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 (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.

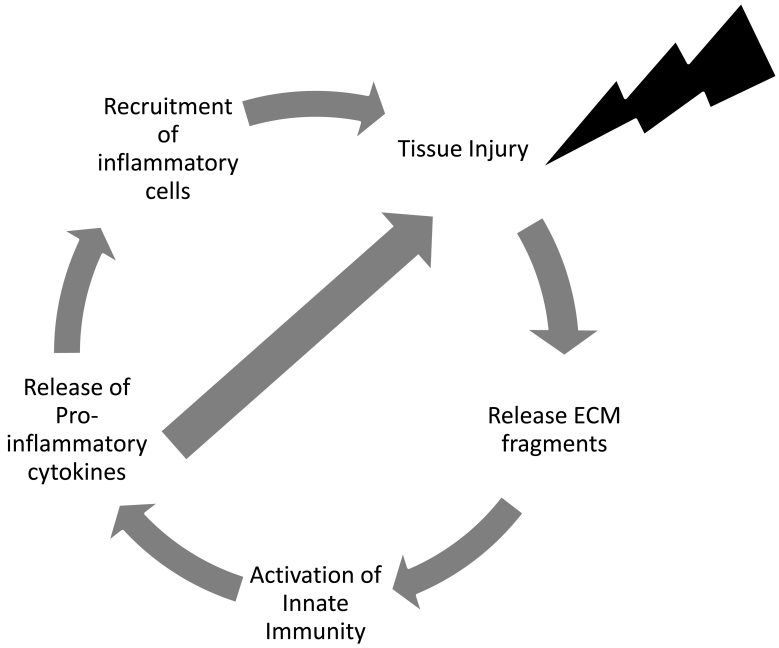

Figure 1. Osteoarthritis (OA) pathogenesis. This figure depicts the self-perpetuating cycle of joint degeneration that characterizes the pathogenesis of OA. An inciting injury to the joint tissue causes the breakdown of the extracellular matrix (ECM), which activates innate immunity and a cyclic cascade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

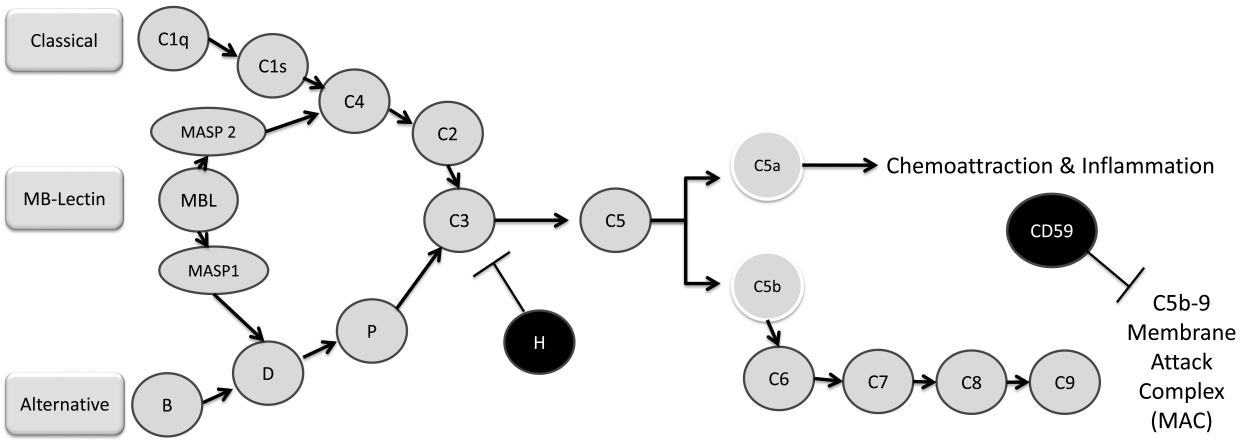

Figure 2. The complement system. The complement cascade is a complex system that can become activated by any of 3 separate pathways: the classical, the mannose-binding lectin (MBL), and alternative pathways. All 3 pathways converge on the C3 protein. C3 cleavage products participate in the activation 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	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; 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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REFERENCES

1. Dequeker J, Luyten FP. The history of osteoarthritis-osteoarthrosis.

Ann Rheum Dis 2008;67:5-10.
2. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64:1697-707.
3. Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson Imaging 1995;13:177-83.
4. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis — results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage 2005;13:361-7.
5. Guermazi A, Hayashi D, Roemer FW, Zhu Y, Niu J, Crema MD, et al. Synovitis in knee osteoarthritis assessed by contrast-enhanced magnetic resonance imaging (MRI) is associated with radiographic tibiofemoral osteoarthritis and MRI-detected widespread cartilage damage: the MOST study. J Rheumatol 2014;41:501-8.
6. Kraus V, McDaniel G, Huebner J, Stabler T, Pieper C, Coleman R, et al. Direct in vivo evidence of activated macrophages in human osteoarthritis. Osteoarthritis Cartilage 2013;21 Suppl:S42-67.
7. Daghestani H, Pieper C, Kraus V. Soluble macrophage biomarkers indicate inflammatory phenotypes in patients with knee osteoarthritis. Arthritis Rheumatol 2014; in press.
8. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804-9.
9. Revell PA, Mayston V, Lalor P, Mapp P. The synovial membrane in osteoarthritis: a histological study including the characterisation of the cellular infiltrate present in inflammatory osteoarthritis using monoclonal antibodies. Ann Rheum Dis 1988;47:300-7.
10. Furuzawa-Carballeda J, Macip-Rodríguez PM, Cabral AR. Osteoarthritis and rheumatoid arthritis pannus have similar qualitative metabolic characteristics and pro-inflammatory cytokine response. Clin Exp Rheumatol 2008;26:554-60.
11. 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.
12. Pelletier J-P, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237-47.
13. Kraus VB. Preclinical osteoarthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt M, Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Mosby Elsevier; 2014.
14. Vincent TL. Targeting mechanotransduction pathways in osteoarthritis: a focus on the pericellular matrix. Curr Opin Pharmacol 2013;13:449-54.
15. Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? Curr Opin Rheumatol 2008;20:565-72.
16. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012;51:249-57.
17. Liu-Bryan R. Synovium and the innate inflammatory network in osteoarthritis progression. Curr Rheumatol Rep 2013;15:323.
18. Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 2010;10:826-37.
19. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis 2013;5:77-94.
20. O'Neill LA, Golenbock D, Bowie AG. The history of Toll-like receptors - redefining innate immunity. Nat Rev Immunol 2013;13:453-60.
21. Radstake TR, Roelofs MF, Jenniskens YM, Oppers-Walgreen B, van Riel PL, Barrera P, et al. Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines interleukin-12 and interleukin-18 via interferon-gamma. Arthritis Rheum 2004;50:3856-65.
22. 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.
23. 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.
24. 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.
25. 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.
26. Abdollahi-Roodsaz S, Joosten LA, Koenders MI, Devesa I, Roelofs MF, Radstake TR, et al. Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis. J Clin Invest 2008;118:205-16.
27. Freria CM, Velloso LA, Oliveira AL. Opposing effects of Toll-like receptors 2 and 4 on synaptic stability in the spinal cord after peripheral nerve injury. J Neuroinflammation 2012;9:240.
28. Rolls A, Shechter R, London A, Ziv Y, Ronen A, Levy R, et al. Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol 2007;9:1081-8.
29. Okamura Y, Watari M, Jerud ES, Young DW, Ishizaka ST, Rose J, et al. The extra domain A of fibronectin activates toll-like receptor 4. J Biol Chem 2001;276:10229-33.
30. Gondokaryono SP, Ushio H, Niyonsaba F, Hara M, Takenaka H, Jayawardana ST, et al. The extra domain A of fibronectin stimulates murine mast cells via toll-like receptor 4. J Leukoc Biol 2007;82:657-65.
31. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. J Immunol 2006;177:1272-81.
32. Taylor KR, Yamasaki K, Radek KA, Di Nardo A, Goodarzi H, Golenbock D, et al. Recognition of hyaluronan released in sterile injury involves a unique receptor complex dependent on toll-like receptor 4, CD44, and MD-2. J Biol Chem 2007;282:18265-75.
33. Frommer KW, Zimmermann B, Meier FM, Schroder D, Heil M, Schaffler A, et al. Adiponectin-mediated changes in effector cells involved in the pathophysiology of rheumatoid arthritis. Arthritis Rheum 2010;62:2886-99.
34. 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.
35. 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.
36. 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.
37. 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.
38. Kalchishkova N, Furst CM, Heinegard D, Blom AM. NC4 domain of cartilage-specific collagen IX inhibits complement directly due to attenuation of membrane attack formation and indirectly through binding and enhancing activity of complement inhibitors C4B-binding protein and factor H. J Biol Chem 2011;286:27915-26.

39. Loeser RF. Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators, and aging collide. Arthritis Rheum 2006;54:1357-60.
40. Kraus VB. Osteoarthritis: the zinc link. Nature 2014;507:441-2.
41. O'Conor CJ, Leddy HA, Benefield HC, Liedtke WB, Guilak F. TRPV4-mediated mechanotransduction regulates the metabolic response of chondrocytes to dynamic loading. Proc Natl Acad Sci U S A 2014;111:1316-21.
42. Vincent T, Hermansson M, Bolton M, Wait R, Saklatvala J. Basic FGF mediates an immediate response of articular cartilage to mechanical injury. Proc Natl Acad Sci U S A 2002;99:8259-64.
43. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6:625-35.
44. Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis 2005;64:1263-7.
45. Scanzello CR, Umoh E, Pessler F, Diaz-Torne C, Miles T, Dicarlo E, et al. Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. Osteoarthritis Cartilage 2009;17:1040-8.
46. Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. Osteoarthritis Cartilage 2007;15:516-23.
47. Ishiguro N, Ito T, Ito H, Iwata H, Jugessur H, Ionescu M, et al. Relationship of matrix metalloproteinases and their inhibitors to cartilage proteoglycan and collagen turnover: analyses of synovial fluid from patients with osteoarthritis. Arthritis Rheum 1999;42:129-36.
48. Yuan GH, Tanaka M, Masuko-Hongo K, Shibakawa A, Kato T, Nishioka K, et al. Characterization of cells from pannus-like tissue over articular cartilage of advanced osteoarthritis. Osteoarthritis Cartilage 2004;12:38-45.
49. Pratta MA, Scherle PA, Yang G, Liu R-Q, Newton RC. Induction of aggrecanase 1 (ADAM-TS4) by interleukin-1 occurs through activation of constitutively produced protein. Arthritis Rheum 2003;48:119-33.
50. Bondeson J, Wainwright SD, Lauder S, Amos N, Hughes CE. The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis. Arthritis Res Ther 2006;8:R187.
51. Sturfelt G, Truedsson L. Complement in the immunopathogenesis of rheumatic disease. Nat Rev Rheumatol 2012;8:458-68.
52. 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.
53. Corvetta A, Pomponio G, Rinaldi N, Luchetti MM, Diloreto C, Stramazzotti D. Terminal complement complex in synovial tissue from patients affected by rheumatoid-arthritis, osteoarthritis and acute joint trauma. Clin Exp Rheumatol 1992;10:433-8.
54. Onuma H, Masuko-Hongo K, Yuan GH, Sakata M, Nakamura H, Kato T, et al. Expression of the anaphylatoxin receptor C5aR (CD88) by human articular chondrocytes. Rheumatol Int 2002;22:52-5.
55. Lepus CM, Song JJ, Wang Q, Wagner CA, Lindstrom TM, Chu CR, et al. Brief report: carboxypeptidase B serves as a protective mediator in osteoarthritis. Arthritis Rheumatol 2014;66:101-6.
56. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008;8:958-69.
57. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 2011;11:723-37.
58. Amos N, Lauder S, Evans A, Feldmann M, Bondeson J. Adenoviral gene transfer into osteoarthritis synovial cells using the endogenous inhibitor I kappa B alpha reveals that most, but not all, inflammatory and destructive mediators are NF kappa B dependent. Rheumatology 2006;45:1201-9.
59. Schroder K, Tschopp J. The inflammasomes. Cell 2010;140:821-32.
60. Dinarello CA. Anti-inflammatory agents: present and future. Cell 2010;140:935-50.
61. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237-41.
62. 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 U S A 2011;108:14867-72.
63. McCarthy G, Cheung H. Point: hydroxyapatite crystal deposition is intimately involved in the pathogenesis and progression of human osteoarthritis. Curr Rheumatol Rep 2009;11:141-7.
64. Denoble AE, Huffman KM, Stabler TV, Kelly SJ, Hershfield MS, McDaniel GE, et al. Uric acid is a danger signal of increasing risk for osteoarthritis through inflammasome activation. Proc Natl Acad Sci U S A 2011;108:2088-93.
65. Yamasaki K, Muto J, Taylor KR, Cogen AL, Audish D, Bertin J, et al. NLRP3/cryopyrin is necessary for interleukin-1beta (IL-1beta) release in response to hyaluronan, an endogenous trigger of inflammation in response to injury. J Biol Chem 2009;284:12762-71.
66. Muehleman C, Li J, Aigner T, Rappoport L, Mattison E, Hirschmugl C, et al. Association between crystals and cartilage degeneration in the ankle. J Rheumatol 2008;35:1108-17.
67. Blom AB, van Lent PL, Libregts S, Holthuysen AE, van der Kraan PM, van Rooijen N, et al. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. Arthritis Rheum 2007;56:147-57.
68. Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF-beta and osteoarthritis. Osteoarthritis Cartilage 2007; 15:597-604.
69. van Lent PL, Blom AB, van der Kraan P, Holthuysen AE, Vitters E, van Rooijen N, et al. Crucial role of synovial lining macrophages in the promotion of transforming growth factor beta-mediated osteophyte formation. Arthritis Rheum 2004;50:103-11.
70. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:455-74.
71. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363-88.
72. Firestein G, Paine M, Littman B. Gene expression (collagenase, tissue inhibitor of metalloproteinases, complement, and HLA-DR) in rheumatoid arthritis and osteoarthritis synovium. Quantitative analysis and effect of intraarticular corticosteroids. Arthritis Rheum 1991;34:1094-105.
73. Bureeva S, Andia-Pravdivy J, Symon A, Bichucher A, Moskaleva V, Popenko V, et al. Selective inhibition of the interaction of C1q with immunoglobulins and the classical pathway of complement activation by steroids and triterpenoids sulfates. Bioorg Med Chem 2007;15:3489-98.
74. Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nat Rev Rheumatol 2012;8:645-55.
75. Fukai A, Kamekura S, Chikazu D, Nakagawa T, Hirata M, Saito T, et al. Lack of a chondroprotective effect of cyclooxygenase 2 inhibition in a surgically induced model of osteoarthritis in mice.

Arthritis Rheum 2012;64:198-203.
76. Clements KM, Price JS, Chambers MG, Visco DM, Poole AR, Mason RM. Gene deletion of either interleukin-1beta, interleukin-1beta-converting enzyme, inducible nitric oxide synthase, or stromelysin 1 accelerates the development of knee osteoarthritis in mice after surgical transection of the medial collateral ligament and partial medial meniscectomy. Arthritis Rheum 2003;48:3452-63.
77. Hunter DJ. Pharmacologic therapy for osteoarthritis—the era of disease modification. Nat Rev Rheumatol 2011;7:13-22.
78. Huebner J, Furman B, Seifer D, Kraus V, Guilak F, Olson S. Assessment of serum and synovial fluid levels of IL-1α and IL-1β in a mouse model of post-traumatic arthritis. Osteoarthritis Cartilage 2009;17:S73-122.
79. Lewis JS Jr., Furman BD, Zeitler E, Huebner JL, Kraus VB, Guilak F, et al. Genetic and cellular evidence of decreased inflammation associated with reduced incidence of posttraumatic arthritis in MRL/MpJ mice. Arthritis Rheum 2013;65:660-70.
80. Caron JP, Fernandes JC, Martel-Pelletier J, Tardif G, Mineau F, Geng C, et al. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. Arthritis Rheum 1996;39:1535-44.
81. Kimmerling K, Furman B, Mangiapani D, Moverman M, Sinclair S, Huebner J, et al. Prolonged intra-articular delivery of IL-1Ra from a thermally-responsive elastin-like polypeptide depot prevents post-traumatic arthritis in mice. Eur Cell Mater 2014; in press.
82. Furman B, Mangiapani D, Zeitler E, Bailey K, Horne P, Huebner J, et al. Targeting pro-inflammatory cytokines following joint injury: Acute intra-articular inhibition of IL-1 following knee injury prevents post-traumatic arthritis. Arthritis Res Ther 2014;16:R134.
83. Kamath R, Hart M, Conlon D, Ghayur T. Simultaneous targeting of IL-1A and IL-1B by a dual-variable domain immunoglobulin (DVD-Ig™) prevents cartilage degradation in preclinical models of osteoarthritis. Osteoarthritis Cartilage 2011;19:S64-126.
84. Kamath RV, Simler G, Zhou C, Hart M, Joshi S, Ghayur T, et al. Blockade of both IL-1A and IL-1B by a combination of monoclonal antibodies prevents the development and reverses established pain in a preclinical model of osteoarthritis. Osteoarthritis Cartilage 2012;20:S62-109.
85. Grunke M, Schulze-Koops H. Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade. Ann Rheum Dis 2006;65:555-6.
86. Fioravanti A, Fabbroni M, Cerase A, Galeazzi M. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. Rheumatol Int 2009;29:961-5.
87. Magnano MD, Chakravarty EF, Broudy C, Chung L, Kelman A, Hillygus J, et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. J Rheumatol 2007;34:1323-7.
88. Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009;61:344-52.
89. Bacconnier L, Jorgensen C, Fabre S. Erosive osteoarthritis of the hand: clinical experience with anakinra. Ann Rheum Dis 2009;68:1078-9.
90. Kraus VB, Birmingham J, Stabler TV, Feng S, Taylor DC, Moorman CT 3rd, et al. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). Osteoarthritis Cartilage 2012;20:271-8.
91. Macor P, Durigutto P, De Maso L, Garrovo C, Biffi S, Cortini A, et al. Treatment of experimental arthritis by targeting synovial endothelium with a neutralizing recombinant antibody to C5. Arthritis Rheum 2012;64:2559-67.
92. Durigutto P, Macor P, Ziller F, De Maso L, Fischetti F, Marzari R, et al. Prevention of arthritis by locally synthesized recombinant antibody neutralizing complement component C5. Plos One 2013;8:e58696.
93. Li J, Hsu H-C, Yang P, Wu Q, Li H, Edgington LE, et al. Treatment of arthritis by macrophage depletion and immunomodulation: Testing an apoptosis-mediated therapy in a humanized death receptor mouse model. Arthritis Rheum 2012;64:1098-109.
94. Forero-Torres A, Shah J, Wood T, Posey J, Carlisle R, Copigneaux C, et al. Phase I trial of weekly tigatuzumab, an agonistic humanized monoclonal antibody targeting death receptor 5 (DR5). Cancer Biother Radiopharm 2010;25:13-9.
95. Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis – a case for personalized health care? Osteoarthritis Cartilage 2014;22:7-16.