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Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis

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Abstract

Osteoarthritis (OA) has long been viewed as a degenerative disease of cartilage, but accumulating evidence indicates that inflammation has a critical role in its pathogenesis. Furthermore, we now appreciate that OA pathogenesis involves not only breakdown of cartilage, but also remodelling of the underlying bone, formation of ectopic bone, hypertrophy of the joint capsule, and inflammation of the synovial lining. That is, OA is a disorder of the joint as a whole, with inflammation driving many pathologic changes. The inflammation in OA is distinct from that in rheumatoid arthritis and other autoimmune diseases: it is chronic, comparatively low-grade, and mediated primarily by the innate immune system. Current treatments for OA only control the symptoms, and none has been FDA-approved for the prevention or slowing of disease progression. However, increasing insight into the inflammatory underpinnings of OA holds promise for the development of new, disease-modifying therapies. Indeed, several anti-inflammatory therapies have shown promise in animal models of OA. Further work is needed to identify effective inhibitors of the low-grade inflammation in OA, and to determine whether therapies that target this inflammation can prevent or slow the development and progression of the disease.

Osteoarthritis (OA) is the most prevalent arthritic disease and a leading cause of disability, with radiographically established OA affecting approximately 37% of the US population over 60 years of age¹. OA can affect the knees, hips, spine, and fingers, and is characterized by progressive breakdown of articular cartilage and remodelling of the underlying bone in the synovial joints. Common clinical features include pain, joint dysfunction, and deformity. Women, older individuals, obese individuals, and individuals with prior joint injuries all have an increased risk of developing OA, as do individuals with certain genetic and biomechanical predisposing factors^{2–4}. Current therapies for OA focus on pain control,

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viscosupplementation (via intra-articular injections of hyaluronic acid), and joint replacement, which all simply target the symptoms of advanced disease. Novel therapeutics are needed to inhibit the processes that drive OA pathology.

The past decade has seen a gradual but fundamental shift in our understanding of the mechanisms underlying OA. We no longer view OA as a prototypical degenerative disease resulting from normal bodily wear and tear, but rather as a multifactorial disorder in which low-grade, chronic inflammation has a central role (BOX 1). This inflammation comes into play early in the course of OA, as a result of interactions between the immune system and factors including local tissue damage and metabolic dysfunction⁵. Further unravelling of the mechanisms underpinning the inflammatory pathophysiology of OA is likely to yield new therapeutic approaches that can modify the course of OA.

In this Review, we examine the emerging evidence for a critical role of low-grade inflammation in the pathogenesis of OA, and discuss the current understanding of the underlying molecular mechanisms. We also explore the potential of therapeutic strategies that target this low-grade inflammation in the prevention or treatment of OA.

OA — a whole-organ disease of the joint

Traditionally, OA has been viewed as a disorder affecting articular cartilage². However, we now know that this disease affects the entire joint structure^{6–10}. The pathologic changes that occur in OA joints are fibrillation and degradation of the articular cartilage, thickening of the subchondral bone, formation of osteophytes, inflammation of the synovium (synovitis), degeneration of ligaments and menisci, and hypertrophy of the joint capsule⁶ (FIG. 1,2). Radiographic evaluation of OA bone reveals the presence of subchondral sclerosis and cysts, and microscopic examination reveals microfractures and microcracks in advanced OA¹¹.

Several cellular and molecular processes are involved in these pathological changes: an increase in cartilage catabolism and a concomitant decrease in cartilage anabolism and repair; hypertrophy and death of chondrocytes; impairment or dysregulation of autophagy; osteoclast-mediated remodelling of bone; and infiltration and activation of immune cells⁶. However, many questions remain about how these processes combine to mediate the pathogenesis of OA. For instance, how does the mechanical and molecular interplay between different joint tissues drive OA pathology?⁶ What is the precise nature of the crosstalk between the affected tissues — that is, which factors produced by one joint tissue cause pathological changes in another? In what sequence do the pathological events occur? What feedback mechanisms are involved? Answering these questions will be important for designing next-generation therapeutic interventions that can prevent, slow, or reverse the development of OA.

The importance of inflammation in OA

Clinically, many individuals with OA have symptoms of joint inflammation, such as morning stiffness, warmth, pain, and joint effusions that arise, in part, from synovial thickening or synovial fluid effusion⁷. Indeed, synovitis, which is detectable by imaging, arthroscopy, or histology, is now recognized as a common finding in OA^{7,12–15}.

Histologically, this synovitis is characterized by infiltration of inflammatory cells into the synovium^{16,17}. Furthermore, molecular evidence of low-grade inflammation in OA is accumulating. As early as 1959 came the discovery that inflammatory plasma proteins are present at abnormally high levels in both the blood and the synovial fluid of patients with OA¹⁸. More recent studies have shown that OA tissue and synovial fluid have abnormally high levels not only of plasma proteins¹⁹, but also of complement components²⁰ and cytokines¹⁹, and that chondrocytes and synovial cells in OA produce or overproduce many of the inflammatory mediators (for example, IL-1 β , TNF, and nitric oxide (NO))²¹ that are characteristic of inflammatory arthritides.

Accumulating evidence supports the association between OA pathology and different markers of inflammation. Imaging studies involving serial MRI scans coupled with histopathologic analysis of synovial tissues have shown that the presence of synovitis in OA is associated with an increased severity of joint symptoms, increased cartilage loss, decreased mobility, and elevated radiographic grades^{12,22–28}. Likewise, the presence of synovitis at the time of arthroscopy is associated with subsequent accelerated destruction of cartilage²⁹.

Whether these associations reflect a causal role for inflammation in OA pathogenesis, or indicate that joint inflammation is merely an epiphenomenon in a process that is primarily degradative or mechanical, remains unclear. The timing of the inflammation, as well as mechanistic plausibility and findings from animal models genetically deficient in specific inflammatory molecules, suggests that inflammation could indeed be pivotal in the pathogenesis of OA. The presence of synovitis often predates the development of radiographic damage in OA³⁰, and mononuclear cell infiltration and overexpression of inflammatory mediators in the synovium are prominent in early OA³¹. Likewise, elevated serum levels of C-reactive protein, a marker of inflammation, are predictive of the development and progression of OA²¹. The inflammatory mediators detected in OA joints are synthesized, in part, in response to tissue injury and breakdown in the joint. They can alter chondrocyte differentiation and function, as well as induce the expression and activation of matrix metalloproteinases (MMPs) and aggrecanases, enzymes that degrade cartilage and are thought to be the downstream effectors of OA pathogenesis^{10,16,32,33}. Finally, evidence from animal models suggests that inflammation contributes to joint degeneration in OA³⁴, and that synovial macrophages are critical for the formation of osteophytes³⁵. Thus, current evidence suggests that targeting inflammation therapeutically has the potential to prevent or reduce multiple pathologic features of OA, and thereby slow the progression of the disease.

In addition to local inflammation in the joint, systemic inflammation might also have an important role in OA pathogenesis. For instance, obesity is known to predispose individuals to OA³⁶ — possibly not only by increasing the mechanical load on joints, but also by causing chronic, systemic inflammation through inflammatory mediators (such as adipokines and other proinflammatory cytokines) that are produced by adipose tissue and released into the bloodstream^{37,38}. Weight loss is associated with a substantial reduction in systemic levels of C-reactive protein and IL-6 in individuals with OA, and can prevent OA onset or alleviate existing OA symptoms^{39,40}. It is possible that the systemic inflammation

associated with chronic inflammatory states, such as obesity or certain chronic diseases, promotes local inflammation in joints that ultimately results in OA.

The inflammation in OA is low-grade

The inflammation observed in OA is generally chronic and low-grade, and is believed to involve an immune response, primarily innate and to a lesser degree adaptive⁴¹. However, this inflammation is fundamentally different from that in rheumatoid arthritis (RA), the prototypical inflammatory arthritis. For example, the increase in levels of inflammatory plasma proteins in the blood and synovial fluid from individuals with OA (relative to healthy controls) is modest compared to that in patients with RA^{18,19}. Histological comparisons reveal that inflammation is also less pronounced in typical OA synovium than in the RA synovium^{14,42–44}. These two types of inflammation differ not only in degree, but also in the cellular and molecular players involved⁴⁵. Whereas the numbers of most immune cells (for example, macrophages and T cells) in synovial tissues are lower in OA than in RA, the number of mast cells in OA is as high as, or sometimes higher than, in RA⁴⁵. The expression of cytokines related to macrophage or T-cell function in OA synovial tissues is also lower than in RA synovial tissues (although higher than in normal tissue)⁴⁵. Finally, systemically blocking the activity of conventional inflammatory cytokines with biologic therapies approved for the treatment of RA (such as anti-TNF or anti-IL-1 β therapies) provides no benefit in generalized OA, and no or only minimal benefit in erosive OA (see below for more discussion on why these trials might have failed)^{32,46–49}. Collectively, these lines of evidence suggest that the inflammatory mechanisms operating in OA differ from those in RA, and that targeting them will require novel approaches to anti-inflammatory therapy.

Molecular inflammatory mechanisms in OA

In the OA joint, acute, subacute, or chronic injuries and joint tissue breakdown, often in the context of other risk factors (such as obesity, advanced age, metabolic disorders, dysregulation of bioenergy sensors, and certain genetic factors), can trigger a progressive cycle of local tissue damage, failed tissue repair, and inflammation, resulting in further cartilage loss and progressive joint degeneration over time^{10,30,42}. In this paradigm (BOX 2, FIG. 3), a number of molecular components and mechanisms could transduce joint trauma, chronic injury, or overuse into inflammatory processes. These factors are discussed in the following sections.

Innate immune mechanisms

The innate immune system recognizes conserved features of pathogens via invariable pattern-recognition receptors (PRRs), which comprise multiple families of cell-surface, endosomal, and cytosolic receptors. PRRs provide a first-line immune response to microbial invaders. However, they recognize not only pathogen-associated molecular patterns, but also damage-associated molecular patterns (DAMPs). Produced during tissue damage, DAMPs are endogenous molecules that signal to innate immune cells (for example, macrophages and mast cells) to trigger a protective response. Once activated by DAMP-PRR signalling, the innate immune system produces an array of inflammatory mediators that normally initiate immune responses, and that ultimately lead to repair. However, prolonged or dysregulated

activation of PRR-DAMP-induced inflammation can be destructive, and has been implicated in the chronic inflammation observed in OA^{30,50}.

Like PRRs, the complement system is an innate immune mechanism by which the body recognizes pathogens^{51,52}, and has also been implicated in inflammation and damage in OA joints⁵³. The complement system enhances the ability of antibodies and phagocytic cells to clear pathogens from an organism^{54,55}. Complement activation leads to chemotaxis, exudation of plasma proteins at inflammatory sites, and opsonization of infectious agents and damaged cells. Interestingly, several products of tissue breakdown in the joint are capable of activating both PRRs and complement⁵⁶⁻⁶¹.

DAMPs—At least four classes of DAMPS are associated with OA (reviewed elsewhere³⁰): the products of extracellular matrix (ECM) breakdown, which occurs at sites of inflammation (such as biglycan, fibronectin, low-molecular-weight hyaluronic acid, and tenascin C); plasma proteins that exude from blood vessels at sites of inflammation-induced or damage-induced vascular leakage (for example, α 1 microglobulin, α 2 microglobulin, fibrinogen, and vitamin D-binding protein); intracellular alarmins released from stressed, damaged, or necrotic cells (for example, HMGB1 and the S100 family of proteins); and microscopic crystals released from cartilage into the synovial space by injury or wear and tear (for example, basic calcium phosphate, calcium pyrophosphate dihydrate, and uric acid).

When inducing inflammation, one of the main classes of PRRs bound by DAMPs are the Toll-like receptors (TLRs). Stimulation of TLRs ultimately leads to activation of inflammatory transcriptional programs via transcription factors such as interferon-regulatory factors, nuclear factor- κ B (NF- κ B), and activator protein 1 (AP-1)⁴². Among the ten functional TLRs in humans, TLR1-TLR7 and TLR9 have been detected in the synovium of individuals with OA or RA (reviewed elsewhere¹⁵). TLR activation has been implicated in the development of synovitis, degeneration of cartilage, and susceptibility to disease in OA¹⁵, although MyD88-dependent TLRs were shown to be dispensable in a mouse model of OA⁶². Indeed, *in vivo* studies of deficiency in DAMPs or TLRs and their agonists have generated mixed results⁶³, and the effects of targeting these molecules in human OA remains to be determined (TABLE 1).

Complement system—Complement can be activated by any of three independent initiation pathways (the classical, alternative, and lectin pathways), which all subsequently converge on complement components C3 and C5, resulting in the formation of C3 and C5 convertases, respectively. Activation of these convertases induces the generation of the effector components of the complement cascade: the C3a and C5a anaphylatoxins promote inflammation by chemoattracting proinflammatory leukocytes, and the membrane attack complex (MAC) promotes tissue damage and inflammation. The MAC binds to the outer surface of cell membranes, and can form a transmembrane pore that results in cell lysis^{64,65}. When bound to a cell surface at sublytic levels, however, the MAC instead induces proinflammatory cell signalling, such as that mediated by mitogen-activated protein kinases, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, and NF- κ B⁶⁶.

Evidence from both human and mouse studies suggests the complement system has a central role in the pathogenesis of OA⁵³. Decades ago, several reports described complement and immunoglobulin deposits in OA cartilage⁶⁷ and synovium⁶⁸, and complement components have since been shown to be produced, in part, by chondrocytes⁶⁹. In 2011, our group reported that OA synovium expresses higher levels of complement effectors and lower levels of complement inhibitors than healthy synovium⁵³. DAMPs present in OA joints, such as cartilage ECM proteins, calcium crystals, and components of apoptotic debris, also bind and activate complement^{56–61}. Findings from mouse studies suggest that this overproduction and hyperactivation of complement in the joint has an important role in OA pathology: deficiency in the complement components C5 or C6 attenuated experimental OA, whereas deficiency in CD59a (a protein that inhibits MAC formation, and hence also MAC activity⁷⁰) worsened it⁵³. Still unknown, however, is whether complement deposition in OA joints is itself a triggering event or whether it is secondary to low-grade inflammation or to the damage of cartilage or joint tissues. These findings suggest that strategies that block complement activation have therapeutic potential for OA, but whether chronic inhibition of complement would be required and what adverse effects this inhibition might have are unclear.

Carboxypeptidase B—Evidence from both human and mouse studies suggests that the enzyme carboxypeptidase B (CPB) protects against the inflammatory destruction of OA joints by inhibiting proinflammatory anaphylatoxins and effectors of the complement system⁷¹. Produced primarily by the liver as a circulating plasma zymogen, CPB is activated by the thrombin-thrombomodulin complex during thrombotic events. In the joint, thrombomodulin expressed by synovial lining cells^{72,73} and neutrophils⁷⁴ forms a 1:1 complex with thrombin, and activates procarboxypeptidase B (also called thrombin-activatable fibrinolysis inhibitor), resulting in the generation of CPB. By cleaving its substrates' C-terminal arginine or lysine, CPB can in turn inactivate several inflammatory proteins, such as fibrin, C5a, C3a, bradykinin, and thrombin-cleaved osteopontin^{75,76}, and thereby protect the joints from inflammatory destruction⁷¹. Whether treatments that target CPB have protective effects in OA clinical trials remains to be determined.

Macrophages and mast cells—Innate immune cells that can be activated by DAMPs and complement include macrophages and mast cells^{77,78}, both of which are implicated in OA pathogenesis. Macrophages in the synovium of OA joints are activated and contribute to cartilage breakdown and osteophytosis by producing cytokines, such as IL-1 β and lymphotoxin-a, as well as pro-MMPs^{17,35,79,80}. Activated mast cells are also present in OA synovial tissues, and higher numbers of mast cells in OA synovial tissues are associated with a greater degree of both synovitis and structural damage in the synovial joints⁴⁵. The mechanisms by which macrophages are activated in the OA joint and contribute to the pathogenesis of OA are currently under investigation.

Mast cells are a heterogeneous group of cells that can be subdivided into those containing only tryptase and those containing both tryptase and chymase⁸¹. The increase in number of mast cells in OA synovial tissue (compared with their numbers in normal tissue) is attributable to the selective expansion of the tryptase-only population of mast cells, in

contrast to the expansion of both mast cell populations that occurs in RA^{82,83}. Furthermore, tryptase activity is higher in mast cells in OA synovial tissues than in normal synovial tissues⁸⁴; mast cell tryptase released into the synovial fluid stimulates the proliferation of fibroblast-like cells and the production of proinflammatory cytokines by these cells⁸⁴, and could in this way contribute to OA pathology. Another classic mast cell mediator is histamine. Compared with those in RA, mast cells in OA synovial tissues have similar or higher histamine content⁸⁵, but lower histamine release^{86,87}. The exact roles of mast cells and their mediators in OA remain poorly understood.

Adaptive immune mechanisms

Levels of antibodies and immune complexes are abnormally high in OA synovial fluid and joint tissues, although the specificities of the antibodies involved and the relevance of these increases in antibody levels are unclear²⁰⁻⁶⁷⁻⁸⁸. It is possible that the cartilage and cellular debris released during cartilage degeneration exposes neoepitopes that are then targeted by antibodies. Natural antibodies, which are typically not affinity-matured and therefore are of low affinity, can bind cartilage or other cellular debris to form immune complexes. These immune complexes might activate innate immune responses and stimulate inflammatory responses; alternatively, they might facilitate the clearance of cartilage debris and thus promote tissue repair, as has been observed in other diseases⁸⁹. Further investigation is needed to define the role of antibodies and of the adaptive immune response in the pathogenesis of OA.

Inflammatory mediators

As mentioned earlier, various soluble inflammatory mediators have been identified in OA joint tissues and fluids, including cytokines, chemokines, growth factors, adipokines, prostaglandins and leukotrienes, and regulators such as CPB (reviewed elsewhere³⁰). These mediators can be produced by different cell types within the joint, including fibroblast-like synoviocytes, chondrocytes, and resident or infiltrating immune cells^{15,90}.

Cytokines—Cytokines are among the most extensively studied mediators of inflammation. Several cytokines, such as TNF, IL-1 β , IL-6, IL-15, IL-17, IL-18, IL-21, and leukaemia inhibitory factor, have been implicated in the pathogenesis of OA^{30,90}. The precise contributions of different cytokines to OA remains to be elucidated, but inflammatory cytokines have been proposed to induce cartilage catabolism as well as inhibit anabolic processes that are critical to cartilage homeostasis^{30,91,92}. For example, IL-1 β and TNF signalling mediated by the transcription factors NF- κ B and AP-1 results in autocrine production of these cytokines, as well as expression of other inflammatory and chondrolytic mediators (including NO, prostaglandin E2 (PGE2), IL-6, MMP1, MMP9, and MMP13), in OA cartilage *ex vivo*⁹³. Despite encouraging results from animal studies, anti-IL-1 β and anti-TNF therapies have not yielded positive results in OA clinical trials⁴⁶⁻⁴⁹. The disappointing results from human trials suggest that targeting a single cytokine (such as IL-1 β or TNF) at the systemic level might not be sufficient to have a beneficial effect on OA; unlike RA, in which TNF drives IL-1 β production, IL-1 β and TNF could act in a parallel, redundant manner in OA³². Failure of these anti-cytokine therapies might also be explained by the inability of systemically administered anti-cytokine therapeutics to

penetrate the joints, or by the evaluation of their efficacy in late-stage OA when the disease process might be less-responsive to such therapies, or by other factors³². Likewise, trials of MMP-blocking therapies in humans have shown a discouraging lack of efficacy and/or unacceptable toxicity^{94–96}. Other cytokines could also be targeted therapeutically, but selecting which cytokine to target in OA will require a thorough understanding of the underlying mechanisms⁹⁰.

Chemokines—Many chemokines (a subset of cytokines that induce the recruitment and trafficking of inflammatory cells and mesenchymal progenitors) are produced within the OA joint^{15,97,98}. Certain chemokines and their receptors (IL-8, CCL5, CCL19, CCR1, CCR2, CCR3, and CCR5, among others) might facilitate the onset and progression of OA¹⁵, not only by inducing the release of MMP3 by chondrocytes and hence the breakdown of cartilage matrix components⁹⁹, but also by promoting osteoclast-mediated remodelling of periarticular bone. Other chemokines might be protective in OA: for instance, stromal cell-derived factor-1 (also called CXCL12) recruits mesenchymal progenitors and thereby promotes tissue repair¹⁰⁰. Yet other chemokines could have a dual role in inflammation, depending on the context in which they are produced¹⁰¹.

Growth factors—Growth factors such as transforming growth factor- β (TGF β), fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF) have been implicated in OA. The TGF β family of growth factors is broadly expressed in cartilage, bone, and synovial tissues¹⁰². TGF β growth factors are normally crucial for maintaining cartilage homeostasis but have been linked to the promotion of osteophytosis and synovial fibrosis in OA^{35,42,103}. Three members of the FGF family expressed in articular cartilage, namely FGF2, FGF8, and FGF18, are involved in cartilage homeostasis and might be associated with OA¹⁰⁴. VEGF, generated by the inflamed synovium, can promote angiogenesis and thereby facilitate infiltration of the joint by immune cells that contribute to inflammation in OA¹⁰⁵. NGF regulates monocyte inflammatory responses and the production of IL-1 β , TNF, IL-6, and IL-8 via the high-affinity NGF receptor (also known as tyrosine kinase receptor-A (TrkA))¹⁰⁶. Inhibiting NGF with monoclonal antibodies, including tanezumab and fulranumab, significantly reduced pain in individuals with OA¹⁰⁷.

Therapeutic approaches that target growth factors hold promise for preserving cartilage or stimulating its repair¹⁰⁸. Several therapies that inhibit VEGF have proven beneficial in animal models of arthritis, and their anti-inflammatory and anti-angiogenic effects in OA are now being evaluated in clinical trials¹⁰⁹. Intraarticular administration of recombinant FGF18 is also being investigated in individuals with OA (TABLE 1). However, local growth factor therapy risks promoting osteochondral bone formation, especially osteophyte outgrowth, whereas systemic diffusion of the growth factor might induce growth in normal tissues or, even worse, in premalignant lesions³².

Adipokines—High systemic and synovial fluid levels of adipokines, a family of cytokines secreted primarily by adipose tissue, are associated with cartilage degeneration and synovial inflammation in OA^{110–112}. Thus, an increase in adipokine levels might explain why obesity (in which altered biomechanics could also have a role) and other features of the metabolic syndrome (hypertension, dyslipidaemia, insulin resistance, and others) increase the risk of

developing OA^{36,111,113,114}. Several adipokines, such as leptin, adiponectin, resistin, visfatin, and nefastin-1, have context-dependent immunomodulatory properties^{115,116} and can induce the production of inflammatory mediators and cartilage-degrading factors, leading to chondrocyte degradation and the development of OA^{112,115,117–124}. Visfatin, for instance, the expression or enzyme activity level of which is regulated by IL-1 β , hypoxia-inducible factor 2 α (HIF-2 α), and other interleukins, not only inhibits the phosphorylation of insulin receptor factors such as IRS1 and AKT, thus reducing proteoglycan production, but also increases the expression of MMPs, NGF, and PGE2, thereby aggravating OA¹²⁰. Adipokines are also produced in the OA joint by infrapatellar fat pads, synovium, chondrocytes, osteoblasts, and osteoclasts^{125,126}, which could additionally serve as local sources of other inflammatory mediators in the joint, such as neuropeptides and the classic inflammatory cytokines IL-1 β , IL-6, and TNF³⁰. Prevention of metabolic syndrome by lifestyle changes might relieve OA symptoms through reductions in adipokine levels and, in the case of weight loss, reduction in joint biomechanical stress.

Prostaglandins and leukotrienes—Lipid mediators, including prostaglandins and leukotrienes, have been detected in the OA joint and might be involved in the pathogenesis of OA^{19,127,128}. In particular, PGE2 is likely to contribute to OA pathology by promoting inflammation, apoptosis, and angiogenesis¹²⁷, whereas leukotriene B4 (LTB4) might act as a powerful leukocyte chemoattractant¹²⁹ and could stimulate the production of IL-1 β and TNF by synovial tissues¹³⁰.

Substantial efforts have been made to elucidate the mechanisms governing prostaglandin and leukotriene production in OA, with a view to their therapeutic targeting. Prostaglandins and leukotrienes are generated from arachidonic acid via distinct enzymatic cascades that can be induced by inflammation or trauma^{127,128,131}, such as that occurring in OA. Prostaglandins are produced by the cyclooxygenase pathway, in which cyclooxygenase-2 (COX2, also known as prostaglandin G/H synthase-2) is the rate-limiting enzyme mediating inducible prostaglandin production. COX2 is overexpressed in inflamed articular tissues¹²⁷, and its expression in human chondrocytes can be induced by proinflammatory cytokines (IL-1 β , TNF, IL-6, and others), as well as by TLR4 stimulation¹³². Likewise, prostaglandin E synthase, the key terminal enzyme in the production of PGE2, is overexpressed in OA cartilage¹³³, and its expression in human OA chondrocytes can be induced by IL-1 β and TNF^{134,135}. Moreover, prostaglandin E synthase localizes to the superficial layers of human OA cartilage, which is where OA damage first occurs¹³³. Upregulation of leukotriene production is also evident in OA joints. Arachidonic acid released from cell membranes in the OA synovial tissues, synovial fluid, cartilage, and subchondral bone^{128,136} can also be converted to the unstable precursor leukotriene A4 (LTA4) via arachidonate 5-lipoxygenase (5LO) and 5LO-activating proteins, with LTA4 in turn being converted to LTB4 by LTA4 hydrolase¹³¹.

NSAIDs and other COX2 inhibitors reduce prostaglandin production and inflammation in OA, but serve only to attenuate pain and are associated with a broad spectrum of adverse effects on the liver, kidney, cardiovascular system, gastrointestinal tract, and skin¹³⁷. Several agents that inhibit both COX2 and COX1 (cyclooxygenase-1, also known as prostaglandin G/H synthase-1) enzymes as well as 5LO are currently in development as inhibitors of

bioactive leukotriene generation, and their safety and efficacy in OA are being evaluated in clinical trials¹³⁸ (TABLE 1).

Nitric oxide—NO might also be involved in inflammatory processes in OA^{139,140}. Cytokines such as those prevalent in OA joints induce the expression of NO via the inducible NO synthase (iNOS) pathway¹⁴¹, and iNOS mRNA and protein have been found in the synovium of individuals with OA¹⁴². Indeed, high levels of nitrite have been detected in arthritic synovial fluid and serum¹⁴³, consistent with the observation that NO production is abnormally high in OA cartilage¹⁴⁴. NO has been proposed to contribute to the cartilage destruction in OA by enhancing expression of MMPs, inhibiting collagen and proteoglycan synthesis, and inducing apoptosis (in a process involving COX2-mediated production of PGE2)^{145,146}. However, NO has also been proposed to have protective effects in OA by inhibiting the activation of proinflammatory pathways¹⁴⁰. Although *in vivo* experiments in animal models suggest that inhibiting NO or iNOS could be an attractive avenue for treating OA³², the selective iNOS inhibitor cindunistat failed to slow the progression of OA in clinical trials¹⁴⁷ (TABLE 1).

Neuropeptides—In the OA joint, neuropeptides have an active role not only in pain modulation, but also in the initiation and perpetuation of inflammation (by activating infiltrating inflammatory cells and by inducing production of proinflammatory cytokines)^{7,148}. Examples of such proinflammatory neuropeptides include substance P, bradykinin, corticotropin-releasing factor, urocortin, and vasoactive intestinal peptide^{7,148}. In OA, substance P is present in the subintimal portion of the synovium and in areas containing osteophytes or cartilage erosions, and can contribute to the inflammatory response by activating immune cells, stimulating the release of cytokines (such as IL-1 β and TNF), inducing synoviocytes to proliferate and produce PGE2 and collagenase, and increasing osteoclast formation and synovial hypertrophy¹⁴⁸. Bradykinin in the OA synovium can contribute to the initiation and maintenance of inflammation by activating synoviocytes and chondrocytes and possibly by synergistically potentiating the proinflammatory effects of cytokines¹⁴⁹. However, intra-articular administration of the specific bradykinin B2 receptor antagonist icatibant in individuals with knee OA had a long-lasting analgesic effect¹⁴⁹ but no detectable anti-inflammatory effect, as assessed by ultrasonography or MRI¹⁵⁰ (TABLE 1).

Circadian clock dysregulation

Disruption of the circadian rhythm could be another mechanism by which chronic inflammation contributes to OA pathogenesis. Findings published in 2016 indicated a role for the circadian clock component aryl hydrocarbon receptor nuclear translocator-like protein-1 (also known as brain and muscle Arnt-like protein-1 (BMAL1)), which is downregulated in OA cartilage, in maintaining homeostasis and integrity of cartilage tissue¹⁵¹. Indeed, environmental disruption of their circadian rhythms predisposes mice to OA-like damage of their knee cartilage¹⁵², and autonomous circadian rhythms in cartilage become dysregulated with age and with chronic inflammation, as well as in mouse models of injury-induced OA^{153,156}. Interestingly, a local circadian clock in pulmonary epithelial cells controls neutrophil recruitment to the lungs in response to local bacterial stimuli¹⁵⁷, which could explain the diurnal variation in symptom severity of inflammatory lung

diseases. Weakening of the local circadian clock in cartilage (and possibly in other joint tissues as well) might likewise contribute to the circadian variation seen in OA symptoms. Disruption of the cartilage circadian clock could conceivably both result from and contribute to inflammation in OA. In such a scenario, a vicious cycle operates in which chronic inflammation weakens the cartilage circadian clock, leading not only to a decrease in expression of proteins involved in cartilage anabolism¹⁵¹, and hence to cartilage loss, but also to an increase in expression of inflammatory cytokines¹⁵¹, and hence to the propagation of inflammation in the joints. Furthermore, circadian rhythms intrinsic to immune cells affect cytokine responses and immune cell trafficking^{158,159} and, therefore, dysregulation of the immune cell clock could potentially contribute to inflammation in OA.

Anti-inflammatory therapeutics for OA

Given the critical role of low-grade inflammation in OA, novel anti-inflammatory therapeutics could offer new opportunities for treating this disease. Although lifestyle changes involving exercise and/or diet-induced weight loss are simple and (in some individuals) effective¹³⁹ ways of slowing the progression of OA, such regimens are difficult to implement in individuals with OA who are elderly or have limited mobility. Currently, only symptom-modifying agents, such as analgesics, NSAIDs, steroids, and hyaluronic acid, have been approved as therapeutic interventions for OA; that is, until joint replacement is needed^{139,160–162}. None of the approved treatments can restore the original structure and function of damaged joints, nor can they slow the progression of OA. Moreover, these medications frequently have deleterious adverse effects. A substantial need remains for safe and effective disease-modifying OA drugs (DMOADs).

Inhibition of the low-grade inflammation in OA could form the basis of such much-needed DMOADs (FIG. 4). Because inflammation is present early in the course of OA, before structural changes have occurred³⁰, therapeutic strategies targeting the low-grade inflammatory processes might be able to not only halt the progression of OA, but also prevent the onset of radiographic OA. Several anti-inflammatory therapeutics have been tested in human OA, but the results have thus far been disappointing^{139,160–162}. Findings from the SEKOIA study suggest that strontium ranelate has disease-modifying effects in individuals with knee OA^{163,164}, possibly through anti-inflammatory mechanisms involving inhibition of IL-1 β ¹⁶⁵ and MMP¹⁶⁶ production. Nonetheless, whether the benefits provided by strontium ranelate can actually prevent or delay joint replacement, and whether individuals with OA will be compliant in taking this drug (which has diverse adverse effects, including gastrointestinal disorders, thromboembolism, cardiovascular disorders, and allergy) for a period of time sufficient to prevent or slow the progression of OA (3 years^{164,167}) remains unclear. Several promising findings showing disease-modifying effects of inhibitors of low-grade inflammation in animal models of OA warrant follow-up in human clinical trials (TABLE 1).

Because of the heterogeneity of OA, the large number of diverse molecules involved in its pathogenesis, and the multifaceted roles of these molecules under normal or pathologic conditions, effective treatment of OA might require a combination of approaches. Furthermore, teasing apart the precise roles of certain inflammatory components in different

contexts will also be important, as targeting these components might not be feasible if they also have protective functions in tissue repair. That is, as we have learned from failed attempts at targeting IL-1 β ^{46–48} and MMPs⁹⁴, anti-inflammatory therapies for OA will likely have to be broad enough to be effective, but selective enough to avoid deleterious off-target effects. Ongoing advances in imaging technologies and biomarker development should facilitate the testing of candidate therapies by enabling antiinflammatory interventions early in the course of OA — when they could be most effective — through earlier diagnosis and better stratification of patients, as well as earlier and more accurate assessment of clinical response to novel therapeutics.

Conclusions

Although the evidence supporting a role of chronic, low-grade inflammation in OA is well-established, only recently have we begun to appreciate that this inflammation has a pivotal role in the pathogenesis of OA. A further shift in our understanding has come with the realization that OA is a disease of the whole joint, affecting not only the articular cartilage, but also the synovium, tendons, muscles, ligaments, subchondral bone, and adipose tissue; perhaps it is even a systemic disease, with inflammation having a critical role in the interplay between the joint tissues. The complexity of the inflammatory mechanisms in OA pathophysiology is becoming apparent. Future work is needed to fully define the molecular pathways mediating the low-grade inflammation in OA, and to use this information either to repurpose existing drugs or candidate therapeutics that target these pathways, or to develop next-generation therapeutics. Ultimately, clinical trials are needed to determine whether targeting low-grade inflammation can indeed prevent or slow the development and progression of human OA.

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References

1. Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008; 58:26–35. [PubMed: 18163497]
2. Felson DT. Clinical practice. Osteoarthritis of the knee. *N Engl J Med.* 2006; 354:841–848. [PubMed: 16495396]
3. Felson DT, et al. Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med.* 2000; 133:726–737. [PubMed: 11074906]
4. Blagojevic M, Jinks C, Jeffery A, Jordan K. P Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage.* 2010; 18:24–33. [PubMed: 19751691]
5. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol.* 2012; 8:729–737. [PubMed: 22907293]
6. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum.* 2012; 64:1697–1707. [PubMed: 22392533]

7. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol.* 2010; 6:625–635. [PubMed: 20924410]
8. Karsdal MA, et al. The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments? *Ann Rheum Dis.* 2014; 73:336–348. [PubMed: 24285494]
9. Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann NY Acad Sci.* 2010; 1192:230–237. [PubMed: 20392241]
10. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. *Nat Rev Rheumatol.* 2015; 11:35–44. [PubMed: 25266449]
11. Brandt KD, Dieppe P, Radin EL. Commentary: is it useful to subset “primary” osteoarthritis?. A critique based on evidence regarding the etiopathogenesis of osteoarthritis. *Semin Arthritis Rheum.* 2009; 39:81–95. [PubMed: 19796724]
12. Guermazi A, et al. Assessment of synovitis with contrast-enhanced MRI using a whole-joint semiquantitative scoring system in people with, or at high risk of, knee osteoarthritis: the MOST study. *Ann Rheum Dis.* 2011; 70:805–811. [PubMed: 21187293]
13. Ishijima M, et al. Relationships between biomarkers of cartilage, bone, synovial metabolism and knee pain provide insights into the origins of pain in early knee osteoarthritis. *Arthritis Res Ther.* 2011; 13:R22. [PubMed: 21320321]
14. Pessler F, et al. The synovitis of “non-inflammatory” orthopaedic arthropathies: a quantitative histological and immunohistochemical analysis. *Ann Rheum Dis.* 2008; 67:1184–1187. [PubMed: 18203762]
15. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone.* 2012; 51:249–257. [PubMed: 22387238]
16. Goldring MB, Goldring SR. Osteoarthritis. *J Cell Physiol.* 2007; 213:626–634. [PubMed: 17786965]
17. Bondeson J, et al. The role of synovial macrophages and macrophage-produced mediators in driving inflammatory and destructive responses in osteoarthritis. *Arthritis Rheum.* 2010; 62:647–657. [PubMed: 20187160]
18. Nettelbladt E, Sundblad L. Protein patterns in synovial fluid and serum in rheumatoid arthritis and osteoarthritis. *Arthritis Rheum.* 1959; 2:144–151. [PubMed: 13638175]
19. Sohn DH, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. *Arthritis Res Ther.* 2012; 14:R7. [PubMed: 22225630]
20. Gobeze R, et al. High abundance synovial fluid proteome: distinct profiles in health and osteoarthritis. *Arthritis Res Ther.* 2007; 9:R36. [PubMed: 17407561]
21. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum.* 2001; 44:1237–1247. [PubMed: 11407681]
22. Roemer FW, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. *Ann Rheum Dis.* 2011; 70:1804–1809. [PubMed: 21791448]
23. Hill CL, et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis.* 2007; 66:1599–1603. [PubMed: 17491096]
24. Torres L, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage.* 2006; 14:1033–1040. [PubMed: 16713310]
25. Baker K, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. *Ann Rheum Dis.* 2010; 69:1779–1783. [PubMed: 20472593]
26. Scanzello CR, et al. Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship to symptoms. *Arthritis Rheum.* 2011; 63:391–400. [PubMed: 21279996]
27. Krasnokutsky S, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis Rheum.* 2011; 63:2983–2991. [PubMed: 21647860]

28. Sowers M, Karvonen-Gutierrez CA, Jacobson JA, Jiang Y, Yosef M. Associations of anatomical measures from MRI with radiographically defined knee osteoarthritis score, pain, and physical functioning. *J Bone Joint Surg Am.* 2011; 93:241–251. [PubMed: 21266638]
29. Ayrat X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis — results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis Cartilage.* 2005; 13:361–367. [PubMed: 15882559]
30. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskeletal Dis.* 2013; 5:77–94.
31. Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis.* 2005; 64:1263–1267. [PubMed: 15731292]
32. Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: hopes and disappointments. *Nat Rev Rheumatol.* 2013; 9:400–410. [PubMed: 23545735]
33. Husa M, Liu-Bryan R, Terkeltaub R. Shifting HIFs in osteoarthritis. *Nat Med.* 2010; 16:641–644. [PubMed: 20526316]
34. Glasson SS. *In vivo* osteoarthritis target validation utilizing genetically-modified mice. *Curr Drug Targets.* 2007; 8:367–376. [PubMed: 17305514]
35. van Lent PL, et al. Crucial role of synovial lining macrophages in the promotion of transforming growth factor β -mediated osteophyte formation. *Arthritis Rheum.* 2004; 50:103–111. [PubMed: 14730606]
36. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med.* 1988; 109:18–24. [PubMed: 3377350]
37. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. *Curr Opin Rheumatol.* 2013; 25:114–118. [PubMed: 23090672]
38. You T, Nicklas BJ. Chronic inflammation: role of adipose tissue and modulation by weight loss. *Curr Diabetes Rev.* 2006; 2:29–37. [PubMed: 18220615]
39. Beavers KM, et al. Effects of total and regional fat loss on plasma CRP and IL-6 in overweight and obese, older adults with knee osteoarthritis. *Osteoarthritis Cartilage.* 2015; 23:249–256. [PubMed: 25450847]
40. Vincent HK, Heywood K, Connelly J, Hurley RW. Obesity and weight loss in the treatment and prevention of osteoarthritis. *PM R.* 2012; 4(5 Suppl):S59–S67. [PubMed: 22632704]
41. Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. *Clin Immunol.* 2013; 146:185–196. [PubMed: 23360836]
42. Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? *Current opinion in rheumatology.* 2008; 20:565–572. [PubMed: 18698179]
43. Krenn V, et al. Grading of chronic synovitis — a histopathological grading system for molecular and diagnostic pathology. *Pathol Res Pract.* 2002; 198:317–325. [PubMed: 12092767]
44. Slansky E, et al. Quantitative determination of the diagnostic accuracy of the synovitis score and its components. *Histopathology.* 2010; 57:436–443. [PubMed: 20840673]
45. de Lange-Brokaar BJ, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. *Osteoarthritis Cartilage.* 2012; 20:1484–1499. [PubMed: 22960092]
46. Cohen SB, et al. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. *Arthritis Res Ther.* 2011; 13:R125. [PubMed: 21801403]
47. Magnano MD, et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J Rheumatol.* 2007; 34:1323–1327. [PubMed: 17516620]
48. Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis.* 2012; 71:891–898. [PubMed: 22128078]
49. Chevalier X, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 2009; 61:344–352. [PubMed: 19248129]

50. Orlowsky EW, Kraus VB. The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. *J Rheumatol.* 2015; 42:363–371. [PubMed: 25593231]
51. Fearon DT, Locksley RM. The instructive role of innate immunity in the acquired immune response. *Science.* 1996; 272:50–53. [PubMed: 8600536]
52. Holers VM, Thurman JM. The alternative pathway of complement in disease: opportunities for therapeutic targeting. *Mol Immunol.* 2004; 41:147–152. [PubMed: 15159060]
53. Wang Q, et al. Identification of a central role for complement in osteoarthritis. *Nat Med.* 2011; 17:1674–1679. [PubMed: 22057346]
54. Rus H, Cudrici C, Niculescu F. The role of the complement system in innate immunity. *Immunol Res.* 2005; 33:103–112. [PubMed: 16234578]
55. Song WC, Sarrias MR, Lambris JD. Complement and innate immunity. *Immunopharmacology.* 2000; 49:187–198. [PubMed: 10904117]
56. Happonen KE, et al. Regulation of complement by COMP allows for a novel molecular diagnostic principle in rheumatoid arthritis. *Arthritis Rheum.* 2010; 62:3574–3783. [PubMed: 20737467]
57. Sjoberg AP, et al. Short leucine-rich glycoproteins of the extracellular matrix display diverse patterns of complement interaction and activation. *Mol Immunol.* 2009; 46:830–839. [PubMed: 18962898]
58. Sjoberg A, Onnerfjord P, Morgelin M, Heinegard D, Blom AM. The extracellular matrix and inflammation: fibromodulin activates the classical pathway of complement by directly binding C1q. *J Biol Chem.* 2005; 280:32301–32308. [PubMed: 16046396]
59. Moreth K, Iozzo RV, Schaefer L. Small leucine-rich proteoglycans orchestrate receptor crosstalk during inflammation. *Cell Cycle.* 2012; 11:2084–2091. [PubMed: 22580469]
60. Rosenthal AK. Crystals, inflammation, and osteoarthritis. *Curr Opin Rheumatol.* 2011; 23:170–173. [PubMed: 21169842]
61. Sofat N. Analysing the role of endogenous matrix molecules in the development of osteoarthritis. *Int J Exp Pathol.* 2009; 90:463–479. [PubMed: 19765101]
62. Nasi S, et al. Dispensable role of myeloid differentiation primary response gene 88 (MyD88) and MyD88-dependent Toll-like receptors (TLRs) in a murine model of osteoarthritis. *Joint Bone Spine.* 2014; 81:320–324. [PubMed: 24703622]
63. Liu-Bryan R. Synovium and the innate inflammatory network in osteoarthritis progression. *Curr Rheumatol Rep.* 2013; 15:323. [PubMed: 23516014]
64. Rosado CJ, et al. A common fold mediates vertebrate defense and bacterial attack. *Science.* 2007; 317:1548–1551. [PubMed: 17717151]
65. Tschopp J, Masson D, Stanley KK. Structural/functional similarity between proteins involved in complement- and cytotoxic T-lymphocyte-mediated cytolysis. *Nature.* 1986; 322:831–834. [PubMed: 2427956]
66. Bohana-Kashtan O, Ziporen L, Donin N, Kraus S, Fishelson Z. Cell signals transduced by complement. *Mol Immunol.* 2004; 41:583–597. [PubMed: 15219997]
67. Cooke TD, Bennett EL, Ohno O. The deposition of immunoglobulins and complement in osteoarthritic cartilage. *Int Orthop.* 1980; 4:211–217. [PubMed: 7009443]
68. Corvetta A, et al. Terminal complement complex in synovial tissue from patients affected by rheumatoid arthritis, osteoarthritis and acute joint trauma. *Clin Exp Rheumatol.* 1992; 10:433–438. [PubMed: 1458695]
69. Bradley K, et al. Synthesis of classical pathway complement components by chondrocytes. *Immunology.* 1996; 88:648–656. [PubMed: 8881771]
70. Kemper C, Atkinson JP. T-Cell regulation: with complements from innate immunity. *Nat Rev Immunol.* 2007; 7:9–18. [PubMed: 17170757]
71. Lepus CM, et al. Brief report: carboxypeptidase B serves as a protective mediator in osteoarthritis. *Arthritis Rheumatol.* 2014; 66:101–106. [PubMed: 24449579]
72. Boffa MC, Burke B, Haudenschild CC. Preservation of thrombomodulin antigen on vascular and extravascular surfaces. *J Histochem Cytochem.* 1987; 35:1267–1276. [PubMed: 2821107]

73. McCachren SS, Diggs J, Weinberg JB, Dittman WA. Thrombomodulin expression by human blood monocytes and by human synovial tissue lining macrophages. *Blood*. 1991; 78:3128–3132. [PubMed: 1660324]
74. Conway EM, Nowakowski B, Steiner-Mosonyi M. Human neutrophils synthesize thrombomodulin that does not promote thrombin-dependent protein C activation. *Blood*. 1992; 80:1254–1263. [PubMed: 1325211]
75. Leung LL, Myles T, Nishimura T, Song JJ, Robinson WH. Regulation of tissue inflammation by thrombin-activatable carboxypeptidase B (or TAFI). *Mol Immunol*. 2008; 45:4080–4083. [PubMed: 18706698]
76. Sharif SA, et al. Thrombin-activatable carboxypeptidase B cleavage of osteopontin regulates neutrophil survival and synoviocyte binding in rheumatoid arthritis. *Arthritis Rheum*. 2009; 60:2902–2912. [PubMed: 19790060]
77. Benoit ME, Clarke EV, Morgado P, Fraser DA, Tenner AJ. Complement protein C1q directs macrophage polarization and limits inflammasome activity during the uptake of apoptotic cells. *J Immunol*. 2012; 188:5682–5693. [PubMed: 22523386]
78. Foell D, Wittkowski H, Roth J. Mechanisms of disease: a ‘DAMP’ view of inflammatory arthritis. *Nat Clin Pract Rheumatol*. 2007; 3:382–390. [PubMed: 17599072]
79. Blom AB, et al. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. *Arthritis Rheum*. 2007; 56:147–157. [PubMed: 17195217]
80. Bondeson J. Activated synovial macrophages as targets for osteoarthritis drug therapy. *Curr Drug Targets*. 2010; 11:576–585. [PubMed: 20199392]
81. Irani AA, Schechter NM, Craig SS, DeBlois G, Schwartz LB. Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci USA*. 1986; 83:4464–4468. [PubMed: 3520574]
82. Buckley MG, Gallagher PJ, Walls AF. Mast cell subpopulations in the synovial tissue of patients with osteoarthritis: selective increase in numbers of tryptase-positive, chymase-negative mast cells. *J Pathol*. 1998; 186:67–74. [PubMed: 9875142]
83. Gotis-Graham I, McNeil HP. Mast cell responses in rheumatoid synovium. Association of the MCTC subset with matrix turnover and clinical progression. *Arthritis Rheum*. 1997; 40:479–489. [PubMed: 9082936]
84. Nakano S, et al. Distinct expression of mast cell tryptase and protease activated receptor-2 in synovia of rheumatoid arthritis and osteoarthritis. *Clin Rheumatol*. 2007; 26:1284–1292. [PubMed: 17205215]
85. Bridges AJ, et al. Human synovial mast cell involvement in rheumatoid arthritis and osteoarthritis. Relationship to disease type, clinical activity, and antirheumatic therapy. *Arthritis Rheum*. 1991; 34:1116–1124. [PubMed: 1930330]
86. Gruber B, et al. Characterization and functional studies of rheumatoid synovial mast cells. Activation by secretagogues, anti-IgE, and a histamine-releasing lymphokine. *Arthritis Rheum*. 1986; 29:944–955. [PubMed: 2427092]
87. Kopicky-Burd JA, et al. Characterization of human synovial mast cells. *J Rheumatol*. 1988; 15:1326–1333. [PubMed: 2462048]
88. Cooke TD. Significance of immune complex deposits in osteoarthritic cartilage. *J Rheumatol*. 1987; 14:77–79. [PubMed: 3625677]
89. Vargas ME, Watanabe J, Singh SJ, Robinson WH, Barres BA. Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. *Proc Natl Acad Sci USA*. 2010; 107:11993–11998. [PubMed: 20547838]
90. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol*. 2011; 7:33–42. [PubMed: 21119608]
91. Goldring MB, Fukuo K, Birkhead JR, Dudek E, Sandell LJ. Transcriptional suppression by interleukin-1 and interferon- γ of type II collagen gene expression in human chondrocytes. *J Cell Biochem*. 1994; 54:85–99. [PubMed: 8126089]

92. Saklatvala J. Tumour necrosis factor a stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature*. 1986; 322:547–549. [PubMed: 3736671]
93. Attur MG, Patel IR, Patel RN, Abramson SB, Amin AR. Autocrine production of IL-1 β by human osteoarthritis-affected cartilage and differential regulation of endogenous nitric oxide, IL-6, prostaglandin E2, and IL-8. *Proc Assoc Am Physicians*. 1998; 110:65–72. [PubMed: 9460084]
94. Krzeski P, et al. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. *Arthritis Res Ther*. 2007; 9:R109. [PubMed: 17958901]
95. Catterall JB, Cawston TE. Drugs in development: bisphosphonates and metalloproteinase inhibitors. *Arthritis Res Ther*. 2003; 5:12–24. [PubMed: 12716443]
96. Clutterbuck AL, Asplin KE, Harris P, Allaway D, Mobasher A. Targeting matrix metalloproteinases in inflammatory conditions. *Curr Drug Targets*. 2009; 10:1245–1254. [PubMed: 19909233]
97. Endres M, et al. Chemokine profile of synovial fluid from normal, osteoarthritis and rheumatoid arthritis patients: CCL25, CXCL10 and XCL1 recruit human subchondral mesenchymal progenitor cells. *Osteoarthritis Cartilage*. 2010; 18:1458–1466. [PubMed: 20709179]
98. Haringman JJ, Smeets TJ, Reinders-Blankert P, Tak PP. Chemokine and chemokine receptor expression in paired peripheral blood mononuclear cells and synovial tissue of patients with rheumatoid arthritis, osteoarthritis, and reactive arthritis. *Ann Rheum Dis*. 2006; 65:294–300. [PubMed: 16107514]
99. Borzi RM, et al. Human chondrocytes express functional chemokine receptors and release matrix-degrading enzymes in response to C-X-C and C-C chemokines. *Arthritis Rheum*. 2000; 43:1734–1741. [PubMed: 10943863]
100. Miller RJ, Banisadr G, Bhattacharyya BJ. CXCR4 signaling in the regulation of stem cell migration and development. *J Neuroimmunol*. 2008; 198:31–38. [PubMed: 18508132]
101. Haringman JJ, Ludikhuizen J, Tak P. P Chemokines in joint disease: the key to inflammation? *Ann Rheum Dis*. 2004; 63:1186–1194. [PubMed: 15082471]
102. Shen J, Li S, Chen D. TGF- β signaling and the development of osteoarthritis. *Bone Res*. 2014; 2:14002. [PubMed: 25541594]
103. Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF- β and osteoarthritis. *Osteoarthritis Cartilage*. 2007; 15:597–604. [PubMed: 17391995]
104. Ellman MB, et al. Fibroblast growth factor control of cartilage homeostasis. *J Cell Biochem*. 2013; 114:735–742. [PubMed: 23060229]
105. Haywood L, et al. Inflammation and angiogenesis in osteoarthritis. *Arthritis Rheum*. 2003; 48:2173–2177. [PubMed: 12905470]
106. Prencipe G, et al. Nerve growth factor downregulates inflammatory response in human monocytes through TrkA. *J Immunol*. 2014; 192:3345–3354. [PubMed: 24585880]
107. Lane NE, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010; 363:1521–1531. [PubMed: 20942668]
108. Thysen S, Luyten FP, Lories RJ. Targets, models and challenges in osteoarthritis research. *Dis Model Mech*. 2015; 8:17–30. [PubMed: 25561745]
109. Henrotin Y, Pésesse L, Lambert C. Targeting the synovial angiogenesis as a novel treatment approach to osteoarthritis. *Ther Adv Musculoskeletal Dis*. 2014; 6:20–34.
110. de Boer TN, et al. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. *Osteoarthritis Cartilage*. 2012; 20:846–853. [PubMed: 22595228]
111. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? *Br Med Bull*. 2015; 115:111–121. [PubMed: 26179188]
112. Malesud CJ. Biologic basis of osteoarthritis: state of the evidence. *Curr Opin Rheumatol*. 2015; 27:289–294. [PubMed: 25784380]
113. Yusuf E, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis*. 2010; 69:761–765. [PubMed: 19487215]

114. Le Clanche S, Bonnefont-Rousselot D, Sari-Ali E, Rannou F, Borderie D. Inter-relations between osteoarthritis and metabolic syndrome: a common link? *Biochimie*. 2016; 121:238–252. [PubMed: 26700146]
115. Conde J, et al. Adipokines and osteoarthritis: novel molecules involved in the pathogenesis and progression of disease. *Arthritis*. 2011; 2011:203901. [PubMed: 22046513]
116. Gomez R, et al. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol*. 2011; 7:528–536. [PubMed: 21808287]
117. Dumond H, et al. Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum*. 2003; 48:3118–3129. [PubMed: 14613274]
118. Filkova M, et al. Increased serum adiponectin levels in female patients with erosive compared with nonerosive osteoarthritis. *Ann Rheum Dis*. 2009; 68:295–296. [PubMed: 19139213]
119. Francin PJ, et al. Association between adiponectin and cartilage degradation in human osteoarthritis. *Osteoarthritis Cartilage*. 2014; 22:519–526. [PubMed: 24462671]
120. Liao, L., Chen, Y., Wang, W. The current progress in understanding the molecular functions and mechanisms of visfatin in osteoarthritis. *J Bone Miner Metab*. 2016. <http://dx.doi.org/10.1007/s00774-016-0743-1>
121. Koskinen A, Vuolteenaho K, Moilanen T, Moilanen E. Resistin as a factor in osteoarthritis: synovial fluid resistin concentrations correlate positively with interleukin 6 and matrix metalloproteinases MMP-1 and MMP-3. *Scand J Rheumatol*. 2014; 43:249–253. [PubMed: 24780007]
122. Goldring MB, Otero M. Inflammation in osteoarthritis. *Curr Opin Rheumatol*. 2011; 23:471–478. [PubMed: 21788902]
123. Jiang L, Bao J, Zhou X, Xiong Y, Wu L. Increased serum levels and chondrocyte expression of nesfatin-1 in patients with osteoarthritis and its relation with BMI, hsCRP, and IL-18. *Mediators Inflamm*. 2013; 2013:631251. [PubMed: 24259949]
124. Yang S, et al. NAMPT (visfatin), a direct target of hypoxia-inducible factor-2 α , is an essential catabolic regulator of osteoarthritis. *Ann Rheum Dis*. 2015; 74:595–602. [PubMed: 24347567]
125. Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? *Joint Bone Spine*. 2008; 75:669–671. [PubMed: 19028435]
126. Presle N, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. *Osteoarthritis Cartilage*. 2006; 14:690–695. [PubMed: 16527497]
127. Martel-Pelletier J, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. *Semin Arthritis Rheum*. 2003; 33:155–167. [PubMed: 14671726]
128. Wittenberg RH, Willburger RE, Kleemeyer KS, Peskar B. A *In vitro* release of prostaglandins and leukotrienes from synovial tissue, cartilage, and bone in degenerative joint diseases. *Arthritis Rheum*. 1993; 36:1444–1450. [PubMed: 8216404]
129. Casale TB, Abbas MK, Carolan EJ. Degree of neutrophil chemotaxis is dependent upon the chemoattractant and barrier. *Am J Respir Cell Mol Biol*. 1992; 7:112–117. [PubMed: 1320901]
130. He W, Pelletier JP, Martel-Pelletier J, Laufer S, Di Battista JA. Synthesis of interleukin 1 β , tumor necrosis factor- α , and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with antiinflammatory cytokines. *J Rheumatol*. 2002; 29:546–553. [PubMed: 11908571]
131. Peters-Golden M, Henderson WR Jr. Leukotrienes. *N Engl J Med*. 2007; 357:1841–1854. [PubMed: 17978293]
132. Geng Y, Blanco FJ, Cornelisson M, Lotz M. Regulation of cyclooxygenase-2 expression in normal human articular chondrocytes. *J Immunol*. 1995; 155:796–801. [PubMed: 7608556]
133. Li X, et al. Expression and regulation of microsomal prostaglandin E synthase-1 in human osteoarthritic cartilage and chondrocytes. *J Rheumatol*. 2005; 32:887–895. [PubMed: 15868626]
134. Masuko-Hongo K, et al. Up-regulation of microsomal prostaglandin E synthase 1 in osteoarthritic human cartilage: critical roles of the ERK-1/2 and p38 signaling pathways. *Arthritis Rheum*. 2004; 50:2829–2838. [PubMed: 15457451]

135. Kojima F, et al. Membrane-associated prostaglandin E synthase-1 is upregulated by proinflammatory cytokines in chondrocytes from patients with osteoarthritis. *Arthritis Res Ther.* 2004; 6:R355–R365. [PubMed: 15225371]
136. Paredes Y, et al. Study of the role of leukotriene B4 in abnormal function of human subchondral osteoarthritis osteoblasts: effects of cyclooxygenase and/or 5-lipoxygenase inhibition. *Arthritis Rheum.* 2002; 46:1804–1812. [PubMed: 12124864]
137. Scarpignato C, et al. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis — an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Med.* 2015; 13:55. [PubMed: 25857826]
138. Steinhilber D, Hofmann B. Recent advances in the search for novel 5-lipoxygenase inhibitors. *Bas Clin Pharmacol Toxicol.* 2014; 114:70–77.
139. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics. *Osteoarthritis Cartilage.* 2014; 22:609–621. [PubMed: 24632293]
140. Abramson SB. Osteoarthritis and nitric oxide. *Osteoarthritis Cartilage.* 2008; 16(Suppl. 2):S15–S20. [PubMed: 18794013]
141. Palmer RM, Hickery MS, Charles IG, Moncada S, Bayliss MT. Induction of nitric oxide synthase in human chondrocytes. *Biochem Biophys Res Commun.* 1993; 193:398–405. [PubMed: 7684906]
142. McInnes IB, et al. Production of nitric oxide in the synovial membrane of rheumatoid and osteoarthritis patients. *J Exp Med.* 1996; 184:1519–1524. [PubMed: 8879223]
143. Farrell AJ, Blake DR, Palmer RM, Moncada S. Increased concentrations of nitrite in synovial fluid and serum samples suggest increased nitric oxide synthesis in rheumatic diseases. *Ann Rheum Dis.* 1992; 51:1219–1222. [PubMed: 1466599]
144. Hashimoto S, Takahashi K, Amiel D, Coutts RD, Lotz M. Chondrocyte apoptosis and nitric oxide production during experimentally induced osteoarthritis. *Arthritis Rheum.* 1998; 41:1266–1274. [http://dx.doi.org/10.1002/1529-0131\(199807\)41:7<1266::AID-ART18>3.0.CO;2-Y](http://dx.doi.org/10.1002/1529-0131(199807)41:7<1266::AID-ART18>3.0.CO;2-Y). [PubMed: 9663485]
145. Notoya K, et al. 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. [PubMed: 10975859]
146. Scher JU, Pillinger MH, Abramson SB. Nitric oxide synthases and osteoarthritis. *Curr Rheumatol Rep.* 2007; 9:9–15. [PubMed: 17437661]
147. Hellio le Graverand MP, et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNQS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann Rheum Dis.* 2013; 72:187–195. [PubMed: 23144445]
148. Sutton S, et al. The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. *Vet J.* 2009; 179:10–24. [PubMed: 17911037]
149. Meini S, Maggi CA. Knee osteoarthritis: a role for bradykinin? *Inflamm Res.* 2008; 57:351–361. [PubMed: 18787773]
150. Song IH, et al. Contrast-enhanced ultrasound in monitoring the efficacy of a bradykinin receptor 2 antagonist in painful knee osteoarthritis compared with MRI. *Ann Rheum Dis.* 2009; 68:75–83. [PubMed: 18375537]
151. Dudek M, et al. The chondrocyte clock gene *Bmal1* controls cartilage homeostasis and integrity. *J Clin Invest.* 2016; 126:365–376. [PubMed: 26657859]
152. Kc R, et al. Environmental disruption of circadian rhythm predisposes mice to osteoarthritis-like changes in knee joint. *J Cell Physiol.* 2015; 230:2174–2183. [PubMed: 25655021]
153. Gossan N, et al. The circadian clock in murine chondrocytes regulates genes controlling key aspects of cartilage homeostasis. *Arthritis Rheum.* 2013; 65:2334–2345. [PubMed: 23896777]
154. Guo B, et al. Catabolic cytokines disrupt the circadian clock and the expression of clock-controlled genes in cartilage via an NF κ B-dependent pathway. *Osteoarthritis Cartilage.* 2015; 23:1981–1988. [PubMed: 26521744]

155. Honda KK, et al. Different circadian expression of major matrix-related genes in various types of cartilage: modulation by light-dark conditions. *J Biochem.* 2013; 154:373–381. [PubMed: 23940085]
156. Takarada T, et al. Clock genes influence gene expression in growth plate and endochondral ossification in mice. *J Biol Chem.* 2012; 287:36081–36095. [PubMed: 22936800]
157. Gibbs J, et al. An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat Med.* 2014; 20:919–926. [PubMed: 25064128]
158. Nguyen KD, et al. Circadian gene *Bmal1* regulates diurnal oscillations of $Ly6C^{hi}$ inflammatory monocytes. *Science.* 2013; 341:1483–1488. [PubMed: 23970558]
159. Gibbs JE, et al. The nuclear receptor REV-ERB α mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci USA.* 2012; 109:582–587. [PubMed: 22184247]
160. Mobasheri A. The future of osteoarthritis therapeutics: targeted pharmacological therapy. *Curr Rheumatol Rep.* 2013; 15:364. [PubMed: 24061701]
161. Mobasheri A. The future of osteoarthritis therapeutics: emerging biological therapy. *Curr Rheumatol Rep.* 2013; 15:385. [PubMed: 24170255]
162. Hunter DJ. Are there promising biologic therapies for osteoarthritis? *Curr Rheumatol Rep.* 2008; 10:19–25. [PubMed: 18457607]
163. Pelletier JP, et al. Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKQIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss. *Ann Rheum Dis.* 2015; 74:422–429. [PubMed: 24297379]
164. Reginster JY, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann Rheum Dis.* 2013; 72:179–186. [PubMed: 23117245]
165. Pelletier JP, et al. Strontium ranelate reduces the progression of experimental dog osteoarthritis by inhibiting the expression of key proteases in cartilage and of IL-1 β in the synovium. *Ann Rheum Dis.* 2013; 72:250–257. [PubMed: 23065732]
166. Tat SK, Pelletier JP, Mineau F, Caron J, Martel-Pelletier J. Strontium ranelate inhibits key factors affecting bone remodeling in human osteoarthritic subchondral bone osteoblasts. *Bone.* 2011; 49:559–567. [PubMed: 21700005]
167. Lafeber FP, van Laar JM. Strontium ranelate: ready for clinical use as disease-modifying osteoarthritis drug? *Ann Rheum Dis.* 2013; 72:157–161. [PubMed: 23292449]
168. Felson DT. Developments in the clinical understanding of osteoarthritis. *Arthritis Res Ther.* 2009; 11:203. [PubMed: 19232065]
169. Midwood K, et al. Tenascin-C is an endogenous activator of Toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. *Nat Med.* 2009; 15:774–780. [PubMed: 19561617]
170. van Lent PL, et al. Active involvement of alarmins S100A8 and S100A9 in the regulation of synovial activation and joint destruction during mouse and human osteoarthritis. *Arthritis Rheum.* 2012; 64:1466–1476. [PubMed: 22143922]
171. Schelbergen RF, et al. Alarmins S100A8/S100A9 aggravate osteophyte formation in experimental osteoarthritis and predict osteophyte progression in early human symptomatic osteoarthritis. *Ann Rheum Dis.* 2016; 75:218–225. [PubMed: 25180294]
172. Joosten LA, Helsen MM, van de Loo FA, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice: a comparative study using anti-TNF α , anti-IL-1 α/β and IL-1Ra. *Arthritis Rheum.* 2008; 58:S110–122. [PubMed: 18240201]
173. Rudolph K, Gerwin N, Verzijl N, van der Kraan P, van den Berg W. Pralnacasan, an inhibitor of interleukin-1 β converting enzyme, reduces joint damage in two murine models of osteoarthritis. *Osteoarthritis Cartilage.* 2003; 11:738–746. [PubMed: 13129693]
174. Zhang Q, Lv H, Chen A, Liu F, Wu X. Efficacy of infliximab in a rabbit model of osteoarthritis. *Connect Tissue Res.* 2012; 53:355–358. [PubMed: 22288847]
175. Urech DM, et al. Anti-inflammatory and cartilage-protecting effects of an intra-articularly injected anti-TNF α single-chain Fv antibody (ESBA105) designed for local therapeutic use. *Ann Rheum Dis.* 2010; 69:443–449. [PubMed: 19293161]

176. Koewler NJ, et al. Effects of a monoclonal antibody raised against nerve growth factor on skeletal pain and bone healing after fracture of the C57BL/6J mouse femur. *J Bone Miner Res.* 2007; 22:1732–1742. [PubMed: 17638576]
177. Moore EE, et al. Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. *Osteoarthritis Cartilage.* 2005; 13:623–631. [PubMed: 15896984]
178. Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy. *Nat Rev Rheumatol.* 2014; 10:11–22. [PubMed: 24189839]
179. Ou Y, et al. Selective COX-2 inhibitor ameliorates osteoarthritis by repressing apoptosis of chondrocyte. *Med Sci Monit.* 2012; 18:247–252.
180. Bresalier RS, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005; 352:1092–1102. [PubMed: 15713943]
181. Drazen JM. COX-2 inhibitors — a lesson in unexpected problems. *N Engl J Med.* 2005; 352:1131–1132. [PubMed: 15713947]
182. Nussmeier NA, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med.* 2005; 352:1081–1091. [PubMed: 15713945]
183. Solomon SD, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005; 352:1071–1080. [PubMed: 15713944]
184. Riendeau D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther.* 2001; 296:558–566. [PubMed: 11160644]
185. Song GG, et al. Relative efficacy and tolerability of etoricoxib, celecoxib, and naproxen in the treatment of osteoarthritis: a Bayesian network meta-analysis of randomized controlled trials based on patient withdrawal. *Z Rheumatol.* 2016; 75:508–516. [PubMed: 26768273]
186. Croom KF, Siddiqui MA. Etoricoxib: a review of its use in the symptomatic treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gouty arthritis. *Drugs.* 2009; 69:1513–1532. [PubMed: 19634927]
187. Ratcliffe A, et al. The *in vivo* effects of naproxen on canine experimental osteoarthritic articular cartilage: composition, metalloproteinase activities and metabolism. *Agents Actions Suppl.* 1993; 39:207–211. [PubMed: 8456630]
188. Svensson O, Malmenas M, Fajutrao L, Roos EM, Lohmander LS. Greater reduction of knee than hip pain in osteoarthritis treated with naproxen, as evaluated by WOMAC and SF-36. *Ann Rheum Dis.* 2006; 65:781–784. [PubMed: 16269428]
189. Coxib and traditional NSAID Trialists' (CNT) Collaboration, et al. Vascular and upper gastrointestinal effects of non-steroidal antiinflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013; 382:769–779. [PubMed: 23726390]
190. Masferrer JL, et al. Pharmacology of PF-4191834, a novel, selective non-redox 5-lipoxygenase inhibitor effective in inflammation and pain. *J Pharmacol Exp Ther.* 2010; 334:294–301. [PubMed: 20378715]
191. Jovanovic DV, et al. In vivo dual inhibition of cyclooxygenase and lipoxygenase by ML-3000 reduces the progression of experimental osteoarthritis: suppression of collagenase 1 and interleukin-1 β synthesis. *Arthritis Rheum.* 2001; 44:2320–2330. [PubMed: 11665972]
192. Raynauld JP, et al. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis.* 2009; 68:938–947. [PubMed: 18653484]
193. Bitto A, et al. Flavocoxid, a nutraceutical approach to blunt inflammatory conditions. *Mediators Inflamm.* 2014; 2014:790851. [PubMed: 25242871]
194. Levy RM, et al. Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects with osteoarthritis of the knee. *Adv Ther.* 2010; 27:731–742. [PubMed: 20845002]
195. Chalasani N, et al. Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: a case series. *Ann Intern Med.* 2012; 156:857–860. [PubMed: 22711078]

196. Stefanovic-Racic M, et al. *N*-Monomethyl arginine, an inhibitor of nitric oxide synthase, suppresses the development of adjuvant arthritis in rats. *Arthritis Rheum.* 1994; 37:1062–1069. [PubMed: 7517676]
197. McCartney-Francis N, et al. Suppression of arthritis by an inhibitor of nitric oxide synthase. *J Exp Med.* 1993; 178:749–754. [PubMed: 7688035]
198. Miyasaka N, Hirata Y. Nitric oxide and inflammatory arthritides. *Life Sci.* 1997; 61:2073–2081. [PubMed: 9395248]
199. More AS, et al. Effect of iNOS inhibitor *S*-methylisothiourea in monosodium iodoacetate-induced osteoarthritic pain: implication for osteoarthritis therapy. *Pharmacol Biochem Behav.* 2013; 103:764–772. [PubMed: 23287799]
200. Brewster M, Lewis EJ, Wilson KL, Greenham AK, Bottomley KM. Ro 32-3555, an orally active collagenase selective inhibitor, prevents structural damage in the STR/ORT mouse model of osteoarthritis. *Arthritis Rheum.* 1998; 41:1639–1644. [PubMed: 9751097]
201. Close DR. Matrix metalloproteinase inhibitors in rheumatic diseases. *Ann Rheum Dis.* 2001; 60(Suppl. 3):62–67.
202. Fujisawa T, et al. Highly water-soluble matrix metalloproteinases inhibitors and their effects in a rat adjuvant-induced arthritis model. *Bioorg Med Chem.* 2002; 10:2569–2581. [PubMed: 12057646]
203. Janusz MJ, et al. Moderation of iodoacetate-induced experimental osteoarthritis in rats by matrix metalloproteinase inhibitors. *Osteoarthritis Cartilage.* 2001; 9:751–760. [PubMed: 11795995]
204. Lewis EJ, et al. Ro 32-3555, an orally active collagenase inhibitor, prevents cartilage breakdown *in vitro* and *in vivo*. *Br J Pharmacol.* 1997; 121:540–546. [PubMed: 9179398]

Key points

- Osteoarthritis (OA) represents the failure of the joint as an organ
- Synovitis is increasingly recognized as a characteristic of the OA joint, and its presence is associated with increased severity of symptoms, joint dysfunction, and cartilage loss
- Studies in humans and animal models demonstrate a key role for chronic, low-grade inflammation in the pathogenesis of OA
- Innate immune pathways, such as the complement and pattern-recognition receptor pathways, are pivotal to the inflammation in OA
- Clinical trials are needed to determine whether anti-inflammatory therapeutics can prevent or slow disease progression in OA

Box 1**Low-grade inflammation in OA**

- Synovitis, indicated by synovial hyperplasia and low-grade inflammatory infiltrates within the synovial lining, is frequently observed in OA
- The inflammation in OA is chronic, low-grade, and differs in its clinical presentations and underlying mechanisms from the ‘high-grade’ inflammation in RA
- Inflammation in OA involves the interplay of the innate immune system and inflammatory mediators, offering opportunities for developing DMOADs for OA

DMOADs, disease-modifying OA drugs; OA, osteoarthritis; RA, rheumatoid arthritis.

Box 2**Inflammatory mechanisms in OA**

- Joint damage, which occurs most often in individuals with risk factors such as advanced age, prior joint injuries, or obesity, triggers an immune response that results in chronic, low-grade inflammation and, ultimately, development of clinical OA
- Key components of the innate immune system implicated in OA include DAMP-TLR signalling, the complement system, CPB, macrophages, and mast cells
- Inflammatory mediators associated with OA include cytokines, chemokines, growth factors, adipokines, prostaglandins, leukotrienes, nitric oxide, and neuropeptides
- Disruption of circadian rhythms might also contribute to the development of OA
- A number of agents that target inflammatory components have shown promise in animal models, but their therapeutic potential in human OA remains to be tested in clinical trials

CPB, carboxypeptidase B; DAMPs, damage-associated molecular patterns; OA, osteoarthritis.

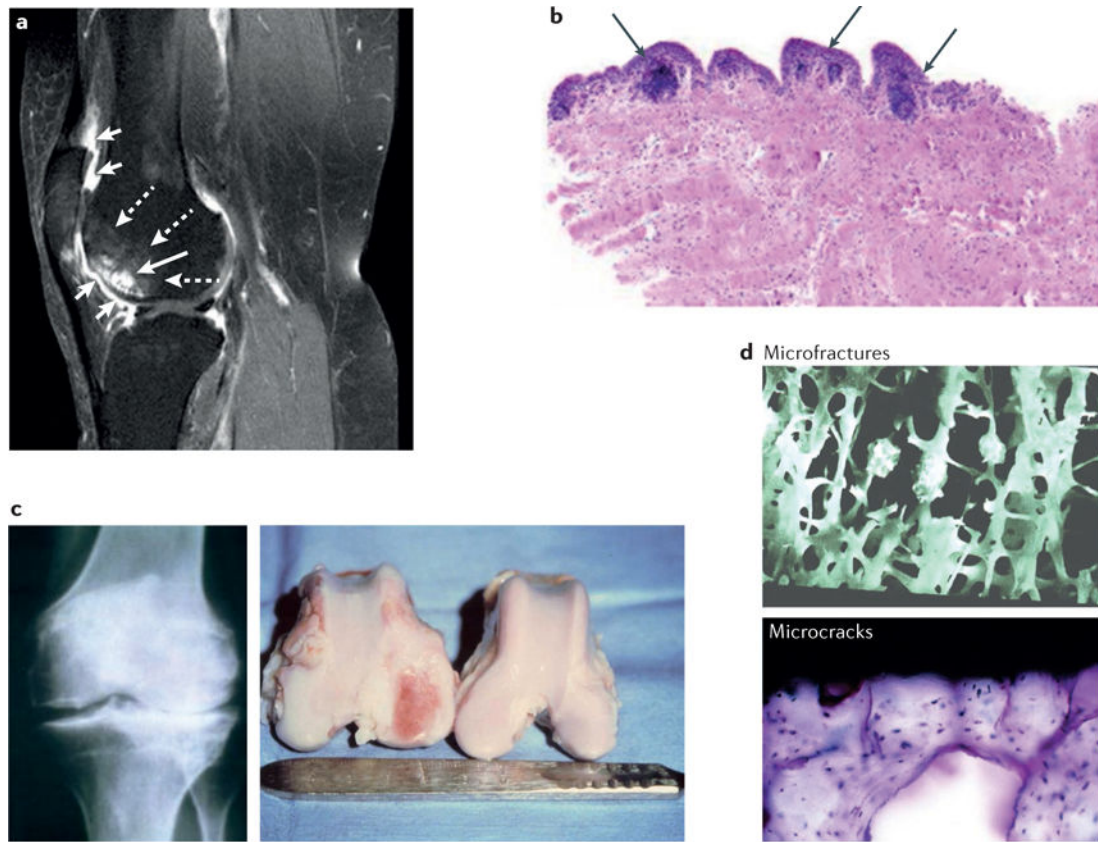


Figure 1. Radiographic and histologic findings in OA: evidence of inflammation and bone remodelling

a | Gadolinium-enhanced MRI (sagittal view) scan of a knee with multiple features typical of OA: synovial inflammation, cartilage degradation, and bone remodelling. Short white arrows indicate marked peripatellar synovitis, dashed white arrows indicate bone marrow lesions, and the long white arrow pointing to bright white structures indicates bone cysts. **b** | A synovial biopsy specimen obtained during meniscectomy from a patient with knee OA, showing histological evidence of inflammation. Arrows indicate the presence of perivascular mononuclear cell accumulation. Original magnification $\times 5$, haematoxylin and eosin stain. **c** | Remodelling of the subchondral bone in OA, as detected by radiography of the knee of an individual with OA (left), and by gross examination of distal femurs of a dog (right) that had undergone unilateral anterior cruciate ligament transection. In the destabilized dog knee, full-thickness ulceration of the articular cartilage has developed on the medial femoral condyle, and striking remodelling of the subchondral bone has occurred, with enlargement of the medial femoral condyle. The articular cartilage and bone on the contralateral dog knee appear grossly normal. **d** | Microfractures and microcracks in subchondral bone of an individual with OA. Part **a** adapted from Felson, D. T. Developments in the clinical understanding of osteoarthritis. *Arthritis Res. Ther.* 11, 203 (2009)¹⁶⁸. The original article is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Part **b** reproduced from Scanzello, C. R. *et al.* Synovial inflammation in patients undergoing

arthroscopic meniscectomy: molecular characterization and relationship to symptoms. *Arthritis Rheum.* 63, 391–400 (2011)²⁶. Parts **c**, **d** reproduced from Brandt, K. D., Dieppe, P. & Radin, E. L. Commentary: is it useful to subset “primary” osteoarthritis? A critique based on evidence regarding the etiopathogenesis of osteoarthritis. *Semin. Arthritis Rheum.* 39, 81–95 (2009)¹¹.

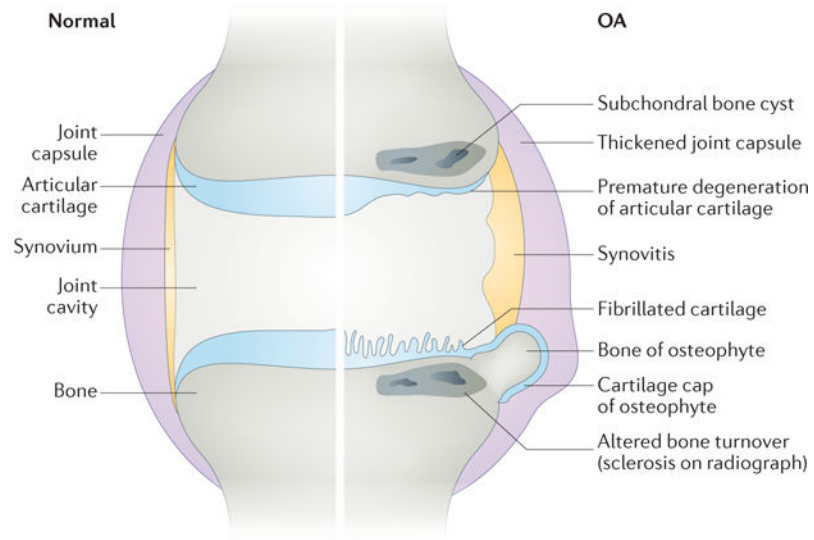


Figure 2. The pathobiology of OA

Comparison of the normal joint (left side) and the OA joint (right side), demonstrating that OA is a disease that affects the entire joint structure, including the articular cartilage, synovium, subchondral bone, joint capsule, and other components of the joint.

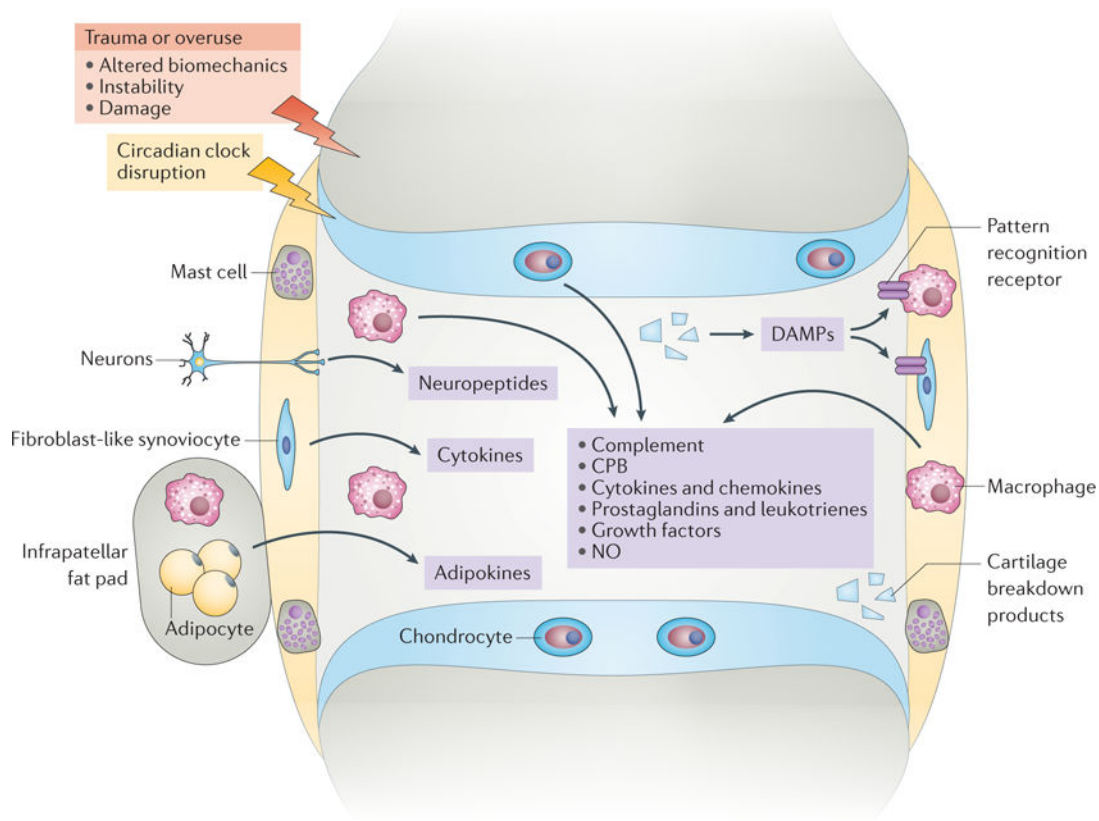


Figure 3. The molecular mechanisms of low-grade inflammation in OA

Several inflammatory pathways and mechanisms are likely to contribute to the pathogenesis of OA. In this paradigm, injury or overuse, often in the context of other risk factors, triggers a vicious cycle of local tissue damage, failed tissue repair, and low-grade inflammation involving a number of molecular components and mechanisms in the joint. This low-grade inflammation contributes to or mediates progressive cartilage loss, pain, and joint dysfunction. CPB, carboxypeptidase B; DAMPs, disease-associated molecular patterns; NO, nitric oxide.

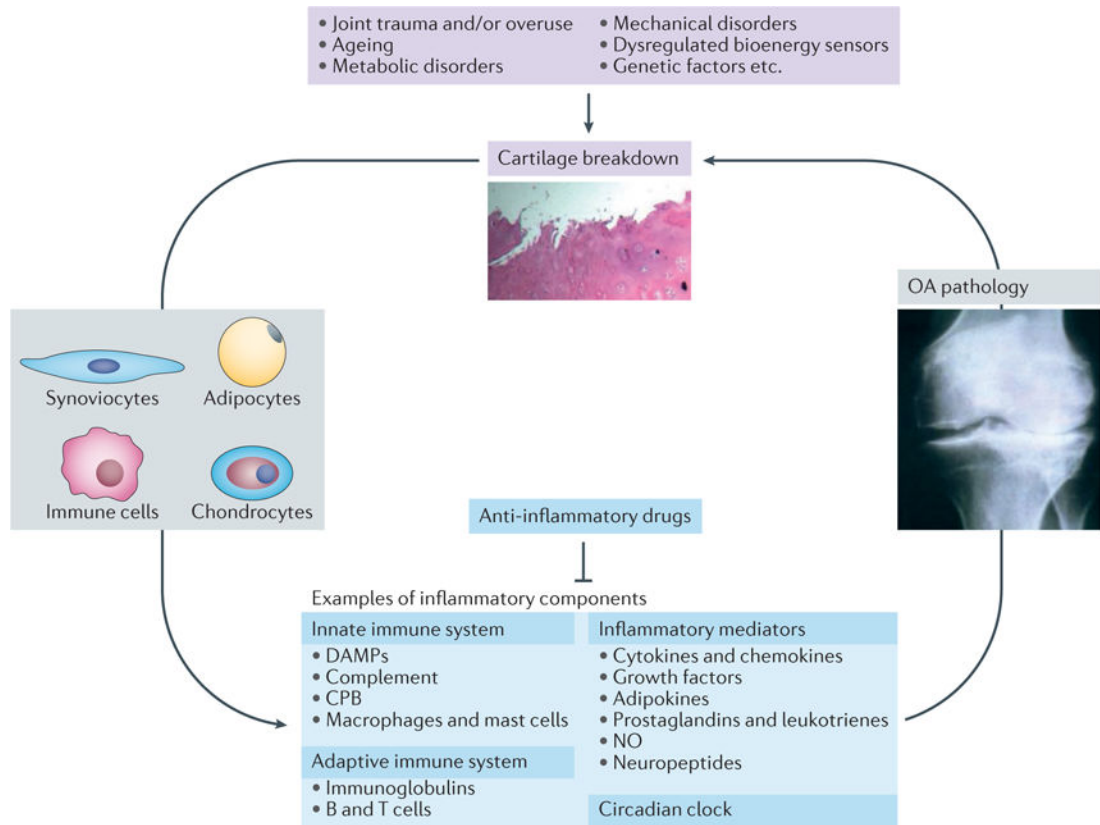


Figure 4. Targeting low-grade inflammation in OA

Can abrogating low-grade inflammatory responses break the feed-forward cycle of joint damage and breakdown leading to inflammation that promotes the pathogenesis of OA? Examples of risk factors for OA, cell types involved in its pathogenesis, and molecular components in the inflammatory pathways that are potential therapeutic targets for preventing or treating OA are shown. CPB, carboxypeptidase B; DAMPs, disease-associated molecular patterns; NO, nitric oxide; OA, osteoarthritis.

Table 1

Examples of genetic and pharmacologic manipulations targeting inflammation in OA

Target	Effects on OA in animal models	Effects on OA in human trials
Tenascin C	<i>Tnc</i> ^{-/-} mice showed resolution of acute joint inflammation and were protected from sustained and erosive joint inflammation; intra-articular injection of tenascin C promoted inflammation ¹⁶⁹	Not tested
S100A8, S100A9	<i>S100A9</i> ^{-/-} mice (also lacking S100A8 at protein level) showed reduced synovial activation, osteophyte formation, and OA cartilage destruction ^{170,171}	Not tested
C5	C5 ⁻ mice showed less cartilage loss, osteophyte formation, and synovitis; treatment with an anti-C5 monoclonal antibody or CR2-rh (a fusion protein that inhibits C3 and C5) attenuated OA ⁵³	Not tested
C6	C6 ⁻ mice were protected from OA development and synovitis ⁵³	Not tested
CD59a	Cd59a ^{-/-} mice developed more severe OA and synovitis ⁵³	Not tested
IL-1 β	Anti-IL-1 β treatment reduced infiltration of inflammatory cells and cartilage damage in collagen-induced arthritis ¹⁷² ; pralnacasan (inhibitor of IL-1 β converting enzyme) reduced OA ¹⁷³	IL-1 β blockade associated with liver toxicity or lack of DMOAD efficacy ^{46,49}
TNF	Intra-articular injection of infliximab (an anti-TNF monoclonal antibody) attenuated OA pathological changes ¹⁷⁴ ; ESBA105 (an anti-TNF scFv antibody) inhibited inflammation and prevented TNF-induced cartilage damage ¹⁷⁵	Lack of DMOAD efficacy in generalized OA; no or minimal benefit in erosive OA ^{47,48}
NGF	An anti-NGF monoclonal antibody improved pain in a fracture model ¹⁷⁶	Treatment with tanezumab (an anti-NGF monoclonal antibody) improved symptoms of OA ¹⁰⁷
FGF18	Intra-articular injection of FGF18 stimulated chondrogenesis and cartilage repair ¹⁷⁷	Trial of intra-articular injection of FGF18 ongoing ¹⁷⁸
COX2	Celecoxib (a COX2 inhibitor) reduced OA-like histological changes and suppressed chondrocyte apoptosis ¹⁷⁹	Celecoxib and rofecoxib (COX2 inhibitors) were associated with cardiovascular toxicity and other adverse effects ¹⁸⁰⁻¹⁸³
	Etoricoxib (a COX2 inhibitor) inhibited acute inflammation and adjuvant-induced arthritis ¹⁸⁴	Etoricoxib improved symptoms of OA ^{185,186}
COX1, COX2	Naproxen (a non-selective COX inhibitor) suppressed MMP activities and the decrease in proteoglycan content ¹⁸⁷	Naproxen improved pain associated with knee OA more than hip OA ¹⁸⁸ , but was associated with upper gastrointestinal complications ¹⁸⁹
5LO	PF-4191834 (a 5LO inhibitor) reduced OA inflammation and pain ¹⁹⁰	Phase II study of PF-4191834 was terminated owing to serious adverse events ¹³⁸
COX1, COX2, 5LO	Licofelone (a COX and 5LO inhibitor) attenuated the progression of OA ¹⁹¹	Licofelone improved OA symptoms and reduced cartilage volume loss ¹⁹²
	Flavocoxid (a COX and 5LO inhibitor) improved inflammatory conditions ¹⁹³	Flavocoxid improved OA symptoms ¹⁹⁴ , but was associated with acute liver injuries ¹⁹⁵
Bradykinin	Icatibant (a bradykinin B ₂ receptor antagonist) reduced inflammation ¹⁴⁹	Icatibant showed an analgesic effect on knee OA ¹⁴⁹ , but no detectable anti-inflammatory effects ¹⁵⁰
CPB	<i>Cpb2</i> ^{-/-} mice showed more severe cartilage damage, osteophyte formation, and synovitis ⁷¹	Not tested
NO, iNOS	L-NMMA (a broad NOS inhibitor) reduced synovial inflammation and tissue damage in animal models of arthritis ¹⁹⁶⁻¹⁹⁸ ; <i>S</i> -methylisothiourea attenuated MIA-induced pain and histopathological changes in the knee joint ¹⁹⁹	Cindunostat (an iNOS inhibitor) failed to slow progression of OA ¹⁴⁷
MMPs	MMP inhibitors prevented the destruction of articular cartilage and bone ²⁰⁰⁻²⁰⁴	PG-116800 (an MMP inhibitor) failed to show benefit and was associated with the development of musculoskeletal toxicity ⁹⁴

Target	Effects on OA in animal models	Effects on OA in human trials
IL-1 β , MMPs	Strontium ranelate reduced the progression of OA structural changes ¹⁶⁵	Strontium ranelate showed disease-modifying effects ¹⁶³

5LO, arachidonate 5-lipoxygenase; COX, cyclooxygenase; CPB, carboxypeptidase B; DMOAD, disease-modifying OA drug; FGF18, fibroblast growth factor 18; LTB4, leukotriene B4; iNOS, inducible NO synthase; L-NMMA, N^G-monomethyl-L-arginine; MIA, monosodium iodoacetate; MMPs, matrix metalloproteinase; NGF, nerve growth factor; NO, nitric oxide; NOS, NO synthase; OA, osteoarthritis; scFv, single-chain variable fragment.