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REVIEW

Toll-like receptors are potential therapeutic targets in rheumatoid arthritis

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Abstract

Toll-like receptors (TLRs) are found on the membranes of pattern recognition receptors and not only play important roles in activating immune responses but are also involved in the pathogenesis of inflammatory disease, injury and cancer. Furthermore, TLRs are also able to recognize endogenous alarmins released by damaged tissue and necrosis and/or apoptotic cells and are present in numerous autoimmune diseases. Therefore, the release of endogenous TLR ligands plays an important role in initiating and driving inflammatory diseases. Increasing data suggest a role for TLR signaling in rheumatoid arthritis, which is an autoimmune disease. Although their involvement is not comprehensively understood, the TLRs signaling transducers may provide potential therapeutic targets.

Key words: Autoimmune disease; Innate immunity; Pattern recognition receptors; Rheumatoid arthritis; Toll-like receptors

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease induced by a combination of genetic, environmental and stochastic mechanisms[1-3]. There is a long-standing hypothesis that microbial infection plays a role in RA and that the infection triggers inflammatory responses recognized by pattern recognition receptors (PRRs). These inflammatory reactions damage the host tissue, release endogenous alarmins that can activate PRRs constituting a positive feedback[4,5]. Furthermore, this sterile inflammation induced by endogenous danger signals is believed to lead to the pathological joint destruction seen in RA[6].

Toll-like receptors (TLRs) were first discovered in drosophila, in the membranes of binding PRRs and are known to target a series of mechanisms leading to the synthesis and secretion of cytokines and activation of other host defense programs that are crucial to the development of innate or adaptive immunity[7-10]. TLRs are present in vertebrates as well as invertebrates. Recently, it was estimated that most mammalian species have 10 to 15 types of TLRs. 13 TLRs (TLR1 to TLR13) have been

identified in humans and mice. The TLR family is summarized in Table 1[8,9,11].

TLRs belong to the Toll/interleukin-1 receptor (TIR) family and all members of this family contain cytoplasmic TIR domains. The endodomain of all TLRs differs from the interleukin (IL)-1R ectodomain in which TLR has leucine rich repeats (LRRs), whereas IL-1R possess Ig-like domains[11]. The TIR domain consists of approximately 160 amino acids, and has three regions of particular importance, termed boxes 1, 2 and 3, and is essential for cellular signaling[12]. The extracellular domains of TLR contain 16-28 LRRs which involve some physiological function[13,14]. The individual LRR module is 20-30 amino acids long and is composed of a conserved "LXX LXLXXN" motif and a variable part. TLR 1 and 2 have two shape structural transitions in the B sheet, and their LRR domains can be divided into 3 subdomains: the N terminal, center, and C terminal. The central domains have one or more α helices inserted in the convex area[15].

TLRs LIGANDS

To date, several types of ligands have been characterized as TLRs ligands. TLR 1, 2, 4 and TLR6 are receptors for lipid-based PAMPs, but TLR 3, 7, 8 and 9 are receptors for nucleic acid based molecules such as ssRNA and unmethylated deoxy-cytidylate-phosphate deoxyguanylate (CpG) (Table 1).

Lipid-based ligands

The main ligands for TLR1 are lipopeptides. TLR2 ligands are the most diverse group among all the TLR ligands[16,17]. TLR1 and TLR2 heterodimers recognize the native mycobacterial lipoprotein, zymosan. The main ligand for TLR4 is lipopolysaccharide (LPS) of gram negative bacteria. TLR6 recognizes mycoplasma lipoprotein and peptidoglycan.

Nucleic acid-based ligands

TLR3 can bind with dsRNA, which indicates that TLR3 might be a key molecule in priming anti-viral immunity. TLR3 can also recognize polyriboinosinic:polyribocytidylic acid, poly (I:C), a synthetic analog of dsRNA[18,19]. Furthermore, mRNA can also act as an endogenous ligand for TLR3[20]. TLR 7/8 recognize the single-stranded RNA (ssRNA) and R-848. Recently, some reports indicated that CL097 is also a ligand of TLR7/8[21-23]. TLR9 is the main receptor for bacterial CpG DNA. Unmethylated CpG-dinucleotide-containing sequences are found much more frequently in bacterial genomes than in vertebrate genomes. Unmethylated CpG oligodeoxynucleotides have immunostimulatory activities including the capability to induce B cell proliferation, and to activate macrophages and dendritic cells (DCs)[24,25].

Endogenous ligands

Recently, some reports have also indicated that TLRs can recognize endogenous ligands called "danger signals" or "alarmins", which are released during tissue damage, infections and cell necrosis and/or apoptosis. These endogenous ligands result in the release of extracellular matrix components, intracellular molecules and stress factors that bind with TLRs to initiate an inflammatory response[6,26].

TLRs SIGNALING

Demonization of TLRs targets the activation of signaling pathways which originate from a cytoplasmic TIR domain. TLRs signaling is composed of at least two pathways[27,28]: a MyD88-dependent pathway that leads to the production of proinflammatory cytokines, and a MyD88-independent pathway associated with the induction of IFN-I genes and upregulation of MHC II and costimulatory molecules in DCs. Both of these pathways induce inflammatory cytokines through nuclear factor (NF)-κB (Figure 1)[29].

MyD88-dependent pathway

MyD88 processes the TIR domain in the C-terminal protein and a death domain in the N-terminal protein[30]. TIR domains of TLRs can associate with MyD88. MyD88 recruits IL-1 receptor-associated kinase 4 (IRAK4) through interaction of the death domains of both molecules. IRAK4 can active IRAK1 with phosphorylation of IRAK1 and then associates with TRAF6. TRAF6 can active AP-1 transcription factors through activation of MAP kinase. In addition, TRAF6 can active TAK1 and TAB complex which enhance activity of the IκB kinase complex. The activation of TAK1 leads to activation of the IKK complex and this complex can active MKK4/7 which in turn can active JNK[31-34]. The activation of these molecules and complexes leads to translocation of NF-κB. MyD88 is essential for inflammatory cytokine production through all TLRs.

MyD88-independent pathway

The MyD88-independent pathway is mediated by TRIF. TLR3 and 4 use TRIF to activate interferon-regulated factor 3 (IRF3). Activation of IRF3 leads to the production of IFN-β[31,33,34]. Lastly, the activation of TRAM (TRIF-related adaptor molecule) is TLR4-induced and leads to TRIF recruitment. TRAM localizes to late endosomes where TAG inhibits IRF3 activation and inflammatory cytokine production induced by TLR2, TLR7 and TLR9 ligands. Phosphorylation and nuclear translocation of IRF3 can introduce TBK1 or IKKi/IKK.

ROLE OF TLR SIGNALING IN RA

Recognition of invading microorganisms by TLRs results in the activation of genes encoding proinflammatory cytokines and chemokines, which initiate local inflammation. In addition, TLR signaling leads to upregulation of costimulatory molecules by antigen presenting cells, facilitating the subsequent activation of adaptive immunity[35-37]. Because of the important role of innate immu-

Table 1 Toll-like receptors, their principal ligands, and the adaptors that serve them

TLRs	Species	Location	Ligands	Adaptors
TLR1/2	Human/mouse	Cell surface	Ac3LP, Glycolipids	MyD88,Tirap
TLR2/6	Human/mouse	Cell surface	Ac2LP, LTA, Zymosan	MyD88,Tirap
TLR3	Human/mouse	Cell compartment	polyI:C, dsRNA	TRIF
TLR4	Human/mouse	Cell surface	LPS, Taxol, Heparan, Hyaluronate, F-prot, RSV, G-prot, VSV, Env prot, MMTV, others	MyD88,Tirap TRIF,TRAM
TLR5	Human/mouse	Cell surface	Flagellin	MyD88
TLR7	Human/mouse	Cell compartment	ssRNA, imiquimod, loxoribine, others	MyD88
TLR8	Human/mouse	Cell compartment	ssRNA, IAQ (R848)	MyD88
TLR9	Human/mouse	Cell compartment	CpG, DNA	MyD88
TLR10	Human	Cell surface	?	?
TLR11	Mouse	Cell surface	Profilin	MyD88
TLR12	Mouse	?	?	?
TLR13	Mouse	?	?	?

TLR: Toll-like receptor.

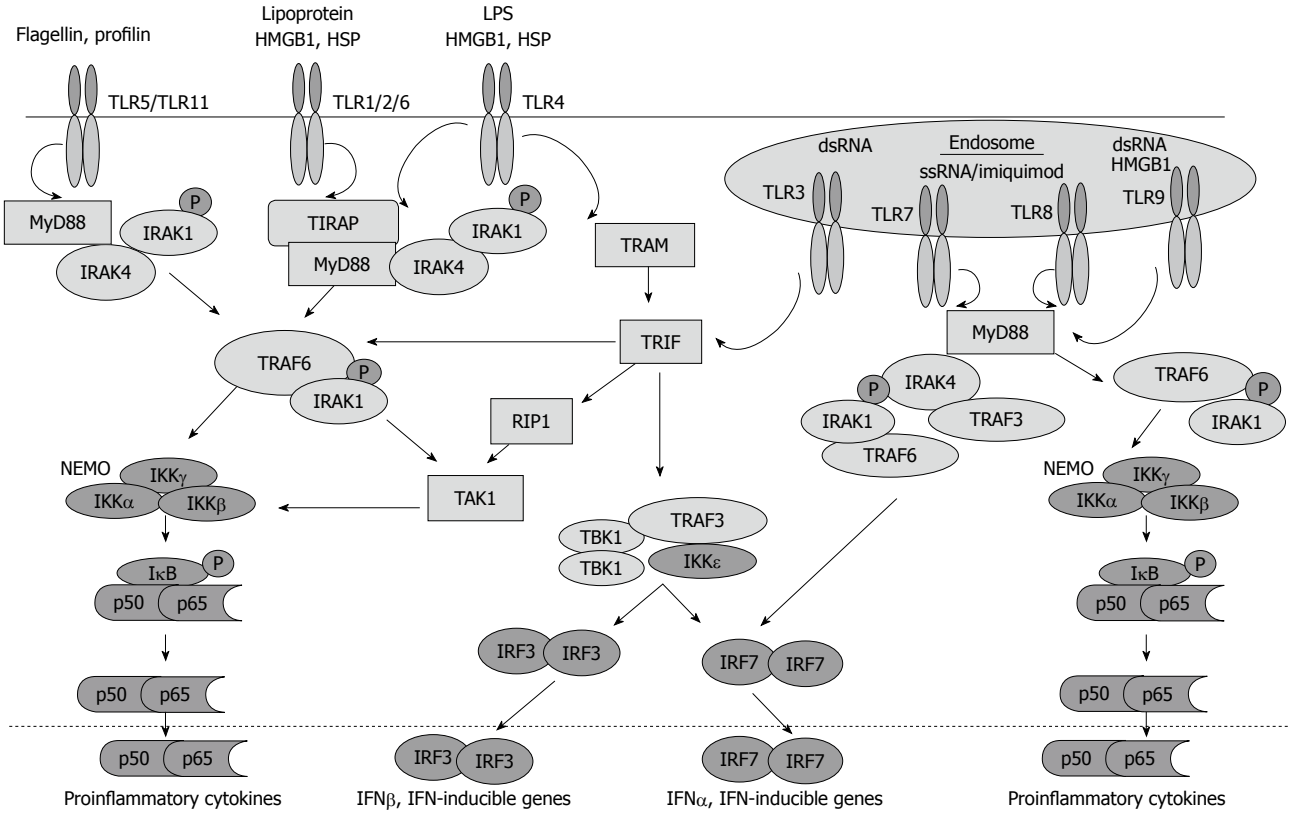

Figure 1 The Toll-like receptor signaling pathway. The ligands of Toll-like receptors, their signaling adaptors and downstream mediators are depicted. LPS: Lipopolysaccharide; HSP: Heat shock protein; TLR: Toll-like receptor; IRAK: Interleukin-1 receptor-associated kinase.

nity, it has been postulated that a dysregulation of innate immune recognition of pathogens may be associated with autoimmunity. However, there is no evidence of a direct link between TLR mutations and a specific autoimmune disease. However, a study in patients with RA and systemic lupus erythematosus (SLE) revealed no evidence of an association with TLR2/4 polymorphisms[38,39]. In spite of the lack of sufficient evidence of a link between TLR mutations and autoimmune diseases, some experimental results suggest the involvement of TLR signaling pathways in the pathogenesis of arthritis. Animal models of arthritis such as adjuvant arthritis or streptococcal cell wall arthritis are dependent on the activation of innate immunity by TLR ligands. Mice deficient in the adaptor molecule MyD88 did not develop streptococcal cell wall-induced arthritis, and TLR2 deficient animals exhibited a significantly reduced severity of arthritis[40]. Moreover, the injection of either staphylococcal peptidoglycan, CpG DNA or dsRNA into the joints of mice results in a self-limited form of arthritis[41-43]. These studies suggested that the availability of TLR ligands might be sufficient to initiate arthritis in a susceptible host. In RA, TLR li-

gands of microbial origin, peptidoglycans and dsDNA, have been detected in the joints of patients. Whether these TLR ligands led to chronic stimulation of innate immunity was unclear. Alternatively, endogenous ligands might specifically activate TLRs and in the absence of regulatory mechanisms cause a pathological immune response. Many endogenous ligands for various TLRs have been described, some of which can be found in the joints of patients with arthritis. Heat shock proteins (HSPs), HMGB1 and hyaluronan are commonly found in inflamed joints and can bind to TLR4. HSPs have previously been implicated in the pathogenesis of arthritis[44,45]. Necrotic cells can also activate TLR2 by an unknown ligand[46]. We postulated that HMGB1 and HSP might be potential ligands of TLRs. Taken together, there is ample evidence for the presence of exogenous as well as endogenous TLR ligands in autoimmune disease. Analysis of synovial tissues from patients with RA revealed TLR2 expression in synovial fibroblasts as well as macrophages[47]. Synovial fibroblasts cultured *in vitro* up-regulated the expression of TLR2 when stimulated with IL-1 and peptidoglycan. A detailed analysis of gene expression following activation of TLR2 with peptidoglycan revealed induction of proinflammatory cytokines such as IL-6, tissue destructive matrix metalloproteinases and adhesion molecules.

TLR signaling may not only be important in the early pathogenesis of arthritis, but also when the adaptive immune system is activated. In the model of murine antibody transferred arthritis, a form of arthritis which is dependent on IL-1, a recent study demonstrated that LPS can substitute for IL-1, and that TLR4 deficient mice have a decreased severity of arthritis[48]. Therefore, TLR signaling has an important function in the development of joint inflammation, even in a situation where T cell and B cell activation has already occurred, and arthritogenic antibodies are present.

In addition, two additional families of PRRs have been described which join the TLRs as key alarmin sensors involved in inflammatory disease. These are NOD-like receptors (NLRs) and RIG-I-like proteins, named RIG-like receptors (RLRs). To date, NLRs have only been shown to detect bacteria, whereas RLRs only recognize viruses. In a similar way to TLRs, some NLRs, in particular, NOD1 and NOD2, activate NF-κB, a key transcription factor for inflammatory and immune gene expression. There is evidence to show that NLRs may also have a role in RA. NOD1 and NOD2, important NLRs, have been shown to be expressed in RA synovial tissue, and the microbial ligand for NOD2, muramyl dipeptide, has been detected in RA synovium[49,50]. In a similar way to anti-viral TLRs, RLRs detect viral nucleic acids and activate certain IRF family members. Therefore, it is apparent that specific NLRs and RLRs can trigger similar responses to TLRs, and are probably involved in the pathogenesis of many infectious diseases[51,52].

TLRs IN OTHER AUTOIMMUNE DISEASES

There is increasing evidence to suggest that the TLRs pathway has a role in SLE[53], atherosclerosis[27], asthma[54], type 1 diabetes[55], multiple sclerosis (MS)[56] and bowel inflammation. SLE is an autoimmune disease characterized by the production of autoantibodies against nuclear antigens. These autoantibodies result in the formation of immune complexes which are deposited in tissues and induce inflammation, thereby contributing to disease pathology. Myelin-specific autoreactive $CD4^+$ T cells contribute to the pathogenesis of EAE and MS. Interestingly, cytokines produced by cells of the innate immune system modulate the differentiation and function of $CD4^+$ T cells, which provides a critical link between TLR signaling and autoreactive T cells that are cooperatively involved in the pathogenesis of autoimmune diseases.

THERAPEUTIC TARGETS OF TLRs IN RA

There has been a furry of activity concerning TLRs, and several TLRs have been shown to respond to various microbial products. In general, the signaling pathways are shared with IL-1R, however, differences are beginning to emerge which indicate specificity. Each TLR induces a common set of genes, but also has its own "private" set, such that the host response to infection can be optimized. The discovery of TLRs has opened up a whole new range of therapeutic possibilities, largely for infectious diseases and sepsis, but also for inflammatory diseases and vaccine development.

A potential target of the TIR domain pathway, apart from inhibiting a specific TLR by preventing ligand binding, is to block signal transduction. Inhibition of common signaling components can block the entire receptor family, including IL-1 and IL-18[28,57]. Single-immunoglobulin interleukin-1 receptor-related (SIGIRR), which is also known as TIR-8, is a member of the TIR domain-containing family of receptors and was first characterized as an inhibitor of interleukin-1 receptor (IL-1R) and TLR signaling. The published data show that SIGIRR is a potential therapeutic target of RA[58]. In addition, targets that are currently being explored include the biochemical characterization of the kinase complex responsible for phosphorylating IκB, the key regulator of NF-κB. Following phosphorylation of Ser32 and Ser36, IκB becomes ubiquinated and is degraded by the proteosome. The kinase responsible for this event is IKK-2, and most of the large pharmaceutical companies and several Biotech companies have discovered small molecule inhibitors of this enzyme[59]. However, these compounds are still in the pre-clinical phase of development. A range of other compounds with anti-inflammatory effects have also been shown to interfere with NF-κB, including non-steroidal anti-inflammatory drugs, glucocorticoids and natural products such as parthenolide[60]. In addition, an inhibitor of the proteosome, PS-1145, has been reported to have beneficial effects in models of inflammation and NF-κB activation, and is showing promise in multiple myeloma[61].

Most drug companies have also initiated programs to

develop inhibitors of p38 and JNK[62]. These two kinases play a role in enhanced transcription through their effects on transcription factors. In addition, p38 stabilizes mRNA containing AU repeats, including genes that encode cyclooxygenase-2 and TNF. Although the precise target of p38 is not known, inhibitors of p38 are in phase II trials for RA and psoriasis. It is a distinct possibility that each of the TLRs trigger a specific set of genes, thereby allowing for tailoring of the innate response to a given pathogen. Such complexities are likely to lend themselves to therapeutic manipulation, although there is still some way to go before we acquire a full understanding of these processes in terms of disease pathogenesis.

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