Cell Biology of Osteoarthritis: The Chondrocyte's Response to Injury

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Cartilage is comprised of a large amount of functional extracellular matrix that is made and maintained by a small number of chondrocytes, the sole resident cell type. Normal cartilage exists in a relatively steady state: that is, the anabolic processes (those that result in the synthesis of cartilage matrix components) are in equilibrium with the catabolic processes (those that result in the normal turnover of matrix molecules). If the functional extracellular matrix is disturbed by physical or molecular means, the cells respond in an attempt to repair the matrix. This stimulated activity does not result in repair due to the extent and complexity of the extracellular matrix. Eventually, the newly synthesized and activated catabolic enzymes degrade the matrix components. This review presents the cellular and molecular mechanisms that account for this activity and provides some possible solutions.

Introduction

Osteoarthritis (OA) is the most common degenerative joint disease. In stark contrast to rheumatoid arthritis (RA), in which the inflamed synovium drives the degradation of the articular cartilage, in OA cartilage degradation is driven by chondrocytes. This does not imply that the surrounding synovium, perichondrium, or bone does not contribute to the OA pathology, but we will assume the process centers in the cartilage. In a recent review of the cell biology of osteoarthritis, we presented the basic cell biology of OA and described the phenotypic response of the cells in OA, varying from recapitulation of development to dedifferentiation, hypertrophy, and even regeneration [1••]. In this review, we propose a new paradigm for understanding OA in the context of cell biology. We have divided the process into three steps (Fig. 1). Step 1 is the assault to the cartilage by direct impact damage (injury), faulty matrix molecules (genetics), or an unknown stimulus. Step 2 is the response of chondrocytes to try to repair the extracellular matrix. This attempt to repair sets up a cycle of anabolism and catabolism that eventually results in cartilage erosion. Step 3 is the final descent into cartilage degradation from which there is no recovery. This review examines the recent evidence that provides a mechanism for this interpretation and possible intervention strategies based on early detection of chondrocyte metabolic activity.

Normal cartilage exists in a relatively steady state; that is, the anabolic processes (those that result in the synthesis of cartilage matrix components) are in equilibrium with the catabolic processes (those that result in the normal turnover of matrix molecules). Chondrocytes express anabolic effectors such as insulin-like growth factors (IGFs), transforming growth factors (TGF), and catabolic effectors such as matrix metalloproteinases (MMPs) that function as autocrine/paracrine effectors of metabolism. The loss of the steady state results in the net loss of articular cartilage the hallmark of OA. Because OA is a chronic condition and most cases are not identified until the later stages of the disease, the specific signals that initiate the changes in the chondrocytes that result in clinical OA remain uncertain. Nonetheless, significant progress has been made in piecing together a picture of some of the changes that occur in the progression of OA. Progression of the disease is a complex process that includes initial up-regulation of matrix synthesis, increased expression of proteolytic enzymes with concomitant suppression of their physiologic inhibitors, increased expression of pro-inflammatory cytokines such as interleukin-1 and -6 (IL-1 and IL-6) and tissue necrosis factor alpha (TNFα), increased cell death through apoptosis, and increased levels of nitric oxide (NO). In addition, in OA cartilage, chondrocytes show an altered phenotype. Re-expression of type IIA procollagen—a chondroprogenitor splice variant of type II procollagen—is observed [2] indicative of a recapitulation of development. The transcription factor Sox9 is a critical enhancer of transcription of type II collagen and other chondrocyte-characteristic genes and is increased in a transgenic mouse model of OA [3•]. Type III collagen is also expressed. A report showed expression of type X collagen in OA cartilage [4], indicating a hypertrophic cell phenotype. These changes in phenotype could indicate the re-initiation of a specific biosynthetic pathway, as discussed by Sandell and Aigner [1••].

In the last 2 years, an important advance in cartilage catabolism was the identification of aggrecanases. Aggrecan is a major component of cartilage that gives elasticity and

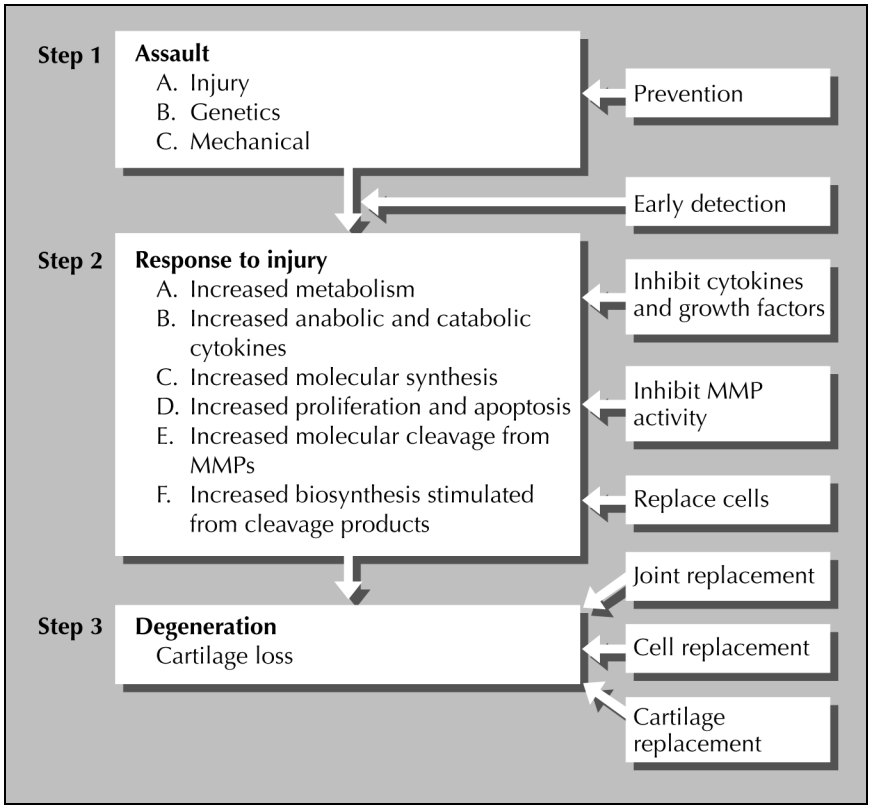

Figure 1. Cellular events in osteoarthritis (OA). In Step 1, the tissue is weakened by injury, genetically altered extracellular matrix molecules, imbalance in biomechanics, or some unknown stimulus. In Step 2, the cell responds to the insult and is stimulated to repair the matrix. Cells may respond slightly differently depending on their place and role in the articular cartilage, but the potential responses are shown. Not all cells need to undergo the same response, but all cells will be affected in some way. Step 2 is self-perpetuating and can last for many years. Step 3 occurs when the cartilage is lost. In the right column potential places for treatment of cellular events of OA are shown.

compressibility to the matrix and thus contributes to the mechanical properties of the articular cartilage. Therefore, loss of aggrecan causes significant impairment of the weight-bearing function of cartilage; this is considered to be one of the central events in OA pathophysiology. In synovial fluid of patients with OA, two major forms of degraded aggrecan were detected, representing two preferential cleavage sites in the aggrecan core protein. In work done nearly a decade earlier, these cleavage sites were pinpointed by amino acid sequencing. Both are located between the two globular domains in N-terminus of the molecule (Table 1). The amino acid sequence at these sites are well conserved among species, suggesting that they could play certain roles in physiologic metabolism of aggrecan. After this, efforts were made to determine the enzymes responsible for this cleavage. Soon after, MMPs were found responsible for the cleavage at one site. All the MMPs examined so far are capable of cleaving the core protein at that site [5]. In 1999, two forms of aggrecanases, aggrecanase-1 and -2 were identified [6•,7]. Both enzymes are members of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family, and were designated as ADAMTS-4 and -5/11, respectively. The expression of aggrecanases was confirmed in cartilage and synovium of patients with OA. Pro-inflammatory cytokines up-regulate their activity [8]. Because accumulating evidence suggests aggrecanases are dominant enzymes in aggrecan catabolism [9], inhibition of their activity could be a new, potent method for OA treatment. This area is controversial, thus future studies will be necessary to determine the order and relative importance of the MMPs and ADAMTSs.

Cartilage Repair Response and Anabolic Cytokines and Growth Factors

What is the first step in the initiation of cellular activity in OA? Scientists and clinicians have pondered this question for decades. Our understanding of cytokines and growth factors cannot define a single factor that could be responsible for all the responses of chondrocytes. It is helpful to view the initial event as a program of response to injury by the chondrocyte—in this response, the chondrocyte tries to repair the damaged matrix. Because synthetic activity of chondrocytes is regulated by anabolic growth factors, such anabolic action in OA cartilage could be related to the expression of growth factors. The enhanced expression or activation of several kinds of growth factors is observed in OA cartilage [10,11]. In contrast to catabolism of OA cartilage, the synthetic side of OA has not received as much attention. By knowing the linkage between the expression of growth factors and unsuccessful repair, we could acquire new insights into the treatment of the disease. This is important because the repair potential of cartilage is gaining more attention as a target for OA treatment.

TGF-beta (TGF-β) is one of the most potent mediators of cartilage matrix synthesis. It up-regulates the expression of several types collagens and proteoglycans (PG) [12]. However, when administered into the joint by direct application or by gene therapy, the cytokine induces osteophyte formation and hyperplasia of the synovium similar to OA [13,14]. TGF-β expression was observed in osteophytes obtained from patients with OA [15]; this cytokine could play a significant role in their formation.

Table 1. Enzymic degradation of structural components in cartilage

Type II collagen	MMPs-1, 8, 13	Fibrillar domain at 3/4 from N terminus
	MMP-3[a]	N-telopeptide region
	Cathepsins B, L[b]	Telopeptide region
Type IX collagen	MMPs-2[c], 3[a], 13[d]	Telopeptide region
	Cathepsins B, L[b]	
Type XI collagen	MMP-3[a]	Gly^{339}–Val^{340}
	MMP-9	Telopeptide region
	Cathepsins B, L[b]	
Aggrecan	MMPs[f]	Interglobular domain, Asn^{341}–Phe^{342}
	ADAMTS-4, 5/11 (aggrecanase-1, 2)[g]	Interglobular domain, Glu^{373}–Ala^{374}
		Glu^{1545}–Gly^{1546}, Glu1714–Gly^{1715}, Glu^{1819}–Ala^{1820}, Glu^{1919}–Leu^{1920}
Link protein	MMPs-1, 2, 3, 9, 10[h]	His^{16}–Ile^{17}
	MMPs-2, 7, 9[h]	Leu^{25}–Leu^{26}
	Cathepsins B, D, G, L[i]	
Cartilage oligomeric matrix protein (COMP)	MMPs-19, 20[j]	

The enzymes in charge of initial cleavage are shown.
*No MMP is known not to cleave at this site.
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Other members of the TGF-β superfamily, the bone morphogenetic proteins (BMPs), are also known to stimulate cartilage matrix synthesis [16]. A recent study has shown that BMP-7 (also called osteogenic protein-1) increases synthesis of hyaluronan and its cell surface receptor CD44. In situ expression of BMP-7 in OA cartilage has also been observed [11].

IGF-I is another growth factor with potent anabolic effects on chondrocytes. Chondrocytes express IGF-I and the concentration of IGF-I increases in OA synovial fluid and in OA cartilage [10]. Induction of IGF-I synthesis in the joint by means of gene transfer resulted in increased PG synthesis [17]. In cartilage obtained from older donors, insulin-like growth factor binding protein-3 (IGFBP-3) was abundant in the territorial matrix [18]. Because IGF-I can prolong chondrocyte survival (possibly through inhibition of apoptosis [19]) increased IGFBP-3 potentially inhibits anabolic activities of chondrocytes, which could be part of the etiology of OA in the elderly population. There is another possible result of increased IGFBP-3 in the territorial matrix. That is, the increased IGFBP-3 may trap and concentrate IGF-I in the cartilage. Then the enzyme MMP-3, up-regulated in OA, degrades IGFBP-3 to non–IGF-binding fragments [20], releasing the IGF-I near the chondrocytes, thereby facilitating the hypersynthetic metabolism seen in OA. Although decreased proteolysis of IGFBP-3 in the synovial fluid of patients with OA has been demonstrated, it is likely a result of the formation of the protease-resistant ternary complex of IGFPB-3 (the acid labile subunit) and IGF-I [21]. The distribution of IGFBPs and IGF-I within the cartilage tissue, the center of the OA disease process, remains unaddressed. Particularly interesting with response to IGF function in cartilage is the observation of Spagnoli *et al.* [22] that IGFPB-3 may have an IGF-independent antiproliferative effect on chondrocytes.

Table 2. Cytokines involved in cartilage metabolism in OA

Proinflammatory	Regulatory	Inhibitory
IL-1β	IL-6	IL-4
TNFα	IL-8	IL-10
IL-17	LIF	IL-13
IL-18		IL-1ra
		sTNF-R

IL—interleukin; IL-1ra—interleukin-1 receptor antagonist; LIF—leukemia inhibitory factor; sTNF-R—soluble TNF receptor; TNF—tumor necrosis factor.

Pro-inflammatory Cytokines in Osteoarthritis

Opposing the anabolic effects of growth factors are pro-inflammatory cytokines. Their role in the progression of OA has attracted considerable attention. The role of cytokines in OA was recently reviewed in depth by Goldring (Table 2) [23••]. Although several pro-inflammatory cytokines are expressed [10], IL-1β and TNFα appear to be principal mediators in OA pathogenesis. These cytokines are synthesized as a cellular response; however, they often stimulate the production of degradative enzymes and suppress protein synthesis. With these cytokines, the anabolic cellular response stimulates a catabolic process.

IL-1β is synthesized as a precursor that requires enzymic processing by IL-1β-converting enzyme (ICE),

also called caspase 1, to become active. ICE expression is enhanced in OA cartilage and synovium, showing distribution similar to IL-1β [24]. Not only is IL-1β codistributed with 6 MMPs in OA cartilage, but it induces the expression of MMPs by articular chondrocytes in vitro [25]. In addition, IL-1β also suppresses the expression of extracellular matrix (ECM) constituents. A recent study has shown IL-1β is responsible for PG depletion through suppression of PG biosynthesis [26] and induction of degradative enzymes.

Recently, it was suggested that a member of ligand-activated transcriptional factors—peroxisome proliferator-activated receptor-γ (PPARγ)—plays an essential role when IL-1β exerts its various inflammatory actions [27]. Thus several ligands for PPARγ are expected to prevent cartilage degradation in OA, suppressing the activity of IL-1β [28].

Another potent cytokine, TNFα is also produced as a precursor, and acquires bioactivity after proteolytic processing by a TNFα-converting enzyme (TACE) at the cellular surface. Two specific cell surface receptors—TNFR55 and TNFR75—have been identified, the former considered to have more biologic significance in OA pathology. Chondrocytes in OA cartilage contain more TNFR55 than TNFR75, especially around the damaged cartilage area. Cartilage containing such chondrocytes were more responsive to TNFα as assessed by PG release [29]. Another study showed that the expression of these receptors is up-regulated by several cytokines including TNFα, suggesting presence of positive feedback mechanism [30]. TNFα is a known inducer of prostaglandin E_2 in synovial cells. A recent study showed that this activity is modulated by other cytokines such as IL-8 and IL-11 [31].

IL-17 and IL-18 are newer members of proinflammatory cytokines. In OA joints, IL-17 is expressed by synoviocytes and is involved in NO production by chondrocytes [32•]. IL-18 expression is observed in OA chondrocytes [24], and has been shown to stimulate chondrocytes to express several other genes involved in cartilage catabolism [33].

Chemokines

Chemokines are emerging as an intriguing topic in OA. Chemokines are a family of cytokines that modulate leukocyte functions at the site of inflammation. Human chondrocytes constitutively express chemokines. In OA, the up-regulation has been observed of their genes and their receptors [34]. The chemokines may be an important link between the various mediators of OA: the chemokine RANTES is stimulated by IL-1 and IL-18. RANTES, in turn, can stimulate inducible nitric oxide synthase (iNOS) and increase PG release from the tissue [35]. Although their exact significance in the pathology is unclear, chemokines could be of potential importance in disease progression in OA.

Nitric oxide

Nitric oxide (NO) is a free radical that is highly reactive and is involved in a variety of diseases. NO is considered to play a significant role in the progression of OA [36]. Patients with OA had an increase of NO concentration in serum and synovial fluid. Chondrocytes are likely a major source of NO in the joint [37]. They produce a large amount of NO when stimulated by IL-1β and TNFα. Recent studies have shown that IL-17 and IL-18 also stimulate NO production in articular chondrocytes [32,33]. NO is synthesized by nitric oxide synthase (NOS). Two classes of enzymes, constitutive NOS (cNOS) and inducible NOS (iNOS, also called NOS2), are known; the latter is considered to be more important in pathologic conditions because it can produce much more NO than can cNOS. Studies on iNOS null mice and using iNOS inhibitors corroborated the significance of NO in progression of OA [38,39,40].

NO inhibits synthesis of ECM components such as type II collagen and PG and increases activity of MMPs. Several different mechanisms seem to be involved in these actions. NO decreases sensitivity of chondrocytes to IGF-I in OA, and reduces endogenous TGF-β production by chondrocytes [41,42]; both of these could down-regulate matrix synthesis. NO is known to suppress expression of the IL-1 receptor antagonist, which enhances catabolic actions of IL-1. Decreased PG synthesis could result from a disturbance in integrin signaling [43]. Inhibition of mitochondrial respiration by NO is another possible mechanism suggested in a recent study [44].

Anti-inflammatory cytokines

In the pathology of OA, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 are expressed together with pro-inflammatory cytokines. Anti-inflammatory cytokines can counteract the actions of pro-inflammatory cytokines [45]. Taking advantage of the suppressive effects, challenges have been made with anti-inflammatory cytokines to suppress progression of OA, either by direct application or by gene transfer [46–49]. The results seem promising.

Cartilage Repair Response: Proliferation and Apoptosis

The issue of cell death in OA has received a great deal of attention in the last 2 years. An increasing number of papers report apoptosis in OA cartilage [49–52], but the descriptions vary and the importance of cell death in OA is controversial. Because cartilage does not contain mononuclear phagocytes, once a chondrocyte dies, space for the dead cell remains as lacuna in cartilage, which possibly causes structural deterioration of the matrix [53,54•]. After cell death, apoptotic bodies stay within and around the lacuna for extended periods due to lack of clearance, and then produce pyrophosphate. Thus chondrocyte apoptosis is considered responsible for cartilage calcification observed with OA and aging [52,53,54•].

Several mechanisms are involved in apoptosis of chondrocytes. Signaling by CD95/Fas is considered an important mechanism for apoptosis [53,54•]. The activity of caspase-8 is necessary in this pathway and is counteracted by transcription factor NF-κB [55]. The mechanism for NO-

induced apoptosis is independent of CD95/Fas signaling [56], but possibly involves c-Jun NH_2-terminal kinase (JNK) [57]. A recent study shows that the mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/Erk) signal transduction pathway inhibits chondrocyte apoptosis, which is induced by loss of cell-matrix interaction [58]. Because NO is a potent inducer of apoptosis, inhibition of iNOS activity may prevent cell death in chondrocytes. An animal study has demonstrated that an iNOS inhibitor prevents cell death, possibly through suppressed expression caspase-3 [39]. Hyaluronan may prevent chondrocyte apoptosis, but the mechanism is unclear [59].

With all these studies, the true significance of apoptosis in OA is still controversial. A recent well-controlled study showed that apoptosis is not a widespread phenomenon in OA, providing a caveat against overestimation of apoptosis in the disease [60•]. The common method for apoptosis detection, the TUNEL reaction, contains several critical steps that significantly affect its specificity [60•]. This potential lack of specificity could explain why recent studies have shown considerable discrepancy in determining the number of apoptotic cells. We may need to be more careful in understanding the roles of apoptosis in OA pathophysiology.

A novel insight into the phenomenon of cell proliferation and clustering is provided by Le Graverand *et al.* [61•] in an interesting study of the formation and phenotype of cell clusters in OA meniscus. Using a model of OA in which the anterior cruciate ligament is cut, they propose that apoptosis and cell proliferation play a role in establishing isolated cell groups. Some cells respond by apoptosis and some by proliferation, each of which can disrupt the cellular network. Then the cell groups undergo a phenotypic and morphologic change that causes them to become more rounded and isolated from the cell matrix. The phenotypic change observed in these cells was to a more hypertrophic phenotype including increased type X collagen, MMP-13, and increased mineralization. It is unknown whether these changes can occur in cartilage chondrocytes.

Biomechanical Stimuli

When a person walks, the knee is exposed to a range of forces, from unweighted to three times body weight. It is unsurprising that such dynamic forces exert a strong influence on the metabolism of chondrocytes. Biomechanical forces can alter the level and activity of a number of anabolic and catabolic regulatory molecules expressed by chondrocytes. This suggests that a lifetime of such forces could play a role in the etiology of OA.

Chondrocytes respond to high magnitude cyclic tensile load with increased mRNA levels of MMP-1,-3,-9, IL-1β, TNFα, and TIMP-1 [62]. In addition, cyclic tensile strain increases the conversion of proMMP-9 to the active form [63].

Biomechanical forces can have anabolic effects on chondrocytes. Xu *et al.* [64] showed that in cultured chondrocytes, low frequency cyclic tensile strain had an antagonistic effect on IL-1β-dependent induction of NOS, cyclo-oxygenase 2 (COX-2), and MMP1. It also abrogated IL-1β-induced suppression of TIMP-2 and type II procollagen, and induced hypersynthesis of aggrecan mRNA [64]. It is likely that compression has a direct effect on chondrocytes through the cytoskeleton; however, fluid flow in cartilage has a significant effect on metabolism.

Dynamic compression increases fluid flow through the porous cartilage matrix. Such fluid flow is necessary for normal cartilage homeostasis. Because cartilage is avascular, flow generated by daily activity serves to promote the influx of small molecules from the synovial fluid and efflux of ECM fragments and factors synthesized by the chondrocytes. The role of fluid flow on the anabolic effects of dynamic compression was demonstrated by Bonassar *et al.* [65•] through experiments that assayed the effects of exogenous IGF-I on protein and PG synthesis by cartilage explants subjected to dynamic compression. Separately, exogenous IGF-I and dynamic compression increased protein and PG synthesis. In combination, IGF-I and dynamic compression synergistically increased protein and PG synthesis. This suggests that increased fluid flow within the cartilage matrix facilitated transport of the IGF-I into the cartilage and enhanced its anabolic effect on the chondrocytes [65•].

Such cellular level responses to mechanical stimulation that negate or diminish catabolic effects and enhance anabolic processes could serve to protect the cartilage from degradation in response to insult, thereby delaying the descent into OA. It is possible that with age, the protective effects of moderate forces become less effective, allowing catabolic forces to overcome anabolism.

OA As an Age-related Disease

Although there are several exceptions such as posttraumatic OA or OA with genetic problems, many patients with OA do not have specific recognizable causes for the disease. Epidemiologic studies show a strong association between older age and OA. These facts suggest that age-related changes in the cartilage matrix and aging of chondrocytes could be responsible for the development of OA. Several age-related biomechanical and biochemical changes are known. Histologic studies show an age-related decrease in the number of chondrocytes in cartilage.

Several new findings have been reported on the age-related changes in chondrocytes. Chondrocytes show many of the same aging and senescence properties of other cells. Martin and Buckwalter [66] recently published evidence that indicates that chondrocytes in human articular cartilage undergo replicative senescence. Using cartilage from donors between 1 and 87 years of age, they found increased activity of senescence-associated β-galactosidase activity and a decrease in mitotic activity and telomere length [66]. Other studies show chondrocytes from elderly donors respond poorly to IGF-I. Increased synthesis of IGFBP-3 could be its

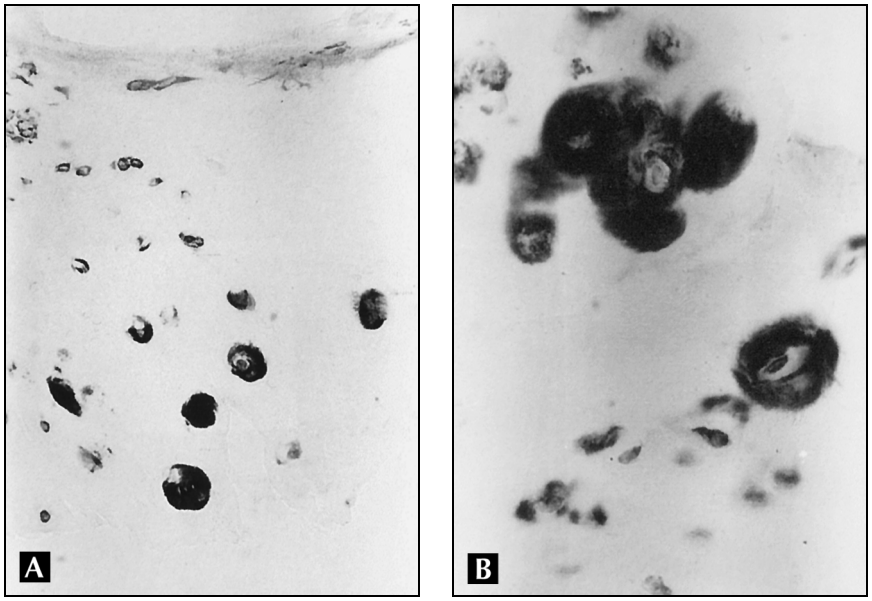

Figure 2. Deposition of newly synthesized products around the chondrocyte, which occurs in type VI collagen, type II collagen, and COMP. **A**, Middle and deep zone of osteoarthritic cartilage (*bar* = 60 microns. **B**, Cell clusters in deep zone of osteoarthritic cartilage (*bar* = 30 microns). (*Figure provided by* Dr. Yong Zhu, Washington University School of Medicine.)

cause. However, another explanation for the decreased response of aged chondrocytes to IGF [67] may be altered signal transduction pathways. When cultured, survival of chondrocyte is influenced by the activity of IGF-I and -II produced by chondrocyte. In addition, the cells from elderly donors depend more strongly on IGF for survival [19]. While age-related reduction in sensitivity to IGF-I may be responsible for decreased chondrocyte density in elderly patients, the direct relationship of the reduced chondrocyte density to OA remains unclear.

Early Detection of OA: Imbalance in Metabolism As a Marker for Disease

The field of markers for OA is becoming increasingly sophisticated. Rather than trying to measure breakdown in serum or urine that may reflect the activity of a synovial joint, techniques and reagents are being developed to monitor the metabolic activity of many tissues of the joint with particular reference to the balance of catabolic and anabolic activities. Therefore, the analysis of response of the chondrocyte to damage in the matrix can be fine-tuned to monitor specific stages and rates in cartilage degeneration. For example, Garnero *et al.* [68•] analyzed disease activity in patients with knee OA by a cross-sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism. They concluded that knee OA is characterized by a systemic decrease of bone turnover and increased cartilage and synovial tissue turnover. They further used a combination of markers, one for chondrocyte anabolism (type IIA collagen N-propeptide) and one for catabolism (type II collagen C-telopeptide), to successfully predict the progression of OA over 1 year (P. Garnero, personal communication). The tissue inhibitor of metalloproteinase-1 (TIMP-1) was used to successfully predict progression of hip OA [69], indicating that a decrease in this inhibitory protein may indicate that the cells can no longer resist the degradation process. Otterness *et al.* [70•] did not find a correlation to any clinical end-points with 14 molecular markers, with the exception of TGF-β1, which was positively correlated with disease progression and the chitenase YKL-40 [71]. Recently, an increase in TGF-β1 in humans has been correlated with OA in a rabbit model. Both are thought to be related to the formation of osteophytes.

Chondrocytes Cannot Repair Cartilage

Evidence points to the conclusion that chondrocytes cannot repair their extracellular matrix, although they are stimulated to try. Currently, there is an accepted, but unproven, hypothesis (or hope) that chondrocytes repair their matrix for a fairly long period of time. Then an event occurs that tips the balance to degradation of the matrix. There is no evidence in favor of this hypothesis. The overwhelming evidence favors an inability to repair. Hembry *et al.* [72] recently addressed this question in a study investigating the chondrocyte response to a partial thickness tear in the superficial cartilage. They concluded that the cartilage was unable to repair its matrix because of a blockage of the lacunar space with accumulated products of metabolism, such as newly synthesized molecules and degradation products (Fig. 2). These studies support other studies that found increased biosynthesis of collagen but no increased collagen content in the extracellular matrix.

Where Does that Leave Us?

Skin and cartilage share many of the same molecules. In addition, the mature cell (fibroblast or chondrocyte) behaves similarly. However, there are several reasons that skin wounds heal while cartilage wounds do not. Essentially, skin heals because it can remove the damaged tissue and can recruit new cells to synthesize new tissue—chondrocytes do

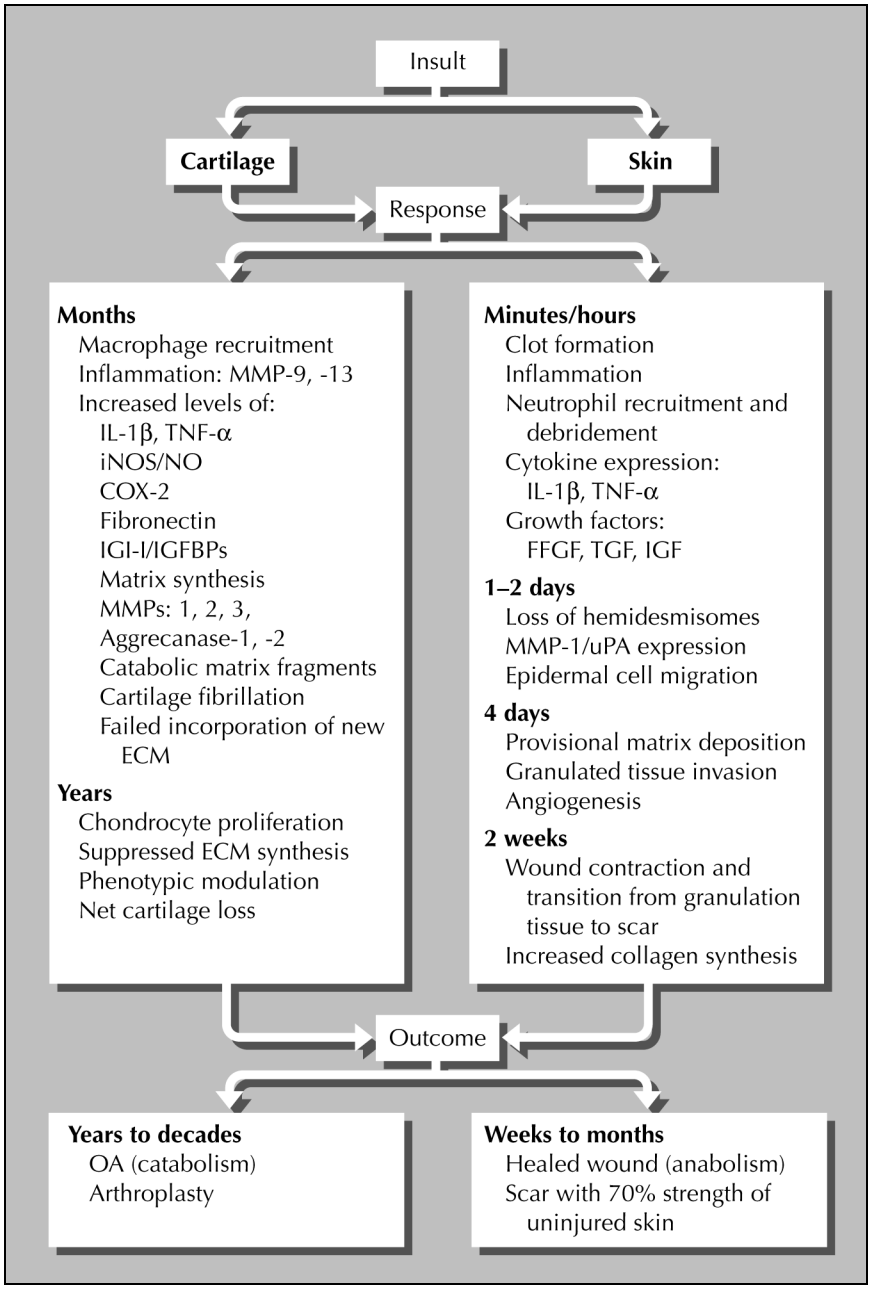

Figure 3. Responses of cartilage and skin to insult. There are similarities and differences in the responses of these tissues to wounding. The differences may be responsible for the inability of cartilage wounds to heal.

not have this option. In skin, there is an inflammatory response that brings in cells secreting cytokines and growth factors that stimulate the recruitment and proliferation of additional cells (Fig. 3). In addition, there is a population of precursor cells in the surrounding tissue that migrate to the wound. The future of cartilage repair would seem to lie in creating techniques to provide components of the wound healing system unavailable in cartilage.

Because cartilage does not heal is any real sense, alternative remedies must be undertaken. The most popular and effective treatment is total joint replacement; however, biologic solutions will soon augment the possible choices for treatment. Realistically, unless the OA is detected very early, it will be impossible to intercede at the level of initial cellular response. A viable possibility is to expand on the use of unaffected chondrocytes or stem cells to make new cartilage in a clean environment in which the degraded cartilage is debrided to remove cytokines and material that is physically in the way. In this manner, "new" cartilage will be formed unimpeded by the need to "repair" degraded tissue. A second realistic treatment will be involve replacing the damaged cartilage with cartilage that can be made in vitro and used to replace the entire tissue. Novel therapies are being developed in all these areas to take advantage of the new information provided by cell and molecular studies.

Conclusions

The chondrocyte is the central player in the damage that occurs to cartilage in patients with OA. The cartilage matrix is damaged by injury, genetic abnormalities in the matrix molecules, or potentially by wear and tear over the years.

The cells are activated to respond to the changes in their extracellular matrix. Upon activation, many events take place to create a "vicious cycle" of degradation and stimulation of synthesis. These events result in very little repair but much damage to the cartilage. We propose that because the chondrocytes cannot draw on other cells to remove the damaged cartilage and replace it with new cells and healthy cartilage, degradation will continue. The treatment strategies rely on total joint replacement and direct inhibition of degradative enzymes. However, progress is being made in the research of early detection of OA, detection of rate of progression of the disease, removal and renewal of the chondrocytes, and biologic replacements through stem cells or "neo" cartilage.

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