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OSTEOARTHRITIS and CARTILAGE

REVIEW

Pathophysiology of osteoarthritis

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Introduction

ALTHOUGH cartilage degeneration characterizes human osteoarthritis (OA), changes also involve the participation of the synovial membrane and the subchondral bone.

In this review, attention will be focused on current knowledge of the major factors participating in the degeneration of OA articular joints tissues. Firstly, we will address the biochemical agents involved in the destruction of cartilage and synovial membrane. This will be followed by a brief survey of the most important modulatory factors of proinflammatory cytokines as well biological agents as potential therapeutics. Emphasis will then be placed on the possibility of an interaction between subchondral bone and cartilage as an integral part of the disease, leading and/or contributing to cartilage destruction in OA; do changes in one cause alterations in the other.

Pathophysiology of osteoarthritis

Osteoarthritis (OA) is an idiopathic disease characterized by a degeneration of articular cartilage. A breakdown of the cartilage matrix leads to the development of fibrillation and fissures, the appearance of gross ulcerations, and the disappearance of the full thickness surface of the joint. This is accompanied by bone changes with osteophyte formation and thickening of the subchondral plate. Moreover, at the clinical stage of the disease, changes caused by OA involve not only the cartilage but also the synovial membrane, where an inflammatory reaction is often observed [1].

A great deal of attention is focused on identifying the protease responsible for the initial occurrence of matrix digestion. Current knowledge indicates an important involvement of matrix metalloproteases (MMP). Of this family, members from three groups in human articular tissues have been identified as being elevated in OA, the collagenases, the stromelysins and the gelatinases. Another group of MMP, localized at the cell membrane surface, has recently been discovered, and named membrane type MMP (MT-MMP). Four members have been identified. Although MT1-MMP possesses properties of collagenase, and both MT1-MMP and MT2-MMP are able to activate gelatinase 72 kD and collagenase-3, the relevance of these enzymes to OA has yet to be determined.

MMP biologic activity is controlled physiologically by specific tissue inhibitors of metalloproteases (TIMP) or by their activation. Enzymes from the serine- and cysteine-dependent protease families, such as the plasminogen activation/plasmin system and cathepsin B respectively, have been proposed as activators, and enhanced levels of urokinase (uPA) and plasmin have been identified in human OA cartilage [2]. Other enzymes have also been found to act as MMP activators. For example, stromelysin-1 activates collagenase-1, collagenase-3 and gelatinase 92 kD; collagenase-3 activates gelatinase 92 kD, MT-MMP activates collagenase-3, and gelatinase 72 kD potentiates the latter activation; MT-MMP also activates gelatinase 72 kD.

Current evidence suggests that proinflammatory cytokines are responsible for the catabolic process occurring in the pathological tissues. They appear to be first produced by the synovial membrane, and diffused into the cartilage through the synovial fluid, where they activate the chondrocytes to produce proinflammatory cytokines. In OA synovial membrane, it is the synovial lining cells that play a major role as inflammatory effectors of which interleukin (IL)-1β, Tumor necrosis factor (TNF)-α, IL-6, leukemic inhibitor factor (LIF) and IL-17 appear most relevant to the disease.

Osteoarthritis data strongly support the concept that IL- 1β, and perhaps TNF-α, are the major catabolic systems involved in the destruction of joint tissues, and may constitute the *in-situ* source

of articular tissue degradation. It is still unclear whether IL-1β and TNF-α act independently or in concert to induce the pathogenesis of OA, or if a functional hierarchy exists between these proinflammatory cytokines. In animal models, it has been shown that blocking IL-1 or its activity is very effective in preventing cartilage destruction [3], whereas blocking TNF-α results in decreased inflammation [4]. Both these cytokines have been found in enhanced amounts in OA synovial membrane, synovial fluid and cartilage.

IL-6 has also been proposed as a contributor to the OA pathological process by: (1) increasing the amount of inflammatory cells in synovial tissue; (2) stimulating the proliferation of chondrocytes; and (3) by inducing an amplification of the IL-1 effects on the increased MMP synthesis and inhibition of proteoglycan production. However, as IL-6 can induce the production of tissue inhibitor of metalloproteases (TIMP), and not MMP themselves, it is believed that this cytokine is involved in the feedback mechanism that limits enzyme damage.

LIF is another cytokine of the IL-6 family that is upregulated in OA synovial membrane and fluid, and produced by chondrocytes in response to the proinflammatory cytokines, IL-1β and TNF-α [5]. This cytokine stimulates cartilage proteoglycan resorption, as well as MMP synthesis and nitric oxide (NO) cellular production [6]. However, its role in OA has not yet been clearly defined.

IL-17 is a newly discovered cytokine of 20–30 kD present as a homodimer and with variable glycosylated polypeptides. The nature of the tissue distribution of IL-17 receptor (R) appears ubiquitous. IL-17 upregulates a number of gene products involved in cell activation including the proinflammatory cytokines, IL-1β, TNF-α and IL-6, as well as MMP, in target cells such as human macrophages [7]. IL-17 also increases the production of NO in chondrocytes [8]. The role of LIF, in OA remains undetermined.

In addition, the inorganic free radical NO has been suggested as a factor that promotes cartilage catabolism in OA. Compared to normal, OA cartilage produces a larger amount of NO, both under spontaneous and proinflammatory cytokine-stimulated conditions [9] resulting in an enhanced expression and protein synthesis of the inducible NO synthase (iNOS). A high level of nitrite/nitrate has been found in the synovial fluid and serum of arthritic patients.

In the inflammatory response of OA articular cells, the changes in cyclooxygenase-2 (COX-2) expression and/or activity seem one of the major determinants for prostaglandin (PG)E_2 production. While the induction of COX-2 and iNOS appear to be separate processes, interaction in some target cells between these two systems was recently reported [10]; the NO stimulation of IL-1β and TNF-α-induced COX-2 expression was suggested to be mediated by cyclic quanosine monophosphate (cGMP). However, in an *in-vitro* study on chondrocytes, it was shown that inhibition of NO production enhanced PGE_2 production [11].

Natural inhibitors capable of directly counteracting the binding of the cytokine to cells or reducing the proinflammatory level have been identified, and can be divided into three categories based on their mode of action. The first inhibitor category is a receptor-binding antagonist of which to date only the IL-1 receptor antagonist has been found. The second category is the soluble receptors for IL-1β and TNF-α that are truncated forms of the receptors. Other natural inhibitors able to reduce proinflammatory cytokine production and/or activity are the cytokines having anti-inflammatory properties. Four such cytokines, namely transforming growth factor (TGF)-β, IL-4, IL-10 and IL-13, have been identified as able to modulate various inflammatory processes including a decreased production of proinflammatory cytokines such as IL-1β and TNF-α, as well as some proteases, and an upregulation of IL-1Ra and TIMP production.

Current therapeutic strategies of antagonizing IL-1β and TNF-α with either receptor blockade (with IL-1Ra) or molecular quenching (with IL-1R or TNF- R soluble receptors) have proven valuable in other arthritic diseases and in animal models of OA. Moreover, *in-vivo* therapeutic effects of a selective inhibitor of iNOS on the progression of lesions in experimental arthritis and OA [12] models have recently been reported.

In addition to degeneration of the articular cartilage, OA involves changes in the surrounding bone. The recently expanded body of knowledge concerning the subchondral bone provides the basis upon which we may assert that this tissue is intimately involved in the pathology of OA. It is suggested that thickening of the subchondral bone may participate in the progression of OA. Whether bone sclerosis initiates or is involved in the progression of cartilage loss remains a matter of debate.

Opposing concepts can explain a stiffening of the subchondral bone. In subchondral bone, the healing of trabecular microfractures, which are present due to repetitive impulsive loading of the joint and remodeling of the bony internal architecture to better resist these stresses, can generate a stiffer bone that is no longer an effective shock absorber [13, 14]. Conversely,

subchondral bone stiffness may be part of a more generalized bone alteration leading to increased bone mineral density/volume.

The hypothesis that abnormal OA osteoblasts directly influence cartilage metabolism has recently been put forward [15, 16]. In one study [15] it was shown that conditioned media from primary osteoblasts of OA patients versus subjects without arthritis significantly altered glycosaminoglycan release from normal cartilage *in vitro*, while cytokine release from these cells remained intact. Recently, Hilal *et al.* [16] reported that *in vitro* primary cultures of osteoblasts from human OA subchondral bone have an altered phenotype, and that the plasminogen activator (urokinase)/plasmin system activity and IGF-1 levels are elevated in these cells, explaining the above observations.

Although cartilage degeneration characterizes human OA, alterations of this disease also involve the participation of the synovial membrane and subchondral bone. Both clinical and laboratory evidence indicate an altered subchondral bone metabolism in OA, possibly due to abnormal osteoblast behavior. Coupled with mechanical/chemical stresses, abnormal OA osteoblasts would then accelerate subchondral bone formation, which would enhance the mechanical pressure on the overlying cartilage in supporting joints, promoting further deterioration and cartilage erosion. The role for a local factor(s) produced by osteoblasts (including PA/plasmin and IGF systems) promoting cartilage breakdown and/or increasing subchondral bone turnover is gaining support.

The current understanding of the factors involved in this disease has evolved greatly during recent years. A better comprehension of the modulating factors as well as the major regulators has and will continue to generate new insights into a more accurate identification of effective targets having therapeutic potential in the treatment of OA. The future holds great promise for the development of new and successful approaches to the treatment of this disease.

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