Review

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

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ABSTRACT. Although osteoarthritis (OA) has existed since the dawn of humanity, 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 innate immune system, the older or more primitive part of the body's immune defense mechanisms. The roles of some of the components of the innate immune system have been tested in OA models *in vivo* including the roles 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 identify patient subsets and give hope for the advent of novel OA therapies. (J Rheumatol First Release Jan 15 2015; doi:10.3899/jrheum.140382)

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OSTEOARTHRITIS   INNATE IMMUNITY   MACROPHAGES   COMPLEMENT

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 peoples[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. OA is no longer thought to be a purely noninflammatory 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 articular chondropathy.

In 1 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 followup arthroscopy. This study did not adjust for baseline severity of OA, which itself is correlated with synovitis[5], so taken alone it cannot directly prove an independent effect of inflammation on structural progression. However, at least 2 other studies more convincingly show a direct effect of inflammation on OA progression. In 1 recent study with the novel imaging agent 99mTc-Etarfolatide, which 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 followup 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 interleukin 1β (IL-1β) and tumor necrosis factor-α (TNF-α), are increased in synovial fluid, and both are produced by synovial membranes and chondrocytes from patients with OA[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[15,16,17]. Thus, OA pathology is the

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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 addresses the innate immune system, including the complement system and synovial macrophages, in the pathogenesis of OA. Although we will discuss the evidence for 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 (ECM) products from trauma, microtrauma (from repetitive overuse), or normal aging generates damage-associated molecular patterns (DAMP) that activate the innate immune system[15,17]. DAMP can be fragments generated from proteins, proteoglycans, or remnants of cellular breakdown, such as uric acid[16,18,19]. DAMP 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 PRR in the cell cytoplasm, such as NOD-like receptors (NLR)[15,17,18].

TLR activation leads to increased expression of proinflammatory cytokines through a number of transcription factors, such as activator protein 1, cyclic AMP responsive element binding protein, interferon regulatory factors, and nuclear factor-κB (NF-κB)[20]; the latter has been found to play a role in OA[15]. The PRR TLR-2 and TLR-4 may be involved 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 samples from patients with OA[22] as well as the synovial membranes of those patients[21]. Human chondrocytes express TLR, and their activation in tissue culture by TLR agonists leads to upregulation of matrix metalloproteases (MMP), nitric oxide, and prostaglandin E2[22]. Tenascin-C, an ECM glycoprotein, has been shown in experimental models to cause persistence of synovial inflammation through TLR-4[23]. The plasma proteins Gc-globulin (vitamin D–binding protein),

α1-microglobulin, and α2-macroglobulin, found to be enriched in OA synovial fluid[24], can signal through 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 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)[35,36,37] (Table 1), 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 proinflammatory cytokines, proteolytic enzymes, and chemokines, and downregulation of anabolic factors, such as antiinflammatory cytokines and growth factors[11]. From a teleological perspective, the ability of DAMP 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 ongoing sterile wound healing cycle resulting in joint tissue pathology (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 antiinflammatory cytokines) and catabolic forces (proteolytic enzymes and proinflammatory cytokines)[43]. The 2 major proinflammatory cytokines implicated in OA are IL-1β and TNF-α[11]; synovial membrane biopsies from patients with early OA (symptomatic but no radiographic changes) had greater immunostaining of these 2 cytokines compared with late

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 through 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 (HA)	Yamasaki, *et al,* 2009[65]	Triggers inflammasome > IL-1β
HA	Scheibner, *et al,* 2006[31]	Triggers TLR-2
HA	Taylor, *et al,* 2007[32]	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.
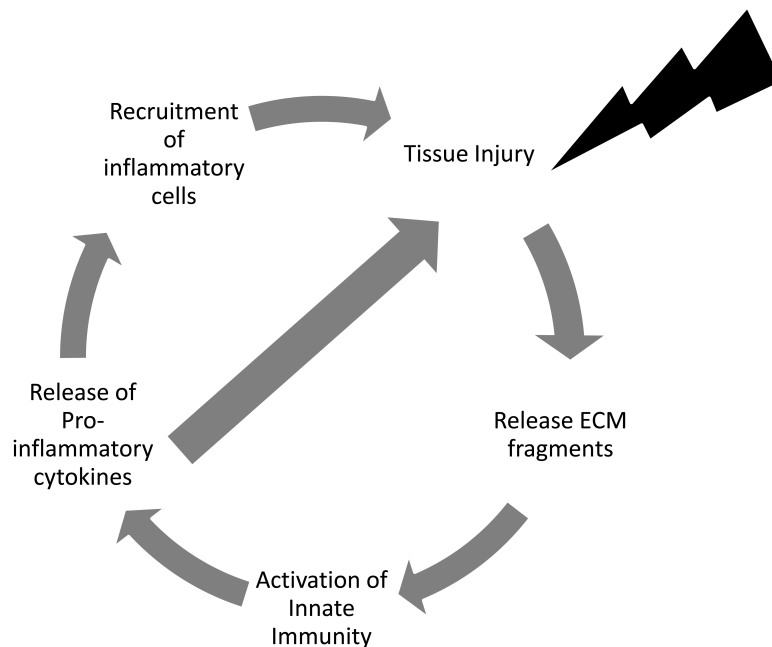

Figure 1. Osteoarthritis (OA) pathogenesis. This figure depicts the self-perpetuating cycle of joint degeneration that characterizes the pathogenesis of OA. An inciting injury to the joint tissue causes the breakdown of the extracellular matrix (ECM), which activates innate immunity and a cyclic cascade of inflammatory events leading to further and ongoing joint damage.

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, intercellular adhesion molecule 1, vascular endothelial growth factor, NF-κB, and cyclooxygenase 2 (COX-2)[44]. Another group found increased concentrations of IL-15 in the synovial fluid of 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 C-reactive protein, 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[11,43].

While the proinflammatory cytokines and chemokines represent the "marching orders," proteolytic enzymes are the actual mediators on the "front line," responsible for actual degradation of the articular cartilage. The 2 main groups of enzymes that mediate this catabolic process are the MMP and ADAMTS[11]. Various MMP and tissue inhibitor of metalloproteinases 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]. Further, RNA expression of ADAMTS from human OA synovial cells can be altered by exposure to IL-1β and TNF-α and pharmacologic blockade of these 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 3 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 studies, MAC forms in response to the presence of certain ECM proteins, such as fibromodulin[35]. Further, MAC also has sublytic properties that can upregulate inflammatory mediators without causing direct cytotoxic effects[35].

Complement proteins (Table 2) have been found to be upregulated in both the synovial membranes as well as the synovial fluid of patients with OA[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 proinflammatory 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 naturally 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 (Table 1).

While this evidence suggests that the complement system is involved in the pathogenesis of OA, a series of 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 antiinflammatory role in the
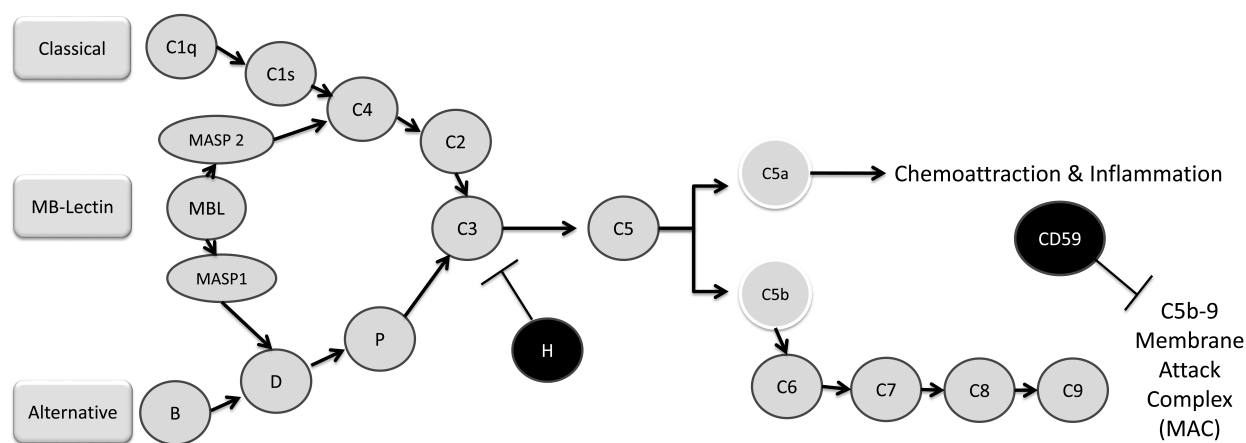

Figure 2. The complement system. The complement cascade is a complex system that can become activated by any of 3 separate pathways: the classical, the mannose-binding lectin (MBL), and alternative pathways. All 3 pathways converge on the C3 protein. C3 cleavage products participate in the activation 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). CD: cluster of differentiation; H: complement factor H; MASP: mannose-binding lectin-associated serine protease. After Wang, *et al,* Nat Med 2011;17:1674-9[35] and Sturfelt and Truedsson, Nat Rev Rheumatol 2012;8:458-68[51].

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 mice	Blom, *et al,* 2007[67]	Depletion of synovial macrophages leads to MMP activity and less severe OA in
Macrophages	van Lent, *et al,* 2004[69]	Macrophages secrete TGF-β that leads to osteophytes

SF: synovial fluid; OA: osteoarthritis; TGF: tissue growth factor; MAC: membrane attack complex.

joint[55]. Finally, in an *in vitro* model, CPB-treated serum decreased MAC formation. Subsequently, they concluded that CPB has an antiinflammatory 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 for the body's defense[56] and play a key role in innate immunity; they are involved in RA as well as OA[9] (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, one of the primary ways is through activation of PRR, 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 proinflammatory 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 patients with knee OA without gout suggested involvement of uric acid–activated NLRP3 inflammasomes in the pathogenesis of OA[64]. In that study, synovial fluid uric acid concentrations correlated with the concentrations of 2 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]. Because 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 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 MMP and aggrecanases, known to be involved in OA[50]. Depletion of synovial macrophages through intraarticular injection of clodronate leads to less MMP activity and less cartilage damage in a mouse model of OA[67]. On the other hand, macrophages also secrete growth factors such as transforming growth factor-β (TGF-β), which can enhance cartilage repair[68]. However, intraarticular injections of TGF-β 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
Because 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 linking the innate immune system with the pathogenesis of OA provides hope that insights into these mechanisms might inform our ability to sort patients into phenotypes. Patients would then stand to benefit the most from a particular therapy because these patient subsets could be treated more specifically than is currently possible. Although currently there are few effective pharmacologic treatment options for symptomatic OA, intraarticular 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 antiinflammatory 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.

The question arises of whether the growing body of knowledge linking the innate immune system to OA pathogenesis provides any hope for new OA treatments. Specifically, can slowing the inflammatory response lead to either symptomatic improvement or halt the progression of OA? Previous animal knockout models for COX-1 and COX-2[75] and IL-1β and IL-1β converting enzyme have failed to show any chondroprotective effect[76] (and may have led to increased disease). Knockout models are not always the most informative ones because it is difficult to ascertain any possible off-target effects (as illustrated 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 pointed out, one of the difficulties facing OA therapeutic studies is the long natural history of the disease[77]. Posttraumatic arthritis models might provide a way to evaluate a critical period of OA pathogenesis where inflammation may be involved. Prior studies from our group have shown that IL-1β is upregulated in the synovial fluid of animals with posttraumatic arthritis[78,79]. A prior study found that recombinant IL-1 receptor antagonist (IL-1RA) used intraarticularly 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 posttraumatic OA[81,82]. Several proof-of-concept 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].

Some of these antiinflammatory therapies have been efficacious in preclinical OA, but it is not certain how close they are to clinical availability. Prior human studies using current RA therapies to block cytokines in OA have met with mixed success. Intraarticular injections of adalimumab, an anti-TNF-α monoclonal antibody, showed some improvement in pain scores for knee OA[85] but no statistically significant improvement in pain for hand OA[86]. Another study showed a reduction in pain but no changes in radiographic scores after 12 months for patients with hand OA who received intraarticular infliximab injections[87]. Intraarticular injections of anakinra, an IL-1RA, have shown mixed results in reducing pain in several small studies[88,89]. In a proof-of-concept study from our group, the effects of intraarticular IL-1RA injections were reviewed following acute joint injury. Patients were randomized to either placebo or intraarticular IL1-RA. Those who received the intraarticular IL1-RA 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 is a growing body of literature on therapies targeting inflamed synovial tissue. 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 2 different animal models of inflammatory arthritis[91]. Another new strategy involved intraarticular injection of a DNA vector encoding an anti-C5 recombinant mini-antibody (MB12/22). This treatment led 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 fewer cellular infiltrates as well as improved clinical scores[93]. Because this therapy is directed toward a subset of inflammatory macrophages, theoretically it should have fewer 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 humans for arthritis.

In addition to serving as our first line of defense, the innate immune system is heavily involved 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; chronic stimulation of the innate immune system 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 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 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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