OsteoArthritis and Cartilage (2004) **12,** S31–S33

doi:10.1016/j.joca.2003.10.002

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Pathophysiology of osteoarthritis

Johanne Martel-Pelletier PhD*

Osteoarthritis Research Unit, Centre Hospitalier de l'Université de Montréal (CHUM) – Hôpital Notre-Dame, Montréal, Québec H2L 4M1, Canada

Key words: Cytokines, Cartilage, Synovial membrane.

Introduction

Osteoarthritis (OA) is characterized by a degeneration of articular cartilage, in which the breakdown leads to matrix fibrillation, fissure appearance, gross ulceration, and full-thickness loss of the joint surface. This is accompanied by hypertrophic bone changes with osteophyte formation and subchondral bone plate thickening. At the clinical stage of the disease, change in the synovial membrane is also found together with an inflammatory reaction.

The principal factors described are involved in two of the major tissues (these being the cartilage and the synovial membrane) implicated in the pathophysiology of this disease. Research has also shown that there is some continuity between bone and cartilage changes in OA, suggesting cross-talk between these tissues. Dr Lajeunesse provides a persuasive overview of this theory in his article, demonstrating that this tissue is more intimately related to the progression and/or the onset of OA, rather than being merely a consequence of this disease.

Hypothesis of the pathophysiology of osteoarthritis

Osteoarthritis has long been considered as being the result of age or trauma. This concept has evolved, and it is now accepted that the etiology of OA is multiple and includes various mechanical, biochemical, and genetic factors. The progression of this disease is generally divided into three broad stages[1]. Stage I is the proteolytic breakdown of cartilage matrix. In stage II, we have fibrillation and erosion of cartilage surface, which is accompanied by the release of breakdown products into the synovial fluid. During stage III, synovial inflammation begins when synovial cells ingest a breakdown product through phagocytosis and produce proteases and proinflammatory cytokines.

Proteases involved in osteoarthritis

A great deal of attention is focused on determining the protease responsible for the first occurrence of matrix digestion. Current knowledge indicates the major involvement of metalloproteases, or the MMP family, in this disease process[2]. From this family, collagenase, which is responsible for collagen degradation, and stromelysin, which is responsible for proteoglycan degradation, play primary roles in the degradation of the extracellular matrix.

Another enzyme named aggrecanase[3,4] is also responsible for proteoglycan fragmentation as seen in OA synovial fluid. This aggrecanase, which was recently cloned, has a disintegrin and MMP domains and belongs to the adamalysin family. Other enzymes from the serine and cysteine-dependent protease families, such as plasminogen activator/plasmin and cathepsin B, respectively, also play key roles but mostly as activators of MMP.

As an irreversible step in OA occurs when collagen is degraded, it was thought that the major enzyme accounting for collagen type II degradation in pathological cartilage was collagenase-1 or MMP-1. Recently, another human collagenase named collagenase-3, or MMP-13, has been identified and our laboratory[5] has shown that this enzyme is involved in the pathophysiology of OA.

Some differential aspects of these collagenases, as they demonstrate a functional role in arthritis, have raised the possibility of therapeutic intervention using specific inhibitors directed against this collagenase-3 activity. The difference between these collagenases point to targeting collagenases-3[6–8]. Hence, in contrast to collagenase-1, collagenase-3 is not present in most of the normal adult tissue, but could be detected in normal cartilage and fetal ossification. Even in pathological conditions, collagenase-3 has a restricted pattern of tissue expression, whereas collagenase-1 has a widespread distribution in human tissues. However, both are present in higher amounts in OA cartilage. Again, and in contrast to collagenase-1, collagenase-3 preferentially cleaves type II collagen, is five to ten times more active on this substrate and has a very high gelatinolytic activity. Indeed, collagenase-3 is 44 times more active against gelatin than collagenase-1.

If we summarize the data on these collagenases in OA cartilage obtained from our laboratory and from that of others, one could hypothesize an involvement of collagenase-1 during the inflammatory process and an implication of collagenase-3 in the remodeling phase of the cartilage.

Cytokines

CATABOLIC PROCESS

The enzymatic alteration in articular cartilage may explain the exhaustive degradation of this tissue but does not provide an explanation for the increased synthesis and

*Address correspondence to: J. Martel-Pelletier, PhD, Centre Hospitalier de l'Université de Montréal (CHUM), Osteoarthritis Research Unit, Hôpital Notre-Dame, Montreal, Québec, Canada H2L 4M1. Tel.: +1-514-890-8000; Fax: +1-514-412-7582; E-mail: jm@martelpelletier.ca

expression of MMP in articular tissues. However, current evidence suggests that the occurrence of synovial membrane inflammation is of importance in the progression of cartilage lesions in OA[1]. A hypothesis of the pathological development of OA at the clinical stage of the disease may be summarized by the following: the cartilage matrix breakdown produced by proteolytic enzymes releases increased amounts of matrix fragments into fluid, which can promote synovial inflammation.

The inflammation of the membrane through the synthesis of mediators creates a vicious cycle with more cartilage being degraded and subsequently provoking more inflammation. Several soluble mediators have been identified in articular tissue from various arthritic diseases. Of the proinflammatory cytokines, interleukin-1β and TNF-α appear to be the principal mediators of joint destruction[9]. Yet, it is claimed, and substantiated by studies on animal models[10–12], that in the disease, IL-1 is of pivotal importance in cartilage destruction and considered to be the principal mover of the enzyme system. TNF-α, however, drives the inflammatory process.

Proinflammatory cytokines, such as IL-1β and TNF-α, have a significant effect on chondrocytes. These cytokines are able (i) to increase the enzyme synthesis, (ii) to inhibit the synthesis of the major physiological inhibitors of these enzymes, and (iii) to inhibit the synthesis of the matrix constituents, such as collagen and proteoglycans. These actions make these two cytokines prime targets for therapeutic approaches. Thus, the action of IL-1β and TNF-α, on the enzyme process, combined with the suppression of matrix synthesis, result in a severe degradation of cartilage and the appearance of conditions known to be characteristic of OA. Understanding the elements involved in the regulation of these two proinflammatory cytokines will therefore provide a better insight into therapeutic strategy.

It is well known that IL-1β is synthesized as an inactive precursor and must be activated by an enzyme to be released in the active form. In mammals, only one protease belonging to the cysteine-dependent protease, and named IL-1β converting enzyme or ICE or caspase-1, can specifically generate mature IL-1β[13]. This enzyme is located in the cells.

Our laboratory has recently demonstrated that ICE is produced in both synovial membrane and cartilage with a marked and significant increase in expression and synthesis in OA tissues[14]. By immunohistochemistry, it was demonstrated that in the normal synovial membrane, only few cells of the lining layer had specific positive ICE staining. In contrast, OA synovial membrane produced a very high amount of ICE. Similarly, this enzyme is present in human articular cartilage and is preferentially located at the superficial level of the cartilage, which is also the location of IL-1β. Morphological analysis of the many specimens of the articular cartilage revealed a statistically significant increase in the level of ICE in OA compared to normal. Again, in this tissue, this enzyme is located preferentially at the superficial zone.

As is well known, cytokines mediate their activities through interactions with high affinity cell surface receptor. Two types of receptors have been identified for IL-1β and TNF-α. These receptors are named IL-1 receptor type I and IL-1 receptor type II for IL-1β[15] and TNF receptor 55 and 75, according to their molecular weight, for TNF-α[16]. These latter receptors function as trimers. Data from our laboratory have shown that the number of type IIL-1 receptors responsible for mediatin the signal is significantly increased in OA tissue[17,18]. We have also shown in our laboratory that TNF receptor 55 is responsible for the TNF signal transduction in both synovial fibroblasts and chondrocytes, and the number of this TNF receptor 55 is significantly increased in OA compared to normal[19].

PHYSIOLOGICAL INHIBITORS

So far, I have highlighted points relating to the catabolic process occurring in OA cartilage or synovial membrane. However, natural or physiological inhibitors capable of directly contracting the binding of cytokines to cells or reducing the proinflammatory level have been identified. In these tissues, they could be divided into three categories based on their mode of action. The first category is a receptor antagonist, which interferes with the binding of the ligand to its receptor by competing for the same binding site. Until now, such an inhibitor has been found only for the IL-1 system and is named IL-1 receptor antagonist, or IL-1Ra.

The second category includes soluble forms of the proinflammatory cytokine receptor, which bind to the free cytokine. These are truncated forms of the receptor. For both IL-1β and TNF-α, they are named according to the classification of their receptor. Thus, for IL-1β, they are named IL-1 receptor type I and type II soluble receptors, and for TNF-α, TNF-soluble receptor 55 and 75. The third category includes molecules able to reduce proinflammatory cytokine production and/or activity. These molecules are named antiinflammatory cytokines and three such cytokines, namely IL-4, IL-10, and IL-13, have been identified.

The following is a summary of how the proinflammatory cytokines, IL-1β and TNF-α, are regulated. To begin with, cytokines bind to specific receptors at the cellular membrane level to mediate their activity. This process can be blocked by natural factors including IL-1Ra for the IL-1 system, which binds competitively to the receptor and blocks access of IL-1β to its receptor. Secondly, there are the soluble receptors, which will bind to the free cytokine and, again, will block its activity. Thirdly, the antiinflammatory cytokine will decrease the synthesis of IL-1β and TNF-α.

The balance between cytokine-driven anabolic and catabolic processes determines the integrity of articular joint tissue. However, not all negative catabolic activity in OA articular cartilage can be attributed to IL-1β or TNF-α. Other cytokines may also be involved, for example, some proinflammatory cytokines, including IL-6, LIF, IL-17, IL-8, and IL-18, have also been shown to be expressed in OA tissues and therefore have been considered potential contributing factors in the pathogenesis of this disease.

Summary

In summary OA is characterized by cartilage degeneration. The breakdown of major macromolecules, such as collagen and proteoglycan, are triggered by enzymatic activity in which MMPs play a dominant role. In this disease, it is now acknowledged that the synovial membrane is also involved. At the clinical stage of the disease, the morphological changes observed in OA include a variable degree of synovial inflammation, which in turn produces inflammatory mediators including IL-1β and TNF-α, which play a pivotal role in mediating the pathophysiological mechanisms. In the last 20 years or so, significant progress has been made in understanding the

mechanisms involved in the pathogenesis of this disease. In addition to the factors mentioned, there is increasing evidence to suggest that alterations in OA also involve the subchondral bone, a situation that may result from abnormal subchondral osteoblast behavior[20].

References

1. Pelletier JP, Martel-Pelletier J, Howell DS. Etiopathogenesis of osteoarthritis. In: Koopman WJ, Ed. Arthritis & Allied Conditions. A Textbook of Rheumatology, 14th edn. Baltimore: Williams & Wilkins 2000; 2195–245.
2. Martel-Pelletier J, Tardif G, Fernandes JC, Pelletier JP. Metalloproteases and their modulation as treatment in osteoarthritis. In: Tsokos GC, Ed. Molecular Rheumatology. Totowa, New Jersey: Humana Press Inc 2000;499–514.
3. Lark MW, Bayne EK, Flanagan J, Harper CF, Hoerrner LA, Hutchinson NI, *et al.* Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. J Clin Invest 1997;100:93–106.
4. Tortorella MD, Burn TC, Pratta MA, Abbaszade I, Hollis JM, Liu R, *et al.* Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science 1999;284:1664–6.
5. Reboul P, Pelletier JP, Tardif G, Cloutier JM, Martel-Pelletier J. The new collagenase, collagenase-3, is expressed and synthesized by human chondrocytes but not by synoviocytes: A role in osteoarthritis. J Clin Invest 1996;97:2011–9.
6. Tardif G, Pelletier JP, Dupuis M, Geng C, Cloutier JM, Martel-Pelletier J. Collagenase 3 production by human osteoarthritic chondrocytes in response to growth factors and cytokines is a function of the physiological state of the cells. Arthritis Rheum 1999; 42:1147–58.
7. Martel-Pelletier J, Pelletier JP. Wanted – the collagenase responsible for the destruction of the collagen network in human cartilage! Br J Rheumatol 1996;35:818–20.
8. Moldovan F, Pelletier JP, Hambor J, Cloutier JM, Martel-Pelletier J. Collagenase-3 (matrix metalloprotease 13) is preferentially localized in the deep layer of human arthritic cartilage in situ: in vitro mimicking effect by transforming growth factor beta. Arthritis Rheum 1997;40:1653–61.
9. Martel-Pelletier J, Alaaeddine N, Pelletier JP. Cytokines and their role in the pathophysiology of osteoarthritis. Front Biosci 1999;4:D694–D703.
10. Caron JP, Fernandes JC, Martel-Pelletier J, Tardif G, Mineau F, Geng C, *et al.* Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis: suppression of collagenase-1 expression. Arthritis Rheum 1996;39:1535–44.
11. Van de Loo FAJ, Joosten LA, van Lent PL, Arntz OJ, van den Berg WB. Role of interleukin-1, tumor necrosis factor alpha, and interleukin-6 in cartilage proteoglycan metabolism and destruction. Effect of in situ blocking in murine antigen- and zymosan-induced arthritis. Arthritis Rheum 1995;38:164–72.
12. Plows D, Probert L, Georgopoulos S, Alexopoulou L, Kollias G. The role of tumour necrosis factor (TNF) in arthritis: studies in transgenic mice. Rheumatol Eur 1995;Suppl 2:51–4.
13. Kronheim SR, Mumma A, Greenstreet T, Glackin PJ, Van Ness K, March CJ, *et al.* Purification of interleukin-1 beta converting enzyme, the protease that cleaves the interleukin-1 beta precursor. Arch Biochem Biophys 1992;296:698–703.
14. Saha N, Moldovan F, Tardif G, Pelletier JP, Cloutier JM, Martel-Pelletier J. Interleukin-1b-converting enzyme/Caspase-1 in human osteoarthritic tissues: localization and role in the maturation of IL-1b and IL-18. Arthritis Rheum 1999;42:1577–87.
15. Slack J, McMahan CJ, Waugh S, Schooley K, Spriggs MK, Sims JE, *et al.* Independent binding of interleukin-1 alpha and interleukin-1 beta to type I and type II interleukin receptors. J Biol Chem 1993; 268:2513–24.
16. Tartaglia LA, Goeddel DV. Two TNF receptors. Immunol Today 1992;13:151–3.
17. Martel-Pelletier J, McCollum R, Di Battista JA, Faure MP, Chin JA, Fournier S, *et al.* The interleukin-1 receptor in normal and osteoarthritic human articular chondrocytes. Identification as the type I receptor and analysis of binding kinetics and biologic function. Arthritis Rheum 1992;35:530–40.
18. Sadouk M, Pelletier JP, Tardif G, Kiansa K, Cloutier JM, Martel-Pelletier J. Human synovial fibroblasts coexpress interelukin-1 receptor type I and type II mRNA: The increased level of the interleukin-1 receptor in osteoarthritic cells is related to an increased level of the type I receptor. Lab Invest 1995; 73:347–55.
19. Alaaeddine N, De Battista JA, Pelletier JP, Cloutier JM, Kiansa K, Dupuis M, *et al.* Osteoarthritic synovial fibroblasts possess an increased level of tumor necrosis factor-receptor 55 (TNF-55) that mediates biological activation by TNF-alpha. J Rheumatol 1997;24:1985–94.
20. Lajeunesse D, Hilal G, Pelletier JP, Martel-Pelleteri J. Subchondral bone morphological and biochemical alterations in osteoarthritis. Osteoarthritis Cart 1999; 7:321–2 [Review].