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Review

The critical role of toll-like receptors — From microbial recognition to autoimmunity: A comprehensive review

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ABSTRACT

Toll-like receptors (TLRs) constitute an important mechanism in the activation of innate immune cells including monocytes, macrophages and dendritic cells. Macrophage activation by TLRs is pivotal in the initiation of the rapid expression of pro-inflammatory cytokines TNF, IL-1β and IL-6 while promoting Th17 responses, all of which play critical roles in autoimmunity. Surprisingly, in inflammatory arthritis, activation of specific TLRs can not only induce but also inhibit cellular processes associated with bone destruction. The intercellular and intracellular orchestration of signals from different TLRs, their endogenous or microbial ligands and accessory molecules determine the activating or inhibitory responses. Herein, we review the TLR-mediated activation of innate immune cells in their activation and differentiation to osteoclasts and the capacity of these signals to contribute to bone destruction in arthritis. Detailed understanding of the opposing mechanisms of TLRs in the induction and suppression of cellular processes in arthritis may pave the way to develop novel therapies to treat autoimmunity.

Contents

Abbreviations: TLRs, Toll-like receptors; RA, Rheumatoid arthritis; PRRs, Pattern Recognition Receptors; ED, Ectodomain; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs, Pathogen Associated Molecular Patterns; HMGB-1, high mobility group box-1; CD14, cluster of differentiation 14; CD36, cluster of differentiation 36; UNC93B1, unc-93 homolog B1; TRAF-6, tumor necrosis-factor-receptor-associated-factor 6; oxLDL, oxidized LDL; MyD88, myeloid differentiation factor 88; TRIF, toll/interferon response factor.

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1. Introduction

Macrophage activation is an integral part of the immune response against infection and a variety of receptors and co-stimulatory molecules are involved in the regulation of the duration, magnitude and the nature of the immune response. The diverse stimuli in different tissues further differentiate and activate tissue resident macrophages and those cells acquire specialized phenotypes such as Kupffer cells in the liver, microglia in the brain, and synovial macrophages and osteoclasts in the joints. The enormous variety of macrophage activating signals is generalized in the concept of classic and alternative activation of macrophages (also termed M1 and M2) which falls short of expectations in elucidating pathogenic mechanisms in inflammatory arthritis and calls for reassessment [1]. Synovial macrophages are activated during infection and tissue injury not only through Toll-like receptors (TLRs), but also through nucleotide-binding and oligomerization domain (NOD)-like receptors, retinoid acid-inducible gene-I (RIG-I)-like receptors, C-type lectin receptors and immunoreceptor tyrosine-based activation motif (ITAM)-associated receptors which exhibit a dual capacity as orchestrators of a cytokine mediated pro-inflammatory response and differentiation to osteoclasts [2]. There has been extensive discussion of toll-like receptors and, in particular, their interrelationships with innate immunity and a variety of signaling pathways in multiple models involving loss of tolerance [3–11]. In this review we focus on the recent advances in structural and molecular biology of TLR signaling and identify unique elements that may enhance our understanding of the pathogenesis of autoimmune models of arthritis and place the data in the context of microbial recognition.

2. Structure and function/recognition of ligands by TLRs

Toll-like receptors (TLRs) are type I transmembrane glycoproteins that play a key role in the immune response against microbes. Ten human TLRs have been identified to date and a subset of TLRs recognizes forms of nucleic acids, including double-stranded RNA, single-stranded RNA, and DNA. TLRs localize in the cell surface such as the case of TLRs 1, 2, 4, 5, 6, 10 or have an endosomal localization as TLRs 3, 7, 8, 9 [12]. All ten TLRs are expressed in human macrophages and mice express TLRs 11, 12, and 13 [13], none of which is represented in humans.

TLRs are composed of an extracellular or ectodomain, a single-path transmembrane domain and an intracellular domain and are classified as Pattern Recognition Receptors (PRRs) as they recognize conserved molecular structures in microbes termed Pathogen Associated Molecular Patterns (PAMPs) [13–15]. The ectodomain is involved in the recognition of ligands, which induce the dimerization of the intracellular domain, termed TIR (Toll/IL-1 resistance) domain and the activation of the signaling pathways. Recent crystal structures of ligands-TLR ectodomains have shed lights to the way that these recognitions take place. The ectodomains of TLRs are composed of an N-terminal cap, a leucine-rich repeat domain (LRR domain), and a cysteine rich domain [13]. The most important ligands for human TLRs are summarized in Table 1.

2.1. The surface TLR receptors

2.1.1. TLR1/2/6/10

TLR2 recognize the broadest range of ligands among TLRs due to its association with other TLRs (TLR1 and TLR6) [15–17]. Crystal structure of TLR2/TLR1 in complex with a triacyl-lipopeptide and TLR2 in complex with a diacyl-lipopeptide showed that the hydrophobic pocket of TLR2 formed by the central LRRs (LRR9 to LRR12) binds the diacylglycerol acyl chains while TLR1 interacts with the N-acyl chains of the ligands (Fig. 1A) [16]. Furthermore, TLR2 also recognize glycolipids such as lipoteichoic acid from Gram-positive bacteria [17,18], lipoarabinomannan from mycobacteria [17,19], and GPI anchor structures from *Trypanosome Cruzi* [20]. We have recently reported that the single hydrophobic pocket of human TLR2 ectodomain is also responsible for binding microbial glycolipids and other lipopeptides [17]. Based on the TLR1/TLR2 and TLR2/TLR6 complex structures, homology models of hTLR10 show a ligand binding pocket similar to TLR2 [21].

Table 1
TLRs and their corresponding endogenous and microbial ligands.

Type of TLR	Microbial ligands (PAMPs)	Potential endogenous TLR ligands (DAMPs)
TLR2 (in association with TLR1 or 6)	Lipomannan (Mycobacterium), Lipoteichoic Acids (Gram-positive bacteria), di-acylated and try-acylated bacterial lipopeptides	HSP 60, HSP70, HSP 96, HMGB-1, gp96, Biglycan, SP-D,
TLR4	LPS (Gram-negative bacteria)	Biglycan, HSP 60, HSP 70, HSP 96, fibrinogen, fibronectin, hyaluronic acid, HMGB-1, OxLDL(in association with TLR6), beta amyloid (in association with TLR6)
TLR5	Flagellin (Gram-negative bacteria)	Undetermined
TLR3	dsRNA (virus)	mRNA (necrotic cells)
TLR7	ssRNA(virus)	ssRNA, imiquimod
TLR8	ssRNA(virus)	ssRNA, microRNAs
TLR9	CpG motif (bacteria, virus)	Self-DNA

2.1.2. TLR4/MD-2

TLR4 requires the association with MD-2 to recognize the lipopolysaccharides (LPS) [22]. MD2 is a 160 amino acid glycosylated soluble protein that associates with the extracellular domain of TLR4 and is required for TLR4 surface expression [22]. The crystal structure of TLR4/MD-2 LPS showed that MD-2 binds to the concave face of TLR4, five acyl chains of LPS binds to MD-2 and the six acyl chain interacts with a hydrophobic patch in TLR4 [23] (Fig. 1B).

2.1.3. TLR 5

TLR5 recognizes bacterial flagellin [24] and has a basolateral localization in intestinal epithelium to respond to flagellin of pathogenic invasive bacteria [25]. TLR5 is also involved in the transport of the pathogenic *Salmonella typhimurium* from intestinal tract to mesenteric lymph nodes [26]. Recently the crystal structure of flagellin TLR5 was solved showing that the first nine N-terminal LRRs of TLR5 are involved in the recognition of the D1 domain of flagellin [27] (Fig. 1C).

2.2. The endosomal TLRs

2.2.1. TLR3

TLR3 recognizes the double stranded RNA (dsRNA) formed during the replication of positive stranded RNA virus [28]. TLR3 has an important role in encephalitis mediated by West Nile virus [29] and herpes simplex virus [30] and participate in the pathogenesis of influenza virus [31]. The N-terminal and C-terminal LRRs of TLR3 are involved in the recognition of dsRNA [32]. The crystal structure of the complex hTLR3ED/dsRNA showed that TLR3 recognizes the phosphate backbone of dsRNA, but not the nitrogenous bases of dsRNA [32] (Fig. 1D).

2.2.2. TLR7, TLR8, TLR9

TLR9 recognize bacterial DNA, which is rich in unmethylated CpG motifs [33] while TLR7 and TLR8 recognize viral single stranded RNA (ssRNA) [34]. The recent crystal structure of TLR8 with ssRNA and degradation products shows that TLR8 expressed as a dimer in the unligated form, has two ligand binding sites, one situated in the heterodimerization domain and one in the concave face and that upon ligand binding the C-terminal LRR domain come close to each other [35,36]. Likewise TLR8, TLR9 has also an insertion between LRR14 and