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The Role of Innate Immunity in Osteoarthritis: When Our First Line of Defense Goes on the Offensive

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Abstract

Although mankind has been suffering from osteoarthritis (OA) dating to the dawn of humankind, its pathogenesis remains poorly understood. OA is no longer considered a “wear and tear” condition but rather one driven by proteases where chronic low-grade inflammation may play a role in perpetuating proteolytic activity. While multiple factors are likely active in this process, recent evidence has implicated the importance of the innate immune system, the older or more primitive part of our body’s immune defense mechanisms. The role of some of the components of the innate immune system have been tested in OA models *in vivo* including the role of synovial macrophages and the complement system. This review is a selective overview of a large and evolving field. Insights into these mechanisms might inform our ability to phenotype patient subsets and give hope for the advent of novel OA therapies.

Key indexing terms

osteoarthritis; innate immunity; macrophages; complement

Introduction

Osteoarthritis (OA) is considered an “old” disease. Not only is it a disease of the elderly but evidence for OA exists in the archeological record of ancient man (1). OA involves the “whole joint”, including articular and meniscal cartilage degeneration and loss, sclerotic changes to the subchondral bone, bony osteophytosis and synovial inflammation (2). Although this disease is widely prevalent, the exact mechanisms involved in its pathogenesis are not well understood. However, OA is no longer thought to be a purely non-inflammatory or a biomechanical (“wear and tear”) process but rather one that has been increasingly recognized to include low grade inflammation, often subclinical (3), that is predictive of

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articular chondropathy. In one study (4), 422 patients (85% with moderate radiographic Kellgren-Lawrence grade 2–3 OA at baseline) underwent knee arthroscopy at the beginning of the study and 12 months later. Those noted to have inflammatory changes in the medial perimeniscal synovium at baseline were more likely to have progression of tibiofemoral cartilage damage observed upon follow-up arthroscopy. This study did not adjust for baseline severity of OA which itself is correlated with synovitis (5), so taken alone cannot directly prove an independent effect of inflammation on structural progression. However, at least two other studies more convincingly show a direct effect of inflammation on OA progression. In one recent study with the novel imaging agent 99mTc-Etarfolatide that detects activated macrophages (6), a soluble macrophage marker (CD163) in synovial fluid was strongly associated with 99mTc-Etarfolatide positivity of the knee and was also associated with OA progression based on osteophyte controlling for baseline osteophyte severity (7). Another study showed that effusion synovitis, assessed by MRI, was an independent predictor of cartilage loss in the tibiofemoral joint at 30 months follow-up in subjects with neither cartilage damage nor tibiofemoral radiographic OA of the knee at baseline (8). Based on histological and cytokine expression profiling, synovial membranes from patients with OA show increased cellular infiltrates (9) and a pannus similar but not as extensive as that observed in rheumatoid arthritis (RA) (10). A number of inflammatory cytokines, most notably IL-1β and TNFα, are increased in synovial fluid, and both are produced by synovial membranes and chondrocytes from OA patients (11, 12).

The latest theories of OA pathogenesis implicate the interplay between mechanical damage and chronic inflammation (13, 14). Activation of the innate immune system is intricately involved in initiation and perpetuation of this low-grade inflammation (15–17). Thus, OA pathology is the result of an imbalance between the anabolic and catabolic processes in the joint (11). It seems only fitting that the innate immune system, considered the older or more “primitive” branch of our body’s defense, plays a key role in this “oldest” known disease of humans (1). This article is a non-systematic review of *in vitro* and *in vivo* studies that examine the role of the innate immune system in OA pathogenesis. We provide a brief overview of innate immunity and the basic mechanisms by which it becomes activated; secondly, we review the literature that implicates the innate immune system, including the complement system and synovial macrophages, in the pathogenesis of OA. Although we will discuss the evidence implicating each, in actuality, this process involves a complex interaction between the various branches of the innate immune system.

Overview of Innate Immunity

How does innate immunity, which serves as our first line of defense, lead to inflammation and joint pathology? The answer lies in how the innate immune system reacts to changes that take place in the joint over time. Unlike the adaptive immune system, innate immunity relies on recognition of conserved motifs generated by pathogens or damage within the body (18). Damage to cellular and cartilage extracellular matrix products from trauma, microtrauma (from repetitive overuse) or normal aging generates damage-associated molecular patterns (DAMPs) that activate the innate immune system (15, 17). DAMPs can be fragments generated from proteins, proteoglycans or remnants of cellular breakdown, such a uric acid (16, 18, 19) (Table 1). DAMPs elicit a sterile inflammatory response

through interaction with particle recognition receptors (PRR), such as toll-like receptors (TLR), on the surface of immune cells, or with PRRs in the cell cytoplasm, such as nod-like receptors (NLRs) (15, 17, 18).

TLR activation leads to increased expression of pro-inflammatory cytokines via a number of transcription factors, such as activator protein 1 (AP1), cyclic AMP responsive element binding (CREB) protein, interferon regulatory factors (IRF) and NF-kB (20); the latter has been found to play a role in OA (15). The PRRs, TLR-2 and TLR-4, have both been thought to play a role in OA. TLR-2 and TLR-4 are upregulated in the synovial tissue from patients with OA, although not to the same extent as those with RA (21). Histological studies have shown increased expression of both TLR-2 and TLR-4 in articular cartilage lesions in OA patient samples (22) as well as the synovial membranes of patients with OA (21). Human chondrocytes express TLRs and their activation in tissue culture by TLR agonists leads to upregulation of matrix metalloproteases (MMPs), nitric oxide, and prostaglandin E2 (PGE_2) (22). Tenascin-C, a ECM glycoprotein, has been shown in experimental models to cause persistence of synovial inflammation via TLR-4 (23). The plasma proteins Gc-globulin (vitamin D-binding protein), a_1-microglobulin, and a_2-macroglobulin, found to be enriched in OA synovial fluid (24), can signal via TLR4 to induce macrophage production of inflammatory cytokines implicated in OA (25). Whereas knockout of TLR-4 resulted in a less severe phenotype in a mouse IL-1 driven model of arthritis, knockout of TLR-2 showed a more severe disease phenotype suggesting its activation may be a countermeasure to joint catabolism (26). Opposing actions of TLR-2 and TLR-4 have also been described in other tissues including presynaptic terminals in the spinal cord and astroglia (27) as well as hippocampal neurons (28). Cell culture studies revealed that the extracellular domain A of fibronectin can trigger TLR-4 to produce an inflammatory response (29, 30). Both *in vitro* cell culture studies as well as an animal model of inflammatory arthritis have suggested that low molecular weight hyaluronic acid (HA) can also trigger either TLR-2 or TLR-4 to produce an inflammatory response (31, 32).

NLR activation leads to inflammasome assembly and activation of the inflammasome mediated inflammatory pathways (33). In addition, in response to inflammatory cytokines, chondrocytes have the ability to produce complement (34), another component of the innate immune response. Various ECM components, such as Cartilage Oligomeric Matrix Protein (COMP) (35–37), and the NC4 domain of type 4 collagen (38), can also fix complement. Finally, activation of mechanoreceptors in the cartilage and the synovium can lead to upregulation of various inflammatory mediators (39)

Once initiated, this inflammatory response leads to upregulation of catabolic factors, such as pro-inflammatory cytokines, proteolytic enzymes and chemokines, and downregulation of anabolic factors, such as anti-inflammatory cytokines and growth factors (11). From a teleological prospective, the ability of DAMPs to trigger the innate immune system probably is meant to promote wound healing and tissue repair (18, 40). However, these events can lead to further tissue breakdown, which contributes to an on-going sterile wound healing cycle resulting in joint tissue pathology (see Figure 1). There are other mechanisms activated in joint tissues in response to injury and an altered mechanical environment including altered mechanoreceptor signaling (41) and release of growth factors such as

fibroblast growth factor (42). The balance of these responses in conjunction with the level of activation of the innate immune response likely orchestrates the net rate and severity of joint tissue catabolism.

Overall, the pathologic response of the joint results from a combination of anabolic (growth factors and anti-inflammatory cytokines) and catabolic forces (proteolytic enzymes and pro-inflammatory cytokines) (43). The two major pro-inflammatory cytokines implicated in OA are IL-1β and TNFα (11); synovial membrane biopsies from patients with early OA (symptomatic but no radiographic changes) had greater immunostaining of these two cytokines compared with late OA (requiring hip arthroplasty) (44), implying that inflammation may play an important role early in the disease course. In these early OA samples they also observed upregulation of indicators of inflammation such as cellular infiltrates, ICAM-1, VEGF, NF-κB and COX-2 (44). Another group found increased concentrations of IL-15 in the synovial fluid from patients with early versus late-stage OA suggesting activation of an innate immune response in the synovial membrane (45). Analysis of synovial membranes from 54 patients requiring arthroplasty for hip or knee OA revealed that the majority (57%) had inflammatory infiltrates (46); the subgroup with inflammatory infiltrates had higher mean levels of plasma high sensitivity CRP, which was strongly correlated with IL-6 concentrations in the synovial fluid (46). In addition, various other inflammatory cytokines and chemokines have possible links to OA pathogenesis; these include IL-8, IL-17, IL-18, IL-21 and leukemia inhibitory factor (LIF) (11, 43).

While the pro-inflammatory cytokines and chemokines represent the “marching orders”, proteolytic enzymes are the actual mediators on “the frontline” responsible for actual degradation of the articular cartilage. The two main groups of enzymes that mediate this catabolic process are the MMPs and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) (11). Various MMPs and tissue inhibitor of metalloproteinases (TIMP) were found to be upregulated in the synovial fluid from patients with OA (47). Also, MMP-1, MMP-3, and MMP-13 were isolated from both OA pannus cells and chrondocytes--with MMP-3 being the most highly expressed from both (48). Both bovine and human chondrocytes have shown the ability to produce ADAMTS protein (49). Furthermore, RNA expression of ADAMTs from human OA synovial cells can be altered by exposure to IL-1β and TNFα and pharmacologic blockade of thes cytokines (50).

The Complement System

The complement system consists of over 30 proteins. It includes serine proteases that contribute to an enzymatic cascade that yields proteins involved with opsonization, chemotaxis, and cell lysis as well as naturally occurring inhibitors, such as CD59 (also known as protectin) and factor H, which serve to keep the complement system in check (51). There are three different pathways by which the complement system can become activated (Figure 2) but all converge into the membrane attack complex (MAC) formed from C5b to C9. The MAC forms a cytotoxic ring-structure that perforates its target (51). As shown by some recent studies, MAC forms in response to the presence of certain extracellular matrix (ECM) proteins, such as fibromodulin (35). Furthermore, MAC also has sublytic properties that can upregulate inflammatory mediators without causing direct cytotoxic effects (35).

Complement proteins (see Table 2) have been found to be upregulated in both the synovial membranes as well as the synovial fluid of OA patients (24, 52, 53). The amount of MAC deposition in the synovial membrane is correlated with the level of synovial inflammation on histology (53). Chondrocytes are also capable of synthesizing complement components whose synthesis in OA can be upregulated by pro-inflammatory cytokines such as IL-1β and TNF-α (34). C5a receptors have been found to be upregulated on the surface of OA chondrocytes but not to the same extent as in RA (54). Other histological studies have found that complement deposition increases during an acute flare of the disease (52). Likewise, complement levels in the synovial fluid are elevated during the earlier acute phases of the disease (35). CD59, a natural occurring complement inhibitor, appears to be continuously upregulated in OA (52) implying that the complement system is chronically activated in OA. As described above, various ECM breakdown products, such as COMP, fibromodulin, and the NC4 domain of type 4 collagen, have all been shown to activate certain components of the complement pathway (see Table 1).

While this evidence has implicated the complement system in the pathogenesis of OA, a series of recent studies in transgenic mouse models have more definitively demonstrated a pathological role of the complement system in OA. For instance, in a medial menisectomy mouse-model, knocking out components of the complement pathway (C5 and C6), attenuated joint damage (35). Conversely, knocking out CD59 (Protectin) increased degenerative changes compared to wild type mice (35). Pharmacologically blocking the complement system by CR2-fH, a fusion protein of a complement receptor and the naturally occurring inhibitor factor H, was associated with less severe joint damage (35). The same group showed that carboxypeptidase B (CPB) appeared to have a protective role in OA by inhibiting the complement system (55). Similar to their previous findings (35), in a medial menisectomy OA model, mice that were deficient for CPB showed more cartilage degeneration, osteophyte formation and synovitis than wild-type mice (55). In addition, they found that levels of CPB correlated to levels of MAC in the synovial fluid of patients with OA; suggesting that CPB has an anti-inflammatory role in the joint (55). Finally, in an *in vitro* model, CPB treated serum decreased MAC formation. Subsequently, they concluded that CPB has an anti-inflammatory effect in OA by inhibiting formation of MAC (55).

Synovial Macrophages

Similar to a war being fought in the air, land and sea, the overall innate immune response requires a concerted effort of multiple lines of defense. In addition to the complement system, innate immune cells, such as macrophages, serve vital functions to our body's defense (56) and play a key role in innate immunity; they are involved in RA as well as OA (9) (see Table 2). Macrophages, as their name implies, are major phagocytic cells of the body, but they also carry out a number of other important functions, such as initiating inflammation, resolving inflammation, and restoring and repairing tissue damage (56, 57). Usually, macrophages exhibit a functional plasticity based on signals from their environment. However, their chronic activation can lead to deleterious effects (56, 57).

Macrophages can be activated in a variety of ways. As mentioned earlier, one of the primary ways is through activation of PRRs, which in turn activate a number of intracellular

pathways, such as NF-κB (58). Another way macrophages can become activated is through inflammasome mediated pathways (59). Inflammasomes are large multimeric intracellular protein complexes that help process caspase-1 which is responsible for producing the mature forms of several pro-inflammatory cytokines such as IL-1β (60). NLRP3 is the most extensively studied of all the inflammasomes (59) and has been associated with crystal-induced inflammation triggered by uric acid and calcium pyrophosphate (61) as well as hydroxyapatite crystals (62, 63). One study of knee OA patients without gout suggested involvement of uric acid activated NLRP3 inflammasomes in the pathogenesis of OA (64). In this study, synovial fluid uric acid concentrations correlated with the concentrations of two cytokines, IL-18 and IL-1β, known to be produced by uric acid activated inflammasomes, and synovial fluid IL-18 was associated with OA progression. Hyaluronan also activates inflammasome pathways (65). Since there is a high degree of correlation of uric acid crystal deposition and cartilage lesions (66), and evidence for inflammasome activation in association with uric acid in OA (62, 64). it has been postulated that the chronic low-grade inflammasome activation helps drive OA progression (62, 64).

Experimental therapies aimed at macrophages have shown the ability to both decrease inflammation and progression of OA. Depletion of macrophages from a cell-culture suspension of human OA synovium decreases the inflammatory response, including both the cytokine response and the activity of proteolytic enzymes, such as matrix metalloproteases and aggrecanases, known to play a role in OA (50). Depletion of synovial macrophages via intra-articular injection of clodronate leads to less MMP activity and less cartilage damage in mouse model of OA (67). On the other hand, macrophages also secrete growth factors, such as TGFβ, that can enhance cartilage repair (68). However, intra-articular injections of TGFβ into the knees of mice can lead to fibrosis and extensive osteophyte formation; this response was abrogated by injecting clodronate beforehand which successfully depleted macrophages from the synovial lining (69). Thus, experimental therapies directed toward macrophages appear to be an attractive future target for OA.

Therapeutic Implications

Since OA has traditionally been thought to be a purely biomechanical disease, patients diagnosed with this condition are primarily treated to palliate symptoms. The growing body of evidence implicating the innate immune system in the pathogenesis of OA provides hope that insights into these mechanisms might inform our ability to phenotype patients who would stand to benefit the most from a particular therapy and treat these patient subsets more specifically than is currently possible. Although currently there are few effective pharmacologic treatment options for symptomatic OA, intra-articular glucocorticoids have shown some efficacy and are recommended by a number of international treatment guidelines (70, 71). Among their many effects, glucocorticoids lower expression of complement (72, 73), and induce macrophage polarization to an anti-inflammatory phenotype (74). However, their effects are broad and associated with numerous adverse effects including decreased bone formation, hyperglycemia and increased risk of infections (74). Development of more targeted therapies is critical for gaining clinical benefit without adverse effects.

Does the growing body of knowledge implicating the innate immune system in OA pathogenesis provide any hope for new treatments of OA in the future? Specifically, can slowing the inflammatory response lead to either symptomatic improvement or halt the progression in OA? Previous animal knockout models for COX-1 and COX-2 (75) and IL-1β and ICE have failed to show any chondroprotective effect (76) (and may have lead to increased disease). Knockout models are not always the most informative as it is difficult to ascertain any possible off-target effects (as illustrated by the previous study by Fukai et al (75)). Instead, are there other *in vivo* study designs that provide a more realistic but accelerated model for OA? As has been previously pointed out, one of the difficulties facing OA therapeutic studies is the long-natural history of the disease (77). As such, post-traumatic arthritis models might provide a way to evaluate a critical period of OA pathogenesis where inflammation may play a key role. Prior studies from our group have shown that IL-1β is upregulated in the synovial fluid of animals with post-traumatic arthritis (78, 79). A prior study found that recombinant IL-1RA used intra-articularly prevented OA development in an experimental animal model (80). More recent studies from our group have shown IL-1 inhibition to be effective in preventing progression of post-traumatic OA (81, 82). Several proof of concepts studies showed that a dual-variable domain immunoglobulin directed to both IL-1α and IL-1β prevented cartilage degradation in an animal model of OA (83, 84).

How close are some of these anti-inflammatory therapies that have been efficacious in preclinical OA, to going from “bench to bedside”? Prior human studies using current RA therapies to block cytokines in OA have met with mixed success. Intra-articular injections of adalimumab, an anti-TNF-α monoclonal antibody, showed some improvement in pain scores for knee OA (85) but showed no statistically significant improvement in pain for hand OA (86). Another small study showed improvement in pain but no changes in radiographic scores after 12 months for patients with hand OA that received intra-articular infliximab injections (87). Intra-articular injections of anakinra, an IL-1 receptor antagonist, have shown mixed results in improving pain in several small studies (88, 89). In a proof of concept from our group, the effects of intra-articular IL1RA injections were looked at following acute joint injury. Patients were randomized to either placebo intra-articular IL1RA. Those who received the intra-articular IL1RA were found to have less pain and improved function (90).

Also, targeting the cells or proteins of the innate immune system holds some promise for OA. There has been a growing body of literature on therapies targeting inflamed synovial tissue. Recently, a new recombinant protein (MT07), representing a fusion of an anti-C5 monoclonal antibody and a synovial-homing peptide, both prevented and successfully treated synovial inflammation in two different animal models of inflammatory arthritis (91). Another new strategy involved intra-articular injection of a DNA vector encoding an anti-C5 recombinant mini-antibody (MB12/22). This treatment lead to *in situ* production of this neutralizing antibody, which resulted in a statistically significant reduction in joint inflammation in a rat model of inflammatory arthritis (92). A human anti-DR5 antibody (TRA-8) was able to selectively induce apoptosis in a subset of inflammatory macrophages in a transgenic mouse model that led to less synovial hyperplasia and cellular infiltrates as

well as improved clinical scores (93). As this therapy is directed toward a subset of inflammatory macrophages, theoretically it should have less off-target effects but further studies are needed. Tigatuzumab, a humanized monoclonal antibody to DR5, has been well tolerated in Phase I cancer studies (94). To the best of our knowledge, these therapies have not been studied in human for arthritis.

Conclusions

In addition to serving as our first line of defense, the innate immune system plays a key role in the pathogenesis of OA. Once activated, innate immunity "goes on the offensive", leading to an inflammatory response that is a major driver of the disease process. The analogy of an innate immune system on the offensive is apt based on the failure of the innate immune response to resolve, which drives OA progression, if not development (43). A greater understanding of the basic mechanisms by which innate immunity becomes activated provides insights into OA pathogenesis. The advent of a much-improved understanding of the pathogenesis of OA is critical for effective phenotyping of OA patient subsets. Only through effective phenotyping will personalized medicine become a reality, the goals of which are to increase drug response rates, decrease adverse event rates, and improve the overall cost-effectiveness of medical therapy (95). It might be imagined that in addition to being able to identify inflammatory subsets of OA, the relative severity and profile of the innate immune response may reveal 'subsets within subsets' of OA. These advances could lead to potential new therapeutics for OA that would be expected to both modify symptoms and structural progression. While OA remains an "old" disease, our new understanding of it offers hope for more effective therapies in the future.

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Glossary of Terms

ADAMTS	a disintegrin and metalloproteinase with thrombospondin motifs
CD	cluster of differentiation
COMP	cartilage oligomeric matrix protein
CPB	carboxypeptidase B
CR	complement receptor
ECM	extracellular matrix
DAMP	damage associated molecular patterns
DR	death receptor
HA	hyaluronic acid

ICAM	intracellular adhesion molecule 1
ICE	IL-1β converting enzyme
IL	interleukin
IL-1RA	interleukin 1 receptor antagonist
MAC	membrane attack complex
MASP	mannan-binding lectin serine protease
MB	mannose binding
MBL	mannose binding lectin
MMP	matrix metalloproteases
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NLR	NOD (nucleotide-binding domain)-like receptor
OA	osteoarthritis
PRR	particle recognition receptor
RA	rheumatoid arthritis
TGF	tissue growth factor
TIMP	tissue inhibitor of metalloproteinases
TLR	toll-like receptor
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor

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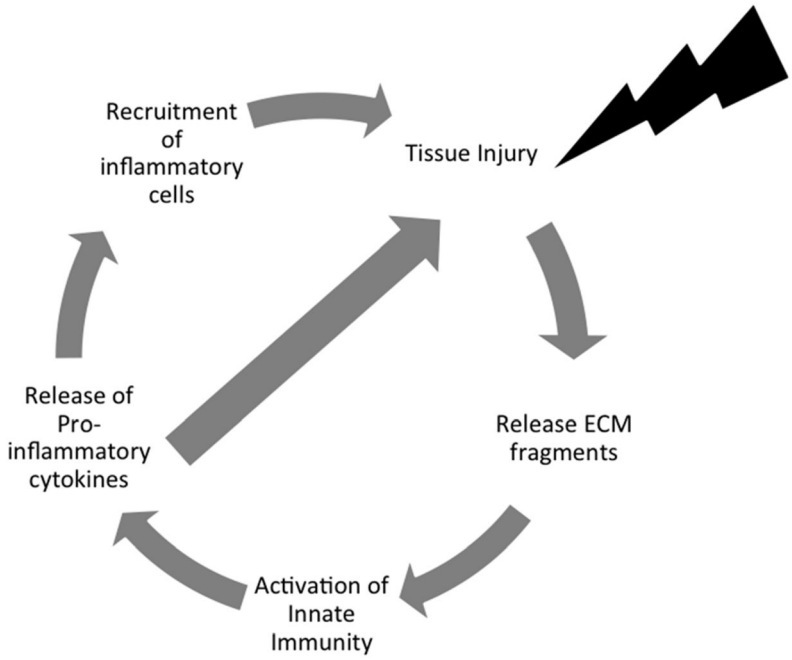

Figure 1. Osteoarthritis Pathogenesis

This figure depicts the self-perpetuating cycle of joint degeneration that characterizes the pathogenesis of osteoarthritis. In this paradigm, an inciting injury to the joint tissue causes the breakdown of the extracellular matrix (ECM), which initiates activation of innate immunity and a cyclic cascade of inflammatory events leading to further and ongoing joint damage.

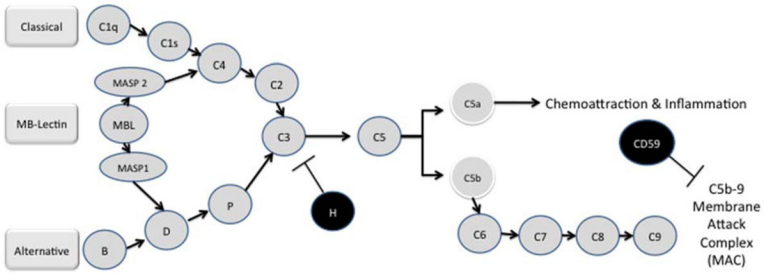

Figure 2. The Complement System

The complement cascade is a complex system that can become activated by one of three separate pathways: the classical, the mannose-binding (MB)-Lectin and alternative pathways. All three pathways converge on the C3 protein. C3 cleavage products participate in the activation of C5 whose cleaved components contribute to a local inflammatory response (C5a) or form part of the membrane attack complex that plays a role in cell lysis (C5b). Abbreviations: CD, cluster of differentiation; H, complement factor H; MAC, membrane attack complex; MASP, mannan-binding lectin serine protease; MB, mannose binding; MBL, mannose binding lectin. Complement effectors=blue, complement inhibitors=red. Adapted from Wang 2011 (35) and Sturfelt 2012 (51).

Table 1

Extracellular matrix breakdown products that can trigger innate immunity.

COMP	**Happonen *et al.* 2010[36]**	**Regulates complement**
Collagen IX (NC4 domain)	Kalchishkova *et al.* 2011[38]	Direct/indirect inhibition of complement
Fibromodulin	Sjoberg A *et al.* 2005[37]	Activates classical complement pathway via C1q
Fibromodulin	Wang *et al.* 2011[35]	Upregulates C5b-9 (MAC) from human OA sera
Fibronectin (EC domain)	Okamura *et al.* 2001[29]	Triggers TLR-4
Fibronectin (EC domain)	Gondokaryono *et al.* 2007[30]	Triggers TLR-4 mast cells
Hyaluronan	Yamasaki *et al.* 2009[65]	HA triggers inflammasome->IL-1β
Hyaluronan	Scheibner *et al.* 2006[31]	HA triggers TLR-2
Hyaluronan	Taylor *et al.* 2007[32]	HA triggers TLR4/CD44/MD-2
Tenascin-C	Midwood *et al.* 2009[23]	TLR-4 agonist leading to persistent synovial inflammation

COMP-cartilage oligomeric matrix protein, MAC=membrane attack complex, OA=osteoarthritis, TLR=toll like receptor

Table 2

Components of Innate Immunity with a Putative Role in Osteoarthritis.

C3c, C5,	Konttinen *et al.* 1996[52]	Increased in synovial membranes of OA patients -Further increased during acute flare
C3	Gobezie *et al.* 2007[24]	Significantly increased from other SF proteins in proteomic assay.
C3a	Wang *et al.* 2011[35]	Increased in SF of OA patients
C4b	Gobezie *et al.* 2007[24]	Significantly increased from other SF proteins in proteomic assay.
C5b-9 (MAC)	Wang *et al.* 2011[35]	Increased in SF of OA patients
C5b-9 (MAC)	Corvetta *et al.* 1992[53]	Increased in synovial membrane of OA patients
C5, C6	Wang *et al.* 2011[35]	Knockout mice for these complement proteins showed less OA damage
CD59 (inhibitor)	Konttinen *et al.* 1996[52]	Chronically upregulated in human OA synovium
CD59 (inhibitor)	Wang *et al.* 2011[35]	Knockout mice for this complement inhibitor showed more severe OA damage
Macrophages	Blom *et al.* 2007[67]	Depletion of synovial macrophages leads to MMP activity and less severe OA in mice
Macrophages	van Lent *et al.* 2004[69]	Macrophages secrete TGF-β that leads to osteophytes

SF=synovial fluid, OA=osteoarthritis; TGF-tissue growth factor