Review

The Interleukin 1ß Pathway in the Pathogenesis of Osteoarthritis

ABSTRACT. Osteoarthritis (OA) is a major disabling disease and is ranked as a major cause of chronic pain in adults. The pathology of the illness is characterized by a loss of articular cartilage leading to narrowing of joint space, increased joint friction, potential structural remodeling, persistent pain, and functional impairment. The proinflammatory cytokine interleukin 1ß (IL-1ß) has several chemical and bioactive characteristics allowing this catabolic protein to be involved in initiation and progression of OA. We review the current understanding of the pathogenesis of OA, and how upregulation of IL-1ß initiates a cascade of intracellular events that can culminate in activation of proteinases, creation of a pro-destructive articular milieu, suppression of anabolic pathways, and a decrease in the synthesis of cartilage extracellular matrix. Therapeutic approaches to block the action of IL-1ß and overcome its signal transduction to curtail disease progression are discussed. (First Release Oct 15 2008; J Rheumatol 2008;35:2306–12; doi:10.3899/jrheum.080346)

Osteoarthritis (OA), a progressive joint disease, is one of the most common forms of arthritis. In the United States, OA affects more than 7% of the population, with the prevalence much higher in elderly and obese individuals. Thus, as the average lifespan and weight of the population is increasing, OA is becoming one of the most prominent chronic diseases, with a tremendous financial burden for its management[1]. Current understanding of the molecular events taking place during joint destruction has implicated interleukin 1ß (IL-1ß) in several pathological features of OA. Thus, it may not be surprising that this cytokine possesses detrimental effects on chondrocyte function as well as integrity of extracellular matrix (ECM).

Involvement of IL-1ß in OA

IL-1ß is primarily produced as a precursor (pro-IL-1ß) that must be cleaved to generate its mature and active cytokine. The intracellular enzyme responsible for this cleavage is caspase-1, also called IL-1ß-converting enzyme (ICE). Indeed, an animal deficient in caspase-1 has no mature IL-1ß. The biological effects of IL-1ß can be inhibited by its natural inhibitors: IL-1 receptor antagonist (IL-1Ra) and type 2 IL-1 decoy receptor (IL-1RII), which can bind IL-1ß without transmission of a signal[2]. Once bound to its type 1 receptor (IL-1RI), IL-1ß can initiate several signal transduction pathways, leading to an increase in intracellular Ca^{2+}, activation of PKC, p38, ERK1/2, and JNK, and nuclear translocation of nuclear factor-κB (NF-κB), activating transcription factor (ATF), and activator protein 1 (AP1).

Several lines of evidence based upon studies of human and animal joints suggest a central role of IL-1ß in OA, as follows.

Human cells and tissues. IL-1ß is localized to chondrocytes in the superficial zone of human OA cartilage, where degenerative changes have been identified on histological examination. Saha, *et al* found upregulation of IL-1ß in human OA cartilage preferentially located at the superficial and upper intermediate layers of articular cartilage, and also found a corresponding upregulation of IL-1ß-converting enzyme in OA tissue where IL-1ß was elevated[3]. In another study, Smith, *et al* reported the presence of IL-1ß in synovial membranes from all patients with OA, with a significant decrease in the ratio of IL-1Ra/IL-1ß with increasing grades of OA[4]. Kubota, *et al* showed that IL-1ß levels in synovial fluid of temporomandibular joints have a positive correlation with OA changes[5]. Loeser, *et al* reported a positive association between the presence of nitrotyrosine, an indicator of oxidative damage, and the presence of IL-1ß on human OA chondrocytes[6]. Additionally, although articular resident cells from normal tissue produce a limited amount of IL-1ß, this cytokine is markedly increased in chondrocytes as well as synovial cells from patients with OA[7]. Marks, *et al* compared patients with anterior cruciate ligament (ACL) deficiency (risk factor for OA) to normal individuals and reported a marked increase in expression of IL-1ß in the synovial fluid of the former group, with a positive correlation between expression of IL-1ß and the severity of chondral damage[8].

Chondrocytes, the major cellular targets for IL-1ß, not only express the receptor for this cytokine, but also express higher IL-1RI in patients with OA. Shlopov, *et al* reported that chondrocytes located in cartilage proximal to macroscopic OA sites bound more IL-1ß compared with chondrocytes isolated from morphologically normal cartilage from the same joint, and that this increase was due to upregulation of IL-1RI[9]. Thus, upregulation of IL-1RI in the chondrocytes renders these cells highly sensitive to the effects of this

cytokine, leading to alteration of chondrocyte gene expression. Aigner, *et al* reported significant alteration in the expression of 79 genes in human chondrocytes following exposure of these cells to IL-1ß, including upregulation of IL-1ß itself[10]. However, from microarray studies of 78 normal and OA samples, Aigner, *et al* surprisingly reported a downregulation of IL-1ß in the OA samples[11]. Yet in the same study the IL-1ß antagonist (IL-1RII) was also reported to be downregulated, and the authors noted the very low level of expression as a concern regarding reliability of data. In a followup study using immunohistochemistry, the same investigators described that while IL-1ß expression and signaling mechanisms, phosphorylated JNK, and p38 were detectable in the upper zones of normal cartilage, they were more pronounced in the upper portions of OA cartilage[12]. The authors also described an autocrine-positive loop following stimulation of chondrocytes by IL-1ß, in that these cells responded not only by producing the inflammatory cytokine IL-6 but also IL-1ß[12]. A remarkable change in catabolic gene expression and signal transduction pathways was also reported by Saas, *et al* using microarray studies in 2 donors[13]. In addition to chondrocytes, IL-1RI has been reported to be expressed in human synovial fibroblasts and to be significantly upregulated in OA synovial cells[14]. Further, in OA synovium, a relative deficit in production of natural antagonists of IL-1 receptor has been reported[15]. Thus the downregulation of IL-1 antagonists, along with upregulation of IL-1ß and its receptors (IL-1RI), may be a molecular explanation for the enhanced catabolic effects of IL-1ß in OA joint tissues.

Genomic studies have also provided some support for the involvement of IL-1ß in OA. Genome-wide scans for genetic loci predisposing to OA revealed potential linkage with an IL-1 gene cluster on chromosome 2. When Loughlin, *et al* performed an association analysis in a case-control cohort of 557 cases, they observed that the IL-1 ligand cluster encodes susceptibility to knee OA[16]. Meulenbelt, *et al* reported an association between IL-1 cluster polymorphisms and the pathogenesis of OA of the hip[17].

Animal cells and tissues. Experimental animal models point to a key role for IL-1ß in the development of OA as well. Pelletier, *et al* reported that dog knee joints subjected to ACL resection had a marked increase in IL-1ß-expressing cells, which promptly decreased following treatment[18]. Wheaton, *et al* reported that biochemical changes similar to those seen in OA were induced with an intraarticular injection of recombinant porcine IL-1ß into the pig knee joint[19]. The same authors demonstrated that 100 ng of IL-1ß injected into the intraarticular regions of porcine joints resulted in a significant decrease in proteoglycan (PG) content, especially in the middle zone of cartilage, along with a marked increase in cell infiltration in synovial fluid. Lai, *et al* reported that IL-1ß activation as a transgene in the joint led to a number of structural changes characteristic of OA, such as cartilage surface fibrillation and erosion[20].

Molecular outcomes of activation of IL-1ß pathway in OA

Destructive effects of IL-1ß in OA include both elevation of cartilage catabolism and suppression of cartilage anabolism.

Elevation of cartilage catabolism. *Induction of proteolytic molecules involved in cartilage degradation*. IL-1ß has been considered the central mediator of cartilage loss in OA, and articular ECM has been reported to be a target of catabolic activity of this cytokine. IL-1ß upregulates the major extracellular proteolytic enzymes in cartilage degradation, such as matrix metalloproteinases (MMP) and A Disintegrin-like and Metalloproteinases with Thrombospondin Motifs (ADAMTS).

Fan, *et al* reported upregulation of MMP-1, -3, and -13, but not MMP-2, in both normal human and OA chondrocytes following IL-1ß treatment[21]. Elliott, *et al* showed induction of MMP-1 and -13 from human primary chondrocytes and human chondrosarcoma cell lines following a 24-hour incubation of these cells with 10 ng/ml of recombinant IL-1ß[22]. Inoue, *et al* described upregulation of MMP-3 release by both chondrocytes and synoviocytes from OA patients following IL-1ß treatment, which was suppressed by IL-1Ra[23]. Kobayashi, *et al* observed upregulation of gene expression of MMP-1, -3, and -13 in articular cartilage from patients with OA, along with an increase in collagen and PG degradation, with all these effects being significantly suppressed by IL-1Ra treatment[24]. Mix, *et al* reported induction of mRNA for MMP-1, -3, and -13 following treatment of human chondrosarcoma cells by 1 ng/ml of IL-1ß[25], and Tetlow, *et al* presented Western blots demonstrating the production and release of MMP-1, -3, and -13 proteins by IL-1ß-stimulated human articular chondrocytes[26]. Apparently the effect of IL-1ß in induction of MMP-1, -3, and -13 is well conserved between different species, as such induction is reported for rabbit, bovine, and equine chondrocytes.

ADAMTS, also called aggrecanases, are enzymes involved in degradation of aggrecans. Fan, *et al* reported upregulation of ADAMTS-4 in normal human and OA chondrocytes by IL-1ß[21], and Bondeson, *et al* observed that both ADAMTS-4 and -5 were upregulated by IL-1ß in human OA synovial fibroblasts[27]. Cortial, *et al* observed that when bovine chondrocytes were cultured with IL-1ß, ADAMTS-4 and -5 were substantially increased[28]. Using human OA chondrocytes, Dai, *et al* reported upregulation of IL-18 by IL-1ß and upregulation of ADAMTS-5 by IL-18[29]. Thus, it is conceivable that some IL-1ß catabolic effects are relayed by other factors, such as IL-18 in this system.

MMP and ADAMTS are not the only proteolytic mediators induced by IL-1ß. For example, Mehraban, *et al* reported upregulation of cathepsin B expression in osteochondrocytes by IL-1ß treatment[30], and Milner, *et al* described IL-

1ß induction of fibroblast activation protein-α (FAPα), a type II integral membrane serine proteinase, in the chondrocytes[31]. Additionally, Schwab, *et al* reported that urokinase-type plasminogen activator receptor (uPAR), which is involved in cartilage degradation by serine proteinases and is upregulated in OA, is stimulated on chondrocytes in a dose-dependent manner by IL-1ß[32]. Shikhman, *et al* reported that stimulation of human chondrocytes with IL-1ß resulted in an increase in extracellular lysosomal glycosidases, a distinct subset of cartilage matrix-degrading enzymes[33].

Induction of inflammatory mediators and cell infiltration. There is evidence of cell infiltration in OA that could be associated with and account for some of the histopathology characteristics such as thickening of the synovial membrane lining layer, increased vascularity, synovial fluid cellularity, and secretion of degradative enzymes. For example, Nakamura, *et al* observed an increase in the T cell population in all of the OA synovial tissues, especially in the perivascular area[34], and Da, *et al* showed that synovial infiltration by B lymphocytes was present in almost half of cases of knee OA[35]. Walsh, *et al* reported an increase in synovial macrophages in patients with OA compared to a control group[36].

In addition, IL-1ß has the capacity to induce several proinflammatory mediators including cytokines, chemokines, angiogenic factors, and proteolytic enzymes involved in the increase of local hematopoietic cells during OA. For example, IL-1ß-induced MMP have been shown to be involved in cell infiltration. Additionally, investigators have reported that IL-1ß stimulation of articular cells such as chondrocytes leads to expression of tumor necrosis factor-α (TNF-α), IL-8, complement factors, and prostaglandin E_2, each having the capacity to induce hematopoietic cell infiltration and propagate local inflammation and tissue damage. Further, IL-1ß induces angiogenic factors such as vascular endothelial growth factor, in addition to several chemokines such as RANTES, and their receptors such as CCR4, leading to inflammatory cell infiltration into the synovia. Several investigators have reported a local increase in mononuclear cells/macrophages during OA progression, with these cells being an important source of proteolytic enzymes and free-radical molecules. Blom, *et al* reported that in experimental models of OA, macrophage depletion led to marked inhibition of osteophytes[37]. Bondeson, *et al* described a decrease in production of MMP-1 and -3 following depletion of synovial macrophages[38]. Hence, once generated, IL-1ß can induce several molecules that act as cell chemoattractants. Thus, an increase in articular hematopoietic cells can induce thickening of the synovial membrane, increases in oxidative burst activity and decreases in O_2 concentration, and generation of additional inflammatory and proteolytic enzymes that can lead to progression of OA.

Suppression of cartilage anabolism. Several studies have shown that apart from increased degradation of ECM, IL-1ß can decrease ECM synthesis by decreasing the anabolic activities of chondrocytes and/or the cell densities of articular cartilage.

Downregulation of PG and collagen biosynthesis. Pfander, *et al* reported a decrease of more than 40% in aggrecan mRNA following treatment of human OA chondrocytes with IL-1ß[39]. Stove, *et al* demonstrated that IL-1ß downregulated aggrecan transcripts in human OA chondrocytes by 2–3 fold[40]. Venkatesan, *et al* revealed a time-dependent decrease in PG synthesis of rat femoral explants by IL-1ß, along with a decrease in PG accumulation[41]. Eger, *et al* showed that both types of chondrocytes from normal human knees and ankles responded to IL-1ß with decreased PG synthesis[42]. Attur, *et al* reported that 5 ng/ml of IL-1ß could significantly suppress PG synthesis from both human and bovine chondrocytes[43]. Stabellini, *et al* described release of matrix sulfated PG into culture media and inhibition of sulfated PG synthesis following IL-1ß treatment of bovine cartilage explants[44]. The deleterious effects of IL-1ß on the anabolism of PG could involve suppression of galactose-ß-1, 3-glucuronosyltransferase I (GlcAT-I), the key enzyme in the biosynthesis of glycosaminoglycan that is linked to PG core proteins. Gouze, *et al* reported suppression of GlcAT-I mRNA (38%) following treatment of rat articular chondrocytes with IL-1ß, which correlated with 32% inhibition of PG synthesis[45].

Collagen, the major articular joint protein, is another target whose synthesis is suppressed by IL-1ß. For example, Shakibaei, *et al* reported the downregulation of type II collagen in human chondrocytes treated with IL-1ß[46]. Using Western blotting, Yudoh, *et al* reported significant reduction in production of type II collagen by rabbit chondrocytes incubated in the presence of 10 ng/ml of IL-1ß[47]. Goldring, *et al* reported downregulation of type II collagen mRNA by Northern blots following treatment of human chondrocyte cell lines[48]. At least some part of the inhibitory effect is due to downregulation of collagen transcription, since IL-1ß suppressed the collagen promoter in a reporter assay. The downregulation was very specific, as several enzymes and transcriptional factors were upregulated by IL-1ß. In a study using human fibroblasts, Nawrat, *et al* reported a 50% reduction in collagen biosynthesis following a 24-hour treatment with 10 ng/ml of IL-1ß[49].

Induction of chondrocyte apoptosis. IL-1ß may also induce apoptosis of chondrocytes. Several investigators have reported reduced numbers of chondrocytes due to an increase in apoptotic chondrocytes in patients with OA, with a potential link to IL-1ß as the possible culprit in these processes. For example, Lopez-Armada, *et al* reported a depolarization of mitochondria and upregulation of proapoptotic Bcl-2 family proteins (characteristics of apoptotic cells) following treatment of human articular chondro-

cytes with IL-1ß[50]. Heraud, *et al* described that in human OA cartilage 18%–21% of chondrocytes showed apoptotic features and that IL-1ß could increase the percentage of apoptotic cells in both normal and OA cartilage in a dose-dependent manner[51]. Also, apoptosis could be significantly induced in rabbit chondrocytes cultured in presence of IL-1ß. Yasuhara, *et al* demonstrated mitochondrial dysfunction and energy depletion of chondrocyte-like ATCD5 cells, eventually leading to an increase in cell death following IL-1ß treatment[52].

How IL-1ß induces the death of chondrocytes is not entirely understood, but nitric oxide (NO) has been strongly suggested as a culpable mediator. For example, Pelletier, *et al* reported that although NO production by normal human cartilage was undetectable, OA cartilage spontaneously produced NO, and this release was upregulated by IL-1ß[53]. In the study by Tenor, *et al*, IL-1ß induced human OA chondrocytes to produce a large amount of NO in a time- and concentration-dependent fashion[54]. Additionally, Clancy, *et al* demonstrated that in bovine chondrocytes, NO mediated IL-1ß-dependent apoptosis under conditions of oxidant stress, where induction of NO led to subsequent accumulation of intracellular oxidants including peroxynitrite and superoxide anion[55]. Thus, IL-1ß may induce chondrocyte apoptosis by increasing NO concentration via upregulation of the enzyme inducible NO synthetase, the inducible enzyme responsible for NO production. This can result in formation not only of NO, but also its derivatives such as peroxynitrite (ONOO-), which can eventually lead to chondrocyte apoptosis. A requirement for reactive oxygen species has been reported for NO-mediated chondrocyte death *in vitro*[56]. Alternatively, IL-1ß may induce cell death through other pathways such as ceramide[57].

Therapeutic inhibition of IL-1ß

While it is not clear whether upregulation of IL-1ß alone is sufficient to induce clinical OA, or whether the elevated level of IL-1ß and its detrimental effects are secondary to OA processes due to other mechanisms such as mechanical insults, the literature as reviewed above has shown a close correlation of IL-1ß and OA changes in human and animal cells and tissues in synovia. Thus, IL-1ß may be a fairly attractive therapeutic target in OA.

In support of the notion of IL-1ß blockade as a potential means to manage OA pathology, almost every current treatment for OA has shown some degree of a decrease in the level of IL-1ß or interference with the downstream effects of IL-1ß. OA treatments interfering with the effects of IL-1ß include steroids, nonsteroidal antiinflammatory drugs (NSAID), hyaluronic acid, glucosamine, analgesics such as morphine, and exercise and weight loss. For example, in a 3-month clinical trial including 30 patients with severe knee OA, the beneficial effects of 200 mg/day of COX-2-specific inhibitor, such as a decrease in cell infiltration and improvement in pain and joint function, were accompanied by a significant decrease in the local protein level of IL-1ß[58]. Thus, one can lean toward the concept that a decrease in IL-1ß level and its signal transduction can be a key element in OA management, as direct suppression of IL-1ß pathways in animal models of OA have shown efficacy in equine, canine, and rabbit models of OA. For example, Frisbie, *et al* reported that intraarticular IL-1Ra gene delivery in an equine model of OA led to significant improvement in clinical measures of pain and disease activity, preservation of articular cartilage, and significant decrease in synovial effusion score[59]. However, the beneficial effects of IL-1ß in animal models of OA should be evaluated with caution, as Clements, *et al* reported that gene deletion of IL-1ß in a murine model of OA accelerated the disease progression[60].

Clinical trials have also generated optimism for anti-IL-1ß therapy as a new stratagem in OA treatment. Chevalier, *et al* performed a safety study of intraarticular injection of IL-1 receptor antagonist in patients with painful knee OA with the secondary objective of ascertaining the efficacy of the treatment[61]. In this phase II double-blinded noncontrolled clinical trial including 13 patients with knee OA, intraarticular injections of 150 mg of a recombinant form of human IL-1Ra, a competitive antagonist of IL-1ß, led to a significant improvement in pain (by visual analog scale, VAS) and the Western Ontario and McMaster Universities (WOMAC) OA index over a 3-month period[61]. These data gain more weight in conjunction with reported outcomes of IL-1Ra treatment of rheumatoid arthritis (RA), where it has shown efficacy as mono- or combination therapy in terms of reduction in clinical symptoms of active disease and diminished rate of joint destruction[62,63].

Diacerein, a symptomatic slow-acting drug with IL-1ß inhibitory properties *in vitro*[64], has also shown promise in OA treatment and has been in clinical use in Europe for several years. In a prospective, multicenter, randomized, double-blind, 3-year, placebo-controlled clinical trial enrolling 521 patients with OA, diacerein was shown to be effective in inducing structure-modifying effects in hip OA as revealed by radiography and measurement of joint space[65]. Louthrenoo, *et al* reported that in a double-blind randomized study, diacerein was effective in reducing pain and improving function in patients with symptomatic knee OA[66]. Fagnani, *et al* described a prospective, randomized, open-label, multicenter clinical trial of patients with knee and hip OA with a minimum of 100 individuals in each of the treatment arms (diacerein plus standard therapy and standard therapy alone)[67]. They reported that the overall assessment of therapy by patients was good or excellent for 60% of those who received diacerein plus standard therapy, compared with 26% of patients who received standard therapy. In a 16-week, randomized, double-blind placebo-controlled trial of 484 patients with knee OA, Pelletier, *et al* reported

Table 1. A summary of IL-1ß effects on chondrocytes.

Pathways	Effects of IL-1ß
Signal transduction pathways	Increased intracellular Ca^{2+}, activation of PKC, p38, JNK, ERK 1 and 2
Transcriptional factors	Nuclear translocation of NF-κB, ATF, and AP1
Proteases	Upregulation of MMP-1, -3 and -13, ADAMTS-4 and -5, FAPα, cathepsin B, and uPAR
Cytokines	Upregulation of IL-6, IL-8, TNF-α, and IL-1ß
Inflammatory mediators	Upregulation of PGE2, NO, RANTES, and CCR4
Anabolic pathways	Downregulation of PG and collagen biosynthesis
Apoptosis	Induction of chondrocytes apoptosis

PKC: protein kinase C, JNK: c-Jun N-terminal kinase, ERK: extracellular signal-regulated kinase, NF-κB: nuclear factor-κB, MMP: matrix metalloproteinase, ADAMTS: A Disintegrin-like and Metalloproteinases with Thrombospondin Motifs, FAPα: fibroblast activation protein-α, IL: interleukin, TNF-α: tumor necrosis factor-α, PG: prostaglandin, NO: nitric oxide.

50 mg diacerein given twice daily significantly improved VAS and WOMAC[68]. The investigators also showed that the primary criterion (VAS) demonstrated significant dose-dependent differences between each of the 3 diacerein dosages and the placebo. Rintelen, *et al* performed a systematic metaanalysis of randomized controlled trials, and suggested that there is evidence for statistically significant and clinically relevant efficacy of diacerein on improvement of pain and function in patients with knee and hip OA[69]. Moreover, diacerein has a carryover effect, providing more pain relief than placebo or NSAID for several weeks after the treatment is stopped[69].

Conclusion

Articular increase in IL-1ß and interaction of this molecule with its receptor IL-1RI can lead to a series of molecular events, each with some degrees of involvement in the pathogenesis of OA (Table 1). Thus, the therapies to decrease local IL-1ß levels, block its specific receptors, or interrupt its signal transduction possess significant clinical value. However, a disease as heterogeneous as OA, with different patterns of expression, and influenced by its anatomical location, may evade any single treatment. Further, however attractive IL-1ß appears as a therapeutic target, it is important to emphasize that as with any key cytokine, IL-1ß blockade might affect one's protective immunity, leading to an increase in the susceptibility to infection and spontaneous tumor development. In addition, it is possible that local production of a small amount of IL-1ß from chondrocytes might serve as a favorable factor for cartilage homeostasis, as IL-1ß knockout animals have defects in their chondrocytes. Thus, a total inhibition of IL-1ß could have a detrimental effect, especially during cartilage repair.

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