Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations

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Abstract: Osteoarthritis (OA) has traditionally been classified as a noninflammatory arthritis; however, the dichotomy between inflammatory and degenerative arthritis is becoming less clear with the recognition of a plethora of ongoing immune processes within the OA joint and synovium. Synovitis is defined as inflammation of the synovial membrane and is characteristic of classical inflammatory arthritidies. Increasingly recognized is the presence of synovitis in a significant proportion of patients with primary OA, and based on this observation, further studies have gone on to implicate joint inflammation and synovitis in the pathogenesis of OA. However, clinical OA is not one disease but a final common pathway secondary to many predisposing factors, most notably age, joint trauma, altered biomechanics, and obesity. How such biochemical and mechanical processes contribute to the progressive joint failure characteristic of OA is tightly linked to the interplay of joint damage, the immune response to perceived damage, and the subsequent state of chronic inflammation resulting in propagation and progression toward the phenotype recognized as clinical OA. This review will discuss a wide range of evolving data leading to our current hypotheses regarding the role of immune activation and inflammation in OA onset and progression. Although OA can affect any joint, most commonly the knee, hip, spine, and hands, this review will focus primarily on OA of the knee as this is the joint most well characterized by epidemiologic, imaging, and translational studies investigating the association of inflammation with OA.

Keywords: Osteoarthritis, inflammation, innate Immunity

Introduction

The classification of osteoarthritis (OA) as a noninflammatory arthritis is an unfortunate consequence of early observations noting fewer leukocytes in OA synovial fluid compared with that of rheumatoid arthritis (RA), reactive arthritis, and even septic arthritis. In spite of this classification, investigators decades ago observed synovial inflammation in so-called 'post-traumatic' synovitis [Soren *et al.* 1976], and similar histopathology has been described among at least a subset of patients with what is now designated primary OA. Given this greater appreciation for synovitis in patients with OA, inflammation has now been strongly implicated in the pathogenesis of OA [Scanzello and Goldring, 2012]. This is not to imply that all OA pathogenesis is related to the synovium. Rather, synovitis is likely a secondary process induced by innate immune activation following cartilage

damage that provides a critical link in the chain of initiation and propagation of OA.

OA is associated with multiple risk factors, most notably age, joint trauma, altered biomechanics, and obesity [Felson, 2006]. Given its complex etiology, OA should not be thought of as a single disease, but rather as the clinical endpoint of numerous disorders leading to the eventual failure of one or more joints of the body. In fact, evidence suggests that the pathologic changes characteristic of OA share a common final pathway that operates to perpetuate joint destruction and eventual failure. The key features of this common final pathway linking biochemical and mechanical processes to progressive joint failure are the subject of this review. Focus will be devoted to the interaction between local tissue damage and the immune system, which

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ultimately leads to a state of low-grade, chronic joint inflammation that drives progression toward the phenotype recognized as clinical OA.

Unlike RA, in which disease-modifying antirheumatic drugs (DMARDs) have revolutionized treatment [Singh *et al.* 2012], therapies used to manage OA are limited to pain control, with no agent to date approved for the prevention or treatment of OA disease progression. Given the high disability burden among patients with OA, there is great need to develop disease-modifying osteoarthritic drugs (DMOADs), and increased understanding of the inflammatory pathways leading to the onset and progression of OA could enable development of targeted therapies.

### Understanding osteoarthritis as an inflammatory disease

Perhaps the first step in understanding OA as an inflammatory disease is to acknowledge that inflammation is not exclusive to RA and the other classical inflammatory arthritidies. Early studies in RA, using OA tissues and fluids as a comparator, noted dramatically increased levels of inflammatory proteins in RA [Farahat *et al.* 1993; Nettelbladt and Sundblad, 1959; Smith *et al.* 1997]. Although largely overshadowed by more pronounced histologic and biochemical abnormalities in RA, even some of these historic studies from as early as 1959 revealed elevated levels of inflammatory plasma proteins in both the blood and synovial fluid of patients with OA [Nettelbladt and Sundblad, 1959: 148]. The authors suggested that, 'This may indicate that the type of permeability change in the synovial tissue is similar in both diseases (OA and RA), although this change is much more marked in rheumatoid arthritis' [Nettelbladt and Sundblad, 1959: 148]. The frequent use of OA fluids and tissues as controls for RA has arguably reinforced the pervasive notion of OA as a noninflammatory arthritis, perhaps leading to the oversight that OA tissue and synovial fluid, when compared with 'normal' fluid or tissue, is highly enriched for plasma proteins, complement components [Gobezie *et al.* 2007], and cytokines [Sohn *et al.* 2012]. In more recent years the field has come to appreciate that, at least in some cases, levels of synovitis between OA and RA tissue can appear nearly indistinguishable [Haraoui *et al.* 1991]. These paradigm-changing studies have freed OA from its reputation as anoninflammatory, 'wear and tear' arthritis, likely transforming the ways in which researchers and clinicians think about and treat the disease.

Using modern tools and techniques, our group has further characterized inflammatory mediators in OA and RA synovial fluid as well as OA, RA, and normal serum [Sohn *et al.* 2012]. Our findings mirrored those of Nettelbladt and Sundblad [Nettelbladt and Sundblad, 1959]. Figure 1 is a heatmap demonstrating a stepwise increase in levels of inflammatory cytokines from normal plasma, to OA plasma, to OA synovial fluid, to RA plasma, and finally to RA synovial fluid. Although RA is clearly associated with higher levels of inflammation, OA is by no means a 'noninflammatory' condition.

Several other studies lend additional support to the observation that systemic inflammation is associated with OA. These include key epidemiologic analyses demonstrating that serum levels of C-reactive protein (CRP) are strongly associated with the presence and progression of knee OA [Spector *et al.* 1997]. Additional studies have impressively demonstrated a positive correlation between levels of serum CRP and histologic evidence of synovitis and synovial fluid interleukin-6 (IL-6) at the time of joint replacement [Pearle *et al.* 2007]. These observations strongly suggest that the systemic inflammation observed in OA is at least partially reflective of local synovial inflammation.

Early osteoarthritis: synovial inflammation precedes structural change

The field of clinical rheumatology often considers OA to be the condition manifest by significant cartilage loss and joint space narrowing. In fact, the current American College of Rheumatology classification criteria for OA require the presence of radiographic changes of bony enlargement or osteophyte formation [Altman *et al.* 1986]. It is now clear that inflammation is present in OA joints well before the development of significant radiographic change. The combination of sensitive imaging modalities as well as direct arthroscopic visualization has suggested that, even at its earliest stages, before visible cartilage degeneration has occurred, OA is already an inflammatory disease. In one study, serial arthroscopies performed on knees with symptomatic but preradiographic OA revealed a clear association between the presence of synovitis and the future development of medial cartilage loss [Ayral *et al.* 2005]. Studies using magnetic resonance imaging (MRI) with or without contrast enhancement have similarly suggested an association between the
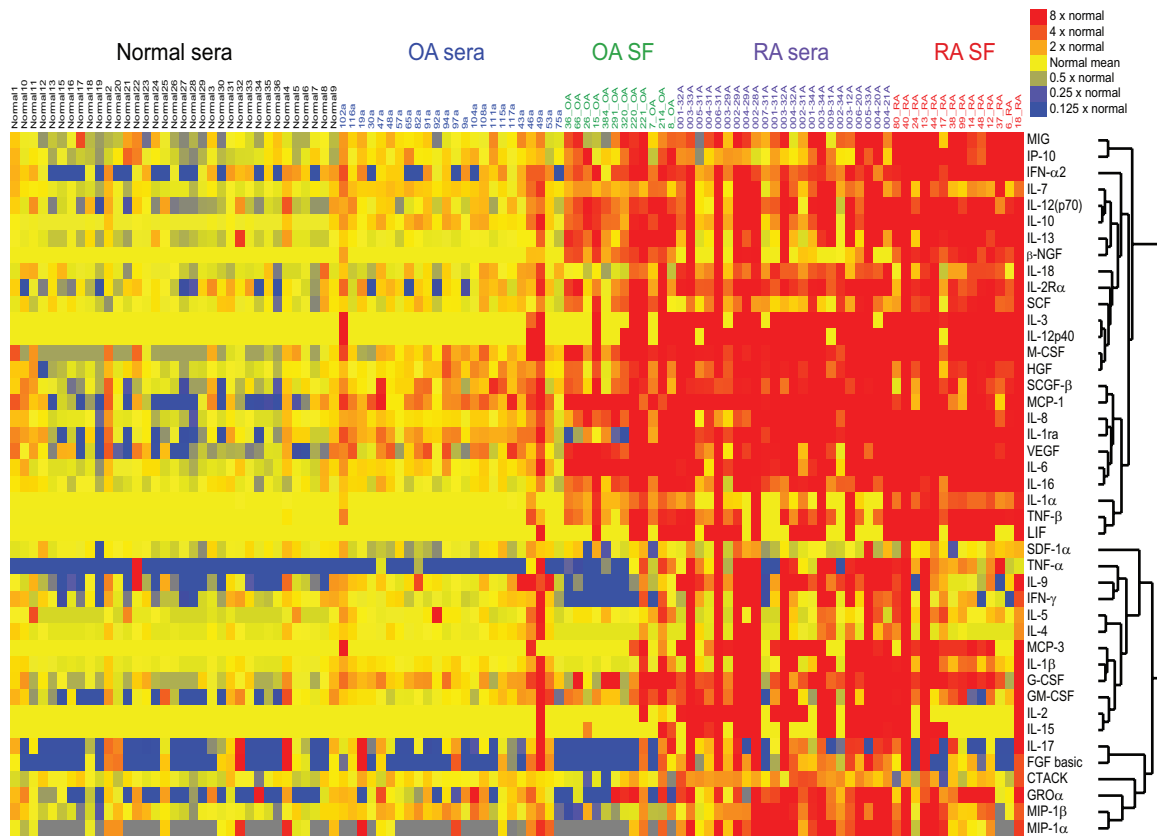
From Sohn et al, 2012.

Figure 1. Inflammatory cytokines are associated with osteoarthritis. Relative cytokine levels in serum and synovial fluid (SF) samples from patients with osteoarthritis (OA) or rheumatoid arthritis (RA) and in serum samples from healthy individuals (normal sera). Cytokine levels were measured with a multiplex bead-based immunoassay. Samples from individual patients are listed above the heatmap, and the individual cytokines are listed to the right of the heatmap. β-NGF, β nerve growth factor; CTACK, cutaneous T-cell attracting chemokine; FGF, fibroblast growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; GROα, growth-regulated oncogene α; G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; IL-2Rα, interleukin-2 receptor α chain; IP-10, interferon γ induced protein 10; LIF, leukemia inhibitory factor; MCP, monocyte chemotactic protein; M-CSF, macrophage colony-stimulating factor; MIG, monokine induced by interferon γ; MIP-1, macrophage inflammatory protein; SCF, stem cell factor; SCGF-β, stem cell growth factor β; SDF-1α, stromal cell-derived factor 1α; VEGF, vascular endothelial growth factor. (Reproduced from Sohn et al. [2012] with permission).

presence of synovitis and OA progression [Krasnokutsky et al. 2011; Felson et al. 2003; Roemer et al. 2011].

Several additional studies support the observation of inflammation in the earliest phases of OA. In one study of 70 synovial tissues spanning a range of radiographic OA severity, severe synovial inflammation was observed in 31% of patients. Notably, synovial inflammation was present in many subjects with minimal radiographic disease [Haywood et al. 2003]. Benito and colleagues went on to compare early and late OA and demonstrated increased mononuclear cell infiltration

and overexpression of inflammatory mediators in early compared with late disease [Benito et al. 2005]. Finally, in a cohort of patients without evidence of radiographic OA who were undergoing arthroscopic meniscectomy to repair traumatic meniscal injury, synovial inflammation was noted in 43% of patients and was associated with more severe preoperative pain and function scores [Scanzello et al. 2011]. These studies, demonstrating significant synovial inflammation in early OA, suggest a window of opportunity may exist in which disease-modifying interventions targeting inflammatory processes might be most efficacious for the prevention and treatment of OA.

Although the synovium is not the only tissue involved in OA-related inflammation, it is a major site of gross and microscopic inflammatory change [Sellam and Berenbaum, 2010] and is thus a major focus of this review. The synovium is normally two to three cell layers thick with notable lack of inflammatory cells. However, in the setting of inflammation there is often marked hyperplasia of the synovial lining cells with an infiltration of inflammatory cells consisting primarily of macrophages but also a smaller but quantifiable number of T and B cells [Bondeson *et al.* 2010], mast cells [Dean *et al.* 1993] and natural killer cells [Skrzeczynska-Moncznik *et al.* 2009]. Notably, the degree of infiltration is highly heterogeneous; some patients possess inflammation resembling that observed in RA, while others exhibit a minimally inflammatory and primarily degenerative histopathology [Benito *et al.* 2005].

It should be noted that the critical role of synovitis in no way excludes involvement of cartilage and the chondrocyte in the pathogenesis of either early or late OA. Cartilage breakdown products in synovial fluid as well as microfissures in articular cartilage are present long before any degeneration can be noted using current MRI technology or gross arthroscopic visualization [Mow *et al.* 1974; Pauli *et al.* 2011]. As discussed later, early cartilage degradation events may in fact play a driving role in the development of inflammation within the OA joint and specifically the OA synovium.

Chronic, low-grade inflammation sets the stage for chronic disease

Data are evolving to suggest that in a significant subset of patients with OA, chronic low-grade inflammation is a major driver of ongoing joint degeneration. It is additionally becoming clear that many of the physiologic maladies of aging are at least associated, if not directly related, to chronic low-grade inflammation. In atherosclerosis, chronic inflammation perpetuates and expands within the atherosclerotic plaque resulting in eventual plaque rupture and acute vascular events such as myocardial infarction or stroke [Libby, 2002]. Similarly, periodontitis is a chronic inflammatory process resulting not only in tooth loss but also in potentially increased rates of atherosclerotic cardiovascular disease, presumably related to locally initiated systemic inflammation [Hasturk *et al.* 2012]. Two additional degenerative diseases common with advancing age and associated with innate immune activation and low-grade inflammation are age-related macular degeneration [Telander, 2011] and Alzheimer's disease [Wyss-Coray, 2006]. Given its role in numerous chronic diseases, chronic inflammation should be considered a key driver of progressive degeneration in OA joints.

The development of chronic inflammation in OA following joint trauma or overuse can be understood as a vicious, self-perpetuating cycle of local tissue damage, inflammation, and repair, such that the OA joint has been likened to a chronic wound [Scanzello *et al.* 2008]. Initial damage, resulting from acute, subacute, or chronic injury, induces a local pathologic inflammatory response that results in further cartilage loss and progressive joint injury over time. This hypothesis is depicted in Figure 2. Biomechanics are central to the development of OA since chronic damage from prior mechanical derangement (such as a meniscal tear or extrusion), overuse, hypermobility, or anatomic misalignment can produce ongoing low-grade damage [Andriacchi *et al.* 2004; Englund *et al.* 2008]. However, in the current paradigm of chronic inflammation, mechanical derangement is the inducing factor.

How do mechanical processes induce and propagate inflammation? It seems unlikely that an isolated injury, even with resultant chronic mechanical instability, could alone result in the chronic inflammatory processes characteristic of OA. Thus, there must be perpetuating factors that can transduce mechanical events into inflammatory signals. These factors will be the focus of our next discussion.

Innate immunity in osteoarthritis: damage fueling the fire of inflammation

Unlike RA, OA does not appear to be associated with a robust adaptive immune response. However, activation of the innate immune system is a central feature of both diseases. Innate immunity refers to host immune responses induced by invariable pattern-recognition receptors (PRRs) that respond to conserved patterns in nature, including, but not limited to, those introduced by invading pathogens such as bacteria, viruses, and fungi [Kawai and Akira, 2010]. PRRs are composed of several families of cell surface, endosomal, and cytosolic receptors. One well characterized family is the toll-like receptors (TLRs) [Kawai and Akira, 2010]. Besides microbial patterns, PRRs also recognize multiple
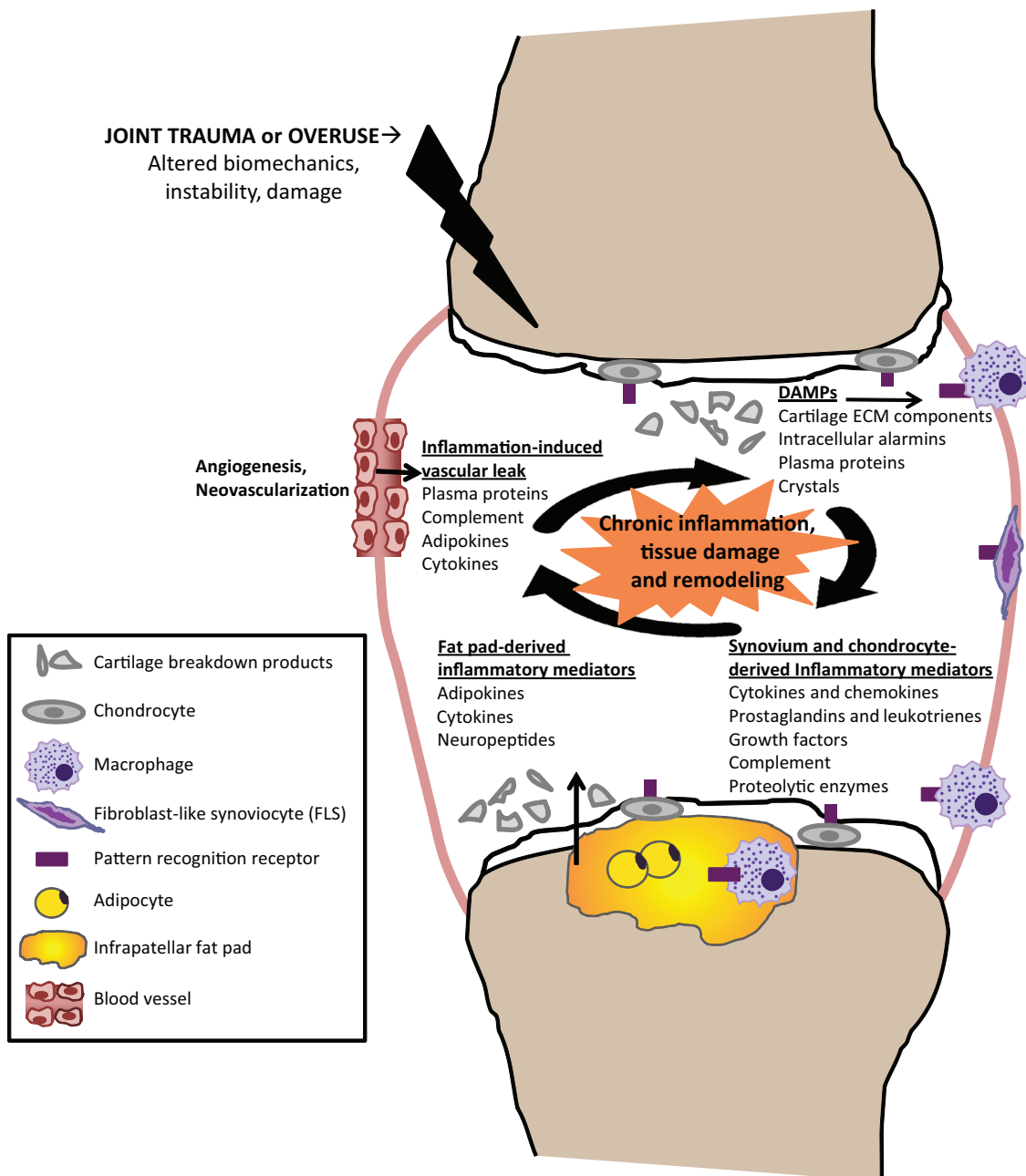
JOINT TRAUMA or OVERUSE→
Altered biomechanics,
instability, damage

DAMPs
Cartilage ECM components
Intracellular alarmins
Plasma proteins
Crystals

**Angiogenesis,
Neovascularization**

**Inflammation-induced
vascular leak**
Plasma proteins
Complement
Adipokines
Cytokines

**Chronic inflammation,
tissue damage
and remodeling**

**Fat pad-derived
inflammatory mediators**
Adipokines
Cytokines
Neuropeptides

**Synovium and chondrocyte-
derived Inflammatory mediators**
Cytokines and chemokines
Prostaglandins and leukotrienes
Growth factors
Complement
Proteolytic enzymes

Cartilage breakdown products

Chondrocyte

Macrophage

Fibroblast-like synoviocyte (FLS)

Pattern recognition receptor

Adipocyte

Infrapatellar fat pad

Blood vessel

Figure 2. Schematic representation of chronic inflammation as a mediator of osteoarthritis. Following joint trauma or overuse, tissue damage results in the production of damage-associated molecular patterns (DAMPs), including cartilage extracellular matrix (ECM) breakdown products and intracellular alarmins that signal through pattern recognition receptors on synovial macrophages, fibroblast-like synoviocytes (FLS), or chondrocytes to induce the local production of inflammatory mediators. Inflammation-induced angiogenesis and increased vascular permeability results in the subsequent influx of plasma proteins also capable of functioning as DAMPs. Acute and chronic production of inflammatory mediators promote further cartilage degradation either directly or indirectly through their induction of proteolytic enzymes, amplifying a vicious cycle of innate immune activation in osteoarthritis.

endogenous 'danger signals' resulting from tissue damage. Thus, in addition to so-called pathogen-associated molecular patterns (PAMPs), there exists another, potentially even more diverse, group of molecules known as damage (or danger) associated molecular patterns (DAMPs). Both PAMPs and DAMPs signal to the immune system a state of stress requiring a protective response to

Table 1. Damage-associated molecular patterns (DAMPs) in osteoarthritis.

DAMP	PRR
Cartilage ECM components	
Biglycan [Melrose *et al.* 2008]	TLR2, TLR4 [Schaefer *et al.* 2005], NLRP3 [Babelova *et al.* 2009]
Fibronectin [Chevalier *et al.* 1996]	TLR2 [Su *et al.* 2005], TLR4 [Okamura *et al.* 2001]
LMW hyaluronic acid [Dahl and Husby, 1985; Liu-Bryan and Terkeltaub, 2010]	TLR2 [Jiang *et al.* 2005], TLR4 [Termeer *et al.* 2002]
Tenascin C [Midwood *et al.* 2009]	TLR4 [Midwood *et al.* 2009]
Plasma proteins	
α1 microglobulin [Gobezie *et al.* 2007; Sohn *et al.* 2012]	TLR4 [Sohn *et al.* 2012]
α2 macroglobulin [Gobezie *et al.* 2007; Sohn *et al.* 2012]	TLR4 [Sohn *et al.* 2012]
Fibrinogen [Gobezie *et al.* 2007; Sohn *et al.* 2012]	TLR4 [Smiley *et al.* 2001]
Gc-globulin [Sohn *et al.* 2012]	TLR4 [Sohn *et al.* 2012]
Intracellular alarmins	
HMGB1 [Li *et al.* 2011; Liu-Bryan and Terkeltaub, 2010]	TLR2 [Park *et al.* 2004], TLR4 [Park *et al.* 2004], RAGE [Hori *et al.* 1995]
S100 family of proteins [van Lent *et al.* 2012]	TLR4 [Schelbergen *et al.* 2012]
Crystals	
Basic calcium phosphate [Gordon *et al.* 1984]	NLRP3 [Pazar *et al.* 2011]
Calcium pyrophosphate dihydrate [Midwood *et al.* 2009]	NLRP3 [Martinon *et al.* 2006]
Uric acid [Denoble *et al.* 2011]	NLRP3 [Denoble *et al.* 2011; Martinon *et al.* 2006]

ECM, extracellular matrix; HMGB-1, high-mobility group box 1; LMW, low molecular weight; NLRP, nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing; PRR, pattern recognition receptor; TLR, toll-like receptor.

either combat infection or initiate repair processes.

Because the list of innate DAMPs is long and rapidly growing, a complete discussion is beyond the scope of this review. However, there exists a shorter, though again expanding, list of molecules implicated in the innate immune response within the damaged joint, each potentially contributing to the chronic inflammation observed in OA. Such molecules include breakdown products from damaged extracellular matrix (ECM) including fibronectin [Okamura *et al.* 2001] and hyaluronan [Termeer *et al.* 2002], as well as known [van Lent *et al.* 2012] and novel plasma DAMPs [Sohn *et al.* 2012], which become elevated in synovial fluid secondary to vascular exudation (Table 1).

Extracellular matrix derived damage-associated molecular patterns

ECM breakdown is ubiquitous at sites of inflammation, including the OA joint [Evans *et al.* 1981]. An early observation by Homandberg and colleagues suggested that ECM breakdown products could promote inflammation and cartilage loss [Homandberg and Hui, 1996]. Even before the resurgence of interest in the innate immune system and the wide appreciation of PRRs, it was observed that fragments derived from the breakdown of fibronectin, when injected into knees of adolescent rabbits, resulted in cartilage damage as evidenced by loss of proteoglycans [Homandberg *et al.* 1993]. Further studies demonstrated that fibronectin fragments induced the production of proinflammatory cytokines, including tumor necrosis factor α (TNFα) and IL-1β, as well as matrix metalloproteinases MMP1 and MMP3, mediators now known to be implicated in chondrolysis [Homandberg and Hui, 1996]. The observations of Homandberg support a model in which damage resulting in ECM breakdown produces DAMPs capable of inciting local inflammatory responses resulting in further chondrolysis and release of additional ECM breakdown products. Notably, several additional ECM breakdown products have been implicated as DAMPs [Midwood *et al.* 2009; Okamura *et al.* 2001; Schaefer *et al.* 2005; Termeer *et al.* 2002] in mediating joint damage, including tenascin C [Midwood *et al.* 2009] and hyaluronic acid [Liu-Bryan and Terkeltaub, 2010].

Plasma protein damage-associated molecular patterns

In addition to ECM breakdown, sites of tissue damage and inflammation are characterized by vascular leak and exudation of plasma proteins [Stahel et al. 2007] capable of acting as DAMPs, including fibrinogen [Smiley et al. 2001]. Proteomic surveys of OA synovial fluid performed by our group [Sohn et al. 2012] and others [Gobezie et al. 2007] observed increased levels of many plasma proteins within OA synovial fluid. We evaluated the potential of a number of these plasma proteins to act as DAMPs in the elicitation of an inflammatory response. We observed that a select group of plasma proteins, including Gc-globulin, α_1-microglobulin, and α_2-macroglobulin, were capable of inducing TLR4-dependent macrophage production of inflammatory cytokines and growth factors implicated in OA, including TNFα, IL-6, IL-1β, and vascular endothelial growth factor (VEGF) [Sohn et al. 2012]. Thus, in addition to local production of DAMPs in the setting of joint injury, there appears to be a subsequent influx of inflammatory mediators resulting from inflammation- and damage-induced vascular leakage that further propagates the intra-articular inflammatory response and cartilage breakdown.

Intracellular alarmins

Intracellular proteins released from stressed, damaged, or necrotic cells can act as a third potential source of DAMPs. These 'intracellular alarmins', normally sequestered within the cell, can signal to the immune system when released from activated, stressed, or dying cells [Foell et al. 2007]. Intracellular alarmins implicated in OA include high-mobility group box 1 protein (HMGB-1) [Liu-Bryan and Terkeltaub, 2010] and the S100 family of proteins [van Lent et al. 2012]. One series of studies by Van Lent and colleagues demonstrated a potential role of the S100 family of proteins in OA-associated inflammation. Analyses of both human OA synovium as well as synovium derived from an animal model of OA revealed increased levels of S100A8 and S100A9 [van Lent et al. 2012]. In vitro studies further demonstrated the ability of these proteins to induce TLR4-dependent cartilage catabolism via upregulation of catabolic mediators, including MMPs 1, 3, 9, and 13, as well as the proinflammatory cytokine IL-6 with concomitant down-regulation of the ECM components aggrecan and type II collagen [Schelbergen et al. 2012]. Moreover, disease severity was reduced in S100A9-deficient animals with collagenase-induced OA [van Lent et al. 2012].

Crystals as damage-associated molecular patterns

Microscopic inorganic crystals, including basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals, are frequently observed in osteoarthritic synovial fluids and tissues. At the time of joint replacement for severe OA, nearly all joints show cartilage deposition of calcium-containing crystals [Rosenthal, 2011]. Examination of 150 knees at autopsy by Gordon and colleagues found evidence of CPPD crystals in 93% of patients with severe OA, but only 24% of those with minimal or no OA. Additionally, they demonstrated an association of radiographic calcification with presence of pathologic synovitis [Gordon et al. 1984]. Although the presence of radiographic chondrocalcinosis was not associated with increased rates of cartilage loss by MRI [Neogi et al. 2006], the lack of precision in identification of chondrocalcinosis as well as the difficulty in radiographic identification of specific crystal types may inadequately represent the contribution of calcium-containing crystals to OA-associated inflammation.

Supporting the potential contributory role of calcium crystals to OA progression are numerous studies suggesting that calcium-containing crystals promote inflammation through their interaction with various components of the innate immune system. A role for both TLRs and Nod-like receptors (NLRs) in mediating the inflammatory properties of calcium-containing crystals has recently been demonstrated. CPPD crystals were able to induce chondrocyte production of nitric oxide in a TLR2-dependent manner [Liu-Bryan et al. 2005]. Furthermore, studies by Martinon and colleagues have demonstrated that CPPD crystals also engage the NLRP3 inflammasome in macrophages to induce the caspase-1-mediated activation and subsequent release of proinflammatory cytokines IL-1β and IL-18 [Martinon et al. 2006]. Similarly, the NLRP3 inflammasome has been shown to drive inflammation by BCP crystals [Pazar et al. 2011]. Additional inflammatory mediators induced by BCP include prostaglandins [Morgan et al. 2004], MMPs [McCarthy and Cheung, 1994], and S100A8 [Cunningham et al. 2012], a DAMP recently implicated in OA pathogenesis [van Lent et al. 2012].

In addition to calcium crystals, recent studies identified a strong association between synovial fluid uric acid levels and radiographic progression of OA [Denoble *et al.* 2011], providing a potential role for uric acid in contributing to inflammatory processes and cartilage degradation in OA. Supporting this hypothesis is the demonstration that monosodium urate (MSU) crystals are potent inducers of IL-1β by the NLRP3 inflammasome [Martinon *et al.* 2006]. Similarly, MSU crystals have been demonstrated to enhance TLR4-mediated production of IL1β through a caspase 1-mediated process [Giamarellos-Bourboulis *et al.* 2009]. Thus, these observations suggest that soluble or crystalline uric acid may prime innate immune responses to OA-associated DAMPs, many of which are known TLR agonists. Indirect support for the role of crystal-induced inflammation in OA was provided by a randomized trial of 60 women with OA in which treatment with colchicine was associated with symptomatic improvement in OA-associated pain [Aran *et al.* 2011].

Cellular mediators of innate immunity

Many cell types within the joint possess PRRs capable of responding to DAMPs. Although much of the innate immune activation and cytokine production in OA is attributed to the action of synovial macrophages [Bondeson *et al.* 2006, 2010], there is also a direct contributory role for other cells of the joint, including fibroblast-like syoviocytes (FLS) and chondrocytes.

FLS contribute to OA pathogenesis by acting as intermediate mediators of local inflammation. Studies have demonstrated that OA FLS produce inflammatory cytokines such as TNFα, IL-1β, and chondrolytic mediators such as MMPs. Additionally, coculture experiments investigating the interaction between FLS and chrondrocytes have demonstrated the ability of FLS-derived IL-1β and TNFα to induce cartilage degradation [Steenvoorden *et al.* 2007]. Further support for the role of FLS as mediators of the innate immune response includes their ability to respond to both inflammatory cytokines as well as TLR ligands [Ospelt *et al.* 2004]. Moreover, a recent study demonstrated that synovial fluid from patients with early OA modulated the FLS response to TLR2 and TLR4 ligands via soluble CD14 (sCD14). This study also observed elevated levels of sCD14 in OA synovial fluid [Nair *et al.* 2012], suggesting that sCD14 may be another factor that promotes innate immune inflammation in the OA joint.

The involvement of chondrocytes as mediators of OA-associated inflammation is supported by studies demonstrating upregulation of TLRs, including TLR2 and TLR4 at sites of OA cartilage lesions [Kuroki *et al.* 2010]. Signaling through these receptors by their respective ligands strongly induces catabolic responses in chondrocytes [Kim *et al.* 2006; Liu-Bryan and Terkeltaub, 2010]. Furthermore, exposure of cartilage explant cultures to TLR-activating fibronectin fragments induces chondrolysis mediated by autocrine regulators of cartilage metabolism, including IL-1, IL-6, TNFα, and MMP3 [Homandberg and Wen, 1998; Homandberg *et al.* 1998].

Complement in osteoarthritis

In addition to the contribution of PRRs, activation of the complement system represents yet another innate immune mechanism by which OA inflammation and cartilage damage may be propagated. Proteomics analyses by our group [Sohn *et al.* 2012] and others [Gobezie *et al.* 2007] revealed increased levels of numerous complement components in osteoarthritic compared with healthy synovial fluids. Moreover, in OA synovium, upregulation of complement effector genes and downregulation of complement inhibitors was demonstrated relative to normal controls [Wang *et al.* 2011]. Further support for a role of complement in OA pathogenesis was provided by animal studies in which mice deficient in complement effectors C5 and C6 were protected in an experimental OA model, whereas disease was aggravated in mice deficient in CD59, a cell surface inhibitor of the membrane attack complex (MAC), C5b-9 [Wang *et al.* 2011]. Activation of complement by cartilage ECM components fibromodulin and aggrecan induced the assembly of MAC [Wang *et al.* 2011], which either through direct chondrolysis or induction of sublytic inflammatory signaling pathways promotes further cartilage damage and production of ECM breakdown products, perpetuating the cycle of complement activation. Notably, other ECM components have been demonstrated to activate complement including cartilage oligomeric matrix protein [Happonen *et al.* 2010], osteoadherin, and chondroadherin [Sjoberg *et al.* 2009].

Mechanical stress-induced immune activation

Another potential mechanism contributing to chronic inflammation, although not classically

Table2. Inflammatory mediators in osteoarthritis.

Cytokines	Chemokines	Growth factors	Adipokines	Prostaglandins/leukotrienes
IL-1 [Dingle *et al.* 1979; Goldring *et al.* 1988; Pfander *et al.* 2004]	Chemerin [Huss *et al.* 2010]	TGFβ [Blaney Davidson *et al.* 2007]	Adiponectin [Conde *et al.* 2011]	PGE2 [Martel-Pelletier *et al.* 2003]
IL-6 [Kaneko *et al.* 2000]	IL-8 [Chauffier *et al.* 2012; Kaneko *et al.* 2000]	VEGF [Haywood *et al.* 2003]	Leptin [Dumond *et al.* 2003]	LTB4 [Wittenberg *et al.* 1993]
IL-15 [Scanzello *et al.* 2009]	MCP-1 [Vangsness *et al.* 2011]		Resistin [Choe *et al.* 2012]	
IL-18 [Olee *et al.* 1999]	MIP-1α [Hsu *et al.* 2004; Vangsness *et al.* 2011]		Visfatin [Chen *et al.* 2010; Gosset *et al.* 2008]	
TNFα [Saklatvala, 1986]	RANTES [Hsu *et al.* 2004]			

IL, interleukin; LTB4, leukotriene B4; MCP, monocyte chemotactic protein; MIP-1, macrophage inflammatory protein; PGE2, prostaglandin E2; RANTES, regulated and normal T-cell expressed and secreted; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

considered part of innate immunity, is the ability of mechanical forces to directly induce production of inflammatory mediators from cartilage and synovium [Loeser, 2006]. However, the presence of subtle cartilage damage at sites of mechanical forces could also be associated with the release of inflammation-inducing DAMPs from ECM damage or necrotic cell death.

Inflammatory mediators in osteoarthritis

Soluble inflammatory factors including cytokines, chemokines, adipokines, neuropeptides, and lipid inflammatory mediators have been implicated in OA pathogenesis. The following discussion and Table 2 provide an overview of these mediators.

Cytokines

Soluble inflammatory factors such as cytokines are central to most inflammatory processes, and several cytokines have been implicated in OA pathogenesis. Studies by Kaneko and colleagues observed increased levels of IL-6 and IL-8 in OA serum and synovial fluid [Kaneko *et al.* 2000], and work from our group [Sohn *et al.* 2012] (Figure 1) identified elevated levels of a large repertoire of cytokines in both blood and synovial fluid of patients with OA. Similarly, work by Scanzello and colleagues demonstrated elevated levels of synovial fluid IL-15 in early knee OA. Furthermore, they revealed a positive correlation between levels of synovial fluid IL-15 with numbers of CD8 T cells within the synovial membrane and levels of synovial fluid MMP1, MMP3, and IL-6 [Scanzello *et al.* 2009].

Although the contribution of these cytokines to OA pathogenesis is not always clear, numerous *in vitro* studies support an overall catabolic role for cytokines elevated in the OA joint. IL-1β and TNFα signaling, culminating in the activation of nuclear factor κB and activator protein 1 transcription factors, can induce autocrine production of IL-1β and TNFα as well as expression of other critical inflammatory and chrondrolytic mediators, including MMP1, MMP9, MMP13, nitric oxide, prostaglandin E2 (PGE2), and IL-6 [Attur *et al.* 1998]. The role of IL-6 in OA is controversial. Elevated at sites of inflammation, IL-6 has been shown to activate B cells, T cells, and mediate the recruitment of inflammatory cells to sites of inflammation [Gabay, 2006]. Additionally, IL-6 receptor blockade is efficacious in the treatment of RA [Jones *et al.* 2010]. However, in the zymosan-induced model of joint inflammation, IL-6 was observed to play a dual role by reducing proteoglycan loss in the acute phase but enhancing osteophyte formation in the chronic phase [van de Loo *et al.* 1997]. This same group also showed that mice deficient in IL-6 displayed increased levels of cartilage loss in a spontaneous aging model of OA [de Hooge *et al.* 2005], again suggesting a potential protective role for IL-6 in the development of OA.

In addition to the ability of inflammatory cytokines to induce cartilage catabolism, many cytokines can also promote OA progression by

inhibiting anabolic processes critical to cartilage homeostasis [Goldring *et al.* 1994; Saklatvala, 1986]. As an example, IL-1β has been demonstrated to inhibit production of cartilage ECM components, including aggrecan [Pfander *et al.* 2004] and types II and IX collagen [Goldring *et al.* 1988].

Adipokines

In addition to traditional cytokines, a new class of soluble mediators known as adipokines has been associated with OA [Conde *et al.* 2011]. So-called because they are primarily (although not exclusively) derived from adipose tissue, adipokines, including leptin [Ku *et al.* 2009], have been associated with OA incidence and severity. The role of adiponectin is less clear. One study observed increased adiponectin levels in patients with erosive disease compared with nonerosive disease [Filkova *et al.* 2009], while others suggest a protective role for adiponectin in OA [Chen *et al.* 2006; Honsawek and Chayanupatkul, 2010]. Also supporting a role for adipokines in OA are several *in vitro* studies demonstrating the ability of adipokines including leptin, adiponectin, visfatin, and resistin to induce inflammatory mediators and chondrolysis [Conde *et al.* 2011]. Recent studies have shown a contributory role for adipokines in the development of obesity-related inflammation and the metabolic syndrome [Qatanani *et al.* 2009]. Thus, epidemiologic studies above demonstrating elevated adipokines in osteoarthritic serum may suggest one potential mechanism by which obesity increases the risk of OA [Felson *et al.* 1988]. However, the association between obesity and knee OA may be confounded by altered biomechanics also associated with obesity.

Although the exact contribution of fat and adipokines to OA pathophysiology remains to be clarified, several recent studies have investigated the role of the infrapatellar fat pad as a local mediator of pain and inflammation in OA. Infrapatellar fat pads derived from knees of patients with OA have been observed to contain not only adipocytes but also increased numbers of macrophages, lymphocytes, and granulocytes [Clockaerts *et al.* 2010]. Studies of fat pad explants have demonstrated the ability of this tissue to produce and secrete large amounts of leptin and adiponectin [Hui *et al.* 2012] as well as inflammatory mediators such as VEGF, TNFα, and IL-6 [Ushiyama *et al.* 2003]. Additionally, the OA fat pad is highly innervated by small C-fiber neurons containing the neuroinflammatory mediator and vasodilator Substance P that mediates not only pain sensation, but also directly acts on a variety of immune cells and the vascular system to induce proinflammatory cytokine (IL-1β and TNFα) production and vascular leak respectively [Bohnsack *et al.* 2005]. Thus, local fatty tissues within the joint including the infrapatellar fat pad may provide an additional source of inflammatory mediators such as adipokines and neuropeptides, as well as more classic soluble mediators of inflammation such as IL-1β, TNFα, and IL-6.

Prostaglandins, leukotrienes, and other lipid mediators

The enzyme cyclooxygenase-2 (COX-2) is upregulated in inflamed joint tissues and is responsible for elevated production of lipid mediators including prostaglandins such as PGE2 in the OA joint [Martel-Pelletier *et al.* 2003]. Studies have suggested that overexpression of COX-2 is likely induced by proinflammatory mediators such as IL-1β, TNFα, and IL-6, as well as via TLR4 stimulation [Geng *et al.* 1995]. There is in fact an extensive literature beyond the scope of this review suggesting that PGE2 is involved in inflammation, apoptosis, angiogenesis, and possibly structural changes that characterize arthritic diseases, which is well reviewed elsewhere by Martel-Pelletier and colleagues [Martel-Pelletier *et al.* 2003].

The biosynthetic pathway producing prostaglandin begins with production of arachidonic acid by the enzyme phospholipase A2. In addition to the generation of prostaglandins by COX enzymes, arachadonic acid can be converted to another class of lipid mediators known as leukotrienes through the action of the lipoxygenase family of enzymes. These mediators, primarily leukotriene B4 (LTB4) and its metabolite LTC4, are produced by OA synovium and to a lesser extent OA bone and cartilage [Wittenberg *et al.* 1993]. In addition to its role as a powerful leukocyte chemoattractant [Casale *et al.* 1992], LTB4 has been demonstrated to stimulate TNFα and IL-1β production from human OA synovial explants [He *et al.* 2002].

Imaging to identify inflammation: epidemiologic tool and clinical potential

Although pathologic evaluation may remain the gold standard for identifying the presence of inflammation in OA, the invasiveness of the synovial biopsy (or the need to wait until time of

surgical intervention such as joint arthroplasty) limits the opportunity to study potential new therapies for OA. However, imaging technologies have advanced significantly and now provide a useful surrogate for identification and quantitation of synovial inflammation. The mainstay of synovial imaging has been MRI, with early studies demonstrating the presence of bone marrow edema along the medial or lateral knee predicting progression of OA in their respective compartments [Felson *et al.* 2003]. It should be noted that medial bone marrow lesions were seen mostly in patients with varus limbs while lateral lesions were seen mostly in those with valgus limbs, and risks were attenuated 37–52% after adjustment for limb alignment. Thus, malalignment and mechanical derangement, although perhaps not the effectors of inflammation, are clearly the harbingers of both development of inflammation and propagation of OA pathology.

Bone marrow edema may be a useful marker of joint inflammation, but whether it is itself associated with joint inflammation or local damage resulting in propagation is unclear. Some have suggested that bone marrow edema represents a local inflammatory process at the bone–cartilage interface and that this interaction forms a functional unit which, when deranged by damage or inflammation, is involved in the initiation of OA [Lories and Luyten, 2011]. Thus the potential primary role of excessive stress at the bone–cartilage interface may yet be an initiating, if not a driving mechanism in the development of OA. The observation of increased levels of inflammatory cytokines within the bone–cartilage unit at sites of early OA support this hypothesis [Lories and Luyten, 2011]. Interestingly, one small study directly investigating the histopathology of MRI bone marrow lesions at the time of total joint arthroplasty did observe low-grade inflammation; however, the predominant findings were more consistent with localized infarction as demonstrated by vascular leak and local fibrinoid reactions with thrombus inclusions [Hunter *et al.* 2009]. One obvious caveat is the late stage at which these lesions were obtained. Notably, however, both cellular necrosis and vascular leak may provide a source of DAMPs capable of contributing to ongoing inflammation.

Further work in MRI has now directly evaluated the joint synovium for pathologic changes of inflammation. Earlier studies of MRI in which gadolinium contrast was not utilized concluded

that the presence of synovitis at a limited number of sites in the joint (infrapatellar fat pad, suprapatellar and intercondylar regions) was associated with increased pain. Notably, the presence of synovitis by these criteria was not associated with future cartilage loss on follow-up MRI [Hill *et al.* 2007]. The same group performed another study in which the presence of joint effusion synovitis, identified without the use of contrast, was associated with risk of subsequent cartilage loss at 30 months. Interestingly, another study by Pelletier and colleagues also observed a small but statistically significant association of noncontrast-enhanced MRI synovitis with loss of cartilage volume only 60 days later by repeat MRI [Pelletier *et al.* 2008].

More recently, imaging has moved toward the use of contrast-enhanced MRI (CE-MRI). A recent translational study comparing non-CE-MRI and CE-MRI demonstrated that although noncontrast T2-weighted sequences could identify fluid and effusion volume, only CE-MRI was able to reliably detect synovitis according to a reference synovial biopsy [Loeuille *et al.* 2011].

It should be noted that MRI is not the only imaging methodology being developed for the evaluation and quantitation of synovitis in OA. A recent study comparing CE-MRI and power Doppler ultrasound (PD-US) noted that PD-US has superior sensitivity compared with non-CE-MRI but not that of CE-MRI. Notably, the use of contrast enhancement for PD-US was potentially even more sensitive than CE-MRI for the identification of effusion synovitis as defined in this study [Song *et al.* 2008]. Additionally, Conaghan and colleagues demonstrated that ultrasound-observed effusion, in combination with radiographic and clinical symptoms, was associated with increased progression to joint replacement at 3-year follow up [Conaghan *et al.* 2010].

Overall, it is clear that advances in imaging by MRI and/or ultrasound to assess inflammation will provide the ability to perform large-scale epidemiologic and translational studies of inflammation in OA. Although the earliest stages of synovial inflammation likely occur before synovitis is detectable by current imaging, the ability to identify radiographic features predictive of future cartilage loss will undoubtedly facilitate the development of therapeutic strategies targeting early OA with the presence of synovitis and visualization of cartilage denudation [Hunter

et al. 2008] as both an entry point and surrogate endpoint to identify promising pathways and therapeutics.

Inflammation as a target for disease modification in osteoarthritis

To date, no agent has been shown to have disease-modifying effects on the structural progression of OA. Current therapies, including nonsteroidal anti-inflammatory drugs, COX-2 selective agents, intra-articular hyaluronic acid injections, and opioids offer only symptomatic relief. Agents that have demonstrated potential efficacy for disease modification include the MMP inhibitor doxycycline [Brandt *et al.* 2005] and the combined lipoxygenase/cyclooxygenase inhibitor licofelone [Raynauld *et al.* 2009]. Despite the clear role of inflammation in OA, recent trials of potent anti-inflammatory therapies, including use of systemic and intra-articular biologic agents to inhibit TNFα and IL-1β, proved disappointing [Hunter, 2008]. Major challenges for the development of DMOADs include the need for improved measures of structural damage (beyond the use of X-rays) as well as improved understanding of the appropriate population and disease stage for intervention. OA is a final common pathway following many predisposing factors and thus therapeutics may have limited, if any, efficacy in those with pre-existing joint damage, biomechanical predisposition, or obesity [Felson and Kim, 2007]. The requirement of radiographic change, a finding observed in those with relatively advanced OA, likely identifies a population less amenable to anti-inflammatory intervention. No studies to date have targeted very early OA at a time when anti-inflammatory intervention might be most effective. Although synovitis is more frequently observed in those with end stage OA [Smith *et al.* 1997], the ability to identify and quantitate synovitis (and *vis à vis* inflammation) before the onset of irreversible joint failure, provides great promise to the targeting of preradiographic inflammation akin to the paradigm now well accepted for the early aggressive treatment of RA [Knevel *et al.* 2010]. Thus, the increasing appreciation of clinical risk factors for the development of OA as well as the advent of highly sensitive imaging modalities capable of visualizing early synovitis and cartilage change holds great promise for the identification of the at-risk population most suitable for very early anti-inflammatory interventions.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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