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Synovium and the Innate Inflammatory Network in Osteoarthritis Progression

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Abstract

This review focuses on the recent advancements in the understanding of innate immunity in the pathogenesis of osteoarthritis, particularly with attention to the roles of damage-associated molecular patterns (DAMPs), pattern recognition receptors (PPRs), and complement in synovitis development and cartilage degradation. Endogenous molecular products derived from cellular stress and extracellular matrix disruption can function as DAMPs to induce inflammatory responses and pro-catabolic events in vitro and promote synovitis and cartilage degradation in vivo via PRRs. Some of the DAMPs and PRRs display various capacities in driving synovitis and/or cartilage degradation in different models of animal studies. New findings reveal that the inflammatory complement cascade plays a key in the pathogenesis of OA. Crosstalk between joint tissues such as synovium and cartilage communicated at the cellular level within the innate immune inflammatory network is implicated to play an important role in OA progression. Further studies on how the innate immune inflammatory network impacts the OA disease process at different stages of progression will lead to the development of new therapeutic strategies.

Keywords

Osteoarthritis; Synovium; Cartilage; Innate immunity; Innate inflammatory network; PRR; DAMPs; Crosstalk; Toll-like receptors

Introduction

Osteoarthritis (OA) is the most common form of arthritis, and is a leading cause of pain and disability [1••]. There is an increasing recognition that OA is a disease of the whole joint [1••]. The major pathological changes of OA include cartilage breakdown, the formation of osteophytes, subchondral bone sclerosis, variable degrees of inflammation of the synovium, degeneration of ligaments and the menisci in the knee, and alteration of the joint capsule [1••]. Multiple lines of evidence suggest that low-grade articular inflammation contributes to OA progression [1••, 2].

Inflammation of the synovium results in synovitis, which can occur in early stages of OA [2]. Although it is generally of a lower grade than that observed in rheumatoid arthritis (RA), synovitis directly contributes to several clinical signs and symptoms including joint swelling and effusion, and reflects the structural progression of the disease [1••, 2, 3].

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Conflict of Interest Ru Liu-Bryan declares that she has no conflict of interest.

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Histologically, OA synovium displays hyperplasia with an increase in number of synovial lining cells, accompanied by infiltration of inflammatory cells consisting of macrophages and lymphocytes [2]. It is still unclear whether morphological changes that occur in the OA synovium are primarily due to a systemic immune response or occur secondarily to cartilage degradation and lesions of the subchondral bone. Nevertheless, soluble inflammatory mediators are detected in OA synovial fluid, including a variety of cytokines and chemokines such as IL-1β TNFα, IL-6, IL-8, IL-15, and IL-17 that may be involved in promoting synovitis [1••, 2]. The molecular products derived from cellular stress and extracellular matrix (ECM) disruption can also cause synovitis [1••, 2, 3]. Innate immunity has been implicated as an active player in the development of synovitis and activation of downstream inflammatory and catabolic events in articular cartilage that lead to OA progression. This review focuses on recent advancements in the understanding of the roles of innate immune players, including pattern recognition receptors (PPRs), damage-associated molecular patterns (DAMPs), and complement in synovitis development and cartilage degradation in OA.

Role of PRRs and DAMPs in OA

The innate immune system plays an essential role not only in the host defense against microbial invasion but also in modulation of multiple forms of tissue injury and repair, and involves the recognition of distinct pathogen-associated molecular patterns (PAMPs) and DAMPs, respectively, by PRRs [4]. Activation of PRRs triggers cell signaling that leads to the production of pro-inflammatory cytokines and chemokines, and the induction of inflammatory responses [4]. These primordial innate immune inflammatory responses are established to mediate many acute and chronic forms of tissue injury [4]. The tissue degradation seen in the OA joint resembles a chronic injury.

Toll-like receptors (TLRs), the type I transmembrane glycoproteins, are members of the largest PRRs [4, 5]. Their extracellular domain contains leucine-rich repeats, which are primarily responsible for mediating ligand recognition [4, 5]. To date, 10 functional TLRs have been identified in humans [4, 5]. All the TLRs, except TLR3, utilize MyD88-dependent signaling pathways to activate transcription factors with NF-κB playing a major role, leading to production of pro-inflammatory mediators including cytokines and chemokines [4, 5]. Many members of the TLR family have been detected in synovial macrophages [6••] and chondrocytes [7, 8] in both OA and RA.

The receptor for advanced glycation end-products (RAGE) is also a member of the PRR family. It is a type I single-pass transmembrane protein, which belongs to the immunoglobulin (Ig) superfamily of cell surface receptors [9]. In the majority of healthy adult tissues, RAGE is expressed at low basal levels. However, up-regulation of RAGE has been associated with diverse pathological events including OA [10], where an inflammatory process is commonly present [9]. Engagement of RAGE triggers multiple signaling pathways leading to inflammatory gene expression via several transcription factors including NF-κB [9].

Endogenous molecular products derived from cellular stress and extracellular matrix disruption can function as DAMPs to activate TLRs and RAGE [11, 12]. Concentrations of some of DAMPs are increased in joint synovial fluid or tissues during joint injury and OA. These include alarmins such as high mobility group box protein 1 (HMGB1) and S100/calgranulin family (e.g., S100A4, the S100A8/A9 heterodimer, S100A11, S100A12), altered or degraded ECM components such as tenascin C (TN-C) and low molecular weight hyaluronan (LMW-HA), modified extracellular proteins (advanced glycation end-products (AGEs), and certain plasma proteins (Table 1) [6••, 11–16, 17•, 18–22]. Numerous studies

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have shown that these DAMPs stimulate synovial cell proliferation, influence hypertrophic chondrocyte differentiation and induce inflammatory and pro-catabolic events in vitro, and promote synovitis and cartilage degradation in vivo in murine OA models [11–16, 17•, 18–25]. Interestingly, HMGB1 and S100A8/A9 heterodimer can function through both TLR and RAGE signaling pathways [26]. A crosstalk between TLR and RAGE has been revealed [27]. Specifically, blocking the functions of TIRAP and MyD88, two intracellular adaptors for both TLR2 and TLR4, inhibits ligand-activated RAGE intracellular signaling [27]. The signaling pathways of TLR and RAGE also converge at some common points [27]. The cooperation between TLR and RAGE may depend on the cell type and particular pathological context [27]. It would be of interest to determine if there is a crosstalk between TLR and RAGE at the cellular level in the OA joint and whether the physiological significance of such cooperation exists.

In vivo studies of deficiency of TLR or RAGE and their agonists in animal models of OA have given mixed results (Table 1). For example, TN-C induces synovitis in a TLR4-dependent manner when injected into the mouse knee [25]. TN-C is not involved in the initiation of inflammation but is required for maintenance of joint inflammation [25]. In contrast, knockout of TN-C leads to worsened cartilage degeneration in the aging-related spontaneous OA and mechanical injury-induced OA mouse models [28•]. Deficiency of TN-C also delays articular cartilage repair in mice [28•]. TLR2 deficiency increased the extent of OA in the collagenase-induced model of mouse knee OA, which is associated with significant synovitis [29••]. However, in the surgically-induced destabilized medial meniscus (DMM) model, which is not associated with marked inflammation, knockout of TLR2 did not decrease experimental OA in mice [29••]. Similarly, S100A9 deficiency did not reduce focal OA cartilage destruction in the DMM model, but significantly decreased synovitis and cartilage destruction in the collagenase-induced model [30••]. RAGE deficiency also had no protective effect in the ACL tear-induced mouse knee OA [31]. The various capacities of these PRRs and DAMPs in driving synovitis and/or cartilage degradation in studies of different animal models could be informative. Each of these PRRs and DAMPs may have differential effects in specific OA phenotypes, and/or in different stages of OA.

Although deficiency of TLR2 and TLR4 attenuates catabolic responses to HMGB1 and LMW-HA in chondrocytes in vitro [20], mice deficient in both TLR2 and TLR4 had only a mild protection against OA in the medial meniscectomy model in vivo (R. Liu-Bryan, unpublished data). Immunohistochemistry analysis of the knee cartilage of these mice showed decreased expression of antioxidant enzymes such as SOD2, catalase, and thioredoxin (R. Liu-Bryan, unpublished data), suggesting a potential role of TLR2 and TLR4 in chondrocyte redox homeostasis. Interestingly, decreased SOD2 expression is seen in the superficial layer of human OA knee cartilage [32], and in the medial tibial condyle cartilage before and after the development of OA-like lesions in the spontaneous OA guinea pig model [33]. Knockdown of SOD2 expression in chondrocytes leads to oxidative damage and mitochondrial dysfunction in chondrocytes in vitro [34]. These data suggest that redox imbalance in chondrocytes could contribute to OA development and progression, and that TLR2 and TLR4 may act as the “double-edged swords” during the process of the disease.

CD14 also belongs to the PRR family. It is a co-receptor for several TLRs including TLR2 and TLR4 [35]. It is anchored into the membrane by a glycosylphosphatidylinositol tail (mCD14). CD14 acts not only as a transporter of ligands but also as a signal amplifier by moving TLRs into kinase-rich environments of lipid raft microdomains, where they associate with Src family kinases and heterodimeric G proteins [35]. A soluble form of CD14 (sCD14) also exists, arising from shedding of mCD14 or directly from intracellular vesicles through secretion [35]. Recent studies have revealed that sCD14 is increased in

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synovial fluid in early stage OA following meniscectomy, as well as in advanced knee OA at the time of total joint replacement, compared with asymptomatic postmortem donors [36•]. The SF levels of sCD14 were significantly higher than in paired serum samples [36•]. In addition, the SF of early OA patients can modulate the inflammatory responses of cultured synovial lining cells to exogenous microbial TLR2 and TLR4 ligands in vitro [36•]. However, it is not known whether CD14 is needed for the signaling of the endogenous TLR2 and TLR4 agonists in the OA joint.

Role of Complement in OA

The complement system is another essential component of innate immunity [37]. It comprises more than 30 plasma and membrane-bound proteins, and can be activated through three pathways: the classical, the alternative, and the lectin pathways [37]. All these result in turnover of C3 and, subsequently, in activation of the terminal pathway and formation of the membrane attack complex (MAC, C5b-9) [37]. The three activation pathways also require an efficient system of regulatory proteins to ensure that complement is not exhausted and to prevent damage to host cells [37]. The main biological function of the complement system is to recognize “foreign” particles and macromolecules, and to promote their elimination either by opsonization or lysis. Complement also plays a role in clearance of damaged or “used” host components [37]. Because complement proteins opsonize or lyse cells, complement can damage healthy host cells and tissues when activated excessively or improperly [37]. This has been linked to certain degenerative diseases including Alzheimer’s disease and age-related macular degeneration [37]. Activation of complement is also among the innate immune drivers of inflammatory arthritis such as RA [38].

Complement deposition is observed in the synovium of patients with cartilage degradation [39], and the components of complement are detected in OA synovial fluid [40]. Recent studies by Wang et al. have shed light on a critical role of the complement cascade in the pathogenesis of OA [41••]. A synovial fluid proteomic screen showed that complement proteins such as C3a and C5b-9 were overexpressed in the synovial fluid (SF) from early stage OA patients, compared with SF from healthy donors [41••], suggesting that complement activation occurs early in the joint during OA development. Additionally, the MAC was also found to be present in the synovium and cartilage from end-stage OA patients [41••]. Moreover, a synovial membrane transcriptome analysis demonstrated that levels of complement effectors transcripts were markedly higher, and levels of complement inhibitor transcripts were considerably lower in the synovium from patients with OA than from healthy donors [41••]. Furthermore, deficiency of C5 (a central component effector) or C6 (a component of the MAC), or addition of complement inhibitory pharmacological agents, protected mice from development of OA following medial meniscectomy [41••]. Conversely, deficiency of CD59a, the MAC inhibitor, promoted increased spontaneous OA in aging mice, and caused more severe OA in mice in the DMM model [41••]. Interestingly, C3 knockout was not chondroprotective in mouse OA in vivo [41••]. The possible explanation is that coagulation factors compensate for the lack of C3, allowing C5 activation to proceed.

How is the complement system activated in OA? Previous studies have demonstrated that the molecular components of extracellular matrix (ECM) such as cartilage oligomeric matrix protein (COMP) and fibromodulin, which are in higher concentrations in OA joint fluids, are capable of activating the complement cascade (Table 1) [42, 43]. A recent study showed that pulverized articular cartilage can induce the formation of MAC [41••]. Interestingly, aggrecan, but not type II collagen, has the capacity to activate complement, despite that both of them are major components of ECM of articular cartilage [41••]. These results suggest that the release or exposure of cartilage ECM due to dysregulation of cartilage remodeling

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and repair could contribute to OA by activation of complement. Other damaged or altered "self" components such as apoptotic and necrotic cells from joint tissues may also have a potential to activate complement in OA. Cartilage damage promoted by the MAC in the studies by Wang et al [41••] is probably not due to chondrocyte lysis, as the MAC stimulates chondrocytes to express genes of proinflammatory cytokines and cartilage-degrading enzymes at sub-cytolytic concentrations [41••]. In addition, sublytic MAC also induces the expression of complement effectors in chondrocytes [41••], indicating that chondrocyte-produced complement may synergize with synovium-derived complement to amplify pathogenic responses in OA. How the MAC stimulates production of inflammatory cytokines and catabolic enzymes remains to be determined.

Is There any Crosstalk Between TLRs and Complement in the OA Joint?

Although TLRs and complement, the two main players of innate immunity, have been studied extensively as separate entities, increasing evidence indicates that there is crosstalk between TLR and complement signaling pathways [44, 45]. Molecular interplay between the two systems can be either protective against microbial invasion by enhancing the immediate immune reaction to better prime the host in mounting a more robust adaptive immune response, or harmful to the host when activated improperly or uncontrolled by synergistic amplification of the inflammatory responses. For example, certain microbial molecules such as LPS (a TLR4 agonist), zymosan (a TLR2/6 agonist), and CpG DNA (a TLR9 agonist) activate complement in addition to initiating TLR signaling [46]. Systemic administration of these molecules to mice lacking decay-accelerating factor (DAF), a major membrane-associated complement inhibitor, induces a synergistic inflammatory response, demonstrated by significantly higher production of TNF-α, IL-1β, and IL-6 relative to wild-type mice [46]. The influence of complement on TLR signaling is exerted predominantly via the C5a receptor (C5aR), involving increased mitogen-activated protein kinase (MAPK) and NF-κB activation [46]. Blockade of the TLR co-receptor CD14 inhibits complement activities [47]. Complement activation also induces up-regulation of CD14, enhancing TLR4-induced inflammatory responses [48]. Cooperative complement–TLR induction of innate responses could be amplified by TLR-induced cytokines, such as IL-6, which promote the expression of C3aR and C5aR [49]. Given the fact that many microbial ligands are capable of activating both TLRs and complement, endogenous agonists derived from damaged tissue such as components of ECM found in OA synovial fluid may also cause coincidental activation of the two pathways, leading to damaging inflammatory responses. Future studies to determine a regulatory link between TLR and complement systems at the cellular level in the OA joint are expected and may lead to novel approaches for therapy.

Role of the Soluble Inflammatory Mediators in the Innate Immune Inflammatory Network

Soluble inflammatory mediators including cytokines and chemokines are increased in OA synovial fluids, and in joint tissues post-injury. Activation of innate immune signaling pathways of PRRs and complement can lead to generation of these soluble inflammatory mediators, produced by a variety type of cells in joint tissues including synovial fibroblasts, macrophages, and chondrocytes [50]. Among these inflammatory mediators, IL-1β and TNFα, the two most extensively studied, have been implicated in the pathogenesis of OA [2, 3]. Both IL-1β and TNFα are thought to diffuse into the synovial fluid and act on chondrocytes to suppress matrix synthesis [2, 3]. In addition, they induce expression of other cytokines such as IL-6 and IL-8, and promote cartilage catabolism by producing matrix-degrading enzymes in both synoviocytes and chondrocytes [2, 3]. Moreover, IL-1β up-regulates expression of certain PRRs such as TLR2 and RAGE [10, 51], induces release of DAMPs such as HMGB1 and low molecular weight hyaluronan [20], and promotes

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synthesis of classical pathway complement components [52] in cultured chondrocytes. These suggest that a positive feedback loop can occur between innate immune players and inflammatory cytokines at the cellular level in the OA joint, resulting in augmentation of synovial inflammation and cartilage breakdown.

It is known that production of active IL-1β requires activation of the NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome, an innate immune complex [53]. Certain DAMPs present in the OA joints, including hydroxyapatite (HA) and calcium pyrophosphate dihydrate (CPPD) crystals, can activate the NLRP3 inflammasome in macrophages [54•, 55]. In the ANK-deficient mice, HA crystals are extensively deposited in articular cartilage and synovial fluid, resulting in joint space narrowing, cartilage erosion, formation of bony outgrowths, and eventually joint immobility. However, both joint inflammation and cartilage degeneration are decreased by knockout of NLRP3 in the ANK-deficient mice [54•]. These results indicate that the NLRP3 inflammasome might be critical for mediating synovitis and joint destruction in the pathogenesis of OA in certain OA phenotypes within specific clinical settings.

Conclusions

Synovial inflammation plays a critical role in the symptoms and structural progression of OA. However, the mechanism by which synovial inflammation is triggered is still unknown. Studies have revealed that crosstalk between the joint tissues such as synovium and cartilage, communicated at the cellular levels within an innate immune inflammatory network, can promote synovitis and cartilage degradation. Innate immunity can also prime chronic and deleterious adaptive immune responses, and could contribute to the reported presence of Th1 cells expressing activation markers in OA synovium [56]. The physiologic impact of this observation warrants further investigation. It should be noted that innate immune effector mechanisms can mediate tissue repair, with protective effects on bone erosion described by Toll/interleukin-1 receptor domain-containing adaptor inducing interferon β (TRIF) modulation of IL-17 in the T cell activation-driven SCW model inflammatory arthritis [57].

Innate immune players (DAMPs, PRRs, complement) and inflammatory cytokines can mutually regulate each other in articular cells. Crosstalk between different PRRs (e.g., TLR and RAGE) and/or between PRRs and complement may exist in articular cells. Some of these innate immune players may have redundant, paradoxical, antagonistic, or various effects in distinct stages of OA, and/or in certain OA phenotypes within specific clinical settings. Targeting single molecules may be insufficient or problematic, or may not be pragmatic in the case of complement. OA is a disorder of the whole joint. Further studies on understanding crosstalk between joint tissues at the cellular level within the innate immune inflammatory network that impacts the disease process at different stages of progression will lead to the development of new therapeutic strategies.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

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1••. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012; 64:1697–707. This excellent review summarizes the key features of OA in various tissues affected, and provides an overview of the currently known mechanisms that contribute to the pathological changes in these tissues. [PubMed: 22392533]

2. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010; 6:625–35. [PubMed: 20924410]

3. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol. 2011; 23:471–8. [PubMed: 21788902]

4. Piccinini AM, Midwood KS. DAMPening inflammation by modulating TLR signalling. Mediators Inflamm. 2010; 2010 pii: 672395.

5. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010; 11:373–84. [PubMed: 20404851]

6••. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012; 51:249–57. This review provides insights into the pathogenic mechanisms underlying the development synovitis in OA. [PubMed: 22387238]

7. Bobacz K, Sunk IG, Hofstaetter JG, Amoyo L, Toma CD, Akira S, et al. Toll-like receptors and chondrocytes: the lipopolysaccharide-induced decrease in cartilage matrix synthesis is dependent on the presence of toll-like receptor 4 and antagonized by bone morphogenetic protein 7. Arthritis Rheum. 2007; 56:1880–93. [PubMed: 17530716]

8. Kim HA, Cho ML, Choi HY, Yoon CS, Jhun JY, Oh HJ, et al. The catabolic pathway mediated by Toll-like receptors in human osteoarthritic chondrocytes. Arthritis Rheum. 2006; 54:2152–63. [PubMed: 16802353]

9. Alexiou P, Chatzopoulou M, Pegklidou K, Demopoulos VJ. RAGE: a multi-ligand receptor unveiling novel insights in health and disease. Curr Med Chem. 2010; 17:2232–52. [PubMed: 20459381]

10. Loeser RF, Yammani RR, Carlson CS, Chen H, Cole A, Im HJ, et al. Articular chondrocytes express the receptor for advanced glycation end products: Potential role in osteoarthritis. Arthritis Rheum. 2005; 52:2376–85. [PubMed: 16052547]

11. Foell D, Wittkowski H, Roth J. Mechanisms of disease: a 'DAMP' view of inflammatory arthritis. Nat Clin Pract Rheumatol. 2007; 3:382–90. [PubMed: 17599072]

12. Sofat N. Analysing the role of endogenous matrix molecules in the development of osteoarthritis. Int J Exp Pathol. 2009; 90:463–79. [PubMed: 19765101]

13. Liu-Bryan R, Terkeltaub R. The growing array of innate inflammatory ignition switches in osteoarthritis. Arthritis Rheum. 2012; 64:2055–8. [PubMed: 22488656]

14. Andersson U, Harris HE. The role of HMGB1 in the pathogenesis of rheumatic disease. Biochim Biophys Acta. 2010; 1799:141–8. [PubMed: 20123076]

15. Yammani RR. S100 proteins in cartilage: role in arthritis. Biochim Biophys Acta. 1822; 2012:600–6.

16. Nakashima M, Sakai T, Hiraiwa H, Hamada T, Omachi T, Ono Y, et al. Role of S100A12 in the pathogenesis of osteoarthritis. Biochem Biophys Res Commun. 2012; 422:508–14. [PubMed: 22609404]

17•. Chockalingam PS, Glasson SS, Lohmander LS. Tenascin-C levels in synovial fluid are elevated after injury to the human and canine joint and correlate with markers of inflammation and matrix degradation. Osteoarthritis Cartilage. 2012 pii: S1063-4584(12)01011-4. This study reported that levels of TN-C are highly elevated in human knee joints after injury or OA that correlated with markers of cartilage degradation and inflammation.

18. Sofat N, Robertson SD, Hermansson M, Jones J, Mitchell P, Wait R. Tenascin-C fragments are endogenous inducers of cartilage matrix degradation. Rheumatol Int. 2012; 32:2809–17. [PubMed: 21874326]

19. Patel L, Sun W, Glasson SS, Morris EA, Flannery CR, Chockalingam PS. Tenascin-C induces inflammatory mediators and matrix degradation in osteoarthritic cartilage. BMC Musculoskelet Disord. 2011; 12:164. [PubMed: 21762512]

20. Liu-Bryan R, Terkeltaub R. Chondrocyte innate immune myeloid differentiation factor 88-dependent signaling drives procatabolic effects of the endogenous Toll-like receptor 2/Toll-like

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receptor 4 ligands low molecular weight hyaluronan and high mobility group box chromosomal protein 1 in mice. Arthritis Rheum. 2010; 62:2004–12. [PubMed: 20506365]

21. DeGroot J, Verzijl N, Wenting-van Wijk MJ, Jacobs KM, Van El B, Van Roermund PM, et al. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. Arthritis Rheum. 2004; 50:1207–15. [PubMed: 15077303]
22. Sohn DH, Sokolove J, Sharpe O, Erhart JC, Chandra PE, Lahey LJ, 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]
23. Schelbergen RF, Blom AB, van den Bosch MH, Sloetjes A, Abdollahi-Roodsaz S, Schreurs BW, et al. Alarmin S100A8 and S100A9 elicit a catabolic effect in human osteoarthritic chondrocytes that is dependent on Toll-like receptor 4. Arthritis Rheum. 2012; 64:1477–87. [PubMed: 22127564]
24. Zreiqat H, Belluoccio D, Smith MM, Wilson R, Rowley LA, Jones K, et al. S100A8 and S100A9 in experimental osteoarthritis. Arthritis Res Ther. 2010; 12(1):R16. [PubMed: 20105291]
25. Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, 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; 15:774–80. [PubMed: 19561617]
26. van Beijnum JR, Buurman WA, Griffioen AW. Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling pathways via high mobility group B1 (HMGB1). Angiogenesis. 2008; 11:91–9. [PubMed: 18264787]
27. Rojas A, Delgado-Lopez F, Gonzalez I, Perez-Castro R, Romero J, Rojas I. The receptor for advanced glycation end-products: A complex signaling scenario for a promiscuous receptor. Cell Signal. 2012; 25:609–14. [PubMed: 23200851]
28•. Okamura N, Hasegawa M, Nakoshi Y, Iino T, Sudo A, Imanaka-Yoshida K, et al. Deficiency of tenascin-C delays articular cartilage repair in mice. Osteoarthritis Cartilage. 2010; 18:839–48. This paper reports worsened cartilage degeneration and delayed cartilage repair in tenascin-C knockout mice in the aging-related spontaneous OA and mechanical injury-induced OA mouse models. [PubMed: 19747998]
29••. Blom AB, van Lent PL, Abdollahi-Roodsaz S, van der Kraan P, van den Berg W. Elusive role for toll like receptor 2 in joint pathology during experimental osteoarthritis. Osteoarthritis and Cartilage. 2011; 19(Suppl 1):25. This study shows that TLR2 deficiency increased the extent of OA in the collagenase-induced model of mouse knee OA (which is associated with significant synovitis), but did not decrease experimental OA in the DMM model.
30••. van Lent PL, Blom AB, Schelbergen RF, Sloetjes A, Lafeber FP, Lems WF, 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(5):1466–76. This study reports that S100A8 and S100A9 play a significant role in synovial activation and joint destruction in the collagenase-induced OA model. [PubMed: 22143922]
31. Cecil DL, Appleton CT, Polewski MD, Mort JS, Schmidt AM, Bendele A, et al. The pattern recognition receptor CD36 is a chondrocyte hypertrophy marker associated with suppression of catabolic responses and promotion of repair responses to inflammatory stimuli. J Immunol. 2009; 182:5024–31. [PubMed: 19342682]
32. Ruiz-Romero C, Calamia V, Mateos J, Carreira V, Martinez-Gomariz M, Fernandez M, et al. Mitochondrial dysregulation of osteoarthritic human articular chondrocytes analyzed by proteomics: a decrease in mitochondrial superoxide dismutase points to a redox imbalance. Mol Cell Proteomics. 2009; 8(1):172–89. [PubMed: 18784066]
33. Scott JL, Gabrielides C, Davidson RK, Swingler TE, Clark IM, Wallis GA, et al. Superoxide dismutase downregulation in osteoarthritis progression and end-stage disease. Ann Rheum Dis. 2010; 69:1502–10. [PubMed: 20511611]
34. Gavriilidis C, Miwa S, von Zglinicki T, Taylor RW, Young DA. Mitochondrial dysfunction in osteoarthritis is associated with a down-regulation of superoxide dismutase 2. Arthritis Rheum. 2012 Nov 8.10.1002/art.37782
35. Finberg RW, Kurt-Jones EA. CD14: chaperone or matchmaker? Immunity. 2006; 24:127–9. [PubMed: 16473824]

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36•. Nair A, Kanda V, Bush-Joseph C, Verma N, Chubinskaya S, Mikezcz K, et al. Synovial fluid from patients with early osteoarthritis modulates fibroblast-like synoviocyte responses to TLR4 and TLR2 ligands via soluble CD14. Arthritis Rheum. 2012; 64:2268–77. This study reports that soluble CD14 is increased in synovial fluid in both early and advanced stages of human knee OA, and that the synovial fluid of early OA patients can modulate cultured synovial lining cell inflammatory responses to exogenous microbial TLR2 and TLR4 ligands. [PubMed: 22492243]

37. Carroll MV, Sim RB. Complement in health and disease. Adv Drug Deliv Rev. 2011; 63:965–75. [PubMed: 21704094]

38. Ballanti E, Perricone C, di Muzio G, Kroegler B, Chimenti MS, Graceffa D, et al. Role of the complement system in rheumatoid arthritis and psoriatic arthritis: relationship with anti-TNF inhibitors. Autoimmun Rev. 2011; 10:617–23. [PubMed: 21549221]

39. Konttinen YT, Ceponis A, Meri S, Vuorikoski A, Kortekangas P, Sorsa T, et al. Complement in acute and chronic arthritides: assessment of C3c, C9, and protectin (CD59) in synovial membrane. Ann Rheum Dis. 1996; 55:888–94. [PubMed: 9014582]

40. Gobezie R, Kho A, Krastins B, Sarracino DA, Thornhill TS, Chase M, et al. High abundance synovial fluid proteome: distinct profiles in health and osteoarthritis. Arthritis Res Ther. 2007; 9:R36. [PubMed: 17407561]

41••. Wang Q, Rozelle AL, Lepus CM, Scanzello CR, Song JJ, Larsen DM, et al. Identification of a central role for complement in osteoarthritis. Nat Med. 2011; 17:1674–9. This study highlights a key role of activation of complement cascade, particularly membrane attack complex assembly, in the pathogenesis of OA. [PubMed: 22057346]

42. Happonen KE, Saxne T, Aspberg A, Morgelin M, Heinegard D, Blom AM. Regulation of complement by cartilage oligomeric matrix protein allows for a novel molecular diagnostic principle in rheumatoid arthritis. Arthritis Rheum. 2010; 62:3574–83. [PubMed: 20737467]

43. 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; 280:32301–8. [PubMed: 16046396]

44. Song WC. Crosstalk between complement and toll-like receptors. Toxicol Pathol. 2012; 40:174–82. [PubMed: 22109714]

45. Hajishengallis G, Lambris JD. Crosstalk pathways between Toll-like receptors and the complement system. Trends Immunol. 2010; 31:154–63. [PubMed: 20153254]

46. Zhang X, Kimura Y, Fang C, Zhou L, Sfyroera G, Lambris JD, et al. Regulation of Toll-like receptor-mediated inflammatory response by complement in vivo. Blood. 2007; 110:228–36. [PubMed: 17363730]

47. Lappegard KT, Christiansen D, Pharo A, Thorgersen EB, Hellerud BC, Lindstad J, et al. Human genetic deficiencies reveal the roles of complement in the inflammatory network: lessons from nature. Proc Natl Acad Sci USA. 2009; 106:15861–6. [PubMed: 19717455]

48. Stevens MG, Van Poucke M, Peelman LJ, Rainard P, De Spiegeleer B, Rogiers C, et al. Anaphylatoxin C5a-induced toll-like receptor 4 signaling in bovine neutrophils. J Dairy Sci. 2011; 94:152–64. [PubMed: 21183027]

49. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol. 2008; 8:776–87. [PubMed: 18802444]

50. 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]

51. Su SL, Tsai CD, Lee CH, Salter DM, Lee HS. Expression and regulation of Toll-like receptor 2 by IL-1beta and fibronectin fragments in human articular chondrocytes. Osteoarthritis Cartilage. 2005; 13:879–86. [PubMed: 15961329]

52. Bradley K, North J, Saunders D, Schwaeble W, Jeziorska M, Woolley DE, et al. Synthesis of classical pathway complement components by chondrocytes. Immunology. 1996; 88:648–56. [PubMed: 8881771]

53. Menu P, Vince JE. The NLRP3 inflammasome in health and disease: the good, the bad and the ugly. Clin Exp Immunol. 2011; 166:1–15. [PubMed: 21762124]

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54•. Jin C, Frayssinet P, Pelker R, Cwirka D, Hu B, Vignery A, et al. NLRP3 inflammasome plays a critical role in the pathogenesis of hydroxyapatite-associated arthropathy. Proc Natl Acad Sci USA. 2011; 108:14867–72. This study shows that the NLRP3 inflammasome mediates synovitis and joint destruction in the pathogenesis of OA associated with deposition of hydroxyapatite. [PubMed: 21856950]

55. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006; 440:237–41. [PubMed: 16407889]

56. Ishii H, Tanaka H, Katoh K, Nakamura H, Nagashima M, Yoshino S. Characterization of infiltrating T cells and Th1/Th2-type cytokines in the synovium of patients with osteoarthritis. Osteoarthritis Cartilage. 2002A; 10:277–81. [PubMed: 11950250]

57. Abdollahi-Roodsaz S, van de Loo FA, Koenders MI, Helsen MM, Walgreen B, van den Bersselaar LA, et al. Destructive role of myeloid differentiation factor 88 and protective role of TIR-containing adaptor inducing interferon β in IL-17-dependent arthritis. Arthritis Rheum. 2012; 64:1838–47. [PubMed: 22147588]

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Key Points

- Innate immunity is an active player in the development of synovitis and activation of downstream inflammatory and catabolic events in articular cartilage.
- DAMPs and PRRs have various capacities in promoting synovitis and/or cartilage degradation, which may be dependent on specific OA phenotype or stage of OA.
- Dysregulation of complement in synovial joints plays a key role in OA pathogenesis.

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Table 1

Innate immunity in OA

Innate immune players	Agonists or DAMPs implicated	Significance (in vivo testing)
Complement: C5, C6, MAC (C5b-9)	• COMP • Fibromodulin • Aggrecan	• C3 knockout: No chondroprotection in the medial meniscectomy model [41••] • C5, C6 knockout (disruption of MAC formation): Decreased OA in the medial meniscectomy model [41••] • CD59 (the MAC inhibitor) knockout: Increased OA in the medial meniscectomy, DMM and spontaneous aging models [41••]
PRRs: TLRs, RAGE, sCD14, NLRP3	• S100A8/A9 (TLR4, RAGE), • S100A4 and S100A11 (RAGE) • S100A12 (RAGE) • HMGB1 (TLR2, TLR4, RAGE) • TN-C (TLR4) • LMW-HA (TLR2, TLR4) • Plasma proteins from OA SF (TLR4) • AGEs (RAGE) • Hydroxyapatite (TLR4, NLRP3) • CPPD (TLR2, NLRP3) Other potential candidates (not reviewed): • Biglycan (TLR2, TLR4) • Necrotic cell debris, oxidized phospholipids (TLR2, TLR4) • HSPs (e.g., Hsp96) (TLR2, TLR4) • Fn extra domain A (TLR4)	• S100A9-knockout: Decreased OA in the collagenase- induced model [30] • TN-C knockout: Increased OA in the ACL and MCL transection model [28] • TLR2 knockout: Increased OA in the collagenase-induced model; no significant effect in the DMM model [29] • TLR2/TLR4 double knockout: Mild chondroprotection in the meniscectomy model (Liu-Bryan, unpublished data) • RAGE knockout: No chondroprotection in the ACL transection model [31] • Increased SF sCD14: Seen in early and advanced human OA [36] • Knockout of NLRP3 in ANK-deficient mice: Less joint inflammation and cartilage degeneration [54•]

ACL anterior cruciate ligament, *AGEs* advanced glycation-end products, *COMP* cartilage oligomeric matrix protein, *CPPD* calcium pyrophosphate dihydrate, *DMM* destabilization of the medial meniscus, *Fn* fibronectin, *HA* hyaluronan, *HSP* heat shock protein, *LMW* low molecular weight, *MAC* membrane attack complex, *MCL* medial collateral ligament, *NLRP3* NACHT LRR and PYD domains-containing protein 3, *PPRs* pattern recognition receptors, *RAGE* receptor for AGEs, *sCD14* soluble CD14, *SF* synovial fluid, *TLR* toll-like receptor, *TN-C* tenascin-C