Restoration of Injured or Degenerated Articular Cartilage

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Abstract

Intra-articular fractures, ligamentous and meniscal injuries, and articular cartilage breakdown are major causes of degenerative joint disease. Lesions on the articular surface seem to have a limited capacity for repair and often progress inexorably toward osteoarthritis. Recent studies on joint immobilization and cartilage atrophy, however, have shown that repair and remodeling of articular cartilage may be possible. Currently used clinical methods of stimulating cartilage repair and remodeling include alteration of the loading on degenerated joints (primarily by using osteotomies), introduction of new cartilage-forming cells by perforation of subchondral bone, and soft-tissue arthroplasty. These procedures provide temporary relief in selected patients, but they often do not predictably restore long-term joint function. Experimentally, cartilage repair has been stimulated successfully with the use of allografts of periosteum and perichondrium, which serve as sources of cells with chondrogenic potential; introduction of cells grown in culture (stem cells or chondrocytes); stimulation by fibrin clot formation; artificial collagen matrices combined with cell transplants; and chondrogenic growth factors. The long-term success of all these methods has not been explored thoroughly, even in animal studies. Nevertheless, some research results are sufficiently encouraging to suggest that repair of the degenerating articular cartilage may be possible in the future.

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The pain and decreased mobility resulting from the loss or degeneration of the articular cartilage in synovial joints compromise the productivity and quality of life of millions of persons.[1-3] Unfortunately, all of the current treatments of synovial joint problems due to damaged or degenerating articular cartilage have significant limitations. Analgesic and anti-inflammatory medications, activity modification, and physical therapy may provide partial symptomatic relief, but they do not restore damaged articular cartilage to its normal state; thus, they rarely allow patients to return to full function for prolonged periods of time.[2] Surgical procedures, including arthrodesis and joint replacement, relieve joint pain, but they also have important limitations, especially for the younger patient who wants to pursue vigorous physical activities. Arthrodesis restricts mobility, causes muscular atrophy, and over time may have undesired effects on adjacent joints. Most artificial joints cannot withstand prolonged and frequent heavy loading, and wear and loosening of the prosthesis may lead to implant failure even in patients who have significantly restricted their activities. For these reasons, substantial efforts have been devoted to the search for biologic methods of restoring degenerating articular cartilage to normalcy before it reaches end-stage osteoarthritis.

The inability of cartilage to repair itself after traumatic injuries and the incapacity of treatment to arrest the osteoarthritic process have been described repeatedly for at least 250 years.[4] However, the clinical experience of treating damaged articular surfaces by osteotomy, abrasion arthroplasty, and fascial, periosteal, and perichondral interposition arthroplasties has shown that there is the potential of restoring some form of cartilaginous articulating surface even in severely injured or degenerated joints.[2,5] In addition, recent advances in cartilage biochemistry and morphology, cellular and molecular biology, and joint and tissue biomechanics[6] suggest that better methods of restoring articular

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surfaces can eventually be developed. This has long been one of the goals of orthopaedic surgery.

This review summarizes some potentially useful approaches to restoring injured or degenerating articular cartilage. It must be borne in mind that although both injury and degeneration involve disruption or loss of the cartilaginous articulating surfaces, the clinical problems, natural history, and potential for restoration of joint function are different.

Form and Function of Articular Cartilage

Articular cartilage consists of a large extracellular matrix with a sparse population of specialized cells, the chondrocytes (Fig. 1, A and B). The extracellular matrix is composed primarily of a mix of collagen (mainly type II) and proteoglycan aggrecan, with smaller amounts of other collagens, proteoglycans, proteins, and glycoproteins.[6] In normal articular cartilage, the collagen network has a well-defined ultrastructure (Fig. 1, C and D), which dictates the tensile stiffness and strength of each cartilage layer.[2,6] Because collagen and proteoglycan form a fiber-reinforced composite material, the collagen network also provides shear stiffness and strength to the tissue. The texture of the normal articular cartilage surface is relatively smooth and is composed of tightly woven sheets of collagen.

In normal articular cartilage, many aggrecan molecules (Fig. 2) bind to a chain of hyaluronan, and this interaction is stabilized by a separate link protein (Fig. 3). Thus, the aggrecans are effectively immobilized within the fine collagen network, which produces a strong, cohesive collagen-proteoglycan solid matrix.[7] An aggrecan molecule comprises many glycosaminoglycan chains (keratan sulfate and chondroitin sulfate), which contain numerous charged carboxyl and sulfate groups. Together with their counterions, they create the swelling pressure of the tissue, which has a major influence on cartilage hydration and hence its deformational properties.[6,8]

The chondrocytes are responsible for the synthesis of the articular cartilage during development, for the maintenance of normal adult cartilage, and for the degradation of cartilage during osteoarthritis.[6] The chondrocytes orchestrate the balance between the synthesis of matrix components, the incorporation of these components into the established extracellular matrix, and the breakdown of matrix as part of the normal maintenance process (Fig. 4). The chondrocytes respond to a variety of factors, including the composition of the surrounding matrix, the mechanical load, and soluble mediators, such as growth factors and cytokines (small proteins that influence multiple cell functions, including migration, proliferation, differentiation, and matrix synthesis).[8-10] In a variety of ways, the chondrocytes are able to receive signals from their environment and transduce these signals into biochemical products, which then maintain a biomechanically normal articular cartilage.

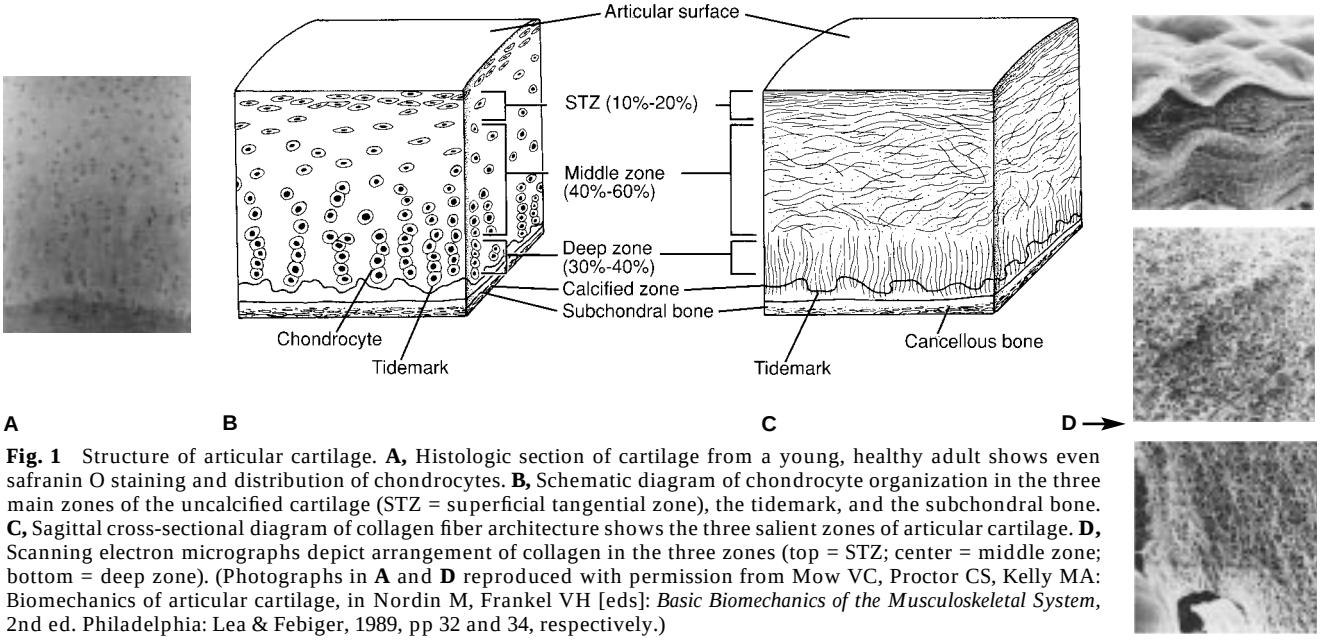

Fig. 1 Structure of articular cartilage. **A,** Histologic section of cartilage from a young, healthy adult shows even safranin O staining and distribution of chondrocytes. **B,** Schematic diagram of chondrocyte organization in the three main zones of the uncalcified cartilage (STZ = superficial tangential zone), the tidemark, and the subchondral bone. **C,** Sagittal cross-sectional diagram of collagen fiber architecture shows the three salient zones of articular cartilage. **D,** Scanning electron micrographs depict arrangement of collagen in the three zones (top = STZ; center = middle zone; bottom = deep zone). (Photographs in **A** and **D** reproduced with permission from Mow VC, Proctor CS, Kelly MA: Biomechanics of articular cartilage, in Nordin M, Frankel VH [eds]: *Basic Biomechanics of the Musculoskeletal System*, 2nd ed. Philadelphia: Lea & Febiger, 1989, pp 32 and 34, respectively.)

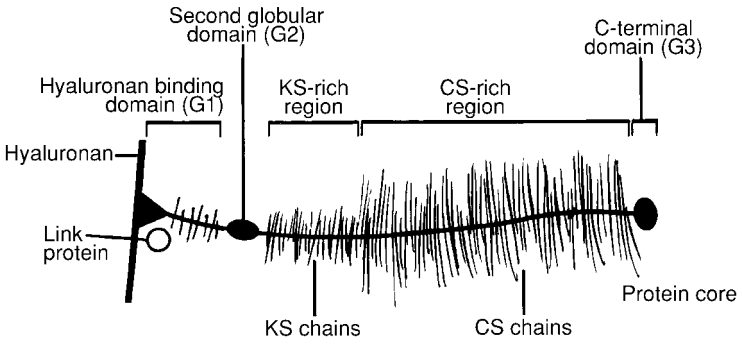

Fig. 2 Diagram of an aggrecan molecule. The protein core has several globular domains (G1, G2, and G3). Other regions contain the keratan sulfate (KS) and chondroitin sulfate (CS) glycosaminoglycan chains. The N-terminal G1 domain is able to bind specifically to hyaluronan; this binding is stabilized by link protein. The total molecular weight of an aggrecan ranges from 0.5 million to 1.0 million daltons. (Reproduced with permission from Simon SR [ed]: *Orthopaedic Basic Science.* Rosemont, Ill: American Academy of Orthopaedic Surgeons, 1994, p 9.)

Articular Cartilage Injury

Mechanical injuries to articular cartilage occur when repetitive and prolonged joint overloading or sudden impact produces high compressive stress throughout the tissue and high shear stress at the subchondral bone junction.[3] These stresses cause injuries that can be separated into three distinct types: (1) microdamage to the cells and matrix without visible disruption of the articular surface, (2) macrodisruption of the articular cartilage alone (chondral fractures), and (3) fracture of the articular cartilage and the subchondral bone (osteochondral fractures).

Cartilage Injury Without Tissue Disruption

A single moderately severe impact or less severe repetitive trauma can damage cartilage. This type of damage is measurable in terms of decreased proteoglycan concentration in the matrix, increased tissue hydration, and possibly altered fibrillar organization of collagen. More important, the trauma can also injure chondrocytes or alter their synthetic and degradative activities.[6,11-13] The exact nature of this type of damage has not been well studied, although the decrease in proteoglycan concentration, the increase in hydration, and the disorganization of the collagen ultrastructure may represent some of the earliest detectable cartilage damage.

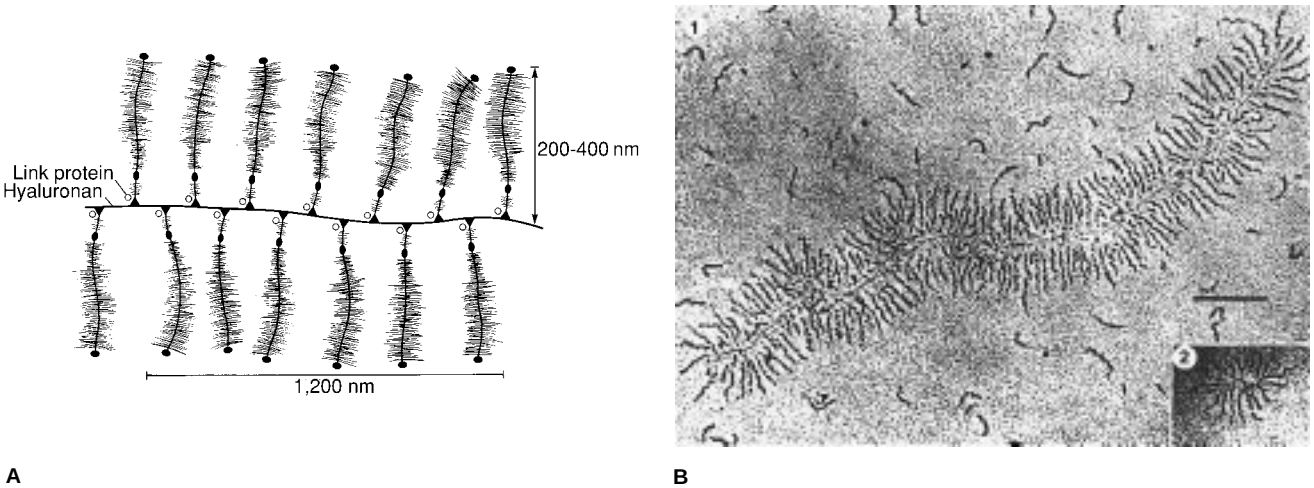

Fig. 3 **A,** A proteoglycan aggregate is composed of a long hyaluronan chain to which many aggrecans are attached, forming macromolecular complexes that are effectively immobilized within the collagen network. The length of the hyaluronan chain determines the size of the aggregate. The total molecular weight may be as high as 200 million daltons in immature cartilage; in adult and aging articular cartilage, the aggregate gradually decreases in size. (Reproduced with permission from Simon SR [ed]: *Orthopaedic Basic Science.* Rosemont, Ill: American Academy of Orthopaedic Surgeons, 1994, p 10.) **B,** Electron micrographs of proteoglycan aggregates in bovine articular cartilage from a skeletally immature calf **(1)** and a skeletally mature steer **(2).** The aggregates consist of a central hyaluronan filament and multiple attached monomers. Bar represents 500 µm. (Reproduced with permission from Buckwalter JA, Kuettner KE, Thonar EJ: Age-related changes in articular cartilage proteoglycans: Electron microscopic studies. *J Orthop Res* 1985;3:251-257.)

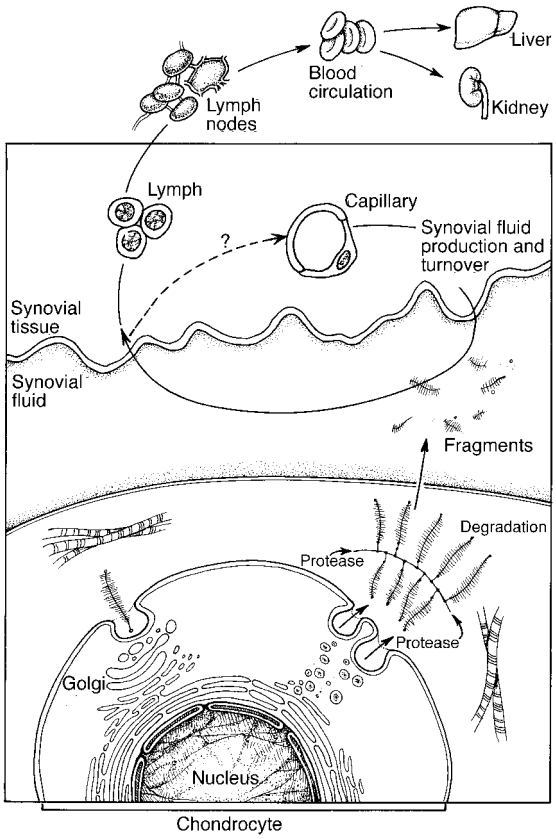

Fig. 4 Schematic representation of the metabolic events controlling the proteoglycans in cartilage. The chondrocytes synthesize and secrete the aggrecans, link protein, and hyaluronan and become incorporated into functional aggregates in the extracellular matrix. Enzymes released by the cells break down the proteoglycan aggregates. The fragments are released from the matrix into the synovial fluid; from there, the fragments are taken up by the lymphatic vessels and moved into the circulating blood.

A slightly more severe impact may produce severe chondrocyte abnormalities and deaths and a weakened collagenous network (Fig. 5). These injuries may also be accompanied by shear damage to the junction between the articular cartilage and the subchondral bone and may cause reactive bone remodeling with increasing replication of the tidemark.[12,14] Loss of proteoglycans and an increase in water content are strongly correlated with a decrease in cartilage stiffness and an increase in its hydraulic permeability. These changes in material properties act to decrease fluid pressurization within the interstitium (i.e., the interstitial fluid can be more easily squeezed from the more permeable cartilage) and thus impair the normal load-carrying capacity of the interstitial fluid.[3] Both of these effects cause greater loading to be exerted on the collagen-proteoglycan solid matrix, thereby increasing the vulnerability of the extracellular matrix to further damage.

In addition to the injuries sustained by cartilage due to mechanical trauma, disruption of the synovial membrane often occurs. This leaves the articular surface exposed to synovial inflammation factors, which can enzymatically cause articular cartilage injury.

Conversely, when synovial joints are immobilized or are otherwise in a state of disuse, an active remodeling process develops within the articular cartilage.[9,15] The attendant functional changes can result in a dramatic loss of proteoglycans from the cartilage. On remobilization, however, the apparently dormant chondrocytes are reawakened to repair the matrix, and the resulting cartilage appears to be able to return to its original form and function. This indicates that the chondrocytes have the potential to repair cartilage, at least for some types of injury. However, this type of repair may require many weeks (possibly months) to restore the affected tissue to normal. There is an overwhelming body of scientific evidence to support the notion that chondrocytes have the ability to detect changes in matrix composition and to sense altered mechanical stresses within the surrounding extracellular matrix, and that they have the capacity to respond to these changes by synthesizing new molecules to repair the damaged extracellular matrix.[9,15] However, the signal-transduction mechanism by which the cells detect these changes and the manner with which the chondrocytes translate these signals into altered metabolic events are unknown.

Following intra-articular injuries, such as a torn meniscus or rupture of the anterior cruciate ligament, the capacity of the chondrocytes for repair is often insufficient to main-

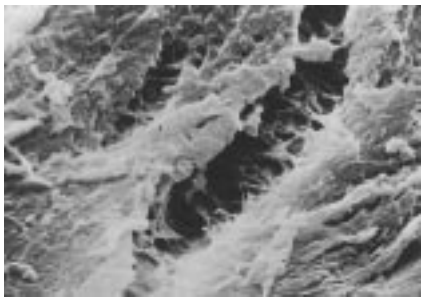

Fig. 5 Scanning electron micrograph of a human cartilage specimen demonstrates fissure in the articular surface. This type of damage not only weakens the surface in tension but also allows large pores to be created in the surface, thus decreasing its effectiveness as a filter and its ability to provide a membrane to limit the rate of fluid exudation (original magnification X3,000). (Reproduced with permission from Mow VC, Mak AF: Lubrication of diarthrodial joints, in Skalak R, Chien S [eds]: ***Handbook of Bioengineering.*** New York: McGraw-Hill, 1986, p 5.)

tain a normal, functioning cartilage. This occurs if the cells fail to repair the microdamages in the extracellular matrix at a sufficiently rapid rate, or if repetitive stress continues to cause microdamage at a more rapid rate. It is not currently known, however, at what point the accumulated microdamage becomes irreversible. Presumably, chondrocytes can restore lost proteoglycans if the rate of loss does not exceed the rate of production. If there is concomitant damage to the collagen network or if a sufficient number of chondrocytes have been destroyed, an irreversible degenerative process ensues.

Reliable, clinically applicable methods of detecting damage to articular cartilage in the absence of surface disruption have yet to be developed, but identification of decreased cartilage stiffness and resiliency by probing the surface during surgery represents a crude method of detecting the severe form of this type of injury. Bone scintigraphy and magnetic resonance imaging can detect alterations in subchondral bone following joint injury, but the relationship between these alterations and cartilage damage has not been defined. The use of biochemical markers in analyzing synovial fluid, serum, and urine offers a potential means of assessing cartilage metabolism and degeneration,[10,11] but such tests are not currently available for clinical use. If biochemical markers could be used to detect the earliest stages of cartilage damage, clinical treatment could be devised for joints that have been subjected to trauma, and the effectiveness of that treatment could be measured.

Chondral Fractures

Compressive forces acting on an articular surface will produce a variety of stresses (tension, compression, shear, and hydrostatic pressure) within the cartilage. These stresses, if sufficiently high, can cause chondral fissures, flaps, and fractures, as well as chondrocyte damage. Loss of significant segments of the articular surface will result in joint effusions, pain, and mechanical symptoms, such as locking and crepitus, and may lead to progressive degeneration of the synovial joint.[2] Because articular cartilage lacks blood vessels, these injuries do not cause hemorrhage or fibrin-clot formation or provoke an inflammatory response. The chondrocytes respond by proliferating and increasing the synthesis of matrix macromolecules near the injury site.[13] Unfortunately, the newly synthesized matrix and proliferating cells do not fill the tissue defect and therefore fail to restore the articular surface. When large defects are present, increased loading of adjacent articular cartilage and underlying subchondral bone can lead to degeneration of the uninjured cartilage; over time, the entire joint is affected.

Current treatments of chondral injuries include sharp debridement of the fractured edges and removal of loose cartilage fragments from the joint. When there is significant loss of articular surface, some surgeons advise abrasion or drilling of the underlying subchondral bone. Experimental work suggests that replacement of cartilage fragments with tissue adhesives or with chondral or osteochondral allografts may be beneficial. At present, there are insufficient long-term studies of the outcome and no guidelines to direct the use of these treatments in acute chondral injuries.

Osteochondral Injuries

Acute joint injuries from more severe impact may also result in fractures that extend through the cartilage into subchondral bone. Unlike injuries that are limited to cartilage, fractures that extend into subchondral bone cause hemorrhage and fibrin-clot formation, thereby activating the inflammatory response. These events fundamentally alter the synovial fluid and the joint environment surrounding the articular cartilage. Soon after injury, blood escaping from blood vessels in the damaged bone forms a hematoma, which temporarily fills the injury site. The fibrin clot extends from the bone for a variable distance into the cartilage defects. Platelets within the clot release vasoactive mediators and growth factors or cytokines. These factors include transforming growth factor beta (TGF-β) and platelet-derived growth factor.

Bone matrix also contains multiple growth factors, including TGF-β, bone morphogenic proteins, platelet-derived growth factor, and insulin-like growth factors. Release of these growth factors may play an important role in stimulating repair of osteochondral defects. In particular, these factors stimulate vascular invasion and migration of undifferentiated cells, proliferation of these cells, and differentiation into chondrocyte-like cells in the chondral portion of the defect. Some of the undifferentiated mesenchymal cells that migrate into the defect assume the rounded form of chondrocytes and begin to synthesize a matrix that contains type II collagen and relatively high concentrations of proteoglycans. These cells produce regions of hyaline-like cartilage in the chondral and osseous portions of the osteochondral defect. The cells within the chondral region produce a repair cartilage that usually contains a high concentration of type II collagen and proteoglycans, but often also contains some type I collagen. The cells in the osseous portion of the defect eventually produce immature bone, which is gradually replaced by mature bone.

The composition of this cartilage repair tissue rarely replicates the structure of normal articular cartilage.[6] This tissue may occasionally

persist unchanged or may progressively remodel to form a more functional joint surface over time.[2] However, in most instances the chondral repair tissue and large osteochondral defects begin to show evidence of depletion of matrix proteoglycans, fragmentation, fibrillation, and loss of chondrocyte-like cells. The remaining cells typically assume the appearance of fibroblasts as the surrounding matrix comes to consist primarily of densely packed type I collagen fibrils. This fibrous tissue usually fragments and often disintegrates within a year, and may leave areas of exposed bone.

Large osteochondral fractures in which the cartilage remains intact with the bone often can be treated by early open reduction and internal fixation of the fracture. If the fracture is not treated soon after injury, the fragments remodel, which makes accurate reduction difficult. The available evidence indicates that the articular surface heals and remodels at the site of anatomically or near-anatomically reduced osteochondral fractures, especially in skeletally immature persons. Smaller osteochondral fractures and those in which the cartilage is not suitable for replacement are currently treated by debridement. Osteochondral allografts have been used successfully as the late treatment of selected osteochondral fractures in which the injured region forms the important frequent-load-bearing region of the joint.

Articular Cartilage Degeneration

The clinical appearance of early degeneration of articular cartilage is characterized by superficial roughening, fibrillation, or fissuring[16] and is apparent at arthroscopy. With time, the fissures extend progressively deeper into the tissue and eventually reach the region of calcified cartilage and subchondral bone. As the disorder progresses, the articular surface becomes weakened (Fig. 6), fragments of the cartilage break free from the surface, and the remaining tissue becomes increasingly fragmented and fibrous.[6,10,11] Eventually, the cartilage may be lost entirely, leaving exposed subchondral bone. The more advanced degenerative changes in the articular surface typically occur simultaneously with increasing density of the subchondral bone, eburnation, and osteophyte formation. Joint-space narrowing, detected radiographically, is evidence of degeneration of the joint at a relatively late stage of the disease.

Many important changes occur in the articular cartilage before the development of clinical osteoarthritis. These preclinical changes in cartilage include not only the disorganization of the collagen ultrastructure (i.e., roughening and fibrillation of the surface zone) but also cell cloning and cell necrosis. In osteoarthritic joints, as opposed to joints in a state of disuse or immobilization, the tensile stiffness and strength of the surface zone are always decreased in association with the disorganization of its collagen network (Fig. 6).[6,8,12] The water content increases, and the proteoglycan content increases initially, followed by a dramatic decrease. The increase in hydration is due to the weakening of the collagen network of the surface zone in tension and the concomitant increase in the swelling pressure resulting from the temporal increase in the proteoglycan content.

These preclinical events may be due strictly to adverse mechanical loading, such as joint instability resulting from disruption of the anterior cruciate ligament, with physical changes in the surface collagen network. Alternatively, these cartilage changes may be mediated by the release by the chondrocytes of matrix-degrading enzymes that actively degrade the collagen and proteoglycan components.[16] This cellular response is certainly ongoing early in the disease process, although it is not clear whether the initiating factor is the mechanical

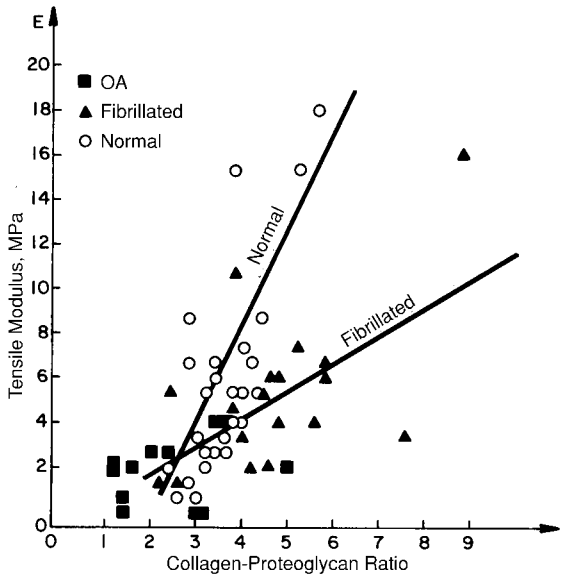

Fig. 6 Knee-cartilage tensile stiffness and collagen-proteoglycan ratio in normal, mildly fibrillated, and osteoarthritic (OA) tissues (the latter obtained from a site adjacent to frank lesions). Note linear correlation in normal and mildly fibrillated tissues. This relationship is lost in OA tissue, likely due to the total disorganization of the cartilage microstructure during advanced stages of OA. (Reproduced with permission from Akizuki A, Mow VC, Muller F, et al: The tensile properties of human knee joint cartilage: I. Influence of ionic conditions, weight bearing, and fibrillation on the tensile modulus. ***J Orthop Res*** 1986;4:379-392.)

event, the cellular event, or a combination of the two.

These degradative changes are also accompanied by an increased rate of chondrocyte mitosis. The resultant cloning of the chondrocyte represents an attempt at repair. However, the newly synthesized proteoglycan and, to a lesser degree, the collagen are often lost into the joint fluid.[10,11] Thus, the reparative responses ultimately fail, the joint progresses to overt degeneration, and clinically apparent osteoarthritis develops.

Synovial joint degeneration typically causes pain and decreased mobility. These symptoms, combined with articular cartilage degeneration and osteophyte formation, are recognized as representing clinical osteoarthritis. However, osteoarthritis is generally not considered to be a single condition and may best be thought of as the clinical result of joint degeneration due to a variety of underlying causes.[16] The degeneration of a synovial joint may be primary, in the sense that there is no known cause, or it may be secondary to conditions such as severe joint trauma, joint instability, lack or loss of joint or limb innervation, joint dysplasia, Paget's disease, and metabolic diseases, including hemochromatosis and ochronosis The natural history of degeneration varies considerably among joints and among individuals. Occasionally, the disorder may spontaneously arrest or appear to improve, but in most instances over a prolonged period of time it progresses. Medical and physical therapy treatments have not been shown to favorably alter this natural history.

Methods of Stimulating Restoration of an Articular Surface

In considering methods of restoring an injured or degenerated articular surface, it is important to distinguish articular cartilage repair from articular cartilage regeneration. Repair refers to the healing of injured tissues or replacement of lost tissues by cell proliferation and synthesis of new extracellular matrix. Unfortunately, the repaired articular cartilage generally fails to replicate the structure, composition, and function of normal articular cartilage.[2] Regeneration in this context refers to the formation of an entirely new articulating surface that essentially duplicates the original articular cartilage.

The success of a given method of restoring an injured or degenerated articular surface has frequently been assessed by determining whether repair tissue fills the chondral defect and by comparing the composition and mechanical properties of the repair tissue with those of normal articular cartilage. However, filling a chondral defect with repair tissue does not necessarily relieve or even decrease pain or improve joint function, nor has it been shown that repair tissue that more closely resembles normal articular cartilage necessarily produces better clinical results. The ultimate measure of the success of any method of restoring the articular surface must be long-term joint function and pain relief.

The available clinical and animal studies show that a number of methods can stimulate the formation of repair tissues, and some recent experimental studies suggest that regeneration of an articular surface may be possible. Methods of stimulating cartilage repair that are currently used in clinical practice include altering the loading of degenerated joints, the introduction of new cartilage-forming cells by penetration of subchondral bone, and soft-tissue arthroplasty. Given the limited ability of mature chondrocytes to repair cartilage defects, one of the potentially most productive approaches to restoring an articular surface is introducing a new cell population into a chondral or osteochondral defect. These cells may be obtained from populations grown in culture and may be combined with artificial matrices and chondrogenesis factors to enhance the formation of new cartilage. Unfortunately, it is difficult to compare methods of restoring articular surfaces because controlled, randomized clinical studies of the outcomes of these treatments have not been performed, and few clinical or experimental studies have investigated the long-term durability of restored articular surfaces and the long-term biomechanical function of the joints.

Altering Loads Applied to Damaged Articular Cartilage

Joint loading and motion can have a significant impact on the progression of joint degeneration and on cartilage repair. Excessive loading of an injured joint can accelerate degeneration and destroy the repair tissue. Prolonged immobilization and unloading of a joint will also contribute to cartilage deterioration and make it susceptible to accelerated degeneration when the joint is suddenly remobilized. However, reducing the level of loading on degenerated cartilage can stimulate repair, and controlled motion and loading, including passive motion, may facilitate repair and maintain or improve joint motion.

Two methods have been used clinically to promote repair of degenerated cartilage surfaces by decreasing the loading of the cartilage: osteotomies and muscle releases. Experimental and clinical evidence shows that these approaches allow and even stimulate some repair of severely damaged articular surfaces. Unfortunately, the clinical results are not predictable, and the relationship between altered loads on degenerative joints and the formation of cartilage repair tissue has not been well defined.

Drilling, Abrasion, or Fracture of Subchondral Bone

Surgical penetration of subchondral bone to disrupt intraosseous blood vessels leads to fibrin-clot formation, releases bone-matrix growth factors, and introduces new cells into the cartilage defect. These cells proliferate and will synthesize a cartilage-repair matrix. The quality and volume of repair tissue following penetration of subchondral bone vary considerably; they are dependent on the size and location of the cartilage defect and probably on the method used for penetrating the subchondral bone, and can be influenced by the loading applied to the joint during the rehabilitation process following the procedure. Partially because of these variables, the clinical results of this approach are difficult to predict. Some patients report symptomatic improvement, and in some instances the repair tissue functions reasonably well as a normal load-bearing articular surface for years; however, other patients experience no improvement.

Periosteal and Perichondral Grafts

Soft-tissue arthroplasties replace degenerated or lost cartilage with grafts of tissues, including fascia, tendon, muscle, periosteum, and perichondrium. The ability of perichondral and periosteal cells (most probably the cells of the cambium layer adjacent to the bone) to form hyaline cartilage makes them an attractive source of new cells to restore an articular surface.[5,17] The availability of periosteum in relative abundance makes this the most likely of the tissues to be used with frequency.

Recent experimental surgical studies with animals have used osteoperiosteal and osteoperichondral grafts as a source of repair tissue in large osteochondral defects that have been created in the patellar groove and the high-weight-bearing region of the femoral condyles. The results indicate that it is possible to form a tissue that fills the defect site, has the gross appearance of hyaline cartilage, and is histologically characteristic of articular cartilage. Biomechanical and biochemical studies indicate that the repair tissue closely resembles articular cartilage.[2,5] Some motion and normal loading of the joint appear to be important in this repair process. The clinical results of periosteal and perichondral grafts vary considerably among individuals and among joints, but there is evidence that this approach produces better results in younger individuals. Success with this approach may be achieved by using highly selected groups of patients in whom repair is reasonably likely (i.e., young patients with focal osteochondral injury).

Implantation of Chondrocytes or Mesenchymal Stem Cells

Cartilage-forming cells can also be introduced into chondral defects by implantation of cells grown and maintained in culture. Experimental investigations of this approach have shown that the transplanted cells can survive and synthesize a cartilaginous matrix that appears to more closely resemble normal cartilage than the fibrous tissue that forms in similar defects not treated with cell transplants. One possible method of applying this approach in humans would be to harvest mesenchymal stem cells or chondrocytes, expand them in culture, implant them in an artificial matrix, and then implant the matrix and the cells in a cartilage defect.

Stimulation of Fibrin-Clot Formation

In vascularized tissues, formation of fibrin clots (including release of growth factors by platelets) probably has an important role in initiating repair. The cytokines released from the clot provide chemotactic and mitogenic stimuli for mesenchymal cells that will migrate into the clot, which may provide a temporary matrix for these cells. Potentially, clot formation could have a similar effect in nonvascularized tissue, such as articular cartilage.

Because the proteoglycans in the cartilage matrix may inhibit clot formation in cartilage defects, investigators have proposed irrigating the defects with saline or enzyme solutions to degrade the proteoglycans and to allow fibrin to clot and adhere to the defects. Experimental studies have provided some evidence that this approach does promote clot formation and adherence and that cell migration into chondral defects does occur.

Chondrogenesis-Stimulating Factors

A variety of polypeptide growth factors (e.g., TGF-β, bone morphogenic proteins, insulin-like growth factor, fibroblast growth factor, and platelet-derived growth factor) influence chondrocyte and other mesenchymal cell functions, such as cell migration, proliferation, matrix synthesis, and differentiation. The effects of these factors on chondrocytes are mediated by cell-surface receptors (integrins). These factors may also directly modify the extracellular matrix and thus modulate the signals (e.g., stresses, strains, and fluid pressure and flow) transmitted to the cells from the surrounding extracellular matrix.

Experimental work has shown that selected growth factors can stimulate formation of cartilaginous tissue in vitro and in vivo. All of the growth factors have shown mitogenic activity on chondrocytes in vitro, and basic fibroblast growth factor, insulin-like growth factor I, and TGF-β have been shown to stimulate matrix synthesis in vivo. In addition, some growth factors potentiate the metabolic effects of

other growth factors. For example, TGF-β can potentiate the mitogenic effects of basic fibroblast growth factor or insulin-like growth factor I, and insulin-like growth factor I and basic fibroblast growth factor act synergistically to increase matrix synthesis. Further work is needed to identify the most effective factors or combination of factors, the optimal doses and methods of delivery, and the best methods of maintaining and releasing them at the site of cartilage injury.

Implantation of Synthetic Matrices

Filling cartilage defects with synthetic matrices can provide a framework that promotes cell migration and gives cells that migrate into the defect a scaffolding they can use to create a new matrix. These matrices can be fabricated from collagen fibers and possibly other substances (for example, carbon fibers or glycosaminoglycan gels) to fill specific defects in articular surfaces, thereby facilitating regeneration of a normal joint contour. A more likely approach is to use such a matrix in vitro as a three-dimensional scaffold in which chondrocytes or cells with chondrogenic potential can be seeded and allowed to establish a three-dimensional cartilage-like matrix. This would then be used as the graft tissue to repair cartilage lesions.

Electromagnetic Fields

Mesenchymal cells respond to electromagnetic fields by altering their synthetic and proliferative activities. In vitro studies have shown that electromagnetic fields can stimulate chondrocytes to proliferate and increase synthesis of proteoglycans. Limited in vivo studies suggest that treatment of osteochondral defects with pulsed electromagnetic fields enhances the volume and quality of repair tissue.[2]

Summary

Treatment of injured or degenerated articular surfaces remains one of the most challenging clinical problems in orthopaedics. Despite the limited capacity of articular cartilage for repair and regeneration, injured and degenerated synovial joints do have some capacity for repairing chondral defects. Formation of cartilage repair tissue can be stimulated with several currently available methods, including decreasing loading on degenerated articular cartilage (primarily through the use of osteotomies), soft-tissue arthroplasty, and introduction of new cell populations to repair chondral defects by penetrating subchondral bone.

Ultimately, the value of a method of restoring an articular surface must be assessed on the basis of outcomes defined by long-term joint function and symptomatic improvement, not just restoration of an articular surface. When this standard is used, none of the clinical methods of stimulating cartilage repair has been shown to predictably restore long-term synovial joint function, although in selected patients they may provide temporary improvement.

Advances in the understanding of the relationships between joint use or loading and articular cartilage degeneration and repair could improve the predictability of these treatments. However, despite significant advances in our knowledge of the biologic, biochemical, and biomechanical processes involved in articular cartilage degeneration, little new information is available on the ability of cartilage to effect the necessary repair and regeneration.

These same recent advances have shown the potential methods necessary to pursue future research to understand the reparative process.[2,6] To some extent, the success of any of these methods of restoring cartilage may vary with the cause of the cartilage loss, that is, whether it is due to an acute mechanical injury or to the osteoarthritic process. The greatest potential for rapid progress in the clinical treatment of articular cartilage damage or loss is most likely in the effort to develop effective methods of restoring articular surfaces following acute mechanical injuries to normal articular cartilage.

Treatment of degenerated articular cartilage presents a more difficult problem. Once the osteoarthritic process has caused substantial cartilage loss and significant alterations in the subchondral bone to the point of eburnation and osteophyte formation, clinical attempts to restore an articular surface and normal joint function are unlikely to be of any real benefit. Prosthetic replacement of the affected joint would then be the orthopaedic treatment of choice. If the osteoarthritic process could be clinically screened sufficiently early by means of markers or some form of radiologic imaging in which the articular cartilage could be clearly delineated, some of the biologic treatment modalities identified in this article could be applied clinically, thus possibly delaying the development of end-stage osteoarthritis. At present, a vast amount of research is being conducted on cartilage biology, biochemistry, and biomechanics. Results from these basic research efforts may provide answers to important questions related to the clinical treatment of this difficult orthopaedic problem.

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