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REVIEW ARTICLE

Osteoarthritis and Therapy

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Introduction

Osteoarthritis (OA) is the leading cause of disability in older persons, affecting ~10% of the population >60 years of age. In the United States alone, there are currently at least 20 million persons afflicted with OA, which costs the economy approximately $60 billion annually. Eighty percent of individuals with OA have limited mobility and 25% cannot perform major daily activities (1). Because the population is aging rapidly, it is anticipated that OA will affect almost 60 million individuals in the United States by 2020, with consequent increased spending on diagnosis, therapy, side-effect prevention, and loss of productivity.

Most cases of OA develop without a known cause of joint degeneration in what is referred to as primary or idiopathic OA. Less frequently, OA develops as a result of joint degeneration caused by traumatic injury or a variety of hereditary; inflammatory; or developmental, metabolic, and neurologic disorders, a group of conditions referred to as secondary OA. Genetic predisposition, age, obesity, female sex, greater bone density, joint laxity, and excessive mechanical loading have been identified as risk factors for primary OA (1). OA diseases are a result of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix, and subchondral bone. Ultimately, OA diseases are manifested by morphologic, biochemical, molecular, and biomechanical changes to both cells and extracellular matrix, which lead to softening, fibrillation, ulceration, loss of articular cartilage, sclerosis, and eburnation of subchondral bone, osteophytes, and subchondral cysts. When clinically evident, OA diseases are characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects (2).

Although intensive research has been carried out on the effects of different cytokines, growth factors, and mechanical loading on the regeneration of cartilage and subchondral bone, there is still no comprehensive understanding of mechanism of OA. Although synovitis is not directly related to the severity of OA (3), it is proposed to be involved with the progression of OA and can be predictive of future chondropathy (4). Therefore, it is imperative to develop a better understanding of how synovitis affects the progression of OA.

Recently, the potential role of subchondral bone in the mechanism of OA has attracted more attention. Several theories relate subchondral bone to OA. First, a stiffer subchondral bone, either caused by healing of trabecular microfacture (5) or abnormal metabolism of osteoblasts (6), is no longer an effective shock absorber and causes damage to cartilage. Second, abnormal function of OA osteoblasts in subchondral bone may lead to an increase in bone volume without a concomitant increase in mineralization due to an inappropriate isoform and structure of collagen, which reduces bone strength (6). Third, bone-derived products (7) and cytokines from subchondral bone (8) may pass through channels and fissures between cartilage and bone to initiate OA (9). Much clinical therapy of OA is focused on improving conditions of OA in subchondral bone.

Embryonic development and cartilage regeneration

Anatomy of cartilage. Articular cartilage possesses a zonal architecture that comprises the superficial, middle, and deep zones, each with distinct cellular phenotype and matrix composition (10) (Figure 1). From the superficial zone to the deep zone, chondrocytes decrease in number and increase in size and metabolic activity (11). Collagen orientation changes in the different layers of articular cartilage, progressing from an isotropic arrangement that runs generally parallel to the articular surface to the frankly anisotropic arrangement of the Benninghoff arcade pattern in which the orientation arises perpendicularly from the basal region and arches over to run parallel to the articular surface (12) (Figure 2). Articular cartilage has no pain

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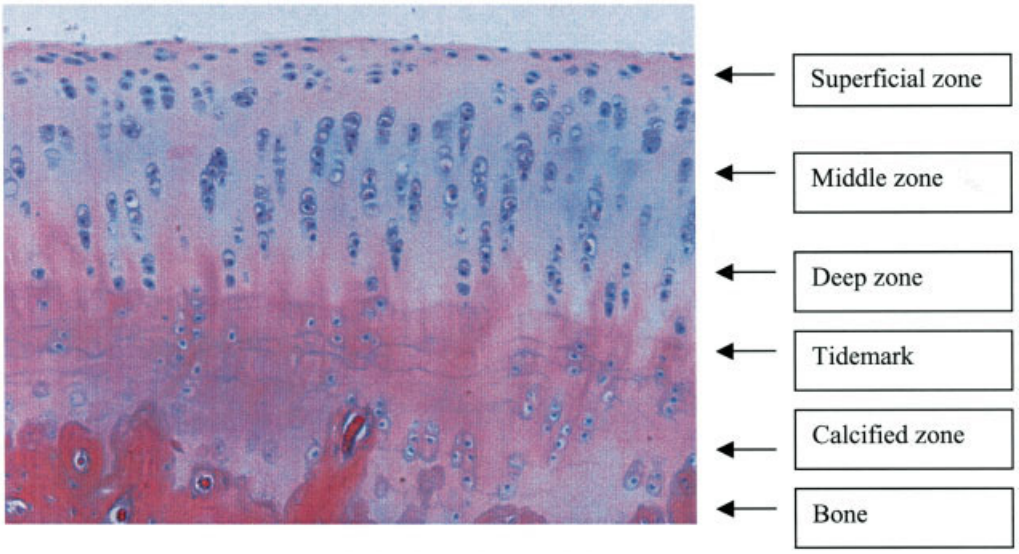

Figure 1. Structure of cartilage. The main difference observed between the chondrocytes in hyaline cartilage is their morphologic variation between the zones. Chondrocytes in the superficial zone are flattened and elongated, whereas the cells in the middle zone appear rounded, and in the deep zone chondrocytes have ellipsoid morphology (82).

fibers or blood vessels. Metabolism is anaerobic and glucose reaches the cells by diffusion both from the joint surface and the underlying bone.

Biochemistry of cartilage extracellular matrix. Collagen content varies from 86% by dry weight in the superficial zone to 67% by dry weight in the deep zone. Type II collagen is the main isoform in articular cartilage while type VI, IX, X, and XI are found in smaller amounts (13). Glycosaminoglycans (GAGs) are negatively charged polysaccharides that increase the compressive capabilities of articular cartilage by sequestering water molecules. Proteoglycans are large molecules with a protein core that are branched with GAGs. Small proteoglycans, such as decorin and biglycan, bind to collagen fibers and thus promote aggregation of the fibers into a collagen meshwork, whereas large proteoglycans with many branching side chains, such as aggrecan and versican, are entrapped in the tissue through frictional interactions with the collagen meshwork.

Endochondral ossification in development. Each limb arises from a small bud of mesodermal cells, which comprise all the progenitors of chondrocytes and connective tissues (14). There are several steps in joint formation: 1) chondrocyte progenitors condensing to skeletal pattern form, 2) programmed cell death and changes in matrix production in the center of the interzone, 3) differentiation of articular cartilage at the 2 edges of the interzone, and 4) accumulation of fluid-filled spaces (joint) (15). Joint devel-

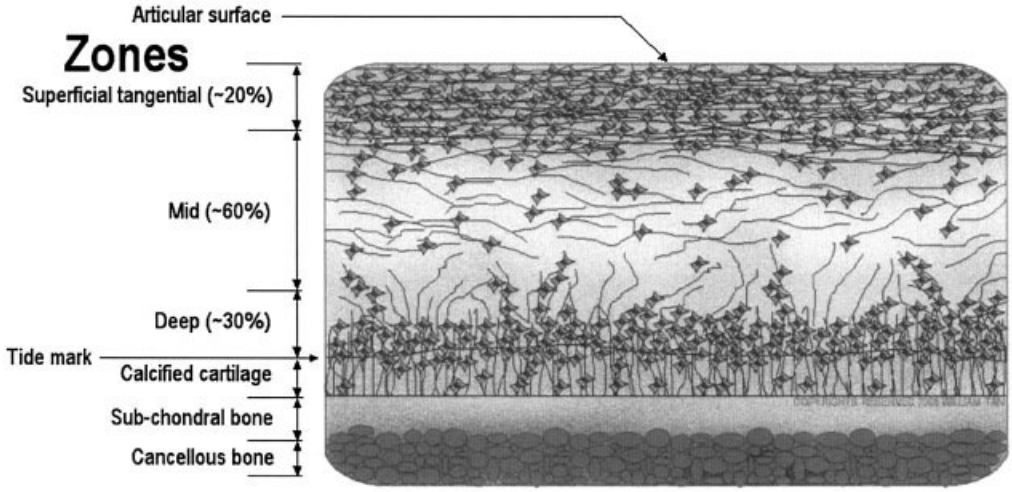

Figure 2. Schematic drawing of collagen fibers and chondrocytes in cartilage. In the superficial zone, the collagen fibers run parallel to the articular surface and lie close to each other in a dense arrangement. The collagen fibers in the middle zone are randomly oriented and are more loosely packed. In the deep zone, the collagen fibers orient themselves perpendicular to the subchondral bone surface.

opment is regulated at the level of gene transcription, cellular signaling, cell-cell and cell-matrix interactions, and systemic modulation. Mediators include transcription factors, growth factors, cytokines, metabolites, hormones, and environmental influences.

Mesenchymal stem cell. Recruitment of mesenchymal stem cells (MSCs) is crucial for both regenerative and developmental chondrogenesis at the cellular level. MSCs have the potential to differentiate into chondrocytes, osteoblasts, adipocytes, fibroblasts, marrow stroma, and other tissues of mesenchymal origin, and they can be harvested from adipose, periosteum, synovial membrane, muscle, dermis pericytes, blood, bone marrow, trabeculare bone, plecenta, and cord blood (16). It is likely that MSCs gain access to various tissues through circulation, adopting characteristics to maintain and repair cartilage in development, but not in regeneration necessarily.

Condensation. Before condensation, mesenchymal cells secrete an extracellular matrix rich in hyaluronan and collagen type I that prevents intimate cell-cell interaction. When condensation begins, an increase in hyaluronidase activity and breakdown of hyaluronan would facilitate condensation (17). Fibronectin may facilitate a matrix-driven translocation of mesenchymal cells into cellular condensations, which may be mediated by the amino-terminal heparin-binding domain (18,19). Cell-cell interactions are involved in triggering ≥1 signal transduction pathways for chondrogenic differentiation. Two cell adhesion molecules, N-cadherin and neural cell adhesion molecule, are initially up-regulated and then down-regulated in differentiating cartilage (20,21). Additionally, cell-cell communication through gap junction is also critically required in precartilage condensation and may operate in conjunction with growth-factor–mediated modulation of chondrogenesis (22). Peanut agglutinin (lectin) is critical in precartilage mesenchymal cell condensation by binding to cell surfaces (23). It provides the scaffold for the formation of the endochondral skeletal elements.

Patterning. Patterning is the delineation of the number, size, and shape of individual elements within the tissue. A feed-forward mechanism of interactions with and across tissue both limits and reinforces the commitment of tissue differentiation. Although important in regeneration, little is known about the mechanism of action of patterning. It is important that proper signals are provided, received, and interpreted to guide the graft to develop into a functionally and structurally normal cartilage, especially when grafted cells or tissues derived from an exogenous source are involved. However, little is known about the mechanism of regeneration, including action of the patterning influences, roles of cytokines, and individual signaling pathways (16).

Cell fate determination. The fate of cells involved in cartilage formation is determined by the combinatorial interactions of genetic and environmental factors. The actions of these determinants include concentration, time, position, interaction between adjacent components of segmental structures, and epithelium and mesenchyme (24). During development of a limb bud, osteoprogenitor and chondroprogenitor cells initiate their differentiation while surrounding cells undergo apoptosis, thus defining the boundaries of the developing skeletal elements. Bone morphogenetic protein (BMP) is a key regulator. Some embryonic cartilages remain as articular cartilage. Differentiated chondrocytes excrete more proteoglycan and collagen type II into the extracellular matrix while gradually becoming round and increasing in size. The hypertrophic chondrocyte starts to secrete more collagen type X and less collagen type II and IX (24).

Challenges in cartilage regeneration. Because there is no evidence that the articular cartilage cell population can be replenished after formation of mature articular surfaces, it can be presumed that there is no endogenous stem cell population within articular cartilage. Additionally, there is no evidence for the ectopic migration of cells from the joint fluid, synovium, or bone to replenish the population of primary chondrocytes within mature cartilage (25).

Adult cartilage regeneration functionally recapitulates embryonic development in that progenitor cells are recruited (or collected in the case of engineered tissues) and induced to differentiate in a patterned manner to give rise to regenerated tissue that possess the shape, form, and functionality of the original tissue. It is highly possible that a considerable number of regulatory mechanisms responsible for cartilage development also operate during regenerative chondrogenesis. Knowledge of developmental chondrogenesis should therefore provide a considerable insight into adult cartilage repair (16). Due to lack of vascularization and innervation in cartilage, humoral factors and recruitment of stem progenitor cells to the site of damage is impossible, which hinders potential regeneration (26). The low cell density within cartilaginous tissue reduces the likelihood of local chondrocytes contributing to self regeneration. Moreover, the proliferative potential of autologous chondrocytes and the number of MSCs decrease with age (27,28).

Synovium and synovial fluid

The synovial lining derives from mesenchymal cells on the inner surface of the developing capsule, which develops at the periphery of the intermediate lamina coincident with joint cavitation (29). The synovium is composed of an inner layer (intima) and a deep layer (subintima). Within the inner layer are 3 types of synovial lining cells that overlap one another in 2 or 3 layers: macrophages, fibroblasts, or undifferentiated precursors of the former 2. The deep layer is composed of adipose, fibrous, or areolar tissue. The synovial cell layer lining the joint is typically 2 cells thick and lacks a basement membrane. This layer has 5 essential functions: to prevent formation of adhesions with articular surface by forming villi, to produce synovial fluid essential to the lubrication of articular cartilage surfaces, to provide nutrients necessary for chondrocyte metabolism, to be part of the immune system that responds to

foreign molecules, and to clear unwanted particles with an intricate system of capillaries and lymphatics (30).

Synovial macrophages participate in all phases of host defense and are the predominant cell type in inflammatory arthritis (31). These cells are usually silent before being activated by antigen-presenting cells that invade the synovium or by macrophages or hematopoietic stem cells that enter the joint directly through synovial capillaries (30). The subsequent inflammatory response can either be destructive to the joint or lead to tissue repair (32).

Synovial fluid, a clear and viscous liquid, is an ultrafiltrate of plasma produced by fibroblasts in synovium. In normal human joints there is ~0.2–0.3 ml of synovial fluid, and it has both fluid and cellular complements. Synovial fluid normally contains 60–200 mononuclear cells per milliliter. Except for the 95% that is water, it also contains plasma solutes, proteins, glycosaminoglycans, proteases, and alkaline phosphatase. Under normal conditions, a state of equilibrium exists between the synovial fluid and the serum, although the concentration of synovial fluid solutes differs from that of plasma. The presence of hyaluronate and lubricin distinguishes synovial fluid from plasma and contributes to its viscosity (30).

Although it is difficult, measuring the concentration of a component in the joint fluid is theoretically the most reliable approach when a component is released. It is easy to correct for possible dilution by measuring the concentration of urea in serum and joint fluid, when necessary (33).

Cytokines and growth factors involved

Although many mediators have been shown to influence chondrocyte activity, little is known about interactions among mediators and their individual importance. Results from many sophisticated studies on perturbations of chondroctye function are difficult to interpret because many basic questions on the normal metabolism of chondrocytes are still unanswered. Furthermore, differences in the biology and response to cytokines of chondrocytes in different joints have increased controversy (34). Age-related difference in cartilage biology has also been reported (27). All of these findings increase difficulties in interpreting the effects of cytokines on cartilage degradation in vivo. In contrast, many cytokine-blocking experiments are reported to protect cartilage.

Cytokines are hormone-like proteins that regulate the intensity and duration of the immune response and are involved in cell-cell interactions. Cytokines and growth factors involved in OA are released from either chondrocytes or synovial cells. Most cytokines influence OA by increasing production of proteinases, such as matrix metalloproteinase and aggrecanase. OA is not a classic inflammatory arthropathy (35), and subsequent synovitis is assumed to be a secondary response to the release of cartilage breakdown products. Although proinflammatory cytokines usually appear in advanced stages of OA, some have been observed in early stages of OA (36). Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the most important and well-studied cytokines in OA. IL-1, released by either synovium (37) or chondrocyte (38), could stimulate chondrocytes to produce most or all of the proteinases involved in cartilage destruction. TNFα, the strongest cytokine to induce cartilage destruction, has effects on chondrocytes similar to IL-1, which is 100–1,000 times weaker on a molar basis (39); however, the combination of the 2 produces strong synergistic effects (40). It is believed that TNFα drives acute inflammation whereas IL-1 has a pivotal role in sustaining inflammation and cartilage erosion; it is unclear whether cytokine synergism happens in OA (41). In addition to catabolic effects, TNFα and IL-1 are also involved in inhibiting the synthesis of proteoglycans and type II collagen (42–44). Cytokines involved in cartilage metabolism can be grouped into 3 categories: catabolic cytokines, which include IL-1α/β, TNFα, IL-17, and IL-18; inhibitory cytokines, which include IL-4, IL-10, IL-11, IL-13, IL-1 receptor antagonist, and interferon-γ; and anabolic cytokines, which comprise insulin-like growth factor 1, TGFβ1, TGFβ2, TGFβ3, fibroblast growth factor [FGF] 2, FGF-4, FGF-8, BMP-2, BMP-4, BMP-6, BMP-7, BMP-9, and BMP-13 (45). Cartilage matrix degradation products, such as those derived from type II collagen, proteoglycans, and fibronectin, are possibly involved in initiating or amplifying inflammation and cartilage destruction (Figure 3) (46).

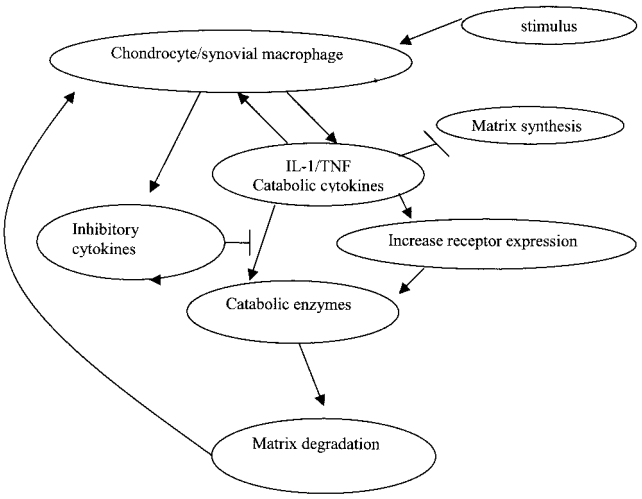

Figure 3. Mechanism of cytokines involved in osteoarthritis. IL-1 = interleukin-1; TNF = tumor necrosis factor.

Current therapeutic strategies

Current treatment efficacy of OA is limited to relieving pain, improving range of motion, and/or promoting partial regeneration in most cases. Current therapeutic strategies for restoration of articular cartilage function include nonpharmacologic, pharmacologic, and surgical procedures such as arthroplasty (47).

Nonpharmacologic therapy. In addition to patient education, self-management programs, and weight control, physical therapy further improves the physical and mental condition of the patient. It usually includes a warm up, range of motion exercises, muscle strengthening techniques, aerobic conditioning, and swimming. Occupational therapy, which aims to assist the patient in achieving the maximum level of independent function, often

helps to improve the quality of life of the patients (48). Osteopathic manipulative treatment consisting of thrust, muscle energy, counterstrain, articulation, and myofascial release can alleviate arthritic pain, promote healing, and increase mobility.

Pharmacologic treatment. Acetaminophen can be used to relieve mild to moderate arthritic pain (49), whereas nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygense 2 (COX-2) selective agents are the preferred drugs for moderate to severe pain. NSAIDs act as analgesics primarily by modulating prostaglandin production (50). Because physiologic levels of prostaglandins may be chondroprotective, NSAIDs may have deleterious effects on disease progression by increasing subchondral bone destruction and preventing cartilage matrix repair. Because COX-2 inhibitors offer the possibility to block cytokine-inducible prostaglandins without affecting physiologic levels due to COX-1 activity, they may slow cartilage and bone destruction (51). Opiate analgesics (i.e., tramadol hydrochloride) can be safely used in treating patients with severe pain resistant to nonopioid medications.

Glucosamine and chondroitin are compounds extracted from animal products that have recently acquired substantial popularity in the treatment of OA. The most important merit is their safety, although they usually have slow and modest effects (52). They appear to be capable of increasing proteoglycan synthesis in articular cartilage (53,54). Oral and intramuscular injection of glucosamine and chondroitin have been reported to be effective and safe.

Interarticular injection is considered only after oral and intramuscular intake result in failed efficacy, because chances of side effects of injection are higher. Nevertheless, the clinical symptoms of OA appear to improve after interarticular injection of chondroitin, glucosamine, sodium hyaluronate, and NSAIDs (55).

Surgery. Surgical treatment is only considered after conservative therapy has been optimized. General medical issues such as cardiopulmonary status, carious teeth, urinary tract infection or prostatic hypertrophy, and airway problems should be evaluated first. Patient education and active involvement with rehabilitation are critical for recovery of cartilage function.

Arthroscopic management. Various techniques include lavage and débridement, abrasion arthroplasty, subchondral penetration procedures (drilling and microfracture), and laser/thermal chondroplasty. Arthroscopic débridement and lavage has long been considered a pain palliative therapy, but is not beneficial to long-term recovery (56). Its beneficial effects are possibly due to removal of inflammatory mediators and loosening bodies within the joint, which cause pain. Greater symptomatic relief and more persistent pain relief can be achieved in patients who have acute onset of pain, mechanical disturbances from cartilage or meniscal fragments, normal lower-extremity alignment, and minimal radiographic evidence of degenerative disease. Arthroscopic chondroplasty techniques provide unpredictable results. Concerns include the durability of fibrocartilage repair tissue in subchondral penetration procedures and thermal damage to subchondral bone and adjacent normal articular cartilage in laser/thermal chondroplasty. With proper selection, patients with early degenerative arthritic and mechanical symptoms of locking or catching can benefit from arthroscopic surgery (57).

Grafting and cell transplantation. Autologous osteochondral transplantation has successfully been used in OA, although it cannot alter progression of preexisting OA changes (58,59). Allografting has been used to treat OA with some degree of success (60), but has been reported to increase antibodies to bone proteins that existed prior to surgery at a relatively low titer (61). Periosteal graft, with autologous chondrocytes, was used successfully to repair deep cartilage defects (62), but not in OA. A commercial autologous chondrocyte implantation product, Carticel, obtained approval from the Food and Drug Administration in 1997. However, it is indicated only for the repair of symptomatic cartilage defects of the femoral condyle due to acute or repetitive trauma in patients, but not for the treatment of cartilage damage associated with OA. So far, only MSCs have been used to treat OA-associated cartilage defects in human clinical cases; use of chondrocytes has not been reported (63).

Osteotomy. Osteotomy (bone cutting) is useful for correcting malalignment arising from disease progression or prior injury that resulted in mechanical overload of a portion of the joint and sparing of another portion of the joint. It is often adopted with other surgical procedures (64).

Arthroplasty. Arthroplasty is used to create an artificial joint to restore the integrity and functional power of a joint as far as possible. It has achieved good short-term results but is limited with relatively short-term results that steadily (after 15 years) deteriorate. Nevertheless, progress on research of new materials has provided hope to overcome current limitations (65).

Arthrodesis. Arthrodesis, the stiffening of a joint by operative means, has a large role in the treatment of OA. It is commonly used in the hand, spine, ankle, and foot, and less commonly in the hip or knee. It can also be used in the knee or hip of young patients who are not good candidates for arthroplasty. It is an excellent salvage procedure and provides excellent pain relief, but with the price of loss of motion (65).

Future therapeutic strategies

Strategy to regenerate cartilage afflicted with OA should include 1) removing the causes or risk factors of OA; 2) inhibiting activities of proteinases and cytokines, which lead to subsequent damage after initial defect; 3) removing osteoarthritic tissues without any chances of recovery and replacing them with scaffolds; 4) introducing proper stem cells or differentiated progenitor cells while creating a suitable microenvironment for cells to proliferate and dif-

ferentiate; and 5) effective rehabilitation to functionalize the regenerated tissues.

Radiofrequency. Radiofrequency energy has been used to ablate diseased cartilage, and the initial results are encouraging. Despite its popularity and promising short-term results, radiofrequency has not been extensively researched in terms of its effect on articular cartilage. Although it has shown inconsistent results from limited clinical trials, it could be a powerful surgical tool under well-controlled conditions (66).

Tissue engineering/scaffold cell transplantation. Tissue engineering has achieved much progress in cartilage regeneration. Due to lack of regenerative ability, cartilage defects need space-filling materials, also known as scaffolds, to allow tissue ingrowth before being replaced totally by regenerated cartilage. Unlike fibrocartilaginous tissue, which is made up of a heterogenous population of chondrocytes and fibroblasts, hyaline cartilage contains only chondrocytes (67). This would suggest that it may be necessary for scaffolds to repel fibroblasts from attaching and growing at the initial stage.

Although there is some progress in using cartilage grafting for OA as well as chondrocyte transplantation for simple cartilage defect, no cell transplantation has been used for the treatment of OA. Adult chondrocytes from nonweighted area should be first choice; however, it is difficult to keep their chondrogenic phenotype during in vitro proliferation within 2-dimensional culture. In vitro 3-dimensional culture may provide a solution (68). In contrast, cartilage defects repaired with chondrocytes degenerate earlier than those repaired with MSCs (69). MSCs, which can differentiate into chondrocytes as well as other mesenchymal cells, could be a solution because they have higher proliferative capacity and are easier to characterize (70). Because mechanical stimulus is important, bioreactors play a critical role in cartilage tissue engineering. Both hydrostatic pressure and direct compression on chondrocyte-seeded scaffolds have been shown to increase extracellular matrix production while other useful parameters have also been incorporated (71,72). More importantly, beyond common requirements for regeneration and tissue engineering, seeded cells should survive, proliferate, and differentiate well in an OA environment.

Integration with surrounding cartilage. There is always concern about the integration of regenerative cartilage with surrounding cartilage, while most regenerated cartilage could not make it at current stage regarding mechanical and histologic integration. Immature tissue implantation provides some clues, although more research is necessary (73).

Gene therapy. OA has a surprising degree of heritability (74) and multiple interacting loci appear to be involved (75); however, it is unlikely that OA can be cured directly by modifying relevant gene mutations in the near future. Much progress has been reported in genetically modifying synovium to enhance synthesis of the cartilaginous matrix, or inhibit its breakdown, or combining both strategies (76,77). Unfortunately, all results are from either animal models or in vitro studies and there is still no human clinical gene therapy trials of OA being reported. However, gene therapy could be a powerful tool in the future. RNA interference, an impressive tool that uses double-stranded RNA to silence sequence-specific genes, can also help to regulate gene expression with high efficiency and relatively few side effects (78).

Anticytokine therapy. Currently, 3 strategies that target the activities of catabolic cytokines include inhibiting the proteinases that degrade cartilage matrix proteins, suppressing cytokine-induced signaling pathways, and inhibiting chondrocyte apoptosis using inducible nitric oxide synthase or caspase inhibitors. Because many proteinases involved in OA share overlapping substrate specificities and structural epitopes, some proteinase inhibitors appear to be effective in both animal models and human clinical trials. Strategies to suppress cytokine-induced signaling pathways include cytokine neutralization, receptor blockade, inhibition of cytokine processing, inhibition of cytokine synthesis or action, and combined therapies (42).

The development of diagnostic markers in serum or synovial fluid can help to monitor progress of OA, which is critical for OA therapy. Molecular markers have been identified for monitoring changes in cartilage metabolism and for assessing joint damage in arthritis (79). The ideal way is possibly to combine anticytokine therapy with gene therapy and tissue engineering to promote cartilage regeneration while inhibiting destruction.

Mechanical stimulus. Mechanical loading plays a major role in the growth and development of articular cartilage. Cartilage that is not mechanically stimulated will atrophy (80), and passive motion is beneficial to cartilage regeneration (81). Although there has been much attention on effects of mechanical stimulus on regeneration of cartilage, there is much to do before it can be used in clinical cases. However, application of mechanical stimulus is critical and essential for regeneration of cartilage.

Overall, it is most important to fully understand the underlined reason and mechanism of OA before it can be properly treated. Safety should be further emphasized while new therapies are being adopted.

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