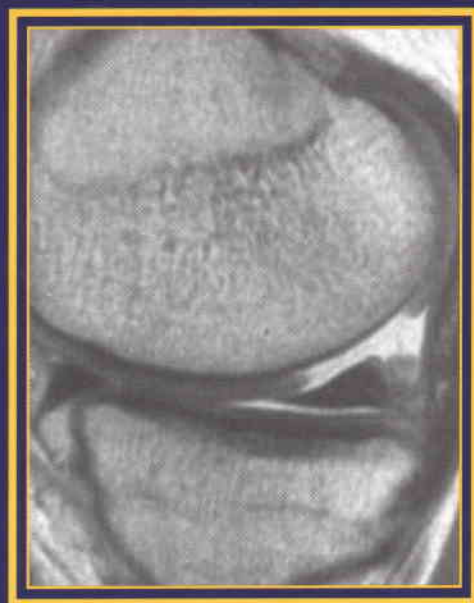


CARTILAGE REPAIR STRATEGIES

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Articular Cartilage

Structure, Biology, and Function

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Summary

The dynamic structure and function of articular cartilage is explored in detail in this chapter. Emphasis is placed on the ultrastructure of cartilage and how this provides for its remarkable physical properties.

Key Words: Hyaline cartilage; chondrocyte; proteoglycan; biomechanics; biology.

INTRODUCTION

Articular cartilage has extraordinary mechanical properties and lasting durability even though it is only a few millimeters thick. Its unique structure and composition provides joints with a surface that combines low friction with high lubrication, shock absorption, and wear resistance while bearing large repetitive loads throughout a person's lifetime. These characteristics are clearly unmatched by any synthetic material.

Despite performing with relatively low metabolic activity within a harsh physical environment, healthy articular cartilage has amazing capacity to sustain itself and carry out its functions. Chondrocytes are active in maintaining the tissue's matrix, yet there is limited capability for repair. Damage to cartilage's high level of organization and molecular architecture from trauma or degeneration is a major source of morbidity.

STRUCTURE AND COMPOSITION

A thorough understanding of the complex structure of articular cartilage is essential for understanding its biology and function. Grossly, articular cartilage is a specialized hyaline cartilage found in diarthrodial joints; it has a firm, smooth, slippery surface that resists plastic deformation (Fig. 1). Microscopically, articular cartilage is made up primarily of extracellular matrix (ECM) surrounding a single cell type, the chondrocyte (Fig. 2). There are no blood vessels, lymphatics, or nerves within articular cartilage. In decreasing concentrations, the ECM consists of water, proteoglycan (PG), collagen (primarily type II), and a variety of other proteins and glycoproteins.

The macrostructure of articular cartilage is best described in four distinct zones: superficial, transitional, deep, and calcified. Within each zone, the structure and composition vary. Light microscopy of the different zones reveals variable chondrocyte appearance; unique collagen fibril size, shape, and orientation; as well as different PG and water contents (Fig. 3). The ECM within each zone can also be divided into distinct regions. These regions have been defined as the pericellular region, territorial region, and interterritorial region.

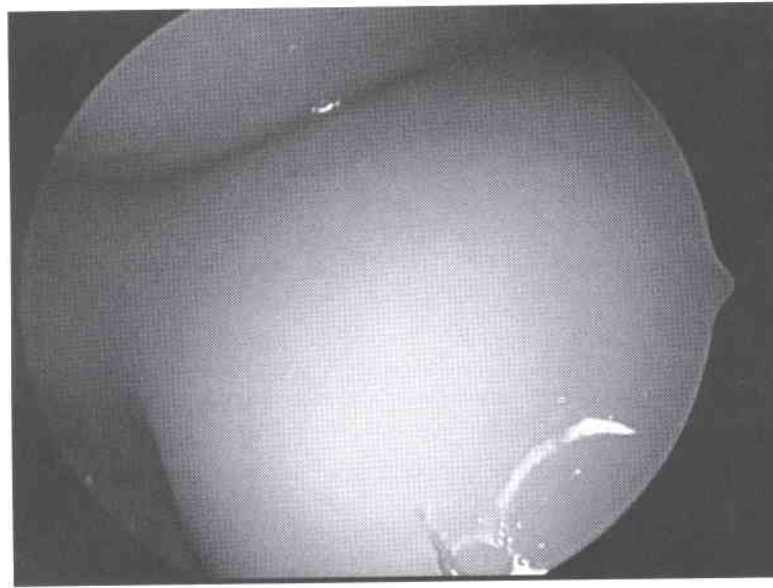


Fig. 1. Gross photograph of human knee articular cartilage.

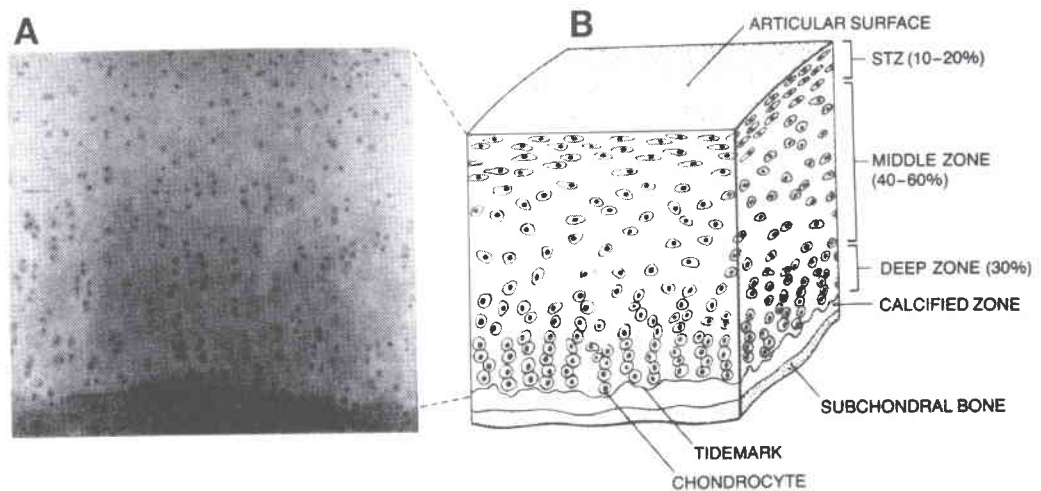


Fig. 2. Healthy articular cartilage structure. Histologic (A) and schematic (B) views of a section of normal articular cartilage. There are four zones: the superficial tangential zone (STZ), the middle zone, the deep zone, and the calcified zone. The cells in the superficial zone have an ellipsoidal shape and lie parallel to the surface; the cells of the other zones have a more spherical shape. In the deep zone, the chondrocytes align themselves in columns perpendicular to the surface. (Reprinted from ref. 24. Used with permission.)

Articular Cartilage Zones

The outermost articular gliding surface, or *superficial zone*, is covered by a fine layer called the lamina splendens. Within the superficial zone, the collagen fibrils are oriented parallel to the surface. The chondrocytes are elongated. The PG content is at its lowest; water content is at its highest.

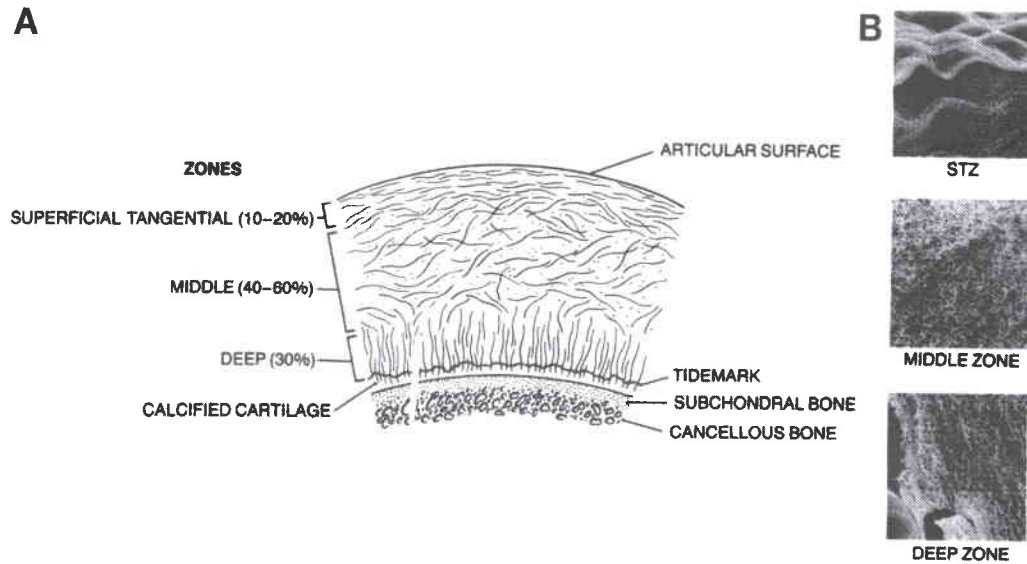


Fig. 3. Schematic (A) and scanning electron micrographs (B) of the interterritorial matrix collagen fibril orientation and organization in normal articular cartilage. In the superficial tangential zone (STZ), the fibrils lie nearly parallel to the surface. In the middle zone, they assume a more random alignment. In the deep zone, they lie nearly perpendicular to the articular surface. (Reprinted from ref. 24. Used with permission.)

The *transitional zone* is below the superficial zone and is characterized by larger diameter collagen fibers with less organization. The chondrocytes in this region are rounder and on electron microscopy appear to have intracellular components consistent with a metabolically active cell (1).

Below this zone is the *deep zone*; it contains large-diameter collagen fibers oriented perpendicular to the articular surface. The chondrocytes appear spherical and are arranged in a columnar pattern. PG concentration is the highest in this zone, and the water content is lowest.

The final zone of articular cartilage is called the *calcified zone*; it is separated from the deep zone by the *tidemark*. This deepest layer is a transitional area that anchors the overlying hyaline cartilage to the subchondral bone (2,3). This stiff zone likely blocks the transport of nutrients from the underlying bone, rendering articular cartilage dependent on synovial fluid for nutritional support. The cells in this zone are small and distributed randomly in a matrix filled with apatitic salts.

Articular Cartilage Regions

The ECM of articular cartilage is also divided into regions based on proximity to the chondrocyte. These regions are the pericellular, territorial, or interterritorial and differ in content and in collagen fibril diameter and organization. The *pericellular matrix* completely surrounds the chondrocyte, forming a thin layer around the cell membrane. This matrix region may play a functional biomechanical role for signal transduction within cartilage during loading (4). The pericellular matrix contains PG and noncollagenous matrix components but little or no collagen fibrils.

The *territorial matrix* surrounding the pericellular region contains thin collagen fibrils that form a fibrillar network at its periphery (5). This possibly provides mechanical protection for

the chondrocytes during loading (4). The *chondron* is defined as the chondrocyte and its surrounding pericellular and territorial matrix regions.

Finally, the *interterritorial region* is the largest of all regions and contributes most to the material properties of articular cartilage (6). This region encompasses the entire matrix between the territorial matrices of the individual cells. Large collagen fibrils and the majority of the PG reside in this region. The collagen fibrils within the interterritorial region change orientation depending on the zone of articular cartilage. The interterritorial collagen fibrils are arranged parallel to the surface in the superficial zone, obliquely in the middle zone, and perpendicular to the joint surface in the deep zone. Because the tensile stiffness and strength of articular cartilage is provided primarily by collagen, and the interterritorial matrix forms most of the volume, it follows that the biomechanical properties should differ in the various cartilage zones. This has been proven experimentally (7).

Chondrocytes

The chondrocyte is the only cell type within articular cartilage. Despite their presence throughout the tissue, chondrocytes occupy less than 10% of the total volume. Each chondrocyte is surrounded by its ECM, has few cell-to-cell contacts, and relies on diffusion for nutritional support. The chondrocyte shape and size varies depending on its zonal position. The superficial cells are ellipsoidal and are aligned parallel to the surface. The transitional cells are spherical and are randomly distributed. The deep cells form columns aligned perpendicular to the tidemark and the calcified zone.

Chondrocytes are derived from mesenchymal cells. Their primary function is to maintain the ECM, the component of articular cartilage that provides its unique material properties. Chondrocytes rarely divide after skeletal growth is completed. The chondrocyte is metabolically active and able to respond to environmental stimuli and soluble mediators, including growth factors, interleukins, and certain pharmaceuticals. They are responsive to mechanical loads, hydrostatic pressure changes, osmotic pressure changes, and injury and degenerative arthritis.

Extracellular Matrix

In normal articular cartilage, 65–80% of the total weight is water (8). Collagens and PGs are the two major load-bearing macromolecules in articular cartilage. Other classes of molecules make up the remaining ECM; these include lipids, phospholipids, proteins, and glycoproteins.

Water

Water content in articular cartilage varies from approx 80% of the wet weight at the surface to 65% in the deep zone (8,9). A small percentage of water is contained in the intracellular space, approx 30% is found within the collagen in the intrafibrillar space, and the molecular pore space of the matrix holds the balance (10). The extracellular tissue fluid contains inorganic dissolved salts of sodium, calcium, chloride, and potassium. The flow of water through cartilage and across the articular surface aids in the transport of nutrients to chondrocytes.

Tissue water has a crucial biomechanical function in cartilage. Together with its interaction with PGs, water provides articular cartilage with tremendous compressive strength. The small pore size of the ECM causes high frictional resistance to fluid flow. It is this frictional resistance coupled with the pressurization of the water within the ECM that is responsible for the compressive strength and ability of articular cartilage to withstand high joint loads. (Details of this important interaction between tissue fluids and large matrix macromolecules

that influences the material properties of articular cartilage are described in the section on biology and function.)

Collagens

A variety of collagen types, synthesized by chondrocytes, compose the major structural macromolecules of the ECM. Collagens contribute approx 60% of the dry weight of cartilage and are distributed throughout the various zones in a relatively uniform concentration but variable orientation as described previously. The unique structure of collagen provides articular cartilage with its tensile strength.

The collagen in articular cartilage is 90–95% type II, with minor contributions by types V, VI, IX, X, and XI. All collagen types are composed of three polypeptide chains (α -chains) wound into a triple helix. The amino acid composition of the polypeptide chains is primarily glycine and proline, with hydroxyproline providing stability via hydrogen bonds along the length of the molecule. In addition, hydroxylysine is involved in creating covalent crosslinks that stabilize the collagen fibrillar structure (9).

The cross-banded fibrils visible on electron microscopy are formed primarily by collagen types II, IX, and XI (11). These extend throughout the tissue to provide tensile stiffness and strength. Importantly, they also act as a meshwork to trap large PGs. Cartilage achieves its compressive strength in part by the swelling of these trapped PGs.

Proteoglycans

Proteoglycans make up approx 10–15% of the wet weight of articular cartilage. Produced by chondrocytes, PGs are secreted into the ECM. The basic structure of a PG is that of a complex macromolecule consisting of a protein core with covalently bound glycosaminoglycan (GAG) side chains. This is called the *PG aggrecan molecule*. The PG aggrecans bind to hyaluronan in the presence of a link protein to form the aggregate. Many aggrecan molecules can bind to a single long hyaluronan chain to form a large PG aggregate (Fig. 4). Aggrecans occupy the interfibrillar space of the cartilage matrix and contribute about 90% to the total cartilage matrix PG (12).

A single GAG is an unbranched chain of repeating disaccharide units, of which there are three major types found in articular cartilage: chondroitin sulfate 4- and 6-isomers, keratan sulfate, and dermatan sulfate. Each disaccharide unit has a negatively charged carboxylate or sulfate group, creating a structure that effectively repels other negatively charged molecules and attracts water and positive counterions such as Ca^{2+} and Na^+ to maintain electroneutrality. These ions are found free floating within the interstitial water. The negative charge of each keratan sulfate and chondroitin sulfate chain repels each other, which tends to maintain the molecules in an expanded form, thus facilitating the trapping of the PGs within the collagen framework.

Hyaluronate, although itself considered a GAG, is not sulfated like those described above, nor is it bound to a protein core. In articular cartilage, hyaluronate is present as large unbranching chains to which the chondroitin and keratan sulfate chains are bound by the link proteins. This provides strong structural stability to this macromolecule, the aggregate. Loss of the link protein to aging or arthritis essentially weakens the ECM of articular cartilage by decreasing the size of the PG aggregate. The length, weight, and composition of an individual aggrecan are variable and are determined primarily by the length of its protein core.

To summarize, the large PG aggregate is composed primarily of chondroitin sulfate and keratan sulfate chains associated with hyaluronic acid filaments and link proteins. In addition,

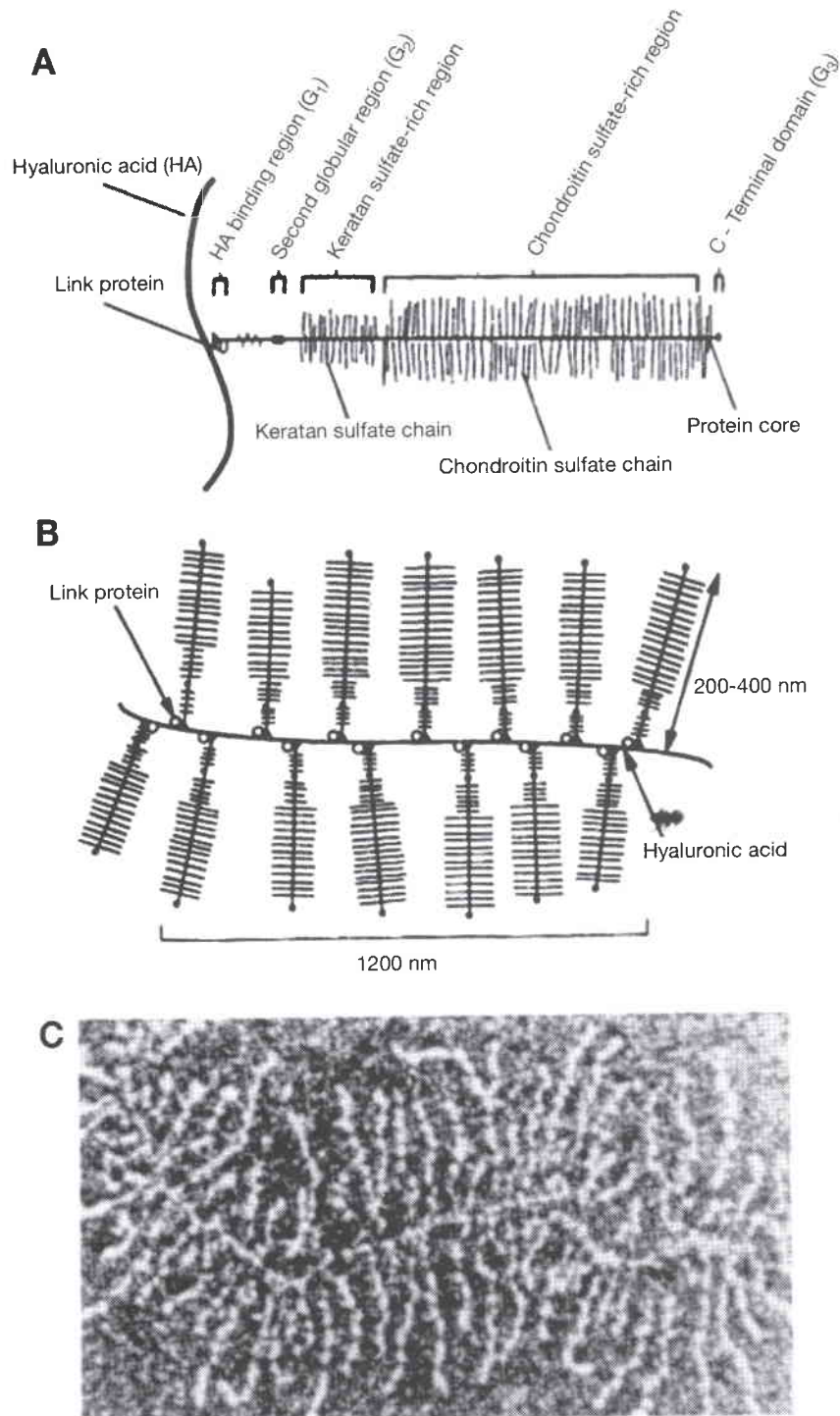


Fig. 4. The structure of proteoglycan. (A) Details of proteoglycan monomer structure showing chondroitin sulfate and keratan sulfate chains and the interaction of the monomer with hyaluronate chain and link protein. (B) Molecular conformation of a typical proteoglycan aggregate showing size of the molecule. (C) An electron micrograph of a proteoglycan aggregate. (Reprinted from ref. 25. Used with permission.)

biglycan and decorin, two smaller, nonaggregating PGs rich in dermatan sulfate, are found in articular cartilage. Although these are much smaller PGs, they equal the larger aggrecan molecule in total number. Biglycan and decorin are found in association with collagen fibrils.

Noncollagenous Proteins and Glycoproteins

The noncollagenous proteins and glycoproteins are poorly studied proteins with occasional monosaccharides and oligosaccharides attached. They are found within the ECM and are likely involved in maintaining structure. These include anchorin CII, a chondrocyte surface protein; cartilage oligomeric protein, an acidic protein found within the territorial matrix; and fibronectin and tenascin.

CARTILAGE BIOLOGY AND FUNCTION

Articular cartilage is a living, active tissue formed and maintained by chondrocytes. These cells are derived from mesenchymal stem cells that differentiate prior to the eighth week of gestation. The chondrocyte survives without blood vessels, lymphatic vessels, or nerves. Standing alone within its matrix, the chondrocyte creates an ordered structure capable of complex interactions that are required to maintain and repair the tissue (1).

It has not been fully elucidated how the chondrocyte obtains nutrition to fuel its metabolism; however, contact between articular cartilage and its vascularized subchondral bone appears to be crucial. In addition, synovial fluid provides chondrocytes with nutrients via diffusion. A double-diffusion barrier requires passage through the synovium first, followed by passage through the ECM to the chondrocyte. Metabolism in articular cartilage is primarily anaerobic in an environment with very low oxygen concentration.

Chondrocytes are metabolically active despite the static appearance of the cells. Basic housekeeping and maintenance of the articular surface requires that chondrocytes turn over the matrix biomacromolecules by replacing degraded matrix components. Chondrocytes must be able to respond to changes in the matrix composition (which occurs with macromolecular degradation) by synthesizing proper types and amounts of these biomacromolecules (1,5).

Biomechanics

Articular cartilage serves the human body by providing for load transmission through joints. The articular cartilage of the knee joint experiences an average load of three times the body weight. With everyday activities, the knee can be exposed to loads ranging up to 10 times body weight during running and 20 times body weight during jumping (13). The structure of articular cartilage enables it to store, transmit, and dissipate this mechanical energy during activity. Articular cartilage must be capable of storing energy; otherwise, it would compress with a permanent loss of thickness, or it would succumb to the forces and tear. In normal conditions, cartilage stores energy as it deforms, and then it dissipates the energy and returns to its form without tearing. Tremendous stresses and strains are developed within the tissue of articular cartilage during normal daily activities.

Articular cartilage has well-defined tensile and compressive properties. The crosslinking among collagen fibrils is primarily responsible for the tensile strength but does little to resist compression. The relationship of PGs and water trapped within the collagen meshwork provides resistance to compression, swelling pressure, and resilience. PGs contain negatively charged GAG chains. These chains attract cations and water and repel each other. By repelling each other, the GAG chains hold the monomers extended, which allows for the filling of the

collagen fibril meshwork with water. Compression of the matrix drives the GAG chains together, which increases resistance to further compression as the desire to repel nearby chains remains. Water is forced out of the macromolecules and returns when the compressive load is released.

Articular cartilage is biphasic. It is important to understand this characteristic of articular cartilage as it is essential to its ability to withstand the high repetitive loads to which it is exposed over decades. The solid phase includes the macromolecular framework of collagens, PGs, and noncollagenous proteins; the fluid phase refers to the tissue water composing 65–80% of the total weight. The biomechanical properties of articular cartilage depend on the interaction of these two phases. In general, it is the fluid phase that accounts for deformational behaviors of hydrated soft tissues (14).

The solid matrix is porous and permeable, allowing the water that resides in the microscopic pores to flow through the matrix when loads are applied. Fluid pressure provides a major part of the total load support, thus minimizing the stress appreciated by the solid matrix. This is referred to as stress shielding of the solid matrix. For healthy cartilage, greater than 95% of the applied load in normal activities will be supported by the interstitial fluid (8,15).

Articular cartilage is viscoelastic. Viscoelasticity describes the material property of having stress-strain behavior dependent on strain rate (14). When a constant compressive stress is applied to cartilage, its deformation will increase with time. There are two mechanisms responsible for viscoelasticity in articular cartilage: flow-independent and flow-dependent mechanisms. The flow-independent aspect of its viscoelastic behavior derives from the intermolecular friction of cartilage's PG matrix. The flow-dependent mechanism depends on interstitial fluid flow and its resultant frictional drag. (A fluid's frictional drag is the reciprocal of the permeability, such that a substance with low permeability will have a high frictional drag.) The drag resulting from interstitial fluid flow is the main source for the viscoelastic behavior of healthy articular cartilage. Cartilage in degenerative joint disease has increased permeability and water content and therefore has lower friction drag and less ability to provide a stress-shielding effect to protect the ECM (8,16).

Articular cartilage also demonstrates creep and stress relaxation. These mechanical properties result primarily from fluid flow through the matrix when articular cartilage is compressed (15). *Creep behavior* refers to a viscoelastic material responding with rapid initial deformation when a constant load is applied, followed by further slow deformation up to an equilibrium state. *Stress relaxation behavior* is when a constant deformation leads to high initial stress followed by a slow progressive decrease in the stress required to maintain the deformation.

In shear, creep and stress relaxation are flow independent and are derived from the intermolecular friction within the collagen-PG matrix and an alteration of the macromolecular framework. The random organization of the collagen architecture through the middle zones contributes most to the shear properties of articular cartilage.

It is the intact collagen fibril meshwork that restrains the expansion of PGs with tissue fluid. Mechanical failure of the matrix and degenerative arthritis result from a disruption of the collagen fibril framework and the subsequent expansion of PGs with an increased water concentration. This decreases cartilage stiffness and increases matrix permeability, making the tissue less capable to support load (15).

Metabolism

Given the low oxygen content and avascular nature of articular cartilage, a surprisingly high level of metabolism exists. The chondrocyte relies primarily on the anaerobic pathway

for energy. Chondrocytes synthesize matrix components, including proteins and GAG chains, and secrete these substances into the ECM. In addition, the chondrocyte is responsible for ECM remodeling via an elaborate group of degradative enzymes. Therefore, it is the chondrocyte that maintains the normal ECM by balancing synthesis of matrix components with their catabolism and release. This metabolic activity of the chondrocyte can be altered by its surrounding chemical and mechanical environment. Cytokines appear to play a role in controlling the balance between matrix macromolecular degradation and synthesis. The ECM plays an important role in transmitting to the chondrocyte chemical, electrical, and mechanical signals created during loading of the articular surface. The chondrocyte responds by altering the matrix structure. Cytokines may be the messenger acting through either autocrine or paracrine means. It is unclear which signals—electrical, mechanical, or physiochemical—are most important in stimulating the activity of the aneural chondrocyte (4,8,17).

PG molecules are synthesized, assembled, sulfated, and secreted into the ECM by the chondrocyte. The control over PG synthesis is responsive to biochemical, mechanical, and physical stimuli. Maintenance of articular cartilage requires continual degradation and release of PGs by articular cartilage. The rate of catabolism is affected by soluble mediators, such as interleukin 1, which accelerates degradation. Joint load can also play a role; for example, immobilization has been found to lead to a loss of PGs from the matrix (17,18). PG fragments such as keratan sulfate can be quantified in body fluids such that synovial fluid concentrations can be used to measure catabolic activity in the cartilage of a particular joint (19,20). Further research on the utility of this information in diagnosis or treatment of early degenerative disease is warranted.

Collagen synthesis and catabolism are both partially under enzymatic control. In addition, growth factors have been found to play an intricate role in cartilage metabolism. The methods by which growth factors influence the chondrocyte are not fully clear; however, cell surface receptor sites are present on the chondrocyte. Platelet-derived growth factor appears to have a mitogenic effect on chondrocytes and may be involved in the healing response in osteoarthritis and lacerative injury (21). Basic fibroblast growth factor, insulinlike growth factors, and insulin are stimulators of deoxyribonucleic acid (DNA) synthesis and matrix production in articular cartilage as well as in the growth plate. Transforming growth factor- β is synthesized by chondrocytes locally and stimulates PG synthesis while suppressing type II collagen synthesis.

Chondrocytes themselves synthesize proteolytic enzymes that are responsible for the breakdown of the cartilage matrix, both in normal turnover and in cartilage degeneration. The primary proteinases involved in cartilage turnover include the metalloproteinases (collagenase, gelatinase, and stromelysin) and the cathepsins (cathepsin B and D), which have the ability to degrade aggrecan. Collagenase is specific in its activity because it cleaves the triple-helical portion of collagen at a single site. Gelatinase then cleaves the denatured α -chains that remain after collagenase activity. Stromelysin acts to break down the protein core of aggrecan. These metalloproteinases all require activation outside the cell by enzymatic modification. For example, collagenase can be activated by plasmin.

Joint motion and loading are required to maintain normal adult articular cartilage structure and function (1). The balance between degradation and synthesis by the chondrocyte is altered when joint loading exceeds or falls below the necessary range (22). Prolonged joint immobilization also leads to cartilage degeneration (1). Normal diffusion of nutrients from the synovial fluid is diminished. In addition, the PG content is decreased, and its structure is altered. Remobilization can reverse the changes in PG (23). Orthopedists today are more

Table 1
Articular Cartilage Composition

<i>Major components</i>	<i>Approximate wet weight (%)</i>
Water	65–80
Type II collagen	10–20
Aggrecan	5
<i>Minor components (<5%)</i>	
Proteoglycans	
Biglycan	
Decorin	
Collagens types V, VI, IX, X, XI	
Link protein	
Hyaluronate	
Fibronectin	
Lipids	

aggressive about maintaining joint motion after injury or surgery because of the increased understanding of the deleterious effects to cartilage of rigid immobilization.

Age-Related Changes

The size of the PG aggregates in the ECM of articular cartilage decreases with age. This occurs as a result of shortening of the hyaluronic acid (HA) chain, such that there are fewer aggrecans attached, or as a result of shortening of the protein core or the GAG chains. In addition, there is a change in the PG at the molecular level such that the concentration of chondroitin sulfate 4 diminishes and chondroitin sulfate 6 increases. However, the overall concentration of chondroitin sulfates decreases and that of keratan sulfate increases. Chondrocytes become larger with aging and acquire increased lysosomal enzymes. The overall protein content increases with aging, and the water content diminishes. As a result of these changes, cartilage stiffness increases, and solubility and elasticity diminish.

Although age-related changes to articular cartilage can be expected eventually in everybody, complex changes to articular cartilage can also result from a variety of intra-articular pathological conditions. It is beyond the scope of this chapter to review the variety of adaptive responses and alterations that take place in articular cartilage in the pathological state.

SUMMARY

Articular cartilage is a dynamic and responsive tissue despite its low metabolic activity and relatively poor ability to heal. The function of articular cartilage is to provide joints with a low-friction and wear-resistant surface that provides shock absorption and high load-bearing capability. The chondrocyte, the only cell type in articular cartilage, is responsible for the production of crucial structural components, including collagen, PGs, and various enzymes, which determine the complex biomechanical properties of the tissue.

The close relationship between articular cartilage's composition and its structural integrity and function enhances our understanding of the effects of aging, degenerative disease, and

injury. Although many growth factors have been discovered in the last decade, future investigations are certain to identify an array of articular cartilage growth factors that may lead to important advances in the treatment of articular cartilage pathology.

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