Commentary

The Novartis–ILAR Rheumatology Prize 2001 Osteoarthritis: from molecule to man

Jean-Pierre Pelletier and Johanne Martel-Pelletier

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

Correspondence: Jean-Pierre Pelletier, MD, Osteoarthritis Research Unit, Centre Hôspitalier de l'Université de Montréal (CHUM) – Hôpital Notre-Dame, 1560 rue Sherbrooke Est, Montréal, Québec, Canada H2L 4MJ. Tel: +1 514 890 8000 ext. 26658; fax: +1 514 412 7582; e-mail: dr@jppelletier.ca

Received: 26 September 2001
Accepted: 4 October 2001
Published: 2 November 2001

Arthritis Res 2002, **4**:13-19

(Print ISSN 1465-9905; Online ISSN 1465-9913)

Abstract

During our careers, we have developed new and innovative concepts pertaining to the pathophysiology of osteoarthritis which have assisted in the development of new therapeutic approaches. Moreover, our laboratory has long sought to develop protective agents for osteoarthritic structural joint tissues. The most significant concepts that have originated from our lab are briefly outlined in this commentary.

Keywords: joint articular tissue, magnetic resonance imaging, osteoarthritis, therapeutic

Introduction

The Novartis–ILAR Rheumatology Prize was awarded at the 20th ILAR Congress of Rheumatology in Edmonton, Canada in August 2001. The Editors-in-Chief would like to inform readers that this Commentary has not undergone peer-review, because it is based upon the acceptance speech for the Prize.

Metalloproteases and their inhibitors

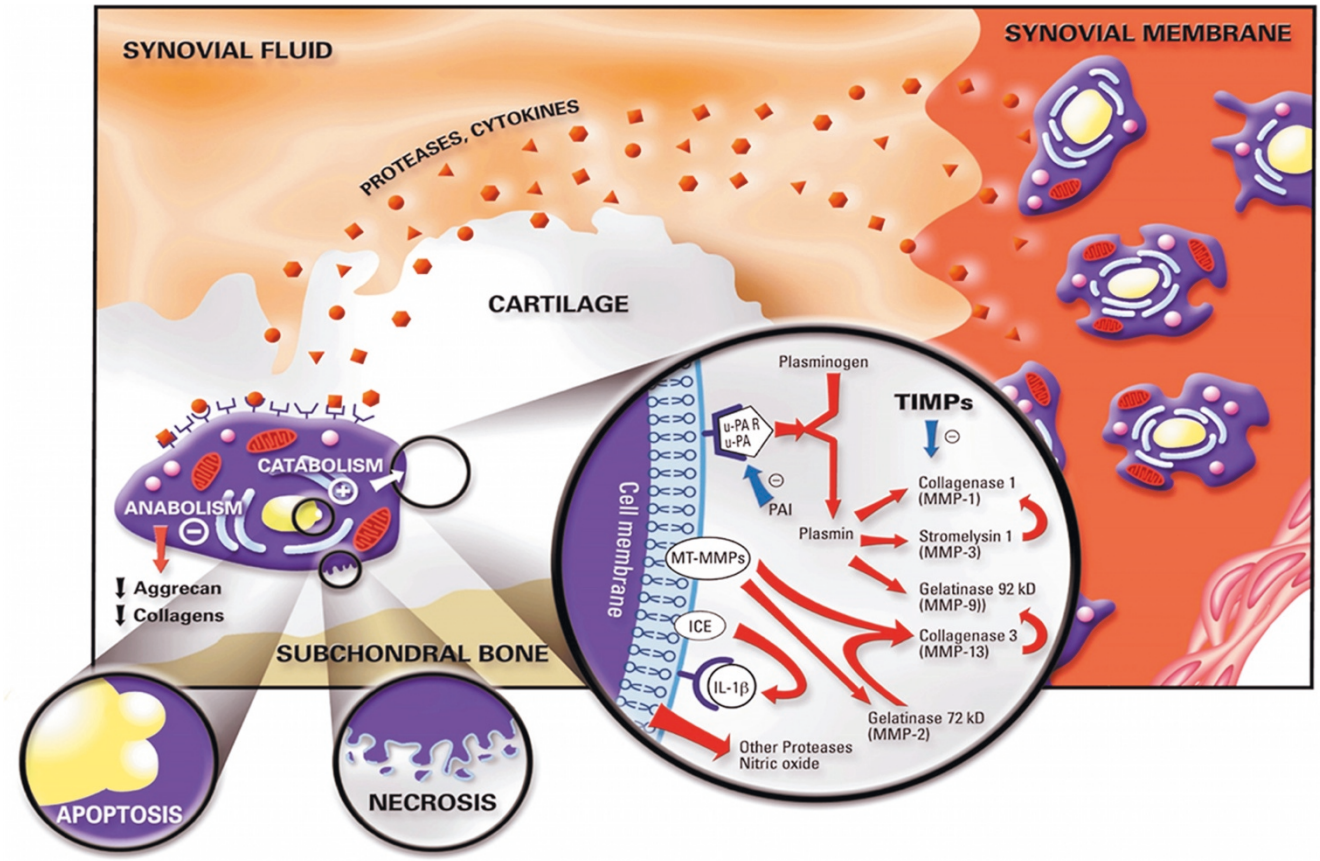
In our work on osteoarthritis, we identified several enzymatic pathways that are intimately related to the development of this disease. More specifically, we demonstrated that, although the matrix metalloprotease (MMP) family is of pivotal importance in the degradation of osteoarthritic cartilage [1–26] (Fig. 1), the serine- and cysteine-dependent proteases [27–30] also play a significant role. We were among the first to introduce and demonstrate the importance of an imbalance in enzymes and their specific inhibitors (tissue inhibitor of MMP, cathepsin B-inhibitors and plasminogen activator/plasmin/plasminogen activator inhibitor-1) in osteoarthritic tissues. This concept is now well recognized as an intimate element in the pathogenesis of osteoarthritis.

In recent years, we have been involved in the discovery of a new collagenase, collagenase-3 (MMP-13), in cartilage and demonstrated its involvement in the osteoarthritis disease process [18]. We were also the first group to clone human collagenase-3 promoter, more specifically its 5′ flanking region (GenBank #U52692) [20]. From the work undertaken in our laboratory, we have come to the hypothesis that collagenase-3, in contrast to collagenase-1 (MMP-1), is involved in the remodeling phase of osteoarthritic cartilage [21–24,26]. Moreover, we also found that, although many cytokines and factors can upregulate collagenase-3, transforming growth factor (TGF)-β appears to be the factor responsible for its upregulation *in vivo* in osteoarthritic cartilage [21,24,26].

Altogether, these findings have proven to be of utmost importance, as some pharmaceutical companies have targeted MMP and tissue inhibitor of MMP as effective ways

IGF = insulin-like growth factor; IL = interleukin; MMP = matrix metalloprotease; PGE = prostaglandin E; TGF = transforming growth factor.

Figure 1



Pathways involved in the osteoarthritis disease process. The evolution of the osteoarthritis disease process is characterized by cartilage degradation caused, at least in part, by proteolytic breakdown of macromolecules, in which matrix metalloproteases (MMPs) play an important role. Further fibrillation and erosion of the cartilage surface result in the release of molecular breakdown products into the synovial fluid. The phagocytosis of cartilage matrix breakdown products and other materials by synovial macrophages induces an inflammatory reaction in the synovial membrane, thereby resulting in local synthesis of proteases and proinflammatory cytokines. The proteases and cytokines released by the synovium diffuse through the synovial fluid and into the cartilage. They induce additional cartilage breakdown by direct macromolecule proteolysis and by stimulation of chondrocyte cytokine production to increase the synthesis of proteases. There is also an increased level of cytokine receptors on the cell. ICE = interleukin-1β-converting enzyme; IL = interleukin; MT-MMP = membrane-type matrix metalloprotease; TIMP = tissue inhibitor of matrix metalloprotease; u-PA = urokinase plasminogen activator; – refers to inhibition; + to stimulation. A part of this figure was adapted from figure 110.1, stage III in [80], a figure produced by Amersham Pharmacia Biotech and reproduced with permission from [80].

to prevent osteoarthritis progression. Moreover, it appears that a specific blockage of collagenase-3 is the preferred candidate in osteoarthritic patients.

Insulin-like growth factor 1

Since there is a dysregulation between matrix synthesis and degradation in cartilage affected by osteoarthritis, researchers have been seeking factors that favor the formation of a durable functional articular surface following damage. Because of its properties, we studied the involvement of insulin-like growth factor-1 (IGF-1) in cartilage and bone [31–39]. Our studies revealed the identification of a metabolic disorder associated with the development of osteoarthritis. We showed that, although more IGF-1 is secreted by osteoarthritic chondrocytes, these cells are hyporesponsive to this growth factor. This phenomenon was not related to a change in IGF-1-receptor expression but rather to an increase in IGF-1 binding proteins that affects the bioavailability of IGF-1. Further studies showed that prostaglandin E_2 (PGE_2) upregulated the levels of IGF-1-binding proteins.

Transforming growth factor ß

We also investigated TGF-β in osteoarthritic cartilage and most specifically its effect on collagenase-3 upregulation. Interestingly our data revealed that TGF-β acts in a differential manner in regulating collagenase-1 (MMP-1) and collagenase-3 (MMP-13). Indeed TGF-β1 and -β2 have an identical pattern in the upregulation of collagenase-3 (MMP-13), which depends on the metabolic state of the chondro-

cytes [24]. In contrast, TGF-β1 upregulates collagenase-1 (MMP-1) and this was not dependent on the metabolic state of the cells. TGF-β2 has no effect on this enzyme. In addition, we recently provided evidence that, in human osteoarthritic cartilage, extracellular activation of TGF-β appears to be controlled by the furin convertase [26].

Proinflammatory cytokines

As a result of the work on the enzymes, and more specifically on MMPs, it became clear that the enzymatic alterations could explain the exhaustive degradation of the articular joint tissue. However, this did not provide an explanation for the increased synthesis and expression of these enzymes and the decreased production of their inhibitors. Another hypothesis that was brought forth, and was a turning point in the understanding of the pathophysiology of osteoarthritis, is the involvement of synovial membrane inflammation. This hypothesis was based on the demonstration of the prime role of the proinflammatory cytokine interleukin (IL)-1β in this disease [40–48].

In addition to demonstrating that IL-1β is responsible, at least in part, for the changes seen in osteoarthritic joint tissues [41,42,45,48,49], we documented the mechanisms by which IL-1β stimulates osteoarthritic cell-biological activity and how this process was modulated. This led to the study of IL-1 receptors (IL-1Rs) as well as to the study of its natural antagonist, IL-1Ra [44,50–56]. In brief, data showed that IL-1β was the major autocrine proinflammatory cytokine involved in the stimulation of catabolic factors, including MMPs. The data also revealed that the type I IL-1R was responsible for mediating the IL-1 activity, the number of this receptor type significantly increased in osteoarthritic cells [44,50,53]. These findings introduced the hypothesis that specifically blocking the activity of IL-1β would protect against structural changes in osteoarthritis.

A relative deficit of IL-1Ra vis-à-vis IL-1β was also found in the diseased tissue, and it was shown that the use of IL-1Ra could reduce IL-1β-induced cartilage degradation [54–56]. In fact, we demonstrated *in vivo* (by intra-articular injections of recombinant IL-1Ra in an experimental OA animal model) that the elevated IL-1Ra level in joint tissues reduces the progression of this disease. Since the administration of proteins is a major weakness for drug delivery, we pursued our research by using gene therapy as a novel therapeutic approach. *In vivo* studies using two experimental animal models and two different strategies were conducted. The first employed an indirect, or *ex vivo*, approach in which the IL-1Ra gene was transferred *in vitro* into the synoviocytes with the use of an adenovirus vector, and the transfected cells reintroduced into the joint. The second used a direct, *in vivo*, gene transfer utilizing a liposome complexed with a DNA plasmid encoding the IL-1Ra gene. Collectively, data demonstrated that the IL-1Ra gene can be transfected into osteoarthritic cells and produce an IL-1Ra protein that results in a significant reduction in the progression of the disease. We are currently increasing our knowledge of gene therapy for its eventual use in human osteoarthritis.

Recently, we also demonstrated that the specific enzyme responsible for the extracellular release of active IL-1β, the IL-1β-converting enzyme (ICE), was present in both human cartilage and synovial membrane, and its level significantly increased in osteoarthritic tissues [57]. We also showed that ICE-specific inhibition in human osteoarthritic cartilage resulted in a complete abrogation of active IL-1β formation. These findings support the notion that blocking this enzyme represents another interesting potential target for osteoarthritis therapy.

Recent work in our laboratory strongly points to the fact that the peroxisome proliferator-activated receptor gamma (PPARγ) system may represent a therapeutic target in osteoarthritis [58,59]. Indeed, we showed in human osteoarthritic chondrocytes and synovial fibroblasts that PPARγ ligands inhibit IL-1β-induced production of MMPs and nitric oxide (NO); this occurred at the transcriptional level.

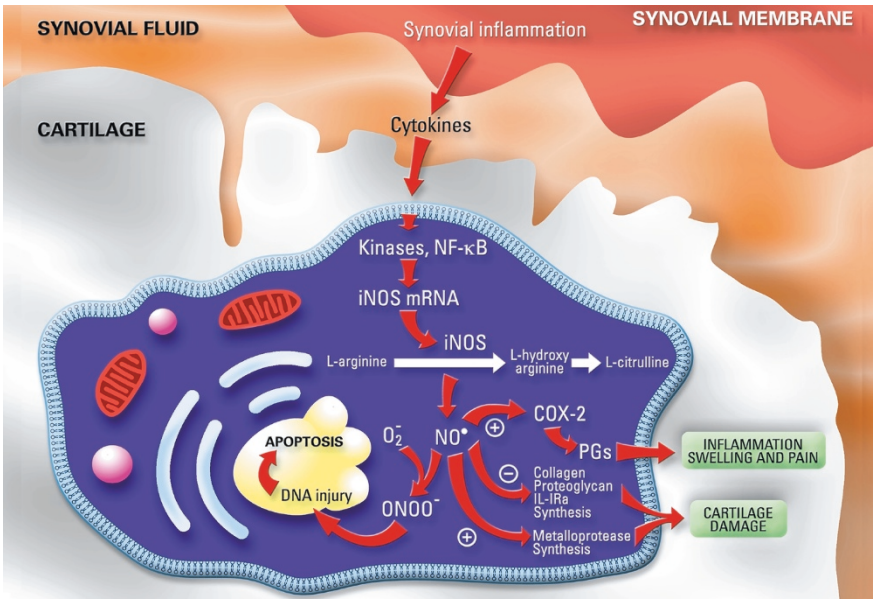
Nitric oxide

Our work also ascertained that another factor, the inducible form of nitric oxide synthase (iNOS), is an extremely important element in regard to the pathophysiology of osteoarthritis [60–65] (Fig. 2). We showed that there is excess production of NO in osteoarthritic cartilage that is generated via an increase in the iNOS level. NO also appears to be responsible for inducing many of the catabolic pathways responsible for osteoarthritic cartilage degradation, such as the reduction of IL-1Ra. Very importantly, we recently demonstrated *in vivo* the potential for the selective inhibition of iNOS to reduce the progression of osteoarthritis in an animal model [61,62,64]. The *in vivo* inhibition of iNOS reduced the severity of structural joint-tissue changes, which was associated with a reduction of MMPs in articular cell tissues and chondrocyte apoptosis, as well as a reduction in the levels of IL-1β and PGE_2 in synovial fluid [62,64]. Recently, we demonstrated that exogenous PGE_2 may sensitize human osteoarthritic chondrocytes to cell death induced by NO [65,66]. These latter data indicate that a possible molecular target for the inhibition of chondrocyte apoptosis is NO and extracellular factors involved in signaling.

Subchondral bone

Earlier, we addressed the idea that cytokines are an interesting link in osteoarthritis for tissue cross-talk (synovium–cartilage) leading to the development and progression of this disease. As a result of data from morphological and clinical studies investigating the subchondral bone in

Figure 2



Pathways of nitric oxide (NO) formation and effects on articular chondrocytes. COX = cyclooxygenase, IL-1Ra = interleukin-1 receptor antagonist, iNOS = inducible nitric oxide synthase, NF = nuclear factor, PGs = prostaglandins, – refers to inhibition; + to stimulation. Reproduced from figure 110.3 with permission from [80].

osteoarthritis, it has been proposed that subchondral bone plays a significant role in the progression of this disease. A question that still remains to be answered is whether the changes in subchondral bone induce or only participate in disease progression.

We recently investigated this concept, and our data provided new substantiated evidence that subchondral bone alterations are likely to be related to the onset or progression of osteoarthritis, rather than being merely consequential ([30,39,67,68] and our unpublished observations). We showed that subchondral bone changes are related, at least in part, to an abnormal subchondral bone osteoblast metabolism. Some local factors produced by subchondral bone osteoblasts, such as alkaline phosphatase, osteocalcin, plasminogen activator/plasmin and IGF-1 systems, and cytokines such as IL-6, as well as PGE_2 and TGF-β, were shown to be associated with osteoarthritis progression.

Therapeutic intervention in humans

Following our *in vitro* and *in vivo* data on humans [19,69–74] and the *in vivo* data on animal models [5,49,75,76], we further explored in humans the *in vivo* effects of intra-articular injections of glucocorticoids. Even though glucocorticoid injections have been used successfully for decades to relieve osteoarthritic symptoms and restore function, there is still debate about whether this drug class has a significant effect on disease progression. We conducted a two-year, double-blind, placebo-controlled study on knee osteoarthritis patients, evaluating the effect of steroids on osteoarthritic symptoms, quality of life and disease progression [77]. Data revealed that repeated steroid injections were found effective for the long-term symptomatic treatment of knee osteoarthritis without having any deleterious effects on the anatomical structure of the joint. Using existing methods to evaluate disease progression, we were not able in this study to see changes even in the placebo group.

We then addressed the question of sensitive and accurate methods for the assessment of the progression of structural changes in osteoarthritic joints in humans when looking at the effect of a drug. Visualization of articular cartilage is now possible with magnetic resonance imaging but quantification of this tissue volume was lacking. We have developed a novel imaging system assessing cartilage volume/thickness using magnetic resonance imaging of the knee. Preliminary data revealed that statistically significant changes in the volume and thickness of osteoarthritic knee cartilage were detectable at 12 months [78,79], which is a considerable improvement over existing X-ray techniques. This technology should significantly improve the investigation of new drugs and their potential to modify the progression of osteoarthritis.

Conclusion

Our research has assisted in the advancement of our knowledge of the mechanisms leading to joint destruction in osteoarthritis. At the same time, we have laid the groundwork for the testing of therapeutic interventions *in vivo* that may be extended to humans. Moreover, the development of software quantifying the volume and thickness of human cartilage as assessed by magnetic resonance imaging will dramatically change the manner in which knee osteoarthritis clinical trials are conducted. Studies will be performed in a timely fashion, allowing the testing of a larger number of molecules that have the potential to retard or stop the progression of the disease.

Acknowledgements

We first would like to thank ILAR and Novartis, the president of ILAR, Dr Jan Dequeker, and the members of the scientific committee for giving us this award. We also want to thank the supervisors we had during our fellowships, Professor DS Howell, Professor RA Altman, and Professor JF Woessner (all at University of Miami, Miami, Florida, USA), who were sources of great inspiration for us, not only during our fellowships but also afterwards. We also would like to thank the rheumatologists and researchers in our Unit at Notre-Dame Hospital, University of Montreal Research Center for their confidence, valuable assistance, collaboration and enthusiasm over the years; we greatly appreciate their support. Many other collaborators have also assisted in the development of our ideas and research, and we thank them all. Finally, we would like to acknowledge the governmental organizations (Canadian Institutes of Health Research, formerly Medical Research Council of Canada, and the Fonds de la Recherche en Santé du Québec), the Arthritis Society and the companies who believed in our research and provided grants or donations for the continuation of our projects.

References

1. Woessner JF Jr, Pelletier JP, Martel-Pelletier J, Enis J, Howell DS: **Direct measurement of cartilage collagenolytic activity in human osteoarthritis.** *Semin Arthritis Rheum* 1981, **11**:58-59.
2. Pelletier JP, Martel-Pelletier J, Howell DS, Ghandur-Mnaymneh L, Enis JE, Woessner JF Jr: **Collagenase and collagenolytic activity in human osteoarthritic cartilage.** *Arthritis Rheum* 1983, **26:** 63-68.
3. Pelletier JP, Martel-Pelletier J, Altman RD, Ghandur-Mnaymneh L, Howell DS, Woessner JF Jr: **Collagenolytic activity and collagen matrix breakdown of the articular cartilage in the Pond-Nuki dog model of osteoarthritis.** *Arthritis Rheum* 1983, **26:**866-874.
4. Martel-Pelletier J, Pelletier JP, Cloutier JM, Howell DS, Ghandur-Mnaymneh L, Woessner JF Jr: **Neutral proteases capable of proteoglycan digesting activity in osteoarthritic and normal human articular cartilage.** *Arthritis Rheum* 1984, **27:**305-312.
5. Pelletier JP, Martel-Pelletier J: **Cartilage degradation by neutral proteoglycanases in experimental osteoarthritis. Suppression by steroids.** *Arthritis Rheum* 1985, **28:**1393-1401.
6. Martel-Pelletier J, Cloutier J-M, Pelletier J-P: **Neutral proteases in human osteoarthritic (OA) synovium.** *Arthritis Rheum* 1986, **29:** 1112-1121.
7. Pelletier JP, Martel-Pelletier J, Cloutier JM, Woessner JF Jr: **Proteoglycan-degrading acid metalloprotease activity in human osteoarthritic cartilage, and the effect of intraarticular steroid injections.** *Arthritis Rheum* 1987, **30:**541-548.
8. Dean DD, Azzo W, Martel-Pelletier J, Pelletier JP, Woessner JF Jr: **Levels of metalloproteases and tissue inhibitor of metalloproteases in human osteoarthritic cartilage.** *J Rheumatol* 1987, **14 (Spec No):**43-44.
9. Martel-Pelletier J, Pelletier JP: **Neutral proteases in human osteoarthritic synovium: quantification and characterization.** *J Rheumatol* 1987, **14:**38-40.
10. Pelletier JP, Martel-Pelletier J, Malemud CJ: **Proteoglycans from experimental osteoarthritic cartilage: degradation by neutral metalloproteases.** *J Rheumatol* 1987, **14:**113-115.
11. Pelletier JP, Martel-Pelletier J, Malemud CJ: **Canine osteoarthritis: effects of endogenous neutral metalloproteoglycanases on articular cartilage proteoglycans.** *J Orthop Res* 1988, **6:**379-388.
12. Dean DD, Martel-Pelletier J, Pelletier JP, Howell DS, Woessner JF Jr: **Evidence for metalloproteinase and metalloproteinase inhibitor imbalance in human osteoarthritic cartilage.** *J Clin Invest* 1989, **84:**678-685.
13. Pelletier JP, Mineau F, Faure MP, Martel-Pelletier J: **Imbalance between the mechanisms of activation and inhibition of metalloproteases in the early lesions of experimental osteoarthritis.** *Arthritis Rheum* 1990, **33:**1466-1476.
14. Zafarullah M, Pelletier JP, Cloutier JM, Martel-Pelletier J: **Elevated metalloproteinase and tissue inhibitor of metalloproteinase mRNA in human osteoarthritic synovia.** *J Rheumatol* 1993, **20:** 693-697.
15. Martel-Pelletier J, McCollum R, Fujimoto N, Obata K, Cloutier JM, Pelletier JP: **Excess of metalloproteases over tissue inhibitor of metalloprotease may contribute to cartilage degradation in osteoarthritis and rheumatoid arthritis.** *Lab Invest* 1994, **70:** 807-815.
16. DiBattista JA, Pelletier JP, Zafarullah M, Fujimoto N, Obata K, Martel-Pelletier J: **Coordinate regulation of matrix metalloproteases and tissue inhibitors of metalloproteinase expression in human synovial fibroblasts.** *J Rheumatol* 1995, **43:**123-128.
17. Zafarullah M, Su S, Martel-Pelletier J, DiBattista JA, Costello BG, Stetler-Stevenson WG, Pelletier JP: **Tissue inhibitor of metalloproteinase-2 (TIMP-2) mRNA is constitutively expressed in bovine, human normal, and osteoarthritic articular chondrocytes.** *J Cell Biochem* 1996, **60:**211-217.
18. 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:**2011-2019.
19. Caron JP, Tardif G, Martel-Pelletier J, Di Battista JA, Geng C, Pelletier JP: **Modulation of matrix metalloproteases 13 (collagenase 3) gene expression in equine chondrocytes by interleukin 1 and corticosteroids.** *Am J Vet Res* 1996, **57:**1631-1634.
20. Tardif G, Pelletier JP, Dupuis M, Hambor JE, Martel-Pelletier J: **Cloning, sequencing and characterization of the 5′-flanking region of the human collagenase-3 gene.** *Biochem J* 1997, **323:**13-16.
21. 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:**1653-1661.
22. Fernandes JC, Martel-Pelletier J, Lascau-Coman V, Moldovan F, Jovanovic D, Raynauld JP, Pelletier JP: **Collagenase-1 and collagenase-3 synthesis in early experimental osteoarthritic canine cartilage. An immunohistochemical study.** *J Rheumatol* 1998, **8:**1585-1594.
23. Martel-Pelletier J, Pelletier JP: **The recently discovered collagenase-3: a key role in osteoarthritis.** In *Advances in Osteoarthritis.* Edited by Hamanishi C, Tanaka H. Tokyo: Springer-Verlag; 1998:121-133.
24. 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:**1147-1158.
25. Su S, Grover J, Roughley PJ, Di Battista JA, Martel-Pelletier J, Pelletier JP, Zafarullah M: **Expression of the tissue inhibitor of metalloproteinases (TIMPs) gene family in normal and osteoarthritic joints.** *Rheumatol Int* 1999, **18:**183-191.
26. Moldovan F, Pelletier JP, Mineau F, Dupuis M, Cloutier JM, Martel-Pelletier J: **Modulation of collagenase-3 in human osteoarthritic cartilage by activation of extracellular transforming growth factor beta: role of furin convertase.** *Arthritis Rheum* 2000, **43:**2100-2109.
27. Martel-Pelletier J, Cloutier JM, Pelletier JP: **Cathepsin B and cysteine protease inhibitors in human OA: Effect of intra-articular steroid injections.** *J Orthop Res* 1990, **8:**336-344.
28. Martel-Pelletier J, Faure MP, McCollum R, Mineau F, Cloutier JM, Pelletier JP: **Plasmin, plasminogen activators and inhibitor in human osteoarthritic cartilage.** *J Rheumatol* 1991, **18:**1863-1871.
29. DiBattista JA, Martel-Pelletier J, Morin N, Jolicoeur FC, Pelletier JP: **Transcriptional regulation of plasminogen activator inhibitor-1**

expression in human synovial fibroblasts by prostaglandin E2: mediation by protein kinase A and role of interleukin-1. *Mol Cell Endocrinol* 1994, **103:**139-148.
30. Hilal G, Martel-Pelletier J, Pelletier JP, Duval N, Lajeunesse D: **Abnormal regulation of urokinase plasminogen activator by insulin-like growth factor 1 in human osteoarthritic subchondral osteoblasts.** *Arthritis Rheum* 1999, **42:**2112-2122.
31. Doré S, Pelletier JP, Di Battista JA, Tardif G, Brazeau P, Martel-Pelletier J: **Human osteoarthritic chondrocytes possess an increased number of insulin-like growth factor 1 binding sites but are unresponsive to its stimulation. Possible role of IGF-1-binding proteins.** *Arthritis Rheum* 1994, **37:**253-263.
32. Doré S, Abribat T, Rousseau N, Brazeau P, Tardif G, Di Battista JA, Cloutier JM, Pelletier JP, Martel-Pelletier J: **Increased insulin-like growth factor 1 production by human osteoarthritic chondrocytes is not dependent on growth hormone action.** *Arthritis Rheum* 1995, **38:**413-419.
33. Tardif G, Reboul P, Pelletier JP, Geng C, Cloutier JM, Martel-Pelletier J: **Normal expression of type 1 insulin-like growth factor receptor by human osteoarthritic chondrocytes with increased expression and synthesis of insulin-like growth factor binding proteins.** *Arthritis Rheum* 1996, **39:**968-978.
34. Di Battista JA, Dore S, Martel-Pelletier J, Pelletier JP: **Prostaglandin E2 stimulates incorporation of proline into collagenase digestible proteins in human articular chondrocytes: identification of an effector autocrine loop involving insulin-like growth factor I.** *Mol Cell Endocrinol* 1996, **123:**27-35.
35. Tavera C, Abribat T, Reboul P, Doré S, Brazeau P, Pelletier JP, Martel-Pelletier J: **IGF and IGF-binding protein system in the synovial fluid of osteoarthritic and rheumatoid arthritic patients.** *Osteoarthritis Cartilage* 1996, **4:**263-274.
36. Di Battista JA, Doré S, Morin N, Abribat T: **Prostaglandin E_2 up-regulates insulin-like growth factor binding-3 expression and synthesis in human articular chondrocytes by a cAMP-independent pathway: Role of calcium and protein kinase A and C.** *J Cell Biochem* 1996, **62:**1-14.
37. Di Battista JA, Doré S, Morin N, He Y, Pelletier JP, Martel-Pelletier J: **Prostaglandin E_2 stimulates insulin-like growth factor binding protein-4 expression and synthesis in cultured human articular chondrocytes: Possible mediation by Ca^{++}-calmodulin regulated processes.** *J Cell Biochem* 1997, **65:**408-419.
38. Martel-Pelletier J, Di Battista JA, Lajeunesse D, Pelletier JP: **IGF/IGFBP axis in cartilage and bone in osteoarthritis pathogenesis [review].** *Inflamm Res* 1998, **47:**90-100.
39. Hilal G, Massicotte F, Martel-Pelletier J, Fernandes JC, Pelletier JP, Lajeunesse D: **Endogenous prostaglandin E2 and insulin-like growth factor 1 can modulate the levels of parathyroid hormone receptor in human osteoarthritic osteoblasts.** *J Bone Miner Res* 2001, **16:**713-721.
40. Pelletier JP, Martel-Pelletier J, Ghandur-Mnaymneh L, Howell DS, Woessner JF Jr: **Role of synovial membrane inflammation in cartilage matrix breakdown in the Pond-Nuki dog model of osteoarthritis.** *Arthritis Rheum* 1985, **28:**554-561.
41. Pelletier JP, Martel-Pelletier J: **Evidence for the involvement of interleukin 1 in human osteoarthritic cartilage degradation: protective effect of NSAID.** *J Rheumatol* 1989, **16:**19-27.
42. Martel-Pelletier J, Zafarullah M, Kodama S, Pelletier JP: ***In vitro* effects of interleukin 1 on the synthesis of metalloproteases, TIMP, plasminogen activators and inhibitors in human articular cartilage.** *J Rheumatol* 1991, **18:**80-84.
43. Haraoui B, Pelletier JP, Cloutier JM, Faure MP, Martel-Pelletier J: **Synovial membrane histology and immunopathology in rheumatoid arthritis and osteoarthritis. *In vivo* effects of antirheumatic drugs.** *Arthritis Rheum* 1991, **34:**153-163.
44. Martel-Pelletier J, McCollum R, Di Battista JA, Faure MP, Chin JA, Fournier S, Sarfati M, Pelletier JP: **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:**530-540.
45. Pelletier JP, Faure MP, Di Battista JA, Wilhelm S, Visco D, Martel-Pelletier J: **Coordinate synthesis of stromelysin, interleukin-1, and oncogene proteins in experimental osteoarthritis. An immunohistochemical study.** *Am J Pathol* 1993, **142:**95-105.
46. Pelletier JP, Di Battista JA, Roughley PJ, McCollum R, Martel-Pelletier J: **Cytokines and inflammation in cartilage degradation** In *Osteoarthritis, Edition of Rheumatic Disease Clinics of North America.* Edited by Moskowitz RW. Philadelphia: WB Saunders Company; 1993:545-568.
47. Sipe JD, Martel-Pelletier J, Otterness IG, Pelletier J-P: **Cytokine reduction in the treatment of joint conditions.** *Mediat Inflamm* 1994, **3:**243-256.
48. Pelletier JP, McCollum R, Cloutier JM, Martel-Pelletier J: **Synthesis of metalloproteases and interleukin 6 (IL-6) in human osteoarthritic synovial membrane is an IL-1 mediated process.** *J Rheumatol* 1995, **22:**109-114.
49. Pelletier JP, Di Battista JA, Raynauld JP, Wilhelm S, Martel-Pelletier J: **The *in vivo* effects of intraarticular corticosteroid injections on cartilage lesions, stromelysin, interleukin-1 and oncogene protein synthesis in experimental osteoarthritis.** *Lab Invest* 1995, **72:**578-586.
50. McCollum R, Martel-Pelletier J, Di Battista JA, Pelletier JP: **Regulation of interleukin 1 receptors in human articular chondrocytes.** *J Rheumatol* 1991, **18:**85-88.
51. Martel-Pelletier J, McCollum R, Pelletier JP: **The synthesis of IL-1 receptor antagonist (IL-1ra) by synovial fibroblasts is markedly increased by the cytokines TNF-alpha and IL-1.** *Biochim Biophys Acta* 1993, **1175:**302-305.
52. Pelletier J-P, Martel-Pelletier J: **The importance of interleukin-1 receptors in osteoarthritis.** *Revue du rhumatisme* 1994, **9:**109S-113S.
53. Sadouk M, Pelletier JP, Tardif G, Kiansa K, Cloutier JM, Martel-Pelletier J: **Human synovial fibroblasts coexpress interleukin-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:**347-355.
54. Caron JP, Fernandes JC, Martel-Pelletier J, Tardif G, Mineau F, Geng C, Pelletier JP: **Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis: suppression of collagenase-1 expression.** *Arthritis Rheum* 1996, **39:**1535-1544.
55. Pelletier JP, Caron JP, Evans CH, Robbins PD, Georgescu HI, Jovanovic D, Fernandes JC, Martel-Pelletier J: ***In vivo* suppression of early experimental osteoarthritis by IL-Ra using gene therapy.** *Arthritis Rheum* 1997, **40:**1012-1019.
56. Fernandes JC, Tardif G, Martel-Pelletier J, Lascau-Coman V, Dupuis M, Moldovan F, Sheppard M, Krishnan BR, Pelletier JP: ***In vivo* transfer of interleukin-1 receptor antagonist gene in osteoarthritic rabbit knee joints: Prevention of osteoarthritis progression.** *Am J Pathol* 1999, **154:**1159-1169.
57. Saha N, Moldovan F, Tardif G, Pelletier JP, Cloutier JM, Martel-Pelletier J: **Interleukin-1β-converting enzyme/Caspase-1 in human osteoarthritic tissues: Localization and role in the maturation of IL-1β and IL-18.** *Arthritis Rheum* 1999, **42:**1577-1587.
58. Fahmi H, Di Battista JA, Pelletier JP, Mineau F, Ranger P, Martel-Pelletier J: **Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-1beta-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes.** *Arthritis Rheum* 2001, **44:**595-607.
59. Fahmi H, Pelletier JP, Di Battista JA, Cheung HS, Fernandes J, Martel-Pelletier J: **Peroxisome proliferator-activated receptor gamma acitvators inhibit MMP-1 production in human synovial fibroblasts by reducing the activity of the activator protein 1.** *Osteoarthritis Cartilage* 2001, **9**:in press.
60. Pelletier JP, Mineau F, Ranger P, Tardif G, Martel-Pelletier J: **The increased synthesis of inducible nitric oxide inhibits IL-1Ra synthesis by human articular chondrocytes: possible role in osteoarthritic cartilage degradation.** *Osteoarthritis Cartilage* 1996, **4:**77-84.
61. Pelletier JP, Jovanovic D, Fernandes JC, Manning PT, Connor JR, Currie MG, Di Battista JA, Martel-Pelletier J: **Reduced progression of experimental osteoarthritis *in vivo* by selective inhibition of inducible nitric oxide synthase.** *Arthritis Rheum* 1998, **41:**1275-1286.
62. Pelletier JP, Lascau-Coman V, Jovanovic D, Fernandes JC, Manning P, Currie MG, Martel-Pelletier J: **Selective inhibition of inducible nitric oxide synthase in experimental osteoarthritis is associated with reduction in tissue levels of catabolic factors.** *J Rheumatol* 1999, **26:**2002-2014.
63. Martel-Pelletier J, Mineau F, Jovanovic D, Di Battista JA, Pelletier JP: **Mitogen-activated protein kinase and nuclear factor kappaB together regulate interleukin-17-induced nitric oxide**

production in human osteoarthritic chondrocytes: possible role of transactivating factor mitogen-activated protein kinase-activated proten kinase (MAPKAPK). *Arthritis Rheum* 1999, **42:**2399-2409.
64. Pelletier JP, Jovanovic DV, Lascau-Coman V, Fernandes JC, Manning PT, Connor JR, Currie MG, Martel-Pelletier J: **Selective inhibition of inducible nitric oxide synthase reduces progression of experimental osteoarthritis in vivo: possible link with the reduction in chondrocyte apoptosis and caspase 3 level.** *Arthritis Rheum* 2000, **43:**1290-1299.
65. Notoya K, Jovanovic DV, Reboul P, Martel-Pelletier J, Mineau F, Pelletier JP: **The induction of cell death in human osteoarthritis chondrocytes by nitric oxide is related to the production of prostaglandin E2 via the induction of cyclooxygenase-2.** *J Immunol* 2000, **165:**3402-3410.
66. Pelletier JP, Fernandes JC, Jovanovic DV, Reboul P, Martel-Pelletier J: **Chondrocyte apoptosis in experimental osteoarthritis is mediated by MEK 1/2 and p38 pathways: Role of COX-2 and iNOS.** *J Rheumatol* 2001, **28**:in press.
67. Hilal G, Martel-Pelletier J, Pelletier JP, Ranger P, Lajeunesse D: **Osteoblast-like cells from human subchondral osteoarthritic bone demonstrate an altered phenotype *in vitro*: Possible role in subchondral bone sclerosis.** *Arthritis Rheum* 1998, **41:**891-899.
68. Benderdour M, Hilal G, Lajeunesse D, Pelletier JP, Duval N, Martel-Pelletier J: **Osteoarthritic osteoblasts show variable levels of cytokine production despite similar phenotypic expression [abstract].** *Arthritis Rheum* 1999, **42:**S251.
69. DiBattista JA, Martel-Pelletier J, Wosu LO, Sandor T, Antakly T, Pelletier JP: **Glucocorticoid receptor mediated inhibition of interleukin-1 stimulated neutral metalloprotease synthesis in normal human chondrocytes.** *J Clin Endocrinol Metab* 1991, **72:**316-326.
70. DiBattista JA, Martel-Pelletier J, Cloutier JM, Pelletier JP: **Modulation of glucocorticoid receptor expression in human articular chondrocytes by cAMP and prostaglandins.** *J Rheumatol* 1991, **27:**102-105.
71. DiBattista JA, Martel-Pelletier J, Antakly T, Tardif G, Cloutier JM, Pelletier JP: **Reduced expression of glucocorticoid receptor levels in human osteoarthritic chondrocytes. Role in the suppression of metalloprotease synthesis.** *J Clin Endocrinol Metab* 1993, **76:**1128-1134.
72. Pelletier JP, Cloutier JM, Martel-Pelletier J: ***In vitro* effects of NSAIDs and corticosteroids on the synthesis and secretion of interleukin-1 by human osteoarthritic synovial membranes.** *Agents Actions* 1993, **39:**181-193.
73. Pelletier JP, Di Battista JA, Ranger P, Martel-Pelletier J: **The reduced expression of glucocorticoid receptors in synovial cells induced by NSAIDs can be reversed by prostaglandin E1 analog.** *J Rheumatol* 1994, **21:**1748-1752.
74. Pelletier J-P, Di Battista, Ranger P, Martel-Pelletier J: **Modulation of the expression of glucocorticiod receptors in synovial fibroblasts and chondrocytes by protaglandins and NSAIDs.** *Am J Therap* 1996, **3:**115-119.
75. Pelletier JP, Martel-Pelletier J: **Protective effects of corticosteroids on cartilage lesions and osteophyte formation in the Pond-Nuki dog model of osteoarthritis.** *Arthritis Rheum* 1989, **32:**181-193.
76. Pelletier JP, Mineau F, Raynauld JP, Woessner JF Jr, Gunja-Smith Z, Martel-Pelletier J: **Intraarticular injections with methylprednisolone acetate reduce osteoarthritic lesions in parallel with chondrocyte stromelysin synthesis in experimental osteoarthritis.** *Arthritis Rheum* 1994, **37:**414-423.
77. Pelletier J-P, Martel-Pelletier J, Lajeunesse D, Jovanovic DJ, Reboul P, Fernandes JC: **Inflammation in osteoarthritis. Fifth World Congress of the Osteoarthritis Research Society International (OARSI) [abstract].** *Osteoarthritis Cartilage* 2000, **8:** S16.
78. Raynauld JP, Kauffmann C, Godbout B, Beaudoin G, Berthiaume MJ, de Guise J, Gagnon R, Bloch D, Altman R, Martel-Pelletier J, Choquette D, Cline G, Meyer J, Pelletier JP: **Knee osteoarthritis progression evaluated by magnetic resonance imaging and a novel quantification software tool [abstract].** *Arthritis Rheum* 2000, **43:**S399.
79. Raynauld JP, Kauffmann C, Berthiaume MJ, Beaudoin G, de Guise J, Camacho F, Bloch DA, Altman RA, Hochberg MC, Meyer JM, Cline G, Martel-Pelletier J, Pelletier JP: **Validation of a quantification imaging system for the normal and osteoarthritic knee [abstract].** *Arthritis Rheum* 2001, **44**:S13.
80. Martel-Pelletier J, Pelletier J-P: **Etiopathogenesis of osteoarthritis.** In *Arthritis and Allied Conditions. A Textbook of Rheumatology*, edn 14. Baltimore: Lippincott, Williams & Wilkins; 2000: 2195-2215.