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REVIEW

Osteoarthritis, an Inflammatory Disease

Potential Implication for the Selection of New Therapeutic Targets

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Osteoarthritis (OA) is a well-known disease that is part of the aging process and also one of the most common diseases among mammals. Although this musculoskeletal disorder has been described in mammals of many ages, having been reported in Egyptian mummies and in dinosaurs, its exact etiology is far from being fully understood. With the graying of the world population, it is of the utmost importance to find out more about the pathogenesis of the disease and thus allow the discovery of new treatments to stop or prevent its progression.

A number of risk factors have lately been identified (1). Mechanical factors, among others, are likely to play a very important role in the initiation of the disease process. Endogenous factors such as type II collagen mutation or dysplastic conditions are also known to be involved in initiating the OA process (2).

There is now strong evidence that the structural changes globally observed in OA are due to a combination of factors, ranging from the mechanical to the biochemical (3,4). The disease process affects not only the cartilage, but also the entire joint structure, including the synovial membrane, subchondral bone, ligaments, and periarticular muscles. In OA synovium, the inflammatory changes that take place include synovial hypertrophy and hyperplasia with an increased number of lining cells, and also an infiltration of the sublining tissue with a mixed population of inflammatory cells. In patients with severe disease, the extent of inflammation can sometimes reach that observed in rheumatoid arthritis (RA) patients at the clinical stage (5,6). Some degree of synovitis has also been reported in even the early stages of the disease (7). Synovial inflammation is clearly reflected in many of the signs and symptoms of OA, including joint swelling and effusion, stiffness, and sometimes redness, particularly at the level of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints.

Role of inflammation in disease progression: what is the evidence?

The question is whether synovitis in OA is an "innocent bystander" or truly participates in the structural changes of the disease. Moreover, is synovial inflammation only relevant during the "flare" of the disease or is it an ongoing process that permanently contributes to the progression of the disease after it is established? From all observations, there are at least 2 major questions that could be raised regarding synovial inflammation and OA. First, what evidence do we have that inflammation is associated with disease progression? Second, what are the inflammatory factors that could possibly be involved in the genesis of OA structural changes?

The association between OA progression, the signs and symptoms of inflammation, and disease activity has been the subject of a number of interesting studies. One must first recognize that there is still some ambiguity in the definition of disease activity with regard to OA. Some of the criteria used address the functionality of the patient, whereas others, such as stiffness, joint effusion, and other related criteria, probably reflect more accurately the state of joint inflammation. Currently, there are no validated measures of disease activity for OA. The disease progression is commonly measured by change in disease status over a period of time. There are a number of methods available for monitoring

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Table 1. Examples of reports on the correlation between biologic markers of inflammation and the appearance, progression, and risk factors of osteoarthritis (OA)

Marker, disease characteristic, measure	First author	Ref. no.
Cartilage oligomeric protein		
Synovitis, cartilage degradation		
Disease progression	Clark AG	10
	Sharif M	9
	Sharif M	12
Risk factor	Petersson IF	11
Hyaluronic acid		
Synovitis		
Joint score (OA)	Goldberg RL	14
C-reactive protein		
Inflammation		
Disease progression	Spector TD	13

disease progression, such as radiography, magnetic resonance imaging (MRI), and arthroscopy, but radiographs are still considered the gold standard. However, radiographs have been proven to have limited sensitivity in the measurement of disease progression. This makes MRI, which provides a more timely and precise structural measurement, a more attractive solution for the future (8).

The main observations that suggest an association between inflammation and the progression of structural changes in OA are derived from clinical studies (9–14). A number of those studies have lately demonstrated an interesting possible association between synovitis, OA inflammation, and progression of structural changes. There are a number of biologic markers that are believed to be associated with OA synovial inflammation, such as cartilage oligomeric protein (COMP), the serum level of C-reactive protein (CRP), and hyaluronic acid (HA) (15–19) (Table 1). It is generally believed that high disease activity suggests a rapid progression of the disease.

COMP is a component of the articular cartilage extracellular matrix and is found in high concentrations in articular cartilage (~0.1% wet weight). Because this protein is formed by activated synovial cells, it is speculated that elevated COMP levels may reflect synovitis (9–11,20). Other studies (12,13) have shown that elevated CRP levels are predictive of radiographic progression of long-term knee OA. Moreover, it was reported that in women with mild-to-moderately severe knee OA whose disease either progressed or showed no progression, a small elevation in CRP levels was of predictive value (13). The level of another biologic marker, HA, rises in concentration during inflammation (14). HA has been reported to be elevated in OA, and plasma HA levels were found to correlate with an objective functional capacity score and with an articular index based on the total amount of cartilage in the involved joints.

A study by Verbruggen and Veys (21) demonstrated that patients with hand OA, involving the distal joints (DIP, PIP), are generally asymptomatic when the disease is "nonerosive" and become symptomatic during inflammatory episodes. The latter are associated with the onset of erosive OA changes, as seen by sequential roentgenograms.

These data strongly suggest, from both the biologic and clinical sides, an association between joint inflammation and the progression of structural changes in OA.

Role of inflammatory mediators in OA: what is the proof?

Although the roles of inflammation and of inflammatory mediators in the pathophysiology of OA have been under extensive scrutiny in the last decade and a great deal of progress has been made, we do not yet understand all of the ramifications of the systems. Many of the etiologic factors responsible for the initiation of the disease, which happens at the cartilage level and is related to the breakdown of the extracellular macromolecules, remain, however, largely unknown. It is largely agreed that the presence of the synovial inflammation that is often associated with the OA process is believed to be a secondary phenomenon related to the destruction of cartilage and the release of cartilage breakdown products in the synovial fluid. In fact, a number of cartilage macromolecules have been demonstrated to have significant immunogenic properties. For instance, evidence has been provided that OA patients express cellular immunity to the cartilage proteoglycan link protein and C1 domain. Moreover, im-

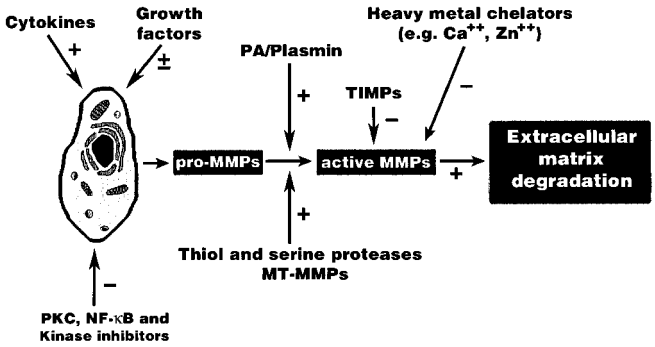

Figure 1. Schematic diagram of activators (+) and inhibitors (−) of matrix metalloprotease (MMP) synthesis and activity. PA = plasminogen activator; TIMPs = tissue inhibitors of matrix metalloproteases; PKC = protein kinase C; NF-κB = nuclear factor κB; MT-MMPs = membrane type matrix metalloproteases.

mune complexes containing antibodies to type II collagen have been detected in the superficial layer of OA cartilage (22). The morphologic changes observed in OA synovium are usually a mild or moderate synovitis that, on occasion, is almost indistinguishable from that in patients with an inflammatory arthritis such as RA (5,6,23,24). This is characterized by an increase in the number of inflammatory mononuclear cells in the sublining tissue, including activated B cells and T lymphocytes (25,26).

Chondrocytes as a source of matrix metalloprotease (MMP) and inflammatory mediator production. There is now strong evidence for major involvement of the MMP family in early cartilage structural changes (3,27). Other enzymes from the serine- and cysteine-dependent protease families, such as the plasminogen activator/plasmin system and cathepsin B, respectively, as well as membrane type MMPs also play a role, but primarily as activators of MMPs (Figure 1). Another protease, aggrecanase (a member of the adamalysin family), appears responsible for proteoglycan cleavage as found in human OA synovial fluid.

It is increasingly appreciated that chondrocytes have the capacity to produce a variety of cytokines and mediators associated with inflammation. Chondrocytes obtained from patients with OA actively produce nitric oxide (NO), prostaglandins, interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), IL-6, and IL-8. Since these cells are sequestered within the lacunae of articular cartilage (a tissue that is avascular and aneural), the production of such mediators by chondrocytes may not be associated with the classic signs of inflammation. However, as will be discussed, there is evidence that these molecules act within cartilage in an autocrine or paracrine manner to promote a catabolic state, which leads to progressive cartilage damage in OA (28).

Proinflammatory cytokines. It is likely that the excessive production of cytokines and growth factors by the inflamed synovium and activated chondrocytes play an important role in the pathophysiology of OA (3,29). These factors are closely associated with functional alterations not only in the synovium, but also in the cartilage and subchondral bone. They appear to be first produced by the synovial membrane, and diffused into the cartilage through the synovial fluid. They activate the chondrocytes, which, in turn, could produce proteases and other catabolic factors such as NO, and are responsible for inducing cartilage catabolism, chondrocyte apoptosis, and other structural changes associated with the disease process.

A large number of cytokines (pro- and anti-inflammatory), antagonists, and growth factors are likely to be involved in OA pathophysiology. Proinflammatory cytokines have been demonstrated to play a pivotal role in the development of this disease process. In particular, IL-1β and TNFα seem prominent and of major importance to cartilage destruction (30,31). IL-1β and TNFα can stimulate their own production and induce chondrocytes and synovial cells to produce other cytokines, such as IL-8, IL-6, and leukocyte inhibitory factor (LIF), as well as stimulate proteases and prostaglandin E_2 (PGE_2) production. Moreover, TNFα has also been shown to induce osteoclastic bone resorption in vitro (32), a phenomenon that may be involved in the remodeling of OA subchondral bone.

IL-1β is primarily synthesized as a precursor, and released in the extracellular milieu in an active form. A protease named IL-1β–converting enzyme (ICE), or caspase 1, which is located in the plasma membrane, is responsible for generating the mature form of this cytokine (33). The level of this enzyme has been shown to be up-regulated in both OA synovium and cartilage (34). The biologic activation of cells by IL-1 is mediated through an association with specific cell-surface receptors (IL-1R). Two receptors have been identified, type I and type II IL-1R (35). The type I receptor, which has a slightly higher affinity for IL-1β than for IL-1α, is responsible for signal transduction. The number of type I IL-1R has been demonstrated to be significantly increased in OA chondrocytes and synovial fibroblasts (36,37), giving these cells a higher sensitivity to stimulation by IL-1β (36). This phenomenon is responsible for potentiating the effect of this cytokine and up-regulating the gene expression of a number of catabolic factors, which, in turn, enhances cartilage destruction. Both types of IL-1R can also be shed from the cell surface,

and these are named soluble IL-1 receptors (sIL-1R). The shed receptor may function as a cytokine antagonist because the ligand-binding region is preserved. They are believed to act as physiologic inhibitors that regulate the activation of IL-1R. Recent observations indicate that the type II receptor may be several-fold more potent than the type I receptor in antagonizing the catabolic effects of IL-1β on cartilage (38). However, the biologic functions of endogenous IL-1 antagonists in OA tissues and their capacity to neutralize the increased level of active IL-1β in situ remain unknown.

In OA, TNFα also appears to be an important mediator of matrix degradation and a pivotal cytokine in inducing synovial membrane inflammation. The proteolytic cleavage of the proform of this cytokine takes place at the cellular surface via a TNFα-converting enzyme named TACE, which belongs to a subfamily of proteases named adamalysin (39). An up-regulation of TACE gene expression in human OA cartilage has recently been reported (40). Once secreted, the cytokine protein oligomerizes to form trimers, which bind to 2 specific receptors (TNFR) on the cell membrane. These 2 TNFR (41,42) are named according to their molecular weight, TNFR55 and TNFR75. TNFR55 seems to be the dominant receptor responsible for mediating TNFα activity in OA chondrocytes and synovial cells. An enhanced expression of TNFR55 has been reported in these cells (43,44).

Adding to the complexity of this cytokine is the recent finding that proteolytic cleavage of the extracellular domain of each TNFR produces sTNFR. The 2 soluble receptors sTNFR55 and sTNFR75 are produced spontaneously by OA synovial fibroblasts and chondrocytes (43,45). These cells have been found to release an increased amount of sTNFR75 (43,45), and an increased level of sTNFR has been found in the synovial fluid of patients with different forms of arthritis (46,47). It is believed that the biologic role of sTNFR varies depending on its concentration in the joint tissues. At low concentrations, sTNFR could stabilize the trimeric structure of TNFα, thereby increasing the half-life of bioactive TNFα. At high concentrations, sTNFR reduces the bioactivity of TNFα by competing for TNF binding with cell-associated receptors. Therefore, the low level of sTNFR found in OA tissues would be another factor favoring the catabolic effects of TNFα.

Other proinflammatory cytokines, including IL-8, LIF, IL-6, IL-11, and IL-17, have been shown to be overexpressed in OA tissue, and should therefore be considered potential contributing factors in the pathogenesis of this disease. Two of them, IL-11 and IL-6, have also shown antiinflammatory properties.

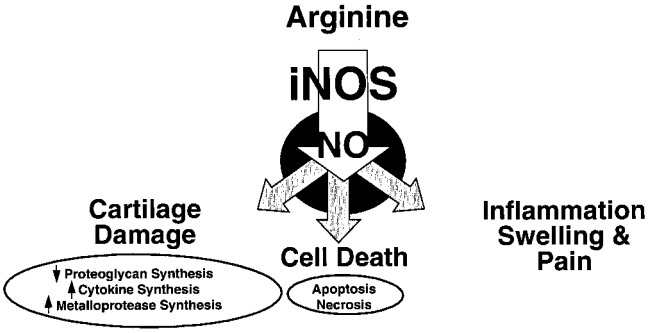

Figure 2. Role of nitric oxide (NO) synthase in osteoarthritis. The up-regulation of the inducible form of nitric oxide synthase (iNOS) causes an excessive production of NO, which is responsible for inducing an inflammatory reaction, tissue destruction, as well as cell death.

Antiinflammatory cytokines and cytokine antagonists. A number of antiinflammatory cytokines, such as IL-4, IL-10, and IL-13, have been shown to be spontaneously elaborated by synovial membrane and cartilage, and are found in increased levels in the synovial fluid of OA patients (48). These cytokines exert their antiinflammatory properties through a number of mechanisms, resulting in a decrease in the production of IL-1β, TNFα, and MMPs, up-regulation of IL-1 receptor antagonist (IL-1Ra) and tissue inhibitor of matrix metalloproteases 1 (TIMP-1), as well as inhibition of PGE_2 release (49–54).

IL-1Ra is a competitive inhibitor of IL-1R and can block a number of catabolic pathways related to OA, including PGE_2 synthesis, collagenase and NO production by chondrocytes, and cartilage matrix degradation. Even though a higher level of IL-1Ra is found in OA articular tissues, the ratio of IL-1Ra to IL-1β is insufficient to deal with the increased level of IL-1β found in those tissues (29,48).

Nitric oxide: a true catabolic factor. NO is a factor that is very likely involved in the promotion of cartilage catabolism in OA through a number of mechanisms (55) (Figure 2). OA cartilage produces a large amount of NO (56,57), and a high level of nitrites/nitrates have been found in the synovial fluid and serum of arthritis patients (58), which is caused by an increased level of the inducible form of NO synthase (iNOS) (59,60). NO can inhibit the synthesis of cartilage matrix macromolecules such as aggrecans, can enhance MMP activity (61,62), and can reduce the synthesis of IL-1Ra by chondrocytes (57). The selective inhibition of iNOS has proven to exert positive effects on the progression of lesions in an experimental canine OA model (63).

Eicosanoids: prostaglandins and leukotrienes (Figure 3). The expression of the inducible cyclooxygenase, COX-2, is increased in OA chondrocytes that

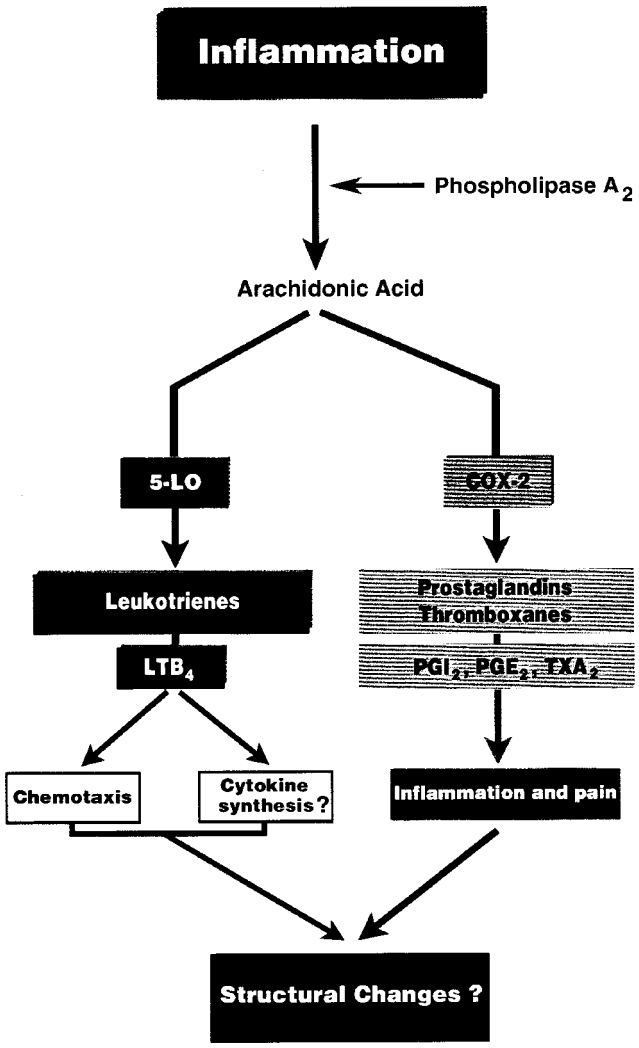

Figure 3. Possible role of eicosanoid in osteoarthritis symptoms and pathophysiology. 5-LO = 5-lipoxygenase; COX-2 = cyclooxygenase 2; LTB_4 = leukotriene B_4; PGI_2 = prostaglandin I_2; PGE_2 = prostaglandin E_2; TXA_2 = thromboxane A_2.

spontaneously produce PGE_2 ex vivo (64). Findings in the literature on the effects of eicosanoid overproduction reveal a variety of both catabolic and anabolic activities. In part, this is due to the fact that different eicosanoid end-products (e.g., PGE_1, PGE_2), acting via different PGE receptors and signaling pathways, have been shown to exert divergent effects on chondrocyte metabolism. Thus, the in vivo consequence of COX-2 overexpression in OA may lead to the production of a variety of prostanoids, of which the net effect on the disease process may be difficult to assess in vitro. However, because of the widespread, prolonged use of COX inhibitors in clinical practice, this is an area that merits further investigation, including the assessment of structural outcomes in the clinic (65).

Moreover, the role of products of the lipoxygenase pathway in OA is unclear at present. Leukotriene B_4 (LTB_4) activity was found to be elevated in the synovial fluid from patients with OA, and both LTB_4 and leukotriene C_4 production have been reported in OA synovial tissue, but not in chondrocytes (66–68). Although the leukotriene mechanism of action is not fully established, LTB_4 was reported to induce IL-1β production in synovial cells (69,70). Since many of these products are produced in only minute amounts and are detected with difficulty by radioimmunoassay or enzyme-linked immunosorbent assay, this is a field that merits further investigation.

Chondrocyte apoptosis: an integral part of the disease process

Morphologic alterations in cartilage involve both extracellular matrix components and chondrocytes. Among the chondrocyte changes is cell cloning. Moreover, there is often an increased number of intracytoplasmic organelles reflecting the hypersynthetic state of these cells (71). There is also an increase in the number of cells exhibiting signs of degeneration or death, a phenomenon that has been shown to be related to both cell necrosis and apoptosis (programmed cell death). The latter involves a complex process related to the activation of several intracellular signaling pathways (72,73). Excess production of NO in OA tissues has been linked with cartilage chondrocyte apoptosis both in vitro and in vivo (74,75). The exact mechanism by which NO mediates apoptosis in OA chondrocytes is not yet completely understood. However, the activation of the caspase cascade seems to play an essential role.

Another possible mechanism that could also contribute to OA chondrocyte apoptosis has recently been identified. A subpopulation of OA chondrocytes (in superficial zones of the cartilage) expresses the Fas antigen, which upon ligand binding, could induce cell apoptosis (76). Interestingly, it is in that zone that most of the apoptotic cells are located. It is presently not known under which condition chondrocytes express Fas ligand, since its only possible source in the OA joint is inflammatory cells in the synovial tissue and fluid.

Inflammation: a therapeutic target

The main objectives in the management of OA are to reduce symptoms, minimize functional disability, and limit progression of the structural changes (77). Our

understanding of the role of catabolic factors in cartilage degradation and the implication of synovial inflammation and cytokines in disease progression has improved substantially in the last 2 decades (3,29). These findings have made possible more precise identification of pathways that have the potential to become therapeutic targets. These pathways can be modified to effectively retard the progression of the disease.

A number of such new agents, referred to as disease-modifying osteoarthritic drugs (DMOADs) (discussed below), are now the subject of preclinical and clinical trials. However, given these new insights, what are the implications for treatment with respect to currently available agents such as nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or intraarticular corticosteroids, or even the use of drugs such as methotrexate? Clinical studies to date have focused on the alleviation of signs and symptoms, for which comparable efficacy has generally been demonstrated for NSAIDs and acetaminophen in stable cohorts of patients with mild-to-moderate OA (78,79). Published data on intraarticular corticosteroids in OA have demonstrated short-term (up to 4 weeks) improvement of signs and symptoms compared with placebo (78,80). The comparative efficacy of these agents in the treatment of episodic crystal-induced inflammatory exacerbations superimposed on chronic OA in selected patients (81), in which one might predict superior efficacy for NSAIDs or corticosteroids over acetaminophen, has not been studied.

However, the current paradigm of inflammatory mediator production in OA focuses less on the induction of signs and symptoms (which has been studied extensively as noted above) than on the potential autocrine/paracrine catabolic actions of these products on cartilage metabolism. Since there are in vitro data to indicate that corticosteroids inhibit synoviocyte and chondrocyte production of IL-1, COX-2, and TNFα (80), there has been speculation that intraarticular corticosteroid administration could exert a disease-modifying role in OA. However, a recent structural outcome study in humans has not been able to validate such a hypothesis (82). Similarly, despite speculation that NSAIDs exert beneficial or harmful effects on the integrity of articular cartilage, there are no validated imaging studies that shed light on this controversy. Predicting the net effects of COX inhibitors on cartilage structure is particularly difficult given the observed pleiotropic effects of individual eicosanoids in vitro on chondrocyte functions, as discussed above. Finally, studies of methotrexate on chondrocyte function, in vitro and in vivo, have failed to show significant effects on cartilage metabolism at clinically relevant concentrations (83).

Thus, although the long-term effects of available antiinflammatory agents on cartilage merit further investigation, there is also significant interest in new agents that have the potential to reduce or stop the progression of the structural changes observed in OA. Such agents offer great promise and are likely to lead to very significant changes in therapeutic approaches in the near future.

The different DMOAD agents presently in development or those targeting pathophysiologic processes and having therapeutic potential can be briefly summarized as follows.

Inhibitors of MMPs (Figure 1). As previously mentioned, some members of the MMP family are intimately involved in articular joint matrix degradation. These enzymes are synthesized as proenzymes and must be activated by proteolytic cleavage. A number of agents that bind the active site of the enzyme can inhibit its catalytic activity. Among these agents are natural MMP inhibitors such as TIMP. Increasing the local synthesis of TIMP would be an effective way to prevent connective tissue turnover and OA progression. However, this natural protein showed limitations with regard to its administration. Nonetheless, therapy with TIMP using recombinant protein and gene therapy has been shown to be effective in antimetastatic treatment (84). These findings, in turn, have generated a regain of interest in the use of TIMP as a therapeutic strategy for OA.

Strategies for the control of MMP synthesis/activity, particularly using synthetic compounds, have been the focus of intensive research over the last decade (27). Although prospects for the prevention of cartilage macromolecule breakdown using synthetic MMP inhibitors look promising, opinions differ as to the best MMPs to target. Stopping the degradation of the collagen network is certainly logical, since it has been shown that its loss leads to irreversible damage. Therefore, collagenases are among the main candidates for inhibition. Collagenase 3 (MMP-13) seems to be a very attractive candidate, because it is the most potent proteolytic enzyme of the 3 collagenases for type II collagen and it is selectively expressed in pathologic conditions such as arthritis (85).

Antibiotics such as tetracycline and its semisynthetic forms (doxycycline and minocycline) have very significant inhibitory properties that impact MMP activity, even in vivo (86). Their main action is mediated by chelating the zinc present in the active site of MMPs. A potential additional therapeutic effect of the tetracyclines may be gained as a result of their capacity to inhibit the expression of iNOS and thereby block NO production (87). A clinical trial is presently underway to

evaluate the therapeutic efficacy of doxycycline in patients with knee OA.

Inhibition of cytokine activity. As mentioned earlier, proinflammatory cytokines are predominant factors involved in the progression of OA. Among these, IL-1β and TNFα play a pivotal role (30,31). Control of cytokine action can be modulated at different levels; therapeutic intervention could target the synthesis, the maturation, or the activity of those cytokines.

Antiinflammatory cytokines. Cytokines such as IL-4, IL-10, and IL-13 were demonstrated to effectively reduce the production of IL-1β and TNFα in vitro while increasing the IL-1Ra production in OA synovium explants. These data suggest that these antiinflammatory cytokines could potentially be useful for the treatment of OA. So far, clinical trials have only evaluated the effects of IL-10 in RA patients and, as yet, no study is underway in OA patients.

IL-1β and TNFα activity inhibition. As mentioned, both IL-1β and TNFα are synthesized as inactive precursors and must be activated by an enzyme before being released extracellularly in their active forms, ICE and TACE, respectively. Therefore, the inhibition of IL-1β and TNFα maturation by specific convertase inhibitors appears to be an attractive therapeutic target. In fact, it was recently shown that an ICE inhibitor can completely abrogate ex vivo the formation of active IL-1β in OA tissue (34). In vivo, in an animal model, data showed that an ICE inhibitor effectively reduced the progression of murine type II collagen–induced arthritis (CIA) (88). The evaluation of the potential of ICE inhibition for the treatment of RA is presently underway.

Receptor blockade or molecular quenching. The IL-1 system is regulated by a natural antagonist of the receptor, namely IL-1Ra. In vivo experiments using intraarticular injections of IL-1Ra or IL-1Ra gene transfection were found to retard the progression of experimental OA (30,89,90). Based on these findings and results from clinical trials in RA patients, it is believed that the use of IL-1Ra for the treatment of OA holds promise. However, to our knowledge, no clinical trial is yet underway for the latter disease.

Another mechanism available to inhibit proinflammatory cytokines is the use of soluble receptors to neutralize the cytokine. Types I or II sIL-1R are potential therapeutic candidates. In human RA, the administration of sTNFR has been shown to be a very effective treatment (91). The role for TNFα in OA cartilage degradation is less clear than that of IL-1, although the production of both TNFα and its converting enzyme, TACE, are increased in OA (40). However, it is possible that both IL-1 and TNFα contribute independently to articular degeneration. Depending on the availability of therapeutic agents with an acceptable risk:benefit ratio, trials that examine TNFα antagonism in OA could be considered.

Table 2. Gene therapy for osteoarthritis*

Potential targets
Cartilage
Catabolic factors (for example, MMPs, NO)
Anabolic factors (growth factors)
Apoptotic factors (for example, caspases, ceramides)
Synovium
Cytokines (for example, IL-1β, TNFα)
Antiinflammatory cytokines (IL-4, IL-10, IL-13)
Cytokine receptor antagonist (IL-1Ra)
Soluble receptors (sIL-1RII, sTNFR)
Strategies
Gene replacement
Gene addition
Gene control

* In both cartilage and synovium, catabolic factors (for example, metalloproteases [MMPs], nitric oxide [NO]) and cytokines (for example, interleukin-1β [IL-1β], tumor necrosis factor α [TNFα]) should be either reduced or eliminated. In contrast, some growth factors and the cytokine receptor antagonist (interleukin-1Ra [IL-1Ra]) or soluble receptors (soluble IL-1 receptor type II [sIL-1RII], soluble tumor necrosis factor receptor [sTNFR]) should be stimulated.

Specific neutralizing antibodies against IL-1 or TNFα have been tested in different systems. The IL-1 antibody has been successfully tested in a CIA murine model of inflammatory arthritis (92). Treatment with an anti-TNFα antibody has also been shown to improve arthritis in an experimental model as well as RA in humans (93). No such treatment has yet been tested in OA.

Inhibition of intracellular signaling pathways. Several postreceptor signaling pathways are involved in the synthesis of cytokines. Two of these pathways, p38 mitogen-activated protein (MAP) kinase and nuclear factor κB (NF-κB), appear to be the major ones involved in mediating the synthesis of several inflammatory cytokines and MMPs and are likely to play a role in these pathways that are activated during the OA process (29).

Pyridinyl imidazole compounds that have the ability to inhibit p38 MAP kinase and block proinflammatory cytokine production have been named cytokine-suppressive antiinflammatory drugs, or CSAIDs. These compounds inhibit synthesis of proinflammatory cytokines such as IL-1 and TNFα at the translational level (94). They have proven therapeutic effectiveness in animal models of inflammatory arthritis (95). In addition, some CSAIDs were also shown to inhibit the production of NO by chondrocytes or by human OA cartilage (96,97).

Drugs that will target NF-κB activity/activation

could have definite potential for the treatment of arthritis. COX-2 and IL-1β are but 2 of several genes modulated by NF-κB activation. A recent report showed that specifically blocking the activation of this factor in vivo in the CIA model induced a marked reduction in the expression of IL-1β and TNFα in synovium, as well as suppressing the degradation of bone and cartilage of the arthritic joint (98).

Inhibition of NO production. The discovery and characterization of the functions of the iNOS isoenzyme have provided the impetus for novel therapeutic approaches toward developing a potential new class of drugs. The challenge lies in making selective inhibitors that target only the inducible form of NOS in order not to down-regulate the constitutive OA physiologic isoform. The use of a selective iNOS inhibitor in a model of experimentally induced OA in dogs (99,100) was demonstrated to reduce in vivo the progression of early lesions, which was then associated with a reduction in cartilage MMP activity and IL-1β in synovium. Moreover, it was shown that the selective inhibition of iNOS decreased in situ the level of chondrocyte apoptosis. These data bring forward the potential of selective iNOS inhibitors, not only as effective agents for the treatment of the signs and symptoms of OA, but also for disease-modifying activity.

Antiapoptotic therapy. Chondrocyte apoptosis is a complex process mediated by the activation of several intercellular signaling pathways (74,75), including the caspase cascade which induces DNA damage (101). Current and future knowledge about its regulatory mechanisms will make it possible to develop a strategy for therapeutic approaches that could be targeted for future OA treatment. Targeting the caspase cascade or the mechanisms involved in caspase activation with the use of specific inhibitors is very appealing, although their potential side effects will require careful evaluation.

Gene therapy: an attractive concept and maybe more. Gene therapy (Table 2) in articular joint tissues can be used as a drug delivery system to modify or reestablish the balance between catabolic/anabolic factors or to modulate proinflammatory cytokines. Ideally, this must be done to the cell or must be tissue specific. The potential for the use of biologic molecules as therapeutic agents is limited. Lately, much attention has been focused on the use of gene transfer techniques. Their potential for the treatment of OA is of very significant interest, since a consistently high local concentration of the therapeutic protein in the joint can be provided and sustained delivery maintained over time. Several strategies to replace defective or deficient protein products are now under study (Table 2). Treatment approaches consist of various ex vivo or in vivo techniques using viral or nonviral vectors (102). One strategy consists of insertion into the cells of a gene enabling the production of a protein not normally expressed or expressed in low and insufficient amounts by the OA cells. The viral system is favored because it generally allows for a very effective transfer to a large percentage of cells while maintaining a sustained high level of protein expression that can be extended over significant periods of time. Ex vivo transfer of marker genes to OA cells has been demonstrated in experimental models with the use of a retroviral vector (89).

The selection or combination of the gene(s) that would offer the best protection against OA remains to be determined. The transfer of genes such as IL-1Ra, IL-10, and IL-13 has been studied using OA or inflammatory animal models (103). However, more specifically with regard to OA, the use of IL-1Ra gene therapy has elicited much attention. The rationale is based mainly on the fact that this antagonist has the ability in vitro to arrest cartilage degradation and in vivo to reduce the progression of experimental OA (30,89,90).

Conclusion

The current understanding of the pathophysiologic pathways involved in OA has evolved greatly in recent years. Specifically, the role of inflammation has been explored and new findings have allowed for a much better understanding of the disease process, the modulating factors, as well as the major regulators, which may have potential therapeutic value by specifically and effectively retarding the progression of this disease. A large amount of new information about OA pathophysiology and new targets for the development of therapeutic strategies has been generated from in vitro and experimental studies. Caution should obviously be exerted in extrapolating this to the clinical situation. Nevertheless, the future holds great promise for the development of new and successful approaches to the treatment of this disease.

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