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Toll-like receptors as an escape mechanism from the host defense

Mihai G. Netea[1,2], Jos W.M. Van der Meer[1,2] and Bart-Jan Kullberg[1,2]

[1]Department of Medicine, University Medical Center, St. Radboud, P.O. Box 9101, Geert Grooteplein 8, 6500 HB Nijmegen, The Netherlands
[2]Nijmegen University Center for Infectious Diseases, P.O. Box 9101, Geert Grooteplein 8, 6500 HB Nijmegen, The Netherlands

Toll-like receptors (TLRs) are probably the most important class of pattern-recognition receptors. Recognition of pathogen-associated molecular patterns (PAMPs) by TLRs, either alone or in heterodimerization with other TLR or non-TLR receptors, induces the production of signals that are responsible for the activation of genes important for an effective host defense, especially those of proinflammatory cytokines. Recent studies also suggest that pathogenic microorganisms can modulate or interfere with TLR-mediated pattern recognition and can use TLRs as an escape mechanism from the host defense. Three major TLR-mediated escape mechanisms have been identified: TLR2-induced immunosuppression, especially through induction of interleukin (IL)-10 release; blockade of TLR recognition; and TLR-mediated induction of viral replication. Thus, TLR signals are not only beneficial to the host, but in certain situations the activation of particular TLR responses by microorganisms might serve as an escape mechanism from the host defense.

Within minutes after the invasion of the host by a pathogenic microorganism, the innate immune system is activated and coordinates the host defense during the initial hours and days of the infection. Although the innate immune system is very effective in dealing with the vast majority of invading pathogens, it has long been believed to be non-specific and non-selective; the specificity would be conferred only by the secondary activation of acquired immunity mediated by T- and B-lymphocytes. This dogma of the non-selective nature of the innate immune response and, in particular, the presumed non-specific recognition of microorganisms by phagocytic cells, has been recently challenged by the discovery of a novel class of receptors, the Toll-like receptors (TLRs). TLRs have been proven to be crucial for recognition of microbes by the innate immune system and for bridging the innate and acquired immune responses.

Toll was initially described as a type I transmembrane receptor with an important role in defense against fungi and Gram-positive bacteria in *Drosophila melanogaster* [1]. The extracellular domain of Toll contains leucine-rich repeats (LRR), whereas the intracellular tail of the receptor shares striking homology with the intracellular domain of interleukin-1 (IL-1) receptor type I, which is designated the Toll–IL-1R (TIR) domain. Initial data suggested that Toll is an important component of the antimicrobial defense of *Drosophila*, and that mammalian homologues might have similar functions. Eleven different TLRs have been identified in mammals [2,3]. TLRs recognize conserved bacterial structures called pathogen-associated molecular patterns (PAMPs): for example, bacterial lipoproteins, lipoteichoic acid and zymosan are recognized by TLR2; double-stranded RNA by TLR3; lipopolysaccharide (LPS) and heat-shock proteins by TLR4; flagellin by TLR5; single-stranded RNA by TLR7 and TLR8; and CpG motifs of bacterial DNA by TLR9 [4–6]. In addition, heterodimerization is reported to be responsible for differential recognition of PAMPs, and this is apparent in the distinction of di- and tri-acylated lipopeptides by TLR2–TLR1 and TLR2–TLR6 heterodimers, respectively [7]. A multitude of studies have reported additional microbial ligands for TLRs, as summarized in other reviews [2,6].

TLRs mediate recognition and protection against microbial pathogens

Recent studies have demonstrated the important role played by TLRs in the recognition of microbial pathogens and the activation of the innate immune system. Absence of intracellular signaling upon TLR engagement by PAMPs [i.e. in mice deficient in the TLR-associated adaptor molecules MyD88 (myeloid differentiation marker-88) and IRAK-4 (interleukin-1 receptor-associated kinase-4)] results in increased susceptibility to a wide variety of microorganisms, including: bacteria, such as *Staphylococcus aureus* [8,9], *Listeria monocytogenes* [10] and *Mycobacterium avium* [11]; fungal pathogens, such as *Candida albicans* [12]; and parasites, such as *Toxoplasma gondii* [13], *Leishmania major* [14] and the intestinal nematode *Trichuris muris* [15]. Similarly, patients with IRAK-4 deficiency display recurrent bacterial infections, especially those caused by pyogenic bacteria [16,17].

Specific roles have been identified for particular TLRs, mainly through the use of knockout mice. On the one hand, TLR2 has been identified as the major receptor for PAMPs of Gram-positive bacteria, such as peptidoglycan and lipoteichoic acids [6], and TLR2−/− mice have an increased susceptibility to infection with *S. aureus* [8,18] or *Streptococcus pneumoniae* [19,20]. On the other hand,

Corresponding author: Mihai G. Netea (M.Netea@aig.umcn.nl).
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mice that do not have a functional TLR4, the major receptor for LPS, are highly susceptible to infections with Gram-negative bacteria (e.g. *Neisseria meningitidis*, *E. coli* [21–24], *Haemophilus influenzae* [25], *Salmonella typhimurium* and *Klebsiella pneumoniae* sepsis [26,27]) and infection with the fungal pathogen *C. albicans* [28,29].

As putative mechanisms that are responsible for TLR-mediated protection, potentiation of cytokine release, mediation of neutrophil recruitment to the site of infection, and the release of oxygen and nitrogen radicals have been demonstrated to contribute to the effects of TLR activation [30]. Sequential activation of the various arms of the immune system under the control of specific TLR-mediated signals appears to coordinate these actions. In line with this, it has been recently shown that during invasive infection with *L. monocytogenes* the initial step of chemokine MCP-1 (monocyte chemoattractant protein-1) secretion and monocyte recruitment is MyD88-independent, whereas the subsequent step of monocyte activation and antibacterial activity requires MyD88-mediated signals [31]. Similarly, different TLRs control early and late activation of the innate immunity to *Salmonella* infection; TLR4 is crucial for early cytokine production and killing of bacteria by monocytes, whereas later activation of macrophages depends on the production of signals that are mediated by TLR2 [32].

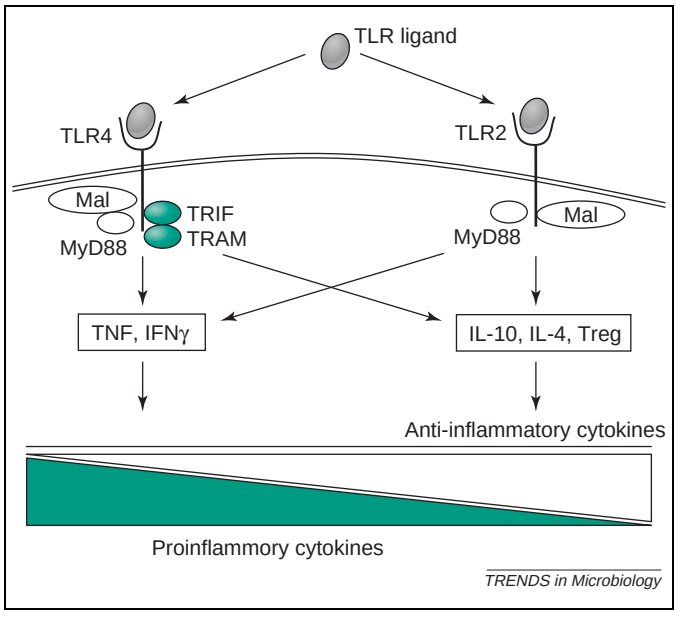

Figure 1. Toll-like receptor (TLR)-signals are involved not only in the primary induction of inflammation, but also in the secondary activation of anti-inflammatory mechanisms. TLRs induce release of both proinflammatory cytokines, such as tumor necrosis factor (TNF) and interferon (IFN)-γ, as well as anti-inflammatory cytokines, such as interleukin (IL)-10, IL-4, IL-5 and IL-13. TLR4-mediated signals induce a more prominent Th1-type response, whereas TLR2 stimulation leads to a more pronounced Th2-type anti-inflammatory cytokine profile.

The ups and downs of inflammation during infection

Following activation of the innate immune system, strong proinflammatory signals are generated, inducing inflammation and activation of the host defense. After proper elimination of the invading microorganisms, subsequent anti-inflammatory signals are responsible for resolution of the inflammation [33]. These signals are crucial not only for the return of the immune system to its homeostatic balance, but also for the protection of the host against the deleterious effects of overwhelming inflammation and for subsequent tissue repair. Probably the best known example of an out-of-control inflammatory reaction during infection is the sepsis syndrome, in which generalized inflammation induced by overproduction of cytokines leads to hypotension, intravascular coagulation, multiple organ failure, and ultimately leads to death [34].

TLR signals are involved not only in the primary induction of inflammation, but also in the secondary activation of anti-inflammatory mechanisms (Figure 1). TLRs are known to induce the release of anti-inflammatory cytokines, such as IL-10, IL-4, IL-5 and IL-13 [35,36]. In addition, TLR2- and TLR4-mediated signals have been shown to mediate the generation of downmodulating T-regulatory cells [37,38]. In line with this notion, the absence of TLR2 or TLR4 results in increased mortality as a result of the occurrence of overwhelming inflammation in certain experimental models, such as pneumococcal meningitis [20] or *Bordetella pertussis* infection [39]. However, although TLR-mediated anti-inflammatory signals are beneficial after the elimination of the pathogens, they can induce dangerous immunosuppressive mechanisms if activated too early during a severe infection; an example of this is detailed below.

The use of TLRs as an escape mechanism

Recent aspects of TLR biology show that although TLRs are crucial for an efficient immune response, certain pathogens use TLR-based strategies to evade the host defense. Three major TLR-mediated escape mechanisms have been identified to-date: (i) TLR2-mediated immunosuppression, due to either premature or biased anti-inflammatory effects; (ii) prevention of TLR recognition; and (iii) TLR-mediated induction of viral replication (Figure 2).

Although TLR2 ligation can induce the production of proinflammatory cytokines, this effect is weaker than that mediated by TLR4 [40]. By contrast, TLR2 signals are strong mediators of anti-inflammatory effects. The TLR2-induced immunosuppression is either an exaggeration or a premature activation of the normal anti-inflammatory effects of TLR stimulation that are needed during the recovery phase of infection for the reversal of the inflammatory process. The first study that investigated the differential effects of TLR2 and TLR4 stimulation on dendritic cells reported the failure of TLR2 ligands to induce the release of IL-12 and interferon (IFN)-γ, favoring a Th2-type response [35]. This initial study is also supported by additional reports [36,41,42]. The molecular mechanisms for the specific TLR2 effects have been also found, showing that engagement of TLR2–TLR1 heterodimers by the bacterial lipopeptide Pam3Cys results in stabilization of the transcription factor c-Fos, a suppressor of IL-12, yielding a Th2 bias [36]. In support of the *in vitro* data that suggest a bias towards Th2-type responses after stimulation of TLR2 are several *in vivo* studies of experimental infections in TLR2−/− mice. In these studies, it has been demonstrated that *Yersinia*

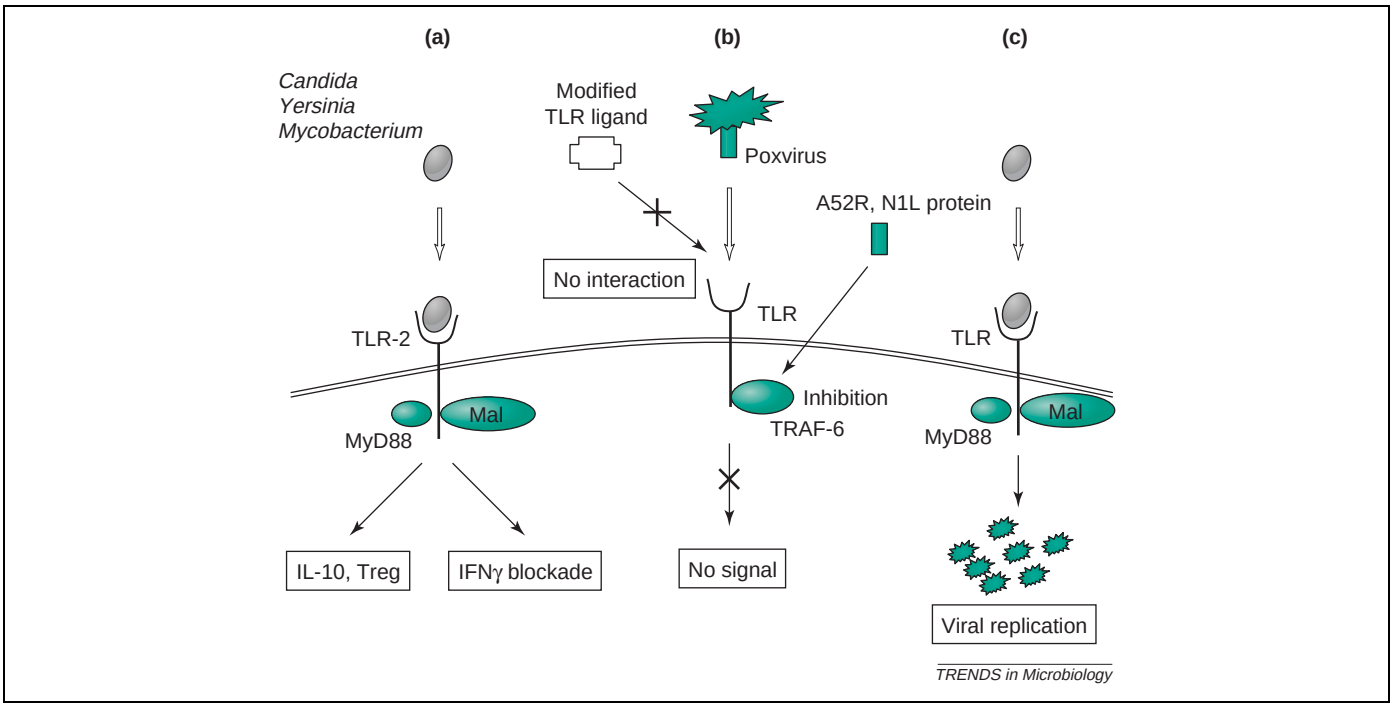

Figure 2. Toll-like receptor (TLR)-mediated signals as escape mechanisms from host defense. Although TLRs are crucial for an efficient immune response, certain pathogens use TLR-based strategies to evade the host defense. Three major TLR-mediated escape mechanisms have been identified to-date: **(a)** TLR2-mediated immunosuppression, due to either premature or biased anti-inflammatory effects; **(b)** obstruction of TLR recognition; and **(c)** TLR-mediated induction of viral replication.

enterocolitica and *C. albicans* induce immunosuppression through TLR2-mediated IL-10 release, and this is further substantiated by the finding that mice lacking TLR2 are more resistant to lethal *Yersinia* and *Candida* infections [12,37,43]. The decreased rate of survival of TLR2−/− mice following *Candida* infection that was reported in another study [44] is probably due to the different experimental design and inappropriate use of control mice with a different background.

In addition to the effects on IL-10 production, in the case of *Candida* infection the immunosuppressive effect of TLR2 signals is obtained through the generation of CD4+CD25+ regulatory T cells [37], and similar data have been reported for schistosomal lyso-phosphatidylserine-induced TLR2 stimulation leading to the generation of IL-10-producing T-regulatory cells (Treg) [45]. The Treg-inducing effects of LPS reported by Caramalho *et al.* [38] are also probably a result of TLR2 contaminants present in their commercial LPS preparation, rather than TLR4-mediated effects [38]. In contrast to TLR2 ligation, stimulation of TLR4 by LPS and TLR9 by CpG induces an inhibition suppressive effects of Treg [46]. In a similar manner to that observed for *Candida*, tolerance induction by *Borrelia burgdorferi* is conferred through TLR2-mediated release of IL-10, and this has been proposed to explain the immunosuppression of chronic Lyme borreliosis with persistence of the microorganisms in immunocompetent hosts [47]. These effects of TLR2 are reminiscent of those of other pathogen-recognition receptors, such as DC-SIGN [dendritic cell-specific intercellular adhesion molecule (ICAM)-grabbing non-integrin] or mannose receptors, which also mediate microbial evasion through their interaction with mannose-capped lipoarabinomannan from mycobacteria and induction of a Th2 bias [48,49].

Another mechanism of TLR2-mediated immunosuppression is represented by inhibition of IFN-γ signaling. Infection of murine macrophages by *M. avium* inhibits IFN-γ signaling through a TLR2-dependent increase in the expression of a dominant-negative STAT1β [50], whereas a *Mycobacterium tuberculosis* 19-kilodalton protein also inhibits IFN-γ-regulated HLA-DR and FcγR1 expression on human macrophages through TLR2-dependent mechanisms [51]. A similar inhibition of IFN-γ-induced signals was found when cells were incubated for long intervals with TLR stimuli, whereas short incubation periods led to amplification of IFN-γ signaling [52].

When these mechanisms (induction of TH2-type cytokines or inhibition of IFN-γ signals) are activated prematurely, or the anti-inflammatory signals are exaggerated, the activation of TLR2 anti-inflammatory pathways can hinder further elimination of the microorganisms (Figure 2a).

In addition to the induction of anti-inflammatory signals by TLRs, certain microorganisms have developed strategies to either block or avoid their recognition by TLRs and subsequent activation of the innate defense. Recently, it has been shown that phospholipid constituents of *Treponema* inhibit cell activation induced by several TLRs (TLR3, TLR4 and TLR9) by blocking the function of LPS-binding protein and CD14 [53,54]. Similarly, the poxvirus protein A52R blocks activation of the transcription factor known as nuclear factor (NF)-κB, which is induced by multiple TLRs (including TLR3) through association with IRAK2 and TRAF6 (tumor necrosis factor receptor-associated factor 6), two key proteins of the intracellular signaling cascade induced by TLRs [55]. By contrast, the poxvirus protein N1L is able

to inhibit NF-κB activation [56] (Figure 2b). A different strategy for escaping TLR recognition is used by the fungus *Aspergillus fumigatus*, which evades immune recognition by germinating into hyphae with subsequent loss of TLR4 recognition, whereas the TLR2-mediated IL-10 pathways remain intact, thus shifting the balance towards a permissive Th2-type profile [57]. Several bacterial pathogens have also modified the structure of particular PAMPs to avoid recognition by TLR4 or TLR5; pathogens, such as *Porphyromonas gingivalis* or *Leptospira,* have LPS structures (normally recognized by TLR4) that only interact with TLR2 [40,58], whereas flagellin of *Helicobacter pylori* is not properly recognized by TLR5, permitting the survival of the bacteria without loss of virulence [59].

A particular form of immune evasion is represented by stimulation of viral replication through TLR activation and is demonstrated specifically by retroviruses (Figure 2c). In this respect, signaling through TLR2, TLR4 and TLR9 significantly enhances human immunodeficiency virus (HIV)-1 replication in either mast cells [60] or transgenic mice [61]. During coinfection with mycobacteria and HIV-1, HIV-1 expression is potentiated by mycobacteria through TLR2 stimulation [62]. Another retrovirus, the mouse mammary tumor virus (MMTV), persists indefinitely in C3H/HeN mice, but not in the TLR4-defective C3H/HeJ mice. The immune escape of MMTV by persistent infection is mediated by TLR4-triggered production of the immunosuppressive cytokine IL-10 [63].

All these data suggest that several microorganisms use specific TLR-mediated signals to escape from the host defense, either by down-modulation of leukocyte function, or amplification of viral replication.

Concluding remarks

The spectacular discoveries of the past few years in the field of pattern recognition receptors have convincingly demonstrated that TLRs are a major class of receptors: they recognize PAMPs of a broad variety of microorganisms; they mediate production of cytokines and activate the microbicidal mechanisms of leukocytes; and they induce maturation and activation of dendritic cells, thereby providing a bridge between innate and acquired immunity. In addition, TLRs also appear to provide signals that are necessary for the resolution of inflammation. However, it appears that certain pathogenic microorganisms have evolved ways to exploit part of this recognition system, for example, induction of TLR-mediated immunosuppression to escape the antimicrobial host mechanisms.

There are still many questions that remain to be answered regarding TLR-mediated immunosuppression:

What are the specific intracellular signals that preferentially lead to tolerance and immunosuppression?

What are the factors that influence the induction of a proinflammatory versus an anti-inflammatory pathway upon triggering of one TLR?

Are co-receptor–receptor complexes involved in the immunosuppressive effects of TLRs?

Can these pathways be used as therapeutic targets?

Learning to modulate this delicate balance between stimulation and suppression at the level of TLRs might provide crucial clues for understanding the regulation of the immune response, and ultimately for finding new strategies to combat infection or autoimmune inflammatory conditions.

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