, forming a fibrillar basket around the cells. This collagenous basket may provide mechanical protection for the chondrocytes during loading and deformation of the tissue. An abrupt increase in collagen fibril diameter and a transition from the basket-like orientation of the collagen fibrils to a more parallel arrangement marks the boundary between the territorial and interterritorial matrices. However, many collagen fibrils connect the two regions, making it difficult to precisely identify the boundary between these regions.

Interterritorial Matrix The interterritorial matrix makes up most of the volume of mature articular cartilage (Figures 1 and 6). It contains the largest diameter collagen fibrils. Unlike the collagen fibrils of the territorial matrix, these fibrils are not organized to surround the chondrocytes, and they change their orientation relative to the joint surface 90° from the superficial zone to the middle zone (Figure 3). In the superficial zone, the fibril diameters are relatively small and the fibrils generally lie parallel to the articular surface. In the transition zone, interterritorial matrix collagen fibrils assume more oblique angles relative to the articular surface, and in the middle (radial or deep) zone, they generally lie perpendicular (or radial) to the joint surface.

Chondrocyte-Matrix Interactions

The interdependence of chondrocytes and the matrix makes possible the maintenance of articular cartilage throughout

life.[69] The relationship between the chondrocytes and the matrix does not end when the cells secrete the matrix macromolecules. The matrix protects the chondrocytes from mechanical damage during normal joint use, and it helps maintain their shape and phenotype. Nutrients, substrates for synthesis of matrix molecules, newly synthesized molecules, degraded matrix molecules, metabolic waste products, and molecules that help regulate cell function (such as cytokines and growth factors) all pass through the matrix and, in some instances, may be stored in the matrix. The types of molecules that can pass through the matrix and the rate at which they can pass depend on the composition and organization of the matrix—primarily the concentration, composition, and organization of the large proteoglycans.

Throughout life, chondrocytes degrade and synthesize matrix macromolecules. The mechanisms that control the balance between these activities remain poorly understood, but cytokines with catabolic and anabolic effects appear to have important roles.[69,75-78] For example, interleukin 1 (IL-1) induces expression of matrix metalloproteinases that can degrade the matrix macromolecules and interferes with synthesis of matrix proteoglycans at the transcriptional level. Other cytokines such as insulin-dependent growth factor I and TGF-β oppose these catabolic activities by stimulating matrix synthesis and cell proliferation. In response to a variety of stimuli, chondrocytes synthesize and release these cytokines into the matrix, where they may bind to receptors on the cell surfaces (stimulating cell activity either by autocrine or paracrine mechanisms) or become trapped within the matrix. The anabolic activities appear in large measure to be responses to structural needs of the matrix or other stimuli, possibly including mechanical loading of the tissue detected by the chondrocytes. The degradative response, conversely, appears to
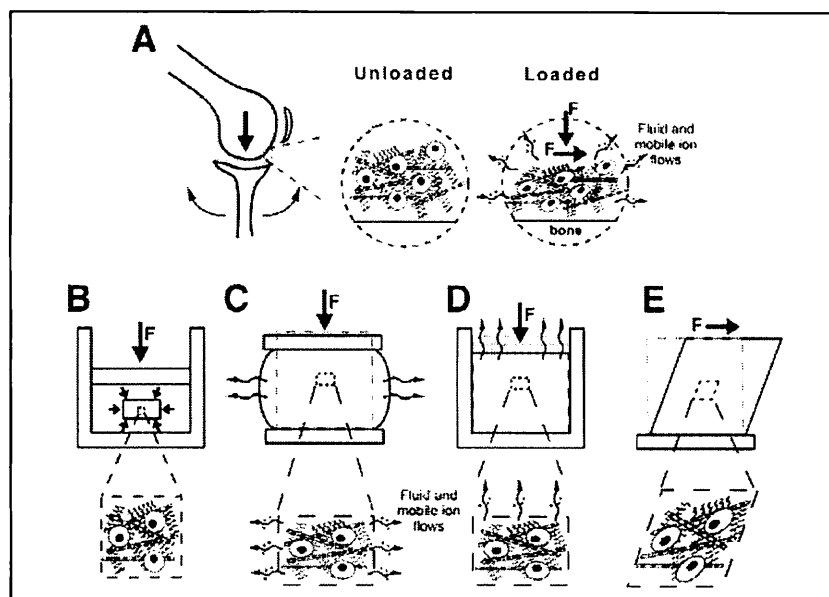
Figure 7 Loading of articular cartilage causes tissue deformation and changes in the cellular microenvironment. During joint motion (A), articular cartilage (gray) is subjected to a complex combination of compression and shear forces, causing deformation of the cells and extracellular matrix as well as fluid and ion flows. Methodologies developed to measure cartilage biomechanical properties under hydrostatic (or osmotic) pressure loading (B), unconfined (C) and confined (D) compression, shear (E), and tension have been used to quantify the metabolic response of articular cartilage to normal and injurious mechanical loads. (Adapted with permission from DeMicco M, Kim YJ, Grodzinsky AJ: Response of the chondrocyte to mechanical stimuli, in Brandt K, Doherty M, Lohmander S (eds): Osteoarthritis. Oxford, England, Oxford University Press, 2003.)

be the result of a complex cascade that includes IL-1, stromelysin, aggrecanase, plasmin, and collagenase being activated or inhibited by factors such as prostaglandins, TGF-β, tumor necrosis factor, tissue inhibitors of metalloproteinases, tissue plasminogen activator, plasminogen activator inhibitor, and other molecules.

Articular Cartilage Biomechanics

Articular cartilage is subjected to a wide range of static and dynamic mechanical loads. Under normal physiologic conditions, in vivo loading can result in peak dynamic mechanical stresses on cartilage as high as 15 to 20 MPa (150 to 200 atm) during activities such as stair climbing.[79,80] These peak stresses occur over very short durations (< 1 second) and,

therefore, lead to small cartilage compressive strains of about 1% to 3%. In contrast, sustained (static) physiologic stresses of approximately 3.5 MPa applied to knee joints for 5 to 30 minutes can result in compressive strains of knee cartilage as high as 35% to 45%.[81]

The ability of cartilage to withstand physiologic compressive, tensile, and shear forces depends on the composition and structural integrity of its extracellular matrix. In turn, the maintenance of a functionally intact matrix requires chondrocyte-mediated synthesis, assembly, and degradation of proteoglycans, collagens, noncollagenous proteins and glycoproteins, and other matrix molecules. Methodologies to measure the biomechanical properties of cartilage in tension, compression, and shear have been devel-

oped over the past decades (Figure 7) and have been used to correlate tissue level behavior with the molecular composition and constituents of the matrix.[79,80] These measurements have revealed that the equilibrium compressive modulus of adult articular cartilage is on the order of approximately 0.5 to 1 MPa, the shear modulus about 0.25 MPa, and the tensile modulus about 10 to 50 MPa. Although strong rope-like collagen fibrils effectively resist tensile and shear deformation forces (Figure 3), the highly charged glycosaminoglycan constituents of aggrecan molecules (Figure 4) resist compression and fluid flow within the tissue. Electrostatic repulsion and osmotic swelling interactions associated with aggrecan contribute more than 50% of the equilibrium compressive stiffness of articular cartilage.

Clinical observations and in vivo animal studies have shown that joint loading can induce a wide range of metabolic responses in articular cartilage.[82-84] Immobilization or reduced loading can cause profound decreases in matrix synthesis and content and result in a softening of the tissue. In contrast, aggrecan concentration is often higher in areas of habitually loaded cartilage and can be further increased by dynamic loading or remobilization of a joint, with concomitant restoration of biomechanical properties. More severe impact or strenuous exercise loading can cause cartilage degradation. Acute and chronic injurious compressive overloads can lead to cartilage degeneration. In vitro studies have demonstrated that static compression within the physiologic range can reversibly inhibit the synthesis of critical components of the cartilage matrix.[82,83] Such static compressive forces can downregulate the gene expression and production of type II collagen, aggrecan core protein, and link protein. In contrast, cyclically applied hydrostatic pressure and compressive strain can stimulate aggrecan core protein and protein synthesis.

Mechanical forces in the microenvironment of the chondrocytes, therefore, can significantly affect the synthesis and degradation of matrix macromolecules. However, the cellular transduction mechanisms that govern chondrocyte response to mechanical stimuli are only beginning to be understood. Recent data suggest that there are multiple regulatory pathways by which chondrocytes sense and respond to mechanical stimuli, including upstream signaling pathways and mechanisms that may lead to direct changes at the level of transcription, translation, posttranslational modifications, and cell-mediated extracellular assembly and degradation of matrix.[79,83,84] Correspondingly, there may be multiple pathways by which physical stimuli can alter not only the rate of matrix production, but also the quality and functionality of newly synthesized proteoglycans, collagens, and other molecules. In this manner, specific mechanical loading regimens may either enhance or compromise the long-term biomechanical function of articular cartilage.

Many physical forces and flows that occur in articular cartilage during loading in vivo have been identified and quantified in vitro.[79,85] Dynamic compression of cartilage results in deformation of cells and extracellular matrix, hydrostatic pressurization of the tissue fluid, pressure gradients and the accompanying flow of fluid within the tissue, and streaming potentials and currents induced by tissue fluid flow. In addition, the local changes in tissue volume caused by static compression also lead to physiochemical changes within the matrix, including alterations in matrix water content, fixed charge density, mobile ion concentrations, and osmotic pressure. Any of these mechanical, chemical, or electrical phenomena in the environment of the chondrocyte may affect cellular metabolism. It is now accepted that these forces and flows constitute a range of physical stimuli that can act in parallel with biologic

factors (such as cytokines and growth factors) to regulate chondrocyte homeostasis in normal and diseased tissue. The understanding of these forces and flows within cartilage has been aided by the development of theoretical models for the mechanical, physicochemical, and electromechanical behavior of the tissue.[79,85] Such models can provide a useful framework for correlating the physical stimuli and cellular responses that occur within articular cartilage during loading.[85]

The functional biomechanical properties of articular cartilage over the long term may be determined in part by the molecular mechanical properties of individual matrix molecules synthesized by the chondrocytes in the injured cartilage. Thus, the biosynthesis of functionally inferior matrix macromolecules that cannot properly contribute to or assemble into a mechanically functional matrix may be one of the hallmarks of the progression of posttraumatic articular cartilage degradation. Recent studies on the mechanics of isolated matrix molecules have focused on the tensile properties of hyaluronan and collagen and the repulsion between chondroitin sulfate chains of aggrecan, using optical tweezers, atomic force microscopy, and high-resolution force spectroscopy.[86] This is an exciting new area of study that should clarify the connection between tissue-level biomechanical properties: molecular mechanical properties of the matrix proteoglycans, glycosaminoglycans, and collagens; and the importance of chondrocyte mechanotransduction as the glue between the tissue, cell, and molecular constituents in cartilage remodeling.[87]

Articular Cartilage Degeneration and Osteoarthritis

Articular cartilage degeneration, the progressive loss of normal cartilage structure and function, leads to the clinical syndrome of osteoarthritis.[8] Osteoarthritis, also referred to as degenerative joint disease, degenerative arthritis, or hyper-

trophic arthritis, consists of a generally progressive loss of articular cartilage accompanied by attempted repair of articular cartilage, remodeling and sclerosis of subchondral bone, and in many instances the formation of subchondral bone cysts and marginal osteophytes.[88-96] In addition to the structural changes in the synovial joint, diagnosis of the clinical syndrome of osteoarthritis requires the presence of symptoms and signs that may include joint pain, restriction of motion, crepitus with motion, joint effusions, and deformity. Osteoarthritis occurs most frequently in the foot, knee, hip, spine, and hand joints,[97] but it can occur in any synovial joint.

Joint degeneration involves all of the tissues that form the synovial joint, including articular cartilage, subchondral and metaphyseal bone, synovium, ligaments, joint capsules, and the muscles that act across the joint; however, the primary changes consist of loss of articular cartilage, remodeling of subchondral bone, and formation of osteophytes.[88,93] The earliest microscopic changes seen in joint degeneration include fraying or fibrillation of the articular cartilage superficial zone extending into the transitional zone, decreased staining for proteoglycans in the superficial and transitional zones, violation of the tidemark by blood vessels from subchondral bone, and subchondral bone remodeling. Some investigators have postulated that stiffening of subchondral bone as a result of remodeling precedes and causes articular cartilage degeneration and that progression of cartilage degeneration requires stiffening of subchondral bone;[98] others have argued that articular cartilage loss leads to increased peak stresses on subchondral bone that cause bone remodeling. It is not clear which of these views is correct or whether either of them is entirely correct; however, in most instances, articular cartilage degeneration and subchondral bone remodeling are both present when patients develop symptoms, and it is the

loss of articular cartilage that leads directly to loss of joint function.

The earliest sign of degeneration visible from the articular surface is localized fibrillation or disruption of the most superficial layers of the articular cartilage. As the disease progresses, the surface irregularities become clefts, more of the articular surface becomes roughened and irregular, and fibrillation extends deeper into the cartilage until the fissures reach subchondral bone. As the cartilage fissures grow deeper, the superficial tips of the fibrillated cartilage tear, releasing free fragments into the joint space and decreasing the cartilage thickness. Enzymatic degradation of the matrix simultaneously decreases the cartilage volume further.[99-102] Eventually, the progressive loss of articular cartilage leaves only dense and often necrotic, eburnated bone.

Many of the mechanisms responsible for the progressive loss of articular cartilage in degenerative joint disease remain unknown, but the process can be divided into three overlapping stages: cartilage matrix damage or alteration, chondrocyte response to tissue damage, and the decline of the chondrocyte synthetic response and progressive loss of tissue.[93,103-108]

In the first stage, either before or with the appearance of fibrillation, the matrix macromolecular framework is disrupted or altered at the molecular level, and the water content increases.[31,93,104-106,109] Although the concentration of type II collagen remains constant, decreases in proteoglycan aggregation and aggrecan concentration and decreases in the length of the glycosaminoglycan chains usually accompany the increase in water content. Simultaneously, alterations in the collagenous framework, including changes in the relationships between the minor collagens and the collagen fibrils, may allow swelling of the aggrecan molecules. Disruption or decreased organization of the macromolecular framework, decreased aggrecan concentration and

aggregation, decreased glycosaminoglycan chain length, and increased water content taken together increase the permeability (that is, the ease with which water and other molecules move through the matrix) and decrease the stiffness of the matrix, alterations that may increase the vulnerability of the tissue to further mechanical damage. This first phase may occur as a result of a variety of mechanical insults, including high-intensity impact or torsional loading of a joint, accelerated degradation of matrix macromolecules as a result of joint inflammation or similar insults, or as a result of metabolic changes in the tissue that interfere with the ability of chondrocytes to maintain the matrix.

The second stage begins when chondrocytes detect the tissue damage or alterations in osmolarity, charge density, or strain and release mediators that stimulate a brisk cellular response. The response consists of both anabolic and catabolic activity, as well as chondrocyte proliferation.[19,93,95,105-108,110,111] Anabolic and mitogenic growth factors presumably have an important role in stimulating synthesis of matrix macromolecules and chondrocyte proliferation; clusters or clones of proliferating cells surrounded by newly synthesized matrix molecules constitute one of the histologic hallmarks of the chondrocytic response to cartilage degeneration.[19,78,93,105-108,110,112] Nitric oxide may have a role in the chondrocyte response because chondrocytes produce this molecule in response to a variety of mechanical and chemical stresses.[113,114] It diffuses rapidly and can induce production of the cytokine IL-1, which stimulates expression of metalloproteases that degrade the matrix macromolecules. Fibronectin fragments or other molecules present in damaged tissue may promote continued production of IL-1 and enhanced release of proteases.[115-118] Degradation of type IX and type XI collagens and other molecules may destabilize the type II collagen fibril meshwork, leaving

many of the type II fibrils intact initially, but allowing expansion of aggrecan and increased water content. Disruption of the superficial zone, a decline in aggregation, and an associated loss of aggrecan resulting from enzymatic degradation, would increase the stresses on the remaining collagen fibril network and chondrocytes with joint loading. Enzymatic degradation also clears damaged and intact matrix components[95,100] and may release anabolic cytokines previously trapped in the matrix that stimulate synthesis of matrix macromolecules and chondrocyte proliferation.

In the second stage of osteoarthritis, the repair response (that is, increased synthesis of matrix macromolecules and to a lesser extent cell proliferation) counters the catabolic effects of the proteases and may stabilize or, in some instances, restore the tissue. The repair response may last for years and in some patients reverses the course of osteoarthritis, at least temporarily. Furthermore, some therapeutic interventions have the potential for facilitating the repair response. For example, studies of osteoarthritic hips and knees following osteotomy show that altering the joint mechanical environment will stimulate restoration of an articular surface in some instances.[25,119-121]

Failure to stabilize or restore the tissue leads to the third stage in the development of osteoarthritis, which is progressive loss of articular cartilage and a decline in the chondrocytic anabolic and proliferative response.[93,105,106,108,110] This decline could result from the mechanical damage and death of chondrocytes that are no longer stabilized and protected by a functional matrix, but it also appears to be related to or initiated by a downregulation of chondrocyte response to anabolic cytokines. This may occur as a result of synthesis and accumulation of molecules in the matrix that bind anabolic cytokines, including dEcoRIn, insulin-dependent growth factor binding protein, and other molecules that can affect cytokine

function. The loss of articular cartilage leads to the clinical syndrome of osteoarthritis, typically characterized by joint pain and loss of joint function. The joint degeneration responsible for osteoarthritis occurs more frequently with increasing age possibly because age-related changes in the cartilage matrix and a decrease in the chondrocyte anabolic response compromise the ability of the tissue to maintain and restore itself.[15,18,19]

Alterations of the subchondral bone that accompany the degeneration of articular cartilage include increased subchondral bone density or subchondral sclerosis, formation of cyst-like bone cavities containing myxoid, fibrous or cartilaginous tissue, and the appearance of regenerating cartilage within and on the subchondral bone surface. This response is usually most apparent on the periphery of the joint where bony and cartilaginous excrescences sometimes form sizable osteophytes. Increased subchondral bone density resulting from formation of new layers of bone on existing trabeculae is usually the first sign of degenerative joint disease in subchondral bone; however, in some joints, subchondral cavities appear before a generalized increase in bone density. At the end stage of the disease, the articular cartilage has been completely lost, leaving thickened, dense subchondral bone articulating with a similarly opposing denuded bony surface. The bone remodeling combined with the loss of articular cartilage changes the shape of the joint and can lead to shortening of the involved limb, deformity, and instability.

In most synovial joints, the growth of osteophytes accompanies the changes in articular cartilage and subchondral and metaphyseal bone. These fibrous, cartilaginous, and bony prominences[122] usually develop around the periphery of the joint (marginal osteophytes typically develop at the cartilage bone interface; capsular osteophytes typically develop along joint capsule insertions). Intra-

articular bony excrescences that protrude from degenerating joint surfaces are referred to as central osteophytes.[123] Most marginal osteophytes have a cartilaginous surface that closely resembles normal articular cartilage and may appear to be extensions of the joint surface. In superficial joints, they usually are palpable and may be tender; and in all joints, they can restrict motion and contribute to pain with motion. Each joint has a characteristic pattern of osteophyte formation. In the hip, they usually form around the rim of the acetabulum and the femoral articular cartilage. A prominent osteophyte along the inferior margin of the humeral articular surface commonly develops in patients with degenerative disease of the glenohumeral joint. Osteophytes are thought to represent a response to degeneration of articular cartilage and subchondral bone remodeling, including release of anabolic cytokines that stimulate cell proliferation and formation of bony and cartilaginous matrices.[124,125]

Loss of articular cartilage leads to secondary changes in the synovium, ligaments, capsules, and the muscles that move the involved joint. The synovial membrane often develops a mild to moderate inflammatory reaction and may contain fragments of articular cartilage.[126] With time, the ligaments, capsules, and muscles become contracted. Decreased use of the joint and decreased range of motion leads to muscle atrophy. These secondary changes often contribute to the stiffness and weakness associated with osteoarthritis.

Osteoarthritis most commonly develops in the absence of a known cause, in which instance it is called primary or idiopathic osteoarthritis. Less frequently, osteoarthritis develops as a result of joint injury, infection, or one of a variety of hereditary, developmental, metabolic, and neurologic disorders, in which instance it is referred to as secondary osteoarthritis (Table 1). The age of onset of secondary osteoarthritis depends on

the underlying cause; thus, it may develop in young adults and even children as well as in the elderly. In contrast, a strong association exists between the prevalence of primary osteoarthritis and increasing age. Numerous suggestions have been made concerning the pathogenesis of primary osteoarthritis, including aging, genetic predisposition, hormonal and metabolic disorders, inflammation, and immunologic disturbances.

Aging

Although the incidence and prevalence of osteoarthritis increase rapidly in those older than 40 years, the age-related changes in the chondrocytes and matrix are typically not those of osteoarthritis. Nonetheless, age-related changes in articular cartilage, particularly the loss of the ability of chondrocytes to maintain and restore the tissue, increase the risk of joint degeneration.[21,22]

Genetic Predisposition

It is evident that some of the disease processes, such as hand and foot deformities, have a genetic and gender-specific origin; however, this factor alone is insufficient evidence to support the frequency and distribution of the disease process as either gender-specific or a genetic predisposition.

Hormonal and Metabolic Disorders

Patients with acromegaly may develop spectacular osteoarthritis, but studies seeking alterations in this and other hormonal influences have failed to locate a single characteristic alteration that could lead to the disease. Similarly, in patients with alkaptonuric ochronosis, osteoarthritis is characteristic, and those with Paget's disease often have severe compromise of joints related to a variation in structural change on the two sides of the joint. Nevertheless, no findings have ever uncovered data to support any hormonal or metabolic factor or joint disease as an identifiable cause of this widespread disorder.

Table 1
Causes of Secondary Osteoarthritis

Cause	Presumed Mechanism
Joint injuries	Damage to articular surface and/or residual joint incongruity and instability
Joint dysplasias (developmental and hereditary joint and cartilage dysplasias)	Abnormal joint shape and/or abnormal articular cartilage
Aseptic necrosis	Bone necrosis leads to collapse of the articular surface and joint incongruity
Acromegaly	Overgrowth of articular cartilage produces joint incongruity and/or abnormal cartilage
Paget's disease	Distortion or incongruity of joints resulting from bone remodeling
Ehlers-Danlos syndrome	Joint instability
Gaucher's disease (hereditary deficiency of the enzyme glucocerebrosidase leading to accumulation of glucocerebroside)	Bone necrosis or pathologic bone fracture leading to joint incongruity
Stickler's syndrome (progressive hereditary arthro-ophthalmopathy)	Abnormal joint and/or articular cartilage development
Joint infection (inflammation)	Destruction of articular cartilage
Hemophilia	Multiple joint hemorrhages
Hemochromatosis (excess iron deposition in multiple tissues)	Mechanism unknown
Ochronosis (hereditary deficiency of enzyme, homogentisic acid oxidase leading to accumulation of homogentisic acid)	Deposition of homogentisic acid polymers in articular cartilage
Calcium pyrophosphate deposition disease	Accumulation of calcium pyrophosphate crystals in articular cartilage
Neuropathic arthropathy (Charcot joints: syphilis, diabetes mellitus, syringomyelia, meningomyelocele, leprosy, congenital insensitivity to pain, amyloidosis)	Loss of proprioception and joint sensation results in increased impact loading and torsion, joint instability and intra-articular fractures

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Inflammation

Inflammatory activist agents, principally those of the interleukin series, may be active materials in the development of joint damage. This appears to relate primarily to the activation of the degradative cascade. The cause of synovial inflammation is not clear, but it may be associated with the release of materials from damaged cartilage. This suggests that inflammatory activist agents do not cause the disease, but perpetuate it.

Immunologic Disturbances

There is ample evidence to suggest that some of the materials present in articular cartilage are not only unique, but under ordinary circumstances are also hidden from the vascular system and the rest of the body. No chemical knowledge or, more importantly, no immunologic knowledge is yet available regarding articular cartilage, which has no blood, nerve, or lymphatic supply and is sealed in a sepulcher with a fibrous membrane at the surface and a tidemark at the bottom. It is possible that when some of the cartilaginous materials escape from the sepulcher, it may cause a significant amount of synovial inflammation, which can cause the release of agents and thereby degrade the cartilage.

Joint Injury and Posttraumatic Osteoarthritis

Injuries to articular surfaces, menisci, joint capsules, and ligaments increase the risk of joint degeneration that leads to a form of osteoarthritis called posttraumatic osteoarthritis.[127-130] Joint injury is a discrete event, and investigating its effects on articular cartilage could potentially clarify the pathogenesis of osteoarthritis in general. Important insights have come from cruciate ligament transection in animal models of knee degeneration, adding to the understanding of how loss of joint stability can cause abnormal loading and proprioception. Clinically, however, despite the development of surgical interventions that can restore mechanical stability and function to a patient's knee joint after ligament damage, these procedures do not appear to greatly reduce the risk for the development of osteoarthritis. This suggests that in addition to the effects of subsequent functional impairment, the initial traumatic event may have irreversible effects on the joint tissues and resident cells.

Groundbreaking insights concerning the molecular mechanisms of cartilage degeneration in vivo have come from a series of analyses of synovial fluid samples taken from Swedish patients after an anterior cruciate ligament or meniscal tear.[131] The concentration of proteoglycan fragments in the synovial fluid was found to be elevated twofold to threefold after injury, which was similar to those concentrations found in patients with primary osteoarthritis. The synovial fluid was also analyzed by enzyme-linked immunosorbent assay for proteins including matrix metalloproteinase stromelysin-1, which represents one of the major pathways for proteoglycan degradation. Matrix metalloproteinase stromelysin-1 levels in synovial fluid were markedly increased at presentation and remained elevated for many years. Joint fluid also showed an initial 15-fold and long-term elevation of the neoepitope Col2CTx in

the C-telopeptide cross-linking domain of type II collagen, indicating digestion of mature, cross-linked collagen by a matrix metalloproteinase. In addition, clinical studies suggest that both proteoglycan and collagen degradation rates are significantly altered within days of the injury and that these changes are not transient and remain altered for years. Thus, the acute response of the joint tissues to the original mechanical insult may initiate an unbalanced degradative process that leads to an increased risk for joint degeneration.

In the past 10 years, in vitro models of acute compressive trauma to articular cartilage have demonstrated events that can occur immediately following cartilage injury.[131-133] In particular, several studies have characterized the resulting damage to the cartilage matrix, including loss of proteoglycan to the culture medium, increased tissue swelling, and increased levels of denatured collagen neoepitopes. In vitro models have also started to focus on identifying the effects of injurious compression on the chondrocytes themselves. Under certain conditions, injury can cause cell death by apoptosis and can abolish the normal upregulation of chondrocyte biosynthesis by dynamic compression. The possibility that apoptosis may be induced at levels of mechanical loading even below the threshold levels that cause macroscopic damage to the cartilage matrix, as assessed by tissue swelling and glycosaminoglycan loss, suggests that apoptosis can be triggered by direct loading injury to the chondrocytes. Joint injury may also initiate or accelerate the age-related loss of chondrocyte function, thereby decreasing the ability of the cells to maintain the tissue.[21]

Summary

The unique biologic and mechanical properties of articular cartilage depend on the design of the tissue and the interactions between chondrocytes and the matrix that maintain the tissue. Chon-

drocytes form the tissue matrix macromolecular framework form three classes of molecules: collagens, proteoglycans, and noncollagenous proteins. The matrix protects the cells from injury caused by normal joint use, determines the types and concentrations of molecules that reach the cells, and helps maintain the chondrocyte phenotype. Throughout life, articular cartilage undergoes continual internal remodeling as the cells replace matrix macromolecules lost through degradation. The available evidence indicates that normal matrix turnover depends on the ability of chondrocytes to detect alterations in matrix macromolecular composition and organization, including the presence of degraded molecules, and respond by synthesizing appropriate types and amounts of new molecules. In addition, the matrix acts as a signal transducer for the cells. Loading of articular cartilage by joint use creates mechanical, electrical, and physicochemical signals that help direct chondrocyte synthetic and degradative activity. Aging leads to alterations in matrix composition and in chondrocyte activity, including the ability of the cells to respond to a variety of stimuli such as growth factors. These alterations may increase the probability of articular cartilage degeneration. Degeneration of articular cartilage that leads to osteoarthritis is among the most common causes of pain and disability for middle-aged and older people. The strong correlation between increasing age and the prevalence of joint degeneration and recent evidence of important age-related changes in chondrocyte function suggest that chondrocyte aging contributes to the development and progression of joint degeneration. Clinical and basic investigations of the pathogenesis of posttraumatic osteoarthritis, the form of osteoarthritis that develops following joint injury, are helping to explain how joint degeneration develops and progresses.

Acknowledgment

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