Published in final edited form as:
Clin Immunol. 2013 March ; 146(3): 185–196. doi:10.1016/j.clim.2012.12.011.

Immunopathogenesis of Osteoarthritis

Abdul Haseeb and **Tariq M. Haqqi***
Department of Anatomy & Neurobiology, Northeast Ohio Medical University, 4209 St. Rt. 44, P.O. Box 95, Rootstown, OH 44272, USA

Abstract

Even though osteoarthritis (OA) is mainly considered as a degradative condition of the articular cartilage, there is increasing body of data demonstrating the involvement of all branches of the immune system. Genetic, metabolic or mechanical factors cause an initial injury to the cartilage resulting in release of several cartilage specific auto-antigens, which trigger the activation of immune response. Immune cells including T cells, B cells and macrophages infiltrate the joint tissues, cytokines and chemokines are released from different kind of cells present in the joint, complement system is activated, cartilage degrading factors such as matrix metalloproteins (MMPs) and prostaglanding E_2 (PGE_2) are released, resulting in further damage to the articular cartilage. There is considerable success in the treatment of rheumatoid arthritis using anti-cytokine therapies. In OA, however, these therapies did not show much effect, highlighting more complex nature of pathogenesis of OA. This needs the development of more novel approaches to treat OA, which may include therapies that act on multiple targets. Plant natural products have this kind of properties and may be considered for future drug development efforts. Here we reviewed the studies implicating different components of the immune system in the pathogenesis of OA.

Keywords

Osteoarthritis; T cells; B cells; Complement system; Cytokines; Chemokines

1. Introduction

Osteoarthritis (OA) is a chronic disease and results from damage to articular cartilage induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors followed by activation of inflammatory response involving the interaction of cartilage, subchondral bone, and synovium [1]. Many factors- some modifiable- contribute to an increased risk of OA and include obesity, genetics, aging and trauma to the joint. In most patients without a strong genetic predisposition, OA is thought to start as a result of damage to the joint tissue by physical forces as a single event of trauma or by repeated

*Correspondence: Tariq M Haqqi, PhD, Department of Anatomy & Neurobiology, Northeast Ohio Medical University, F-144, 4209 St. Rt. 44, P.O. Box 95, Rootstown, OH 44272, USA, thaqqi@neomed.edu.

microtrauma due to altered mechanical loading of the joint [2]. Chondrocytes respond to the physical injury by stopping the production of anabolic factors and by releasing more catabolic enzymes such as MMPs, which results in further damage to the cartilage [3], and this further leads to the release of matrix components, which elicit inflammatory mechanisms [4]. Involvement of an immune response, both innate and adaptive, in OA is now widely accepted based on the following evidence:

1. An inflammatory synovium/synovitis has been linked to increased cartilage damage [5] and pain [6] in recent epidemiological studies on large number of OA patients.
2. Infiltrates of immune cells including T-cells, B-cells and macrophages have been detected in synovial tissue of OA patients [7,8,9].
3. Immunoglobulins and immune complexes against cartilage components are detected in cartilage, synoium and plasma in OA patients [4].
4. Key role of complement activation in OA synovium has been identified [10].

Here we provide a review and recent updates on the involvement of major aspects of immune system, including innate and adaptive immune responses, in the pathogenesis of OA.

2. Innate immunity

2.1 Cellular Factors: Monocytes/macrophages and other cells of innate immunity in OA

Macrophages are among the most abundant cell type present in the cellular infiltrates found in the inflamed synovium in OA [7,11,12]. Macrophage-derived cytokines, including IL-1β and TNF-α are the major players in the cartilage breakdown in OA [discussed later in this review]. Several chemokines responsible for chemotaxis of macrophages have been implicated in the development of OA. Using a collagenase-induced mouse model it was shown that depletion of synovial macrophages by injection of clodronate-laden liposomes resulted in decreased TGF-β-induced osteophyte formation [13]. Using the same model Blom et al showed that the activation of synovial macrophages is required for the production of MMPs and cartilage damage [14]. Bondeson et al developed a macrophage depleted synovial cell culture model by using CD14-conjugated magnetic beads. Specific removal of synovial macrophages from these cultures resulted in significantly decreased production of cytokines, IL-1β and TNF-α, indicating that the source of these cytokines were synovial macrophages. Further, macrophage depletion also resulted in decreased production of IL-6, IL-8, MMP-1 and MMP-3 [15].

Presence of natural killer cells was reported in synovial tissues obtained from patients undergoing total joint replacements, which constituted about 30% of the CD45+ mononuclear cell infiltrate [16]. These cells showed a quiescent phenotype consistent with post-activation exhaustion. Presence of low level of activated dendritic cells was also reported in OA synovium [17]. Recently, dendritic cell infiltrates were detected in the synovial tissue of rabbits with surgically induced OA in the early stages of the disease (2 and 4 weeks post-operation) [18]. However, the role of both NK cells and dendritic cells in OA pathogenesis has not yet been elucidated in detail.

2.2 Humoral Factors

2.2.1 Activation of complement system in OA—The complement system constitutes a crucial effector mechanism in the immune system to clear the pathogens and immune complexes and consists of a cascade of very tightly regulated array of proteins, improper regulation of which may lead to self tissue damage. The deposition and activation of complement factors in OA cartilage has been documented in several early studies in OA patients as well as in animal models of OA [19,20,21,22]. Tarkowski et al observed expression of decay accelerating factor (DAF) in the synovial lining cell layer both in rheumatoid arthritis (RA) and in osteoarthritis (OA) along with C5b-9 terminal complement complex suggesting an activation of complement-mediated response [23]. Corvetta et al found a correlation of terminal complement complex deposits in synovial tissue with the extent of inflammatory synovitis, irrespective of whether the synovitis was in RA or OA patients [24]. Doherty et al found C3 activation to be associated with RA and gout but not with OA [25]. A recent study looking specifically at the levels of lectin pathway proteins found a significant association of the level of these proteins in plasma and synoial fluid (SF) with RA and OA [26]. Several proteomic studies have identified components of complement system as differentially expressed proteins in synovial fluid [27,28], serum [29] and cartilage [30] samples from OA patients. A transcriptome analysis of damaged versus smooth articular cartilage obtained from OA patients revealed decay accelerating factor (DAF) and complement factor I (IF) as two of the six genes up-regulated in the affected cartilage [31]. Results obtained from several studies point to a local synthesis and secretion of these factors within SF instead of resulting from a leakage from the blood [30,31,32,33,34,35]. Chondrocytes have been shown to over-express the C5a receptor (C5aR/CD88) during RA and OA and C5aR/CD88 was found to be up-regulated upon treatment with IL-1 in RA chondrocytes but not in OA chondrocytes suggesting a differential role of C5aR/CD88 in RA and OA [36]. Functional studies have shown that one of the complement components 1s acts as a serine protease and degrades chondroprotective trophic factor IGFBP-5 in cartilage and inhibition of C1s results in improved OA symptoms [37,38]. In a recent report using three mouse models of OA, Wang et al showed that mice deficient in the ability to synthesize the membrane attack complex (MAC) are protected from developing OA while mice deficient in MAC-inhibitor CD59a developed more severe OA as compared to wild type mice [10]. This study also showed that MAC's cartilage destruction was mediate by an over-expression of cartilage degradation enzymes and pro-inflammatory cytokines instead of lysis of the chondrocytes by the MAC itself [10].

2.2.2 Role of cytokines in OA—Inflammation of the synovial membrane/synovitis is emerging as the main feature of OA even in the early stages of the disease [reviewed recently in 39]. Several soluble factors such as cytokines and chemokines released from the inflamed synovium result in further progression of OA symptoms. During OA, the normally tightly regulated anabolic and catabolic process responsible for maintenance of cartilage homeostasis is disturbed due to the stimulation of inflammatory mechanisms and release of several cytokines. IL-1β and TNF-α are the two major pro-inflammatory cytokines responsible for the shift of cartilage homeostasis towards more catabolism and degradation of cartilage.

2.2.2.1 IL-1β: IL-1β is over-expressed during OA in cartilage as well as in the synovial tissue with a concomitant decrease in the expression of IL-1R antagonist (IL-1Ra) [40,41,42,43]. Over-expression of IL-1RI was observed in chondrocytes located in cartilage proximal to the macroscopic OA lesions resulting in increased binding of IL-1β making those cells more susceptible to the effects of this cytokine [44]. IL-1RI has also been reported to be over-expressed in human OA synovial fibroblasts [45]. Several studies in animal models of OA have also highlighted the important role played by IL-1β in development of symptoms associated with OA [46,47]. IL-1β has been shown to up-regulate the expression of MMP family of catabolic enzymes, MMP-1, -3 and -13 [48,49,50] and to stimulate the production of ADAMTS-4 and -5 (aggrecanases) in human chondrocytes [51], in human OA synovial fibroblasts [52] and bovine chondrocytes [53]. IL-1β also suppresses the anabolic mechanism in cartilage tissue by inhibiting the expression of type II collagen [54,55] and proteoglycans [56,57] in chondrocytes, the two major components of the cartilage extra-cellular matrix (ECM) in cartilage. The mechanism of action of IL-1β on the anabolism of proteoglycan was shown to involve the repression of galactose-beta-1,3-glucuronosyltransferase I (GlcAT-I), a key enzyme in the biosynthesis of glycosaminoglycans [58]. A decrease in the number of chondrocytes during OA has been reported and IL-1β has been attributed as the cause of apoptosis in chondrocytes. In fact, apoptotic features such as mitochondrial depolarization and upregulation of pro-apoptotic Bcl-2 family of proteins have been reported in chondrocytes treated with IL-1β [59,60]. IL-1β may induce apoptosis by increasing the production of NO via up-regulation of iNOS [61,62] or by generation of ROS in chondrocytes [63,64,65].

2.2.2.2 TNF-α: TNF-α shows similar effects on articular cartilage and may act synergistically with IL-1β during OA. TNF-α, similar to IL-1β, has been shown to be over-expressed in OA cartilage [66,67] and was detected in OA synovium [68]. TNF receptor expression is increased in OA cartilage and OA synovium [69,70]. TNF-α was shown to stimulate resorption and inhibit the synthesis of proteoglycan in cartilage explants [71]. TNF-α has also been shown to stimulate the expression of MMP-1, MMP-3 and MMP-13 [72,73]. mRNA expression of TNF-α converting enzyme (TACE), which mediates the conversion of pro-TNF-α to mature TNF-α, was also found to be elevated in OA cartilage [74]. Looking at the success of anti-TNF therapy in RA and given the important role played by IL-1β and TNF-α in OA, any optimism regarding the success of therapies aimed at blocking these cytokines in OA won't be unjustified, but the few clinical trials conducted did not show much success in OA patients [reviewed recently in 75,76,77]. This may be attributed to a more complex interplay of various pathogenetic factors in OA, than those regulated by these cytokines alone.

2.2.2.3 IL-6: IL-6 is a pro-inflammatory cytokine, which activates the transcription of its target genes via formation of an IL-6 receptor complex involving a membrane bound IL-6 receptor (IL-6R), soluble IL-6R (sIL-6R) and gp130 followed by activation of STAT1/STAT3 pathway [78]. Guerne et al showed the release of IL-6 from synoviocytes in response to IL-1 and detected IL-6 activity in synovial fluids obtained from OA patients, though less than those from RA patients [79]. Later, the same group showed the release of IL-6 from human chondrocytes in response to cytokines, including IL-1 and TNF-α and

certain growth factors [80]. Type II collagen stimulated the production of IL-6 from human chondrocytes [81]. PGE_2 has also been shown to stimulate the synthesis of IL-6 in synovial fibroblasts [82] and human chondrocytes [83,84,85]. A prospective population study on a cohort of British women showed a correlation of higher BMI and elevated serum levels of IL-6 with development of radiographic knee OA [86]. IL-6 has been shown to exert its effect on catabolic mechanism in cartilage by upregulating the expression of MMP-1 and MMP-13 expression in combination with IL-1β and oncostatin M (OSM) in human and bovine cartilage explants [87,88]. IL-6 has also been shown to affect the anabolic process in cartilage by inhibiting the expression of type II collagen by inhibiting the binding of Sp1/Sp3 to the type II collagen promoter [89].

2.2.2.4 Other Cytokines: Role of other pro-inflammatory cytokines including oncostatin M (OSM), IL-7, IL-8, leukemia inhibitory factor (LIF), IL-11, IL-17 and IL-18 and anti-inflammatory cytokines including IL-4, IL-10 and IL-13 has also been reported in chondrocytes metabolism and development of OA [reviewed in 75,77].

2.2.3 Role of Chemokines in OA—Chemokines are small secretory molecules responsible for chemotaxis of immune cells. Chemokines are classified based on the motif displayed by the first two cysteines residues near the N-terminus into four groups: CC-, CXC, C- and CXXXC. Chemokines act through seven transmembrane Gi-protein coupled receptors [90]. Several chemokines including IL-8/CXCL-8, GROα/CXCL-1, MCP-1/CCL-2, RANTES/CCL-5, MIP-1α/CCL-3 and MIP-1β/CCL-4 were reported to be expressed by human chondrocytes and some of them were shown to be over-expressed in OA [91]. Pro-inflammatory cytokine IL-1β has been shown to stimulate the expression of chemokines in OA chondrocytes [92], while anti-inflammatory factors TGF-β and IL-10 did not show any effect on the expression of these molecules [93]. Expression of several chemokine receptors on the surface of chondrocytes was later reported, which also showed their functionality by inducing the release of MMPs upon binding with their lignads [94,95, 96]. Alaaeddine et al reported the over-expression of RANTES/CCL-5 and its receptors in OA chondrocytes and in normal chondrocytes upon stimulation with IL-1β. Treatment of normal chondrocytes with RANTES/CCL-5 induced the markers of cartilage degradation [69]. Expression of several chemokines and chemokine receptors were also reported in PBMCs and synovial tissue from RA, OA and reactive arthritis [97]. Endres et al reported the chemokine profile of synovial fluid from OA, RA and normal subjects and showed the presence of several chemokines in diseased synovium that may cause the migration of mesenchymal progenitor cells in the microfracture caused during arthritis [98]. A global gene expression analysis in rat model of OA revealed differential expression of MCP-1/CCL-2 and CXCR-4 in chondrocytes [99]. Interestingly, much higher levels of MIP-1β/CCL4 were found in synovial fluid of OA patients (18.0 +/− 8.9 ng/ml) as compared to RA patients (6.1 +/− 2.9 ng/ml) [100]. MIP-1γ/CCL-9 was shown to be produced from activated CD4+ T cells present in the synovium of a mouse model of OA, which also resulted in increased formation of osteoclasts in joints [101]. GRO-α/CXCL-1 and SDF-1/CXCL-12 have been shown to induce cell death in human chondrocytes in apoptotic and necrotic manner, respectively [102, 103]. SDF-1/CXCL-12 was also shown to stimulate IL-6 expression in human synovial fibroblasts [104]. Merz et al showed that IL-8/CXCL-8 and

GRO-α/CXCL-1 induced hypertrophic differentiation and calcification in chondrocytes, highlighting the role of inflammation in altered differentiation of chondrocytes [105]. Expression of IL-8/CXCL-8/Kc was, recently, shown to be stimulated by mechanical, inflammatory and metabolic stresses [106]. Hsu et al reported higher levels of eotaxin-1/CCL-11 in OA patients compared to controls and there was an increase in expression of eotaxin-1/CCL-11 upon treatment of chondrocytes with IL-1β and TNF-α [107]. Further, treatment of chondrocytes with eotaxin-1/CCL-11 resulted in increased expression of its receptors CCR-3 and CCR-5 and cartilage degradation enzymes MMP-3 and MMP-13 [107]. Brul et al detected the expression of CCR-5 on synovial fibroblasts from OA and RA patients. Activation of CCR-5 with its ligands CCL-19 and CCL-21 resulted in cell migration and increased secretion of VEGF [108].

3. Adaptive immunity

3.1 T cells and cellular immunity in OA

Mononuclear cell infiltrates in synovial tissues have been reported in OA [40,109,110,111,112] and have been shown to contain primarily CD3+ T cells [113]. Both CD4+ and CD8+ cells were found in OA synovium at similar levels as in RA synovium. The Th1 subset of T cells were found to be about 5 times more than Th2 cells [113] and higher levels of Th1 cytokines, IL-2 and IFNγ, were detected in most of OA patients [110]. T-cells in lymphocytic aggregates in OA synovium were shown to bear early (CD69), intermediate (CD25 and CD38) and late (CD45RO) activation markers. These observations suggest the presence of an active cell-mediated immune response in majority of OA patients. Analysis of α/β T cell receptor diversity revealed the presence of oligoclonal populations of T cells in OA patients [9,114,115]. This suggested that those cells were undergoing clonal expansion in response to specific antigens within the synovium. Although there are no conclusive data on the antigens, which drive the immune response in OA, several candidate antigens have been proposed. T cells derived from peripheral blood and synovial fluid of OA patients showed a strong response to autologous chondrocyte and fibroblast membrane preparations [116]. In another study OA chondrocytes were shown to stimulate autologous T cell response in vitro [117]. Cellular immunity to type III collagen and proteoglycan was detected after partial meniscectomy in rabbits [118]. Higher cellular immunity was observed in OA patients compared to normal subjects when their peripheral blood lymphocytes were stimulated with human cartilage link protein and G1 globular domain of proteoglycan [119]. More specifically, peptides representing amino acid regions 16–31 and 263–280 located in G1 domain of proteoglycan were more frequently recognized by PBMCs isolated from OA patients compared to healthy controls [120]. These studies suggest a role for cartilage components as autoantigens responsible for oligoclonal T cell response observed in OA patients. The role of CD4+ T cells in OA was highlighted by a recent study in anterior cruciate ligament-transection (ACLT)-induced OA mice where these cells were found to be involved in increased production of MIP-1γ followed by increased infiltration of macrophages in synovium and increased expression of MMP-9 [101]. In another study, when chondrocytes from OA patients were co-culture with autologous T cells, they produced higher amounts of RANTES and MMP-1, MMP-3 and MMP-13 [121].

3.2 B cells and humoral immunity in OA

Cellular infiltrates in the inflamed OA synovium have been reported to contain activated B cells along with other cell types [7]. A clonal analysis of B cells in OA synovium revealed their oligoclonal nature suggesting an antigen driven activation instead of non-antigenic activation [122]. Moreover, several studies found antibodies against cartilage components highlighting the activation of humoral adaptive immune response in OA. When cartilage cell surface proteins were used as substrate in an ELISA and sera from OA patients were applied, an elevated antibody titer was detected compared to controls [123]. Similarly, autoantibodies were found in OA patients against cartilage derived proteins osteopontin [124], cartilage intermediate layer protein (CILP) [125], YKL-39, [126], fibulin-4 [127] and collagen [128]. Anti-CCP antibodies were detected in 7 out of 136 OA patients [129], while another group also detected them in OA patients but at significantly lower levels compared to RA patients [130]. Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of OA patients [131]. Using proteomic approach, Xiang et al identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA [127]. Other studies have reported autoantibodies in animal models of OA including horses [132] and dogs [133]. The role of the autoantibodies against cartilage components in development of OA has been further highlighted by studies showing their deposition [134,135] and cytotoxic effects on cartilage [136], which may be one of the mechanisms playing important role in cartilage degeneration in OA.

4. Major signaling pathways involved in OA

4.1 Involvement of TLRs in OA

TLRs (TLR1 through 10 in humans) are a group of motif recognition receptors important in eliciting an initial innate response against pathogens. They are constitutively expressed on the surface of many immune cells including macrophages but their expression may be induced in other cell types. Upon tissue injury, TLRs may be activated by endogenous damage-associated molecular patterns (DAMPs) also called as alarmins such as hyaluronan, HMGB-1 and S100 family of proteins. The damage to the joint in OA resembles a chronic wound [137]. It involves the release of several DAMPs derived from the damaged extracellular matrix of the joint that act through activation of TLRs such as fibronectin [138], tenascin [139,140], hyaluronan [141,142,143] and biglycan [144 145,146].

TLR-2 and TLR-4 were detected in OA synovial membrane, though less than in RA synovium [147]. However, in vitro, synovial cells from OA and RA patients were equally responsive to the TLR-4 agonist lipopolysaccharides [148] and to the TLR-2 agonist bacterial peptidoglycan [149]. Human chondrocytes have also been shown to express TLRs [150,151] and activation of the TLRs by their ligands leads to the activation of catabolic pathways in chondrocytes [152]. TLR-2 and TLR-4 were found to be upregulated in damaged cartilage in patients with advanced osteoarthritis [150,151]. Zhang et al showed that activation of different TLRs had a differential effect on collagenase gene expression [153]. TLR-4 gene expression was increased in the synovial tissue of stifle joints with OA induced by cranial cruciate ligament transection in dogs, but expression of TLR-2 remained

unchanged [154]. MyD88 dependent TLR2/TLR4 signaling was demonstrated as crucial in mediating catabolic responses to low molecular weight hyaluronan (LMW-HA) and HMG-B1 in murine cartilage explants [155]. Alarmins S100A8 and S100A9 were shown to induce cartilage catabolism in human OA chondrocytes by activating TLR-4 [156]. In this study, OA chondrocytes were found to be more sensitive to S100 stimulation compared to normal chondrocytes. Plasma proteins found in the synovial fluid of OA patients Gc-globulin, α1-microglobulin, and α2-macroglobulin were shown to stimulate pro-inflammatory cytokine production from macrophages via TLR-4 mediated pathway [157]. More recently, CD14, a co-receptor for TLRs, was shown to sensitize the synovial fibroblasts from OA patients to TLR-2 and TLR-4 lignads [158].

4.2 Role of NF-κB pathway in OA

Transcription factor NF-κB is the master regulator involved in control of expression of several proteins involved in inflammation, immune response and apoptosis. It is present in the cytoplasm in inactive form associated with the inhibitory κB (IκB) proteins. In response to a broad range of stimuli, including TNF-α, IL-1β, bacterial and viral products, UV radiation and free radicals, a cascade of signaling events result in phosphorylation of IκB by activated IKKs through ubiquitination-dependent degradation by the proteasome leading to the activation and nuclear translocation of NF-κB. NF-κB then binds to the DNA elements present in its target genes and facilitates their transcription. Numerous studies have reported a central role for NF-κB proteins in cartilage metabolism and development of OA [reviewed in 159]. More direct evidence for the involvement of NF-κB in OA development came from a series of studies in cultured synovial fibroblasts from OA patients [52,160]. Using adenoviral vector over-expressing IκB in cultured synovial fibroblasts resulted in decreased baseline expression of IL-6, IL-8, MCP-1/CCL-2 and MMPs [160]. In a subsequent study, IL-1β induced expression of ADAMTS-4 was inhibited by IκB over-expression while ADAMTS-5 expression remained unaffected [52]. In a rat model of surgically induced OA, NF-κB was inhibited by adenoviral vector mediated delivery of the siRNA specific for NF-κB-p65 [161]. This approach resulted in inhibition of the expression of p65, reduced stimulation of IL-1β and TNF-α in synovial fluid, reduced inflammation of the synovium and reduced cartilage damage [161].

Due to its central role in the regulation of genes involved in OA, NF-κB pathway has been an important target of several strategies aimed at developing novel therapies for the treatment of OA [162]. NF-κB activity can be inhibited by inhibiting different steps of the NF-κB activation pathway [159]. Inhibition of IKKβ, proteasomal machinery and DNA binding activity of NF-κB subunits using small molecules or siRNA are some of the most popular approaches under study in OA drug discovery. The biggest challenge in these approaches is the side effects of these drugs because of the involvement of NF-κB in normal cellular functioning [163]. A number of natural products including curcumin and resveratrol have been studied as modulators of NF-κB pathway without showing severe side effects [164]. Studies from our group showed a cartilage protective role of a polyphenol rich extract from pomegranate via inhibition of the NF-κB pathway [165].

5. Conclusion

The accumulating evidence suggesting the involvement of all aspects of the immune response in OA, along with other mechanical and biochemical factors, put OA into the category of one of the most complex disorders (Fig. 1). This is contrary to earlier perception of OA as a simple degradation of the joint cartilage due to advanced age. The complexity of the pathogenesis makes it extremely difficult to develop therapeutic approaches to treat OA. Most of the current approaches employed for the treatment of OA provide symptomatic relief from pain and inflammation and effective disease modifying OA drugs (DMOADs) are still elusive. Success of anti-cytokine therapy in RA raised enthusiasm in the field of OA also, but all the recent trials showed limited or no success in modifying the disease condition in OA patients [75] (Table 1). Therefore, it becomes imperative to look for some novel approaches to treat this complex disease. There should be more research and human trials on natural health products with multiple targets and low side effects, which are supported by traditional wisdom as well as new scientific data.

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Highlights

- OA is the most common and painful disease of the joints among the elderly.
- Pathogenesis of OA is complex and both the innate and adaptive immunity play a role.
- Use of biologics to treat OA has not met with the same success as in RA.
- There is a need to identify novel therapeutic targets and agents for treating OA.

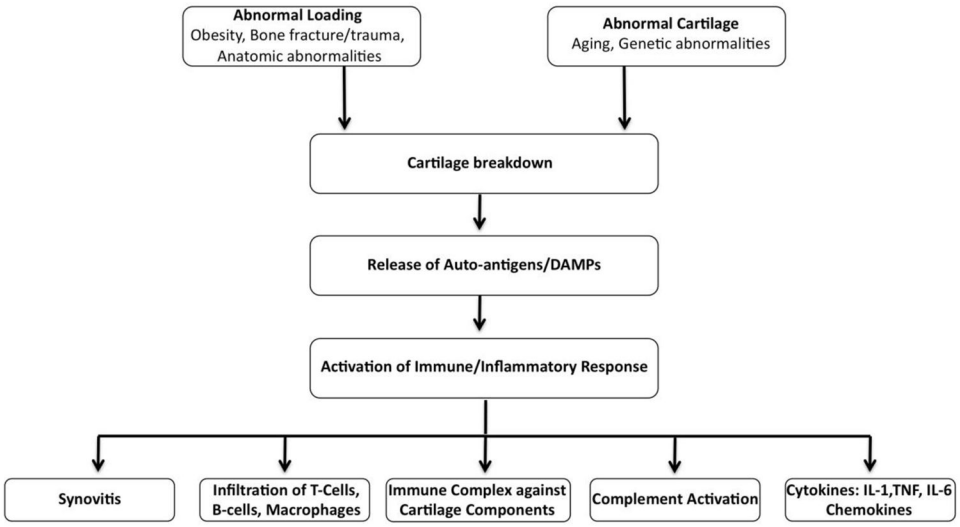

Figure 1. Schematic representation of immunopathogenesis of OA

Several genetic, metabolic as well as environmental factors lead to the damage of cartilage resulting in the release of cartilage specific autoantigens, which in turn activate the immune/inflammatory response. There is increased infiltration of T-cells, B-cells and macrophages in the joint tissues. These immune cells along with other cells of the joint tissue get activated and release several molecules such as cytokines, chemokines and other cartilage degrading factors such as MMPs and PGE_2 resulting in further degradation in the cartilage. DAMPs: damage-associated molecular patterns

Table 1

Selected in vivo studies targeting IL-1β, TNF-α and NF-κB for the treatment of OA.

Target	Authors [Ref.]	Therapy	Type of study (model)	Main findings
IL-1β				
	Pelletier et al [166]	IL-1Ra gene therapy	Pre-clinical (dogs)	Reduced lesion severity and progression
	Fernandes et al [167]	IL-1Ra gene therapy	Pre-clinical (rabbits)	Reduced lesion severity and progression
	Frisbie et al [168]	IL-1Ra gene therapy	Pre-clinical (horses)	Significant improvement in pain, disease activity and cartilage preservation
	Zhang et al [169]	IL-1Ra+IL-10 gene therapy	Pre-clinical (rabbits)	Significant reduction in cartilage breakdown
	Caron et al [170]	Recombinant IL-1Ra (Anakinra)	Pre-clinical (dogs)	Protection from OA lesions and reduction in collagenase-I expression
	Chevalier et al [171]	Recombinant IL-1Ra (Anakinra)	Clinical trial	Drug found to be safe and well-tolerated
	Chevalier et al [172]	Recombinant IL-1Ra (Anakinra)	Clinical trial	Not effective in relieving disease symptoms
	Bacconnier et al [173]	Recombinant IL-1Ra (Anakinra)	Case report (3 female patients)	Improvement in pain and global handicap in erosive OA of the hand
TNF-α				
	Grunke et al [174]	Monoclonal anti-TNF antibody (Adalimumab)	Case report (single 68 yr old male patient)	Relief from pain, improved movement and improved disease symptoms
	Magnano et al [175]	Monoclonal anti-TNF antibody (Adalimumab)	Pilot clinical trial (12 patients)	Well-tolerated, modest improvement in disease symptoms in erosive OA of the hand
	Fioravanti et al [176]	Monoclonal anti-TNF antibody (Infliximab)	Pilot clinical trial (10 female patients)	Well-tolerated and relief from pain but modest improvement in lesion in erosive OA of the hand
NF-κB				
	Hashimoto H et al [177]	NF-κB decoy oligodeoxynucleotde	Pre-clinical (rats)	Decrease in OA lesion (assessed by Mankin score), significant decrease in IL-1β and TNF-α levels in synovium and cartilage
	Chen et al [161]	Adenoviral vector-mediated NF-κBp65-specific siRNA	Pre-clinical (rats)	Reduced synovial inflammation, cartilage degradation and IL-1β and TNF-α levels in the synovium in early phase of experimental OA