Chapter

# Osteoarthritis as a Chronic Inflammatory Disease: A Review of the Inflammatory Markers

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## Abstract

Osteoarthritis (OA) is the most prevalent joint disease and a common cause of joint pain, functional loss, and disability. In addition to macroscopic features, such as cartilage degradation with subchondral bone remodeling, hypertrophy of the joint capsule, and osteophytes formation, several cellular and molecular alterations are present in OA, which lead to a chronic low-grade inflammation. Inflammatory mediators observed in OA joints are thought to be the downstream effectors of the pathogenesis of the disease. Although cytokines are among the most extensively studied mediators of inflammation, such as IL-1β and TNF, there has been an increase in studies showing the contribution of chemokines and adipokines in OA progression. This fact is supported by recent progress, which has considerably improved knowledge of the factors involved in the development of OA and the mechanisms responsible for its progression. Therefore, the aim of this chapter is to discuss the involvement of the inflammatory response in OA maintenance, focusing on the main inflammatory markers observed in studies with OA.

**Keywords:** osteoarthritis, immune response, inflammation, biomarkers, cytokines

## 1. Introduction

Osteoarthritis (OA) is a common disease that can affect joints from any part of the body, and it represents a major cause of disability and joint pain worldwide [1, 2]. OA most commonly affects the knee, hip, and shoulder, and it was estimated that more than 25 million people in the USA were affected by some form of OA in the last decade [3]. In addition, OA presents a high susceptibility to affect female gender, elderly people, and obese individuals [4].

The progression of OA leads to cartilage degradation with subchondral bone remodeling, hypertrophy of the joint capsule, and osteophytes formation, causing pain [1, 5, 6]. Although the development of OA is considered a heterogeneous process, which comprises a number of genetic and environmental causes, the presence of local causes, such as trauma and hypermobility of the joint, may worsen OA [2, 7].

The accurate identification of osteoarthritic features has been studied in order to radiographically grade the stages of OA. The Kellgren-Lawrence classification is the most widely used, especially in clinical researches. This classification evaluates the appearance of osteophytes and cysts, joint space loss, and sclerosis, and it grades the severity from 0 to 5 points. The radiological features found in OA joints were

graded as follows: (1) formation of osteophytes on joint margins or on tibia spines for knee OA; (2) periarticular ossicles in relation to distal and proximal interphalangeal joints; (3) narrowing of joint cartilage and sclerosis of subchondral bone; (4) pseudocystic areas with sclerotic walls in the subchondral bone; and (5) altered shape of the bone ends [8]. Some of these criteria were adopted by the World Health Organization (WHO) as the standard for studies on OA.

Current options for the treatment of OA focus on reducing pain (non-steroidal anti-inflammatory drugs—NSAIDs) and joint viscosupplementation (intra-articular injections of hyaluronic acid) [1]. Besides presenting a short-term effect, the chronic use of some of these medications, especially NSAIDs, may cause serious adverse events, including toxicity and risk of thromboembolism [9, 10]. In severe cases, surgical procedures, mostly joint replacement, are suggested [1]. Novel alternative therapies, called orthobiologics, have emerged from the need of tissue regeneration. Clinical trials using orthobiologics, which comprise platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), fat graft (Biofat), and expanded mesenchymal stem cells, have shown promising results for the treatments of OA from any origin [11–14].

Moreover, monoclonal antibody (mAb) therapy represents one of the alternative treatments that aim to control inflammation and slow structural progression [15]. This approach focuses on blocking specific molecules responsible for the maintenance of OA. Preclinical studies with ADAMTS mAbs reported a significant decrease in histological scores after 3 months of treatment [16]. Adalimumab is an anti-TNF-α therapy used in diverse immune-mediated diseases, and it presents a protective role for OA as it reduces the severity of the cartilage lesion and improves the structure of subchondral bone [17]. Since IL-1 family may induces the production of metalloproteinases (MMP), it has also become a target for mAb therapy, and, in a randomized controlled trial with patients who presented knee OA, it was reported great improvement on pain relief [18].

In addition to macroscopic features, several cellular and molecular alterations are present in OA, such as catabolism and anabolism events; hypertrophy and, consequently, death of chondrocytes; and impaired autophagy process [19]. Also, a chronic low-grade inflammation interplayed with immune system has been considered to present a crucial role in the maintenance of OA [1]. This fact is supported by recent progress, which has considerably improved the knowledge regarding factors involved in the OA development and the mechanisms responsible for its progression.

## 2. Osteoarthritis and immune response

The inflammation observed in OA is believed to involve innate immune response prior to a mild degree of adaptive immunity [20]. During tissue damage, a group of endogenous molecules, called damage-associated molecular pattern (DAMP), signals the immune cells to induce a protective response against the tissue, causing tissue repair. However, a prolonged signaling of DAMP to immune cells leads to an exacerbated cytokine release, which can be destructive to the tissue [21, 22].

Innate immune cells activated by DAMP include macrophages and mast cells, which have shown to present (displayed or demonstrated) a key role in the pathogenesis of OA. Mast cells are considered regulators of vascular permeability, and they may play a crucial role in OA joint inflammation as they facilitate leukocyte infiltration [23].

Macrophages exhibit a functional plasticity based on the environment in which they are located or present [22]. However, their chronic activation can lead to the

production of proinflammatory cytokines, which worsen the osteoarthritic joints [24]. *In vitro* studies of human OA synovium-derived cells showed that macrophage depletion results in diminishing of inflammatory response by decrease of proteolytic enzyme expression, such as metalloproteinases (MMP) This fact is supported by *in vitro* studies with cell culture suspension of human OA synovium, which reported that, after macrophage depletion, there was a decrease in the production of inflammatory response by less activity of proteolytic enzymes, such as metalloproteinases (MMP) [25]. Although macrophages may also present a protective role, as they are known to secrete transforming growth factor β (TGF-β), which would enhance cartilage repair, intra-articular injection of TGF-β in mice knee led to osteophyte formation and fibrosis [26].

In addition, natural killer (NK) infiltrates are commonly found in synovial tissue from patients who underwent joint replacement surgeries, and a subset of NK cells ($CD56^{bright}$) was found to be greatly expanded in patients with inflammatory arthritis who have not undergone joint replacement surgeries. However, the effect of these cells on the development of OA has not been elucidated yet [27–29]. NK cells secrete protease enzymes called granzyme type A and B, which correlate to cytolytic potency. Granzymes can be released during degranulation of cytotoxic cells and, when delivered intracellularly to the target cells, they induce apoptosis. Granzyme A also stimulates the production of tumor necrosis factor (TNF-α), IL-6, and IL-8, while granzyme B may intensify the degradation of extracellular matrix [30, 31]. Tak et al. identified both types of granzymes in synovia from OA and rheumatoid arthritis. However, another study later showed that NK cells within OA synovia were granzyme negative with potential to produce the interferon-γ (IFN-γ) when expanded with IL-2 and stimulated with cytokines known to trigger IFN-γ production in blood NK cells, such as IL-12 and IL-18 [27, 32].

The presence of IFN-γ has a role in the bone resorption and consequently in the osteoclastogenesis process, but the studies have shown controversial results in this regard: *in vitro* evidence reported that IFN-γ, via TRANCE pathway, strongly suppresses osteoclastogenesis in culture of mononuclear phagocyte cells, which are the osteoclast precursors [33], whereas in culture of peripheral blood it may enhance osteoclast production as IFN-γ increases superoxide generation by neutrophils [34]. In addition, experimental studies in which IFN-γ receptor was silenced suggested a more rapid onset of collagen-induced arthritis [35]. Although IFN-γ plays a key role in angiogenesis, there is no evidence that this cytokine is able to promote angiogenesis in OA.

Proteins from complement system have been found to play a role in OA, especially in early stages, as they were upregulated in both synovial membrane and fluid [23, 36]. Additionally, the deposition of the membrane attack complex (MAC, C5b-9) is correlated with the presence of inflammation on histology of synovial membrane, and it was present in chondrocytes in late OA [36]. MAC can lead to chondrocyte destruction as it stimulates catabolic events through the increase of leukocytes and, consequently, the production of MMP [23]. Also in the studies with experimental knockout models for C5 and C6, the joint damages were attenuated [36].

Cellular infiltrates from adaptive immune response have also been observed in synovial fluid from OA joints. Although the main cell type present in this infiltrate is CD3+ T cells, both CD4+ and CD8+ cells have also been found in OA [37]. Th1 cells, and consequently their secretory cytokines, such as IL-2 and INF-γ, appear to be expressed five times greater than Th2 in most of OA patients [37]. Based on lymphocyte aggregates, there is a suggestion of an active cell-mediated immune response since T-cells in lymphocytic aggregates in OA synovium were shown to bear early (CD69), intermediate (CD25 and CD38), and late (CD45RO) activation markers [38].

## 3. Inflammatory markers in osteoarthritis

### 3.1 Cytokines

Inflammatory mediators observed in OA joints are thought to be the downstream effectors of the pathogenesis of the disease. Cytokines are among the most extensively studied mediators of inflammation. Several cytokines have been reported to play a role in the progression of OA, such as TNF, IL-1β, IL-6, IL-15, IL-17, IL-18, IL-4, and IL-10. Although their precise mechanism of action has not been completely elucidated yet, it has been proposed that their presence influences cartilage homeostasis as they induce catabolic events as well as inhibit anabolic processes [21, 39, 40].

#### *3.1.1 IL-1β and TNF*

Interleukin (IL)-1β and tumor necrosis factor (TNF) are considered the major mediators in the pathophysiology of OA. They both are secreted not only by immune cells, especially mononuclear cells, but also by chondrocytes and osteoblasts. In OA joints, these cytokines are increased in both synovial fluid and membrane. They are known to drive the inflammatory cascade, and their increased expression induces catabolic events as they enhance MMP [39]. IL-1β and TNF downregulate the synthesis of major extracellular matrix (ECM) components by inhibiting anabolic activities of chondrocytes [40] and reducing type II collagen production [41].

IL-1β is activated through the binding of its specific receptor type I (IL-1RI). Overexpression of IL-1RI in cartilage proximal to the macroscopic injury in OA joints resulting in increased binding of IL-1β was observed [42]. IL-1β has also been reported to be responsible for the catabolic events present in OA: its expression combined with TNF induces the production of MMP-1, -3, and -13 and stimulates the production of aggrecanases (ADAMTS)-4 and -5 in human and bovine chondrocytes [43, 44]. TNF receptor type I (TNFRI) is overexpressed in OA chondrocytes [45]. High levels of TNF-α in cartilage explants seem to inhibit the synthesis of proteoglycan and stimulate resorption [40].

In OA joint, IL-1β and TNF amplify the arthritic condition by inducing the production of proinflammatory cytokines, such as IL-6, IL-8, and monocyte chemoattractant protein 1. In addition, chondrocytes treated with IL-1β and TNF increase the production of nitric oxide (NO), cyclooxygenase 2 (COX-2), and prostaglandin E2 (PGE2), which contribute to articular inflammation and cartilage destruction as they enhance MMP activity, inhibit the production of anabolic products such as collagen and proteoglycan, and induce chondrocyte apoptosis [39].

The catabolic events observed (the catabolic events that occur due to the presence of...) in the presence of IL-1β and TNF are mediated through the activation of signaling pathways, including nuclear factor-κB (NF-κB) signaling. NF-κB pathway induces the expression of the genes related to the inflammatory mediators cited above and also contributes to the induction of MMP-1 and -13 and ADAMTS-4 [46]. However, some signaling pathways are involved in the downregulation of the IL-1β and TNF effects in OA, such as peroxisome proliferator-activated receptor-γ (PPAR-γ). The activation of PPAR-γ seems to reduce the progression of cartilage lesion in experimental models of OA as it assists the downregulation of inflammatory and catabolic responses mediated by IL-1β and TNF [47, 48].

#### *3.1.2 IL-6*

IL-6 is a proinflammatory cytokine, whose signaling pathway involves the activation of receptors, such as membrane-bound IL-6 receptor (IL6R), soluble

IL-6R (sIL-6R), and gp130, followed by the activation of STAT1 and STAT3 pathways [39]. In physiological conditions, the production of IL-6 by chondrocytes is considerably low. However, the exact mechanism of IL-6 action in OA is unknown, but its production can be stimulated by the number of cytokines and growth factors present in OA, including IL-1β, TGF-β, and $PGE_2$ [25, 49].

Increased levels of IL-6 in synovial fluid and serum have been correlated with the severity of lesions in X-ray imaging [50]. *In vitro* studies have shown that IL-6, in combination with IL-1β and TNF, upregulates the production of MMP-1 and -13 in human and bovine chondrocytes and induces proteoglycan and type II collagen degradation [51, 52]. The effect of IL-6 in studies with animal models has shown uncertain results. IL-6 knockout mice revealed more advanced degenerative changes compared to wild-type animals [53]. However, when IL-6 was injected in the joint cavity of IL-6-deficient mice, the reduction in the loss of proteoglycans in the acute phase of inflammation was observed [54].

One of the most considered active components in OA is the change in subchondral bone tissue, and IL-6 has been a critical mediator in this regard. Its effect, together with IL-1β and TNF, is based on promoting osteoclast formation and, consequently, bone resorption [55]. In response to IL-6, osteoblasts stimulate the production of receptor activator of NF-κB ligand, IL-1β, and $PGE_2$, which activate osteoclasts [56]. In addition, osteoblasts activated by these cytokines produce MMPs, which adversely affect the surrounding cartilage [57].

### *3.1.3 IL-15*

Despite a better documented involvement in rheumatoid arthritis [58], the knowledge regarding IL-15 and its action in OA is still poor. It acts based on the stimulation and proliferation of T cells and NK cells, and it may also induce the production of MMP [59]. IL-15 levels are elevated in synovial fluid in early stages of OA, and this concentration correlates with pain and severity of lesions seen on X-ray imaging [60, 61].

### *3.1.4 IL-17*

Due to its inflammatory effects, IL-17 family has been implied to play a role in OA [62]. IL-17 is mainly stimulated by CD4+ T cells and mast cells, which are present in the cellular infiltrates observed in OA joints [63]. Within the joints, IL-17 primarily targets chondrocytes and fibroblast-like synoviocytes, which express IL-17 receptor (IL-17R) on their surface [64]. It was reported that IL-17 is able to inhibit proteoglycan synthesis by chondrocytes and increase the production of MMPs [65]. Also, high levels of IL-17 in both serum and synovial fluid were correlated with radiographic lesions in OA [66].

The genetic correlation between IL-17 and OA was suggested: a polymorphism in the gene IL-17A G-197A could be associated with the susceptibility to the development of OA [67]. In addition, IL-17 is produced by a specific T cell lineage called T helper 17, and it is able to cause hypertrophy of synovial membrane as its presence influences the secretion of vascular endothelial growth factor (VEGF), which leads to excessive blood vessel formation [68]. It can also indirectly affect cartilage by inducing the production of cytokines responsible for tissue degradation, such as IL-1β, TNF, IL-6, NO, and $PGE_2$ [64].

### *3.1.5 IL-18*

The active form of IL-18 results from the activation of caspase-1, which has been reported to be elevated in articular cartilage and synovium of OA, leading to great

promotion of IL-18 and IL-1β. The production of IL-18 in joints is mainly determined by chondrocytes, osteoblasts, and macrophages [69]. IL-18 affects cartilage by upregulating the production of IL-18Rα on chondrocyte surface and stimulates excessive production of MMP-1, -3, and -13 [70]. Also, IL-18 negatively influences the production of proteoglycans, aggrecan, and type II collagen and may cause morphological changes typically observed in apoptotic processes [71, 72].

The increased concentration of IL-18 observed in synovial fluid, synovium, cartilage, and even blood serum from patients with OA has been correlated with the severity of lesions seen in radiographic imaging [73]. Also, studies have correlated the development of OA and lumbar disc degeneration with polymorphisms in the gene encoding IL-18 and its receptor (IL-18R) [74, 75].

*3.1.6 IL-4*

Anti-inflammatory cytokines also present a role in the maintenance of OA. IL-4 is associated with chondroprotective effects as it is shown to reduce MMP production and, consequently, inhibit the degradation of proteoglycans in the articular cartilage [76]. However, chondrocytes from OA joints have shown a decreased susceptibility to this IL-4 protective effect, leaving the cartilage unprotected, quickening the degeneration via the action of the proinflammatory cytokines cited above [77]. In addition, a polymorphism in the gene encoding IL-4 and its main receptor (IL-4Rα) could predetermine the development of OA in hand and knee joints [78, 79]. It was also further reported that, when compared with healthy patients, OA patients present an elevated level of soluble IL-4Rα (sIL-4Rα) [80].

The activation of IL-4 depends on intracellular signal transduction by gradual phosphorylation of IL-4Rα, which leads to the expression of several proinflammatory genes [81]. IL-4 production is mainly determined by T cells, especially Th2, which are present in the cellular infiltrates observed in OA [37]. It was reported that IL-4 alone or in combination with IL-10 is able to reduce the production of diverse proinflammatory mediators, such as IL-1β, TNF-α receptors, IL-6, $PGE_2$, and COX-2 [82–84].

*3.1.7 IL-10*

Due to its anti-inflammatory features, IL-10 is another cytokine that presents chondroprotective effects, and it is linked to the release of IFN [62]. *In vitro* studies have shown increased proteoglycan and type II collagen syntheses after the administration of IL-10 in chondrocytes [62]. The protective effects that IL-10 exhibits are likely due to a stimulation of the synthesis of IL-1β antagonist and a tissue inhibition of MMP-1 (TIMP-1) [85]. Also, IL-10, as well as IL-4, reduces apoptotic events in chondrocytes and production of MMP [86, 87].

IL-10 induces the expression of bone morphogenetic protein-2 and -6 (BMP2 and BMP6), which are related to chondrogenesis as they belong to TGF-β family [88]. Together with BMP production, IL-10 activates signaling pathways, such as NKX-3.2/SOX9, that induce the differentiation of mesenchymal stem cells into chondrocytes [89]. Also, by reducing the expression of TNF-α receptors, IL-10 is able to attenuate the effect of TNF-α on synovial fibroblasts. A decrease in COX-2 production was also noted in the same study [90].

The secretion of IL-10 can be influenced by physical exercises. Patients with and without OA had synovial fluid and periarticular tissue harvested from their knee before, during, and after they underwent exercise practice for 3 hours. A significant increase in IL-10 levels was observed in these patients after the exercise. Although it is not clear what exact mechanism led to this result, this observation is

likely attributed to an increase in intra-articular pressure and subsequent effects on cellular secretion [91, 92].

### 3.2 Chemokines

Chemokines comprise small proteins that act as chemoattractants to assist cells to migrate to injured tissue. Diverse chemokines have gained attention in the development of OA. Some of them including their receptors, such as IL-8, CCL5, CCL19, CCR1, CCR2, CCR3, and CCR5, may induce the production of MMP-3 by chondrocytes and increase the breakdown of cartilage matrix components, which trigger the onset of OA [60, 93]. However, some chemokines might present a protective role in OA, such as stromal cell-derived factor-1 (also called CXCL12), whose main function is to recruit mesenchymal stem cells to the injured area in order to promote tissue repair [94].

Several chemokines were reported to be overexpressed in OA, such as IL-8/CXCL-8, GROα/CXCL-1, MCP-1/CCL-2, RANTES/CCL-5, MIP-1α/CCL-3, and MIP-1β/CCL-4. Some of these chemokines are stimulated by IL-1β, which is upregulated in OA, and they induce MMP production upon binding to their ligands, causing tissue degradation [93]. Levels of INF-γ-inducible protein 10 (IP-10), also called as CXCL-10, in plasma and synovial fluid have been correlated with radiographic knee OA. CX3CL1, a serum fractalkine, has also been reported to be significantly elevated in severe knee OA in a study that compared OA patients with healthy patients [95].

To support the role of macrophage in the inflammatory response observed in OA, MCP-1, also known as chemokine ligand-2 (CCL2), has been reported to recruit macrophages into adipose tissue and atherosclerotic lesions [96]. Also, MCP-1 levels in both serum and synovial fluid has been associated with self-reported pain and disability in patients who present knee OA [97]. In addition, it was observed that, in severe knee OA, the levels of macrophage-derived chemokine (MDC) and IP-10 in synovial fluid were elevated, while eotaxin levels, an eosinophil chemotactic protein, were lower when compared with healthy patients [98].

### 3.3 Adipokines

Adipokines have been associated with the incidence and severity of OA [99]. *In vitro* studies reported that the presence of adipokines, such as leptin, adiponectin, visfatin, and resistin, increases the production of inflammatory mediators and also induces chondrolysis [99]. Although the exact mechanism of how these cytokines derived from adipose tissue act on arthritic joints has not yet been elucidated, researchers have studied the role of fat pad as a local inflammation mediator in OA, particularly in knee OA due to the infrapatellar fat pad, which has proven to be infiltrated with macrophages, lymphocytes, and granulocytes [100]. These findings support the thought that obesity supports the development of OA more through biochemical pathways rather than biomechanical overload risks on a weight-bearing joint.

### 3.4 Lipid mediators

The COX-2 enzyme is responsible for the production of lipid mediators, including PGE2 and leukotrienes, and it is also upregulated in OA joints. In addition, the overexpression of COX-2 in OA has been associated with the increased production of IL-1β, TNF, and IL-6 via toll-like receptor-4 (TLR-4) [101]. Besides assisting the production of MMPs and other functions already cited above, $PGE_2$ is also involved in apoptosis and structural changes that characterize arthritic disease [102].

Leukotrienes have also been investigated for their role in OA. These mediators are converted from arachidonic acid, which also produces $PGE_2$ via the activity of the enzyme phospholipase A2 [21]. Leukotrienes, mainly leukotriene B4 (LTB4), are present, to a lesser extent, in OA synovium, bone, and cartilage. Also, LTB4 has been reported to stimulate the production of IL-1β and TNF in arthritic synovium [103].

## 4. Conclusions

The cumulative evidences over the years have shown that increased expression of proinflammatory cytokines, in particular IL-1β, TNF, and IL-6, in cartilage as well as synovial fluid and membrane, has played a key role in the pathogenesis of OA. Inflammatory processes linked with immune responses have characterized OA as a complex disease and not as a simple age-related cartilage degeneration as it is thought to be. The understanding of individual roles of inflammatory mediators and their compounds is of utmost importance to target new therapies for OA, since the current options are elusive and may be noneffective, invasive, or even capable of presenting serious side effects. Due to advancements in molecular tools, the overall aim would be to dissect the role of each cytokine in the pathophysiology of OA and, together with drug delivery systems, to develop specific anticytokine therapy, given that inflammatory responses contribute substantially to OA maintenance.

## Conflict of interest

The authors have no conflict of interest to declare.

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