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The role of TLR2 in infection and immunity

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Toll-like receptors (TLRs) are recognition molecules for multiple pathogens, including bacteria, viruses, fungi, and parasites. TLR2 forms heterodimers with TLR1 and TLR6, which is the initial step in a cascade of events leading to significant innate immune responses, development of adaptive immunity to pathogens and protection from immune sequelae related to infection with these pathogens. This review will discuss the current status of TLR2 mediated immune responses by recognition of pathogen-associated molecular patterns (PAMPS) on these organisms. We will emphasize both canonical and non-canonical responses to TLR2 ligands with emphasis on whether the inflammation induced by these responses contributes to the disease state or to protection from diseases.

Keywords: TLR2, TLR1, TLR6, TLR2 ligands, polymorphisms, co-receptors

INTRODUCTION

The innate immune system contains germline-encoded pattern recognition receptors (PRRs) that detect pathogens threat and trigger prompt responses against them. PRRs recognize microbial components termed pathogen-associated molecular patterns (PAMPs), which play crucial roles in microbial pathogenesis, survival and replication. Examples of PAMPs include integral cell membrane and cell wall components, bacterial toxins, DNA RNA, etc. A cascade of events occurs following PAMP recognition by PRRs, which activate host defense mechanisms to prevent or fight off infections and initiate and enhance a subsequent adaptive immune response (West et al., 2006). A well-known group of PRRs discovered in the 1990s are the toll-like receptors (TLR; Gay and Gangloff, 2007), a family of very similar proteins containing leucine-rich repeats, that are widely expressed by a variety of cells in many animal species (Akira et al., 2006). TLRs and TOLLs (in the fruit fly) are evolutionarily ancient mediators of innate host defense (Leulier and Lemaitre, 2008). The most recent Nobel Prize in Medicine and Physiology was partially awarded for this discovery. To date, 13 TLRs have been identified, 10 human TLRs (TLR1-10), and 12 mouse TLRs (TLR1-9, TLR11, TLR12, mice do not express TLR10; Beutler, 2009).

TLR2 identification, molecular characterization, and cloning were first published in 1998, together with TLR1, TLR3, TLR4, and TLR5 (Rock et al., 1998). More than a decade of extensive research has demonstrated the importance of TLR2 in the vertebrate immunity. This receptor is the only TLR described so far to form functional heterodimers with more than two other types of TLRs. TLR2 also interacts with a large number of non-TLR molecules, allowing for recognition of a great number and variety of PAMPs (Zähringer et al., 2008). This diversity comprises different types of molecules from all microbial phyla including viruses, fungus, bacteria, and parasites. TLR2 expression has been detected in immune cells, endothelial, and epithelial cells (Flo et al., 2001; Brzezińska-Blaszczyk and Wierzbicki, 2010). This ubiquity is consistent with the wide range of roles and function of TLR2.

TLR2 LIGANDS FOR PATHOGEN RECOGNITION

Toll-like receptor receptors are type I integral transmembrane glycoproteins composed of a conserved intracellular toll–interleukin-1 receptor (TIR) homology domain, a single transmembrane helix domain and a solenoid ectodomain (Kumar et al., 2009). The ectodomain is responsible for pathogen recognition and is composed of 16–28 diverse leucine-rich-repeat (LRR) modules (Akira et al., 2006). TLRs can be divided into six major families, according to the repeat number of LRRs and the motifs of two cysteine clusters flanking the LRRs. TLR2, together with TLR1, TLR6, and TLR10, are members of the TLR1 subfamily (Matsushima et al., 2007).

Ligand specific recognition and signaling through TLR2 occurs via heterodimerization with TLR1 or TLR6. TLR2/TLR1 and TLR2/TLR6 heterodimers are thought to be pre-formed on the cell surface. In the absence of TLR1 and TLR6, TLR2 homodimerization was proposed but it has not been observed with current techniques (Jin et al., 2007). The crystal structure of both heterodimers where determined, showing that LRR modules confers a horse-shoe shaped structure to the ectodomain and each heterodimer forms an "m" shaped complex with the ligand, stabilizing the two receptors. Without the ligand, the pre-formed heterodimers most likely have no interaction between their intracellular moieties and therefore there is no downstream signaling (Jin et al., 2007; Kang et al., 2009). New studies also describe the existence of TLR2/TLR10 pre-formed dimers, although their function is unclear (Guan et al., 2010). TLR1 and TLR10 were described to form dimers with TLRs from the same subfamily (Hasan et al., 2005), while TLR6 can form a heterodimer with TLR4 in response to endogenous ligands, promoting sterile inflammation (Stewart et al., 2010).

The wide array of TLR2 ligands includes molecules with diacyl and triacylglycerol moieties, proteins and polysaccharides (**Table 1**). The biochemical diversity of such ligand structures consequently raises questions about receptor specificity. For a long time the identity of most putative TLR ligands was doubted, due to potential lipoprotein contamination. A recent study claims that only lipoproteins/lipopeptides (LPs) are "true" TLR2 ligands, sensed at physiological concentrations by this receptor (Zähringer et al., 2008). To assess such potential contamination, treatment with lipoprotein lipase (Hashimoto et al., 2006, 2007), high temperatures (Liang et al., 2007a), and solvent washes (Ikeda et al., 2008) have been used, according to the molecular structure and physicochemical properties of the hypothetical TLR2 ligand. However, some of these methods were applied in the absence of proper ligand molecular structure analysis, leading to mistaken conclusions. An example is the use of lipoprotein lipase to assess lipoprotein contamination of diacylglycerol preparations, such as Lipoteichoic Acid (LTA), which are also cleaved by the lipase (Seo and Nahm, 2009).

Endogenous ligands have also been described for TLR2, known as "alarmins" and indicating tissue damage, necrosis, or potential tumor cells. For example, human β-defensin-3, hyaluronan fragments, heat shock proteins, and high mobility group box 1 protein were identified as TLR2 endogenous ligands (Scheibner et al., 2006; Funderburg et al., 2007; Curtin et al., 2009; Erridge, 2010). Although it seems plausible that these molecules contribute to host responses to infections leading to this type of damage, there is no evidence, thus far, that endogenous ligands that engage TLR2 can modulate the course of microbial infections. Another complicating factor regarding studies with these TLR2 "endogenous ligands" is that contamination of the preparations with other non-endogenous TLR2 ligands was not always ruled out (Tsan and Gao, 2007).

The major TLR2 ligand characterized thus far are lipoproteins, ubiquitous to all bacteria and highly expressed in the outer membrane of Gram-positive bacteria. They present a unique NH3-terminal lipo-amino acid, *N*-acyl-*S*-diacylglycerol cysteine and usually three lipid chains (triacyl), except for those found in mycobacteria that can have two lipid chains (diacyl). These molecules have a variety of functions and are described in an extensive database (Babu et al., 2006). Triacyl LPs are recognized by TLR2/TLR1 while diacyl LPs are recognized by TLR2/TLR6 (Beutler et al., 2006). This has been described in detail by crystallographic techniques, demonstrating that the TLR1 ectodomain has a channel that binds the amide-bound lipid chain of the triacylated LP (Jin et al., 2007), while the same channel in TLR6 is obstructed by amino acid residues (Kang et al., 2009). TLR2 has a hydrophobic pocket that interacts with the remaining lipid chains in a less specific manner, allowing slight variations in length and chemical structure of lipid or hydrophobic moieties of its ligands (Kang et al., 2009). No matter which of the two dimers is activated, the classical signaling cascade triggered was found to be the same (Farhat et al., 2008), although the kinetics could be different depending on the ligands, and lead to different physiological outcomes (Depaolo et al., 2008; Long et al., 2009). TLR10 appears to recognize the same ligands as TLR1 and requires the same intracellular adaptor myeloid differentiation primary-response gene 88 (MyD88). However, the activated TLR2/TLR10 dimer could not trigger the common signaling cascade, suggesting a different role for this dimer yet to be defined (Guan et al., 2010). Recognition of lipopeptides through TLR2 in the absence of TLR1 or TLR6 participation was observed using either TLR-knockout mice or modified ligands (Buwitt-Beckmann, 2005). However, there is no demonstration that ligand recognition by TLR2 alone actually occurs at physiological concentrations in the course of an infection (Buwitt-Beckmann, 2005).

TLR2 RECEPTOR COMPLEXES AND ACCESSORY MOLECULES

TLR2 forms heterodimers with its co-receptors, which increases the diversity of molecules recognized by the receptor. Recently, a number of accessory molecules and co-receptors have been described to concentrate microbial products on the cell surface or inside phagosomes to facilitate TLR2 responses. A new ligand complex was just proposed for activation by diacylglycerol ligands, including lipopeptides: CD36 may bind ligands and transfer them to the accessory molecule CD14, which, in turn, loads the ligand onto TLR2/TLR6 heterodimers (FSL-1, MALP-2, and LTA) or on TLR2/TLR1 (lipomannan) heterodimers (Jimenez-Dalmaroni et al., 2009). The ligand delivery occurs within lipid rafts, where CD14 and CD36 molecules are anchored, resulting in complex internalization to the Golgi apparatus, and this trafficking may be dependent on the TLR2 ligand. Despite this finding, activation does appear to occur at the cell surface and is independent from internalization (Triantafilou et al., 2006; Jimenez-Dalmaroni et al., 2009). The ectodomain of CD14 and CD36 is the active receptor moiety for ligand delivery (Jimenez-Dalmaroni et al., 2009). It is notable that, even though CD14 and CD36 are not an absolute requirement (Hoebe et al., 2005; Nakata et al., 2006) for TLR2 signaling, the role of these molecules is to enhance responses, lower the threshold of the concentrations needed for receptor recognition and signaling. A similar mechanism likely occurs with GPI anchors from some protozoan parasites, since they also contain the diacylglycerol moiety and are known to be TLR2 ligands. Accordingly, CD36−/− macrophages have an impaired cytokine response compared to wild-type macrophages when stimulated with *Plasmodium falciparum* GPI (Patel et al., 2007). *Trypanosoma cruzi* GPI needs CD14 to fully activate TLR2 (Almeida and Gazzinelli, 2001). However, this function of CD14 cannot be extended to all GPIs, since CD14 does not participate in *Toxoplasma gondii* GPI stimulation of TLR2 and TLR4. Instead, galectin-3 seems to deliver *T. gondii* GPIs for these TLRs (Debierre-Grockiego et al., 2010).

Interestingly, vitronectin, an extracellular matrix glycoprotein also present in the blood, has been reported as essential for triacyl LP engagement of TLR2. This protein, in its extended conformation, binds to triacyl LPs and is recognized by the integrin β3 receptor, which is part of the pre-formed TLR2/TLR1 signaling complex in resting monocytes (Gerold et al., 2008). CD14 (but not CD36) also concentrates and delivers triacyl LPs to TLR2/TLR1, without directly binding to the dimer (Hoebe et al., 2005; Nakata et al., 2006), and can contribute to the inflammatory response in phagocytes (Drage et al., 2009). Other researchers identified radioprotective 105 kDa (RP105) as a receptor able to bind mycobacterial lipoproteins, mostly TLR2/TLR1 agonists, acting as an accessory molecule for the TLR2 receptor complex in

Table 1 | TLR2 microbial ligands.

Ligand	Origin	TLRS	Ligand delivery	Reference
	Bacterium			
Diacyl lipopeptides (MALP-2/FSL-1)	*Mycoplasma*	TLR2/TLR6	RP105 (B cells)/ CD14/CD36	Jimenez-Dalmaroni et al. (2009), Blumenthal et al. (2009)
Heat-labile enterotoxins (b subunit)	*Escherichia coli*, *Vibrio cholerae*	TLR2/TLR1	CD14/GD1a	Liang et al. (2007b), Connell (2007)
Lipomannan/ lipoarabinomannan	*Mycobacterium*	TLR2/TLR1	CD14/CD36	Jimenez-Dalmaroni et al. (2009), Birch et al. (2010)
Lipoprotein	*Mycobacterium*	TLR2/?	CD14/CD36/RP105	Jimenez-Dalmaroni et al. (2009)
Lipoteichoic acid (LTA)	Gram-positive bacteria	TLR2/TLR6	CD14/CD36/MBL	Jimenez-Dalmaroni et al. (2009), Ip et al. (2008), Tawaratsumida et al. (2009)
Peptidoglycan (PG)*	*Staphylococcus*	TLR2/?	CD14	Natsuka et al. (2008), Müller-Anstett et al. (2010)
Porins	*Neisseria*, *Salmonella*, *Shigella*	TLR2/TLR1	Unknown	Massari et al. (2006), Cervantes-Barragán et al. (2009), Biswas et al. (2009)
Triacyl lipopeptides (LPs)	Bacteria	TLR2/TLR1	CD14/vitronectin + integrin β3	Beutler et al. (2006), Gerold et al. (2008)
	Fungus			
Glucuronoxylomannan	*Cryptococcus neoformans/gaati*	TLR2/TLR1– TLR2/TLR6	CD14/not dectin-1	Fonseca et al. (2010)
Phospholipomannan	*Candida albicans*	TLR2/TLR6	CD14/dectin-1	Jouault et al. (2003), Netea et al. (2006)
Unknown	*Paracoccidioides brasiliensis*	TLR2/?	Dectin-1	Bonfim et al. (2009)
Unknown	*Penicillium marneffei*	TLR2/?	Dectin-1	Nakamura et al. (2008)
Unknown	*Aspergillus fumigatus*	TLR2/?	Dectin-1	
Yeast phase-specific protein (Yps3p)	*Histoplasma capsulatum*	TLR2/?	Dectin-1***	Aravalli et al. (2008)
Zymosan**	*Saccharomyces cerevisiae*	TLR2/TLR6	CD14/dectin-1	Ikeda et al. (2008), Beutler et al. (2006), Gantner et al. (2003)
	Protozoan/helminth			
Glycosylphosphatidylinositol (GPI) anchors	*Trypanosoma*, plasmodium, toxoplasma (protozoans)	TLR2/TLR1**** and TLR4	CD36/(likely) CD14	Jimenez-Dalmaroni et al. (2009), Debierre-Grockiego et al. (2007), Gowda (2007)
Lipopeptidophosphoglycan	*Entamoeba histolytica* (protozoan)	TLR2/TLR6 and TLR4		Wong-Baeza et al. (2010)
lipophosphoglycan	*Leishmania* (protozoan)	TLR2/?		Kavoosi et al. (2010)
Lysophosphatidylserine	*Schistosoma mansoni*, *Ascaris lumbricoidis* (helminth)	TLR2/?		van Riet et al. (2009)
	Virus			
EBV-encoded dUTPase	Epstein–Barr	TLR2/?	Not CD14	Ariza et al. (2009)
Glycoprotein B	Cytomegalovirus	TLR2/TLR6	CD14	Barbalat et al. (2009), Klouwenberg et al. (2009), Compton et al. (2003)
Hepatitis B capsid*****	Hepatitis B	TLR2/?	CD14	Cooper et al. (2005)
hepatitis C core and NS3 protein	Hepatitis C	TLR2/TLR6	Unknown	Chang et al. (2007)
Unknown	Measles	TLR2/TLR6	Unknown	Klouwenberg et al. (2009), Bieback et al. (2002)
Unknown	Herpes simplex (1/2)	TLR2/TLR6	Unknown	Klouwenberg et al. (2009), Sorensen et al. (2008)
Unknown	Vaccinia	TLR2/?	Unknown	Barbalat et al. (2009)
Unknown	Lymphocytic choriomeningitis	TLR2/?	CD14	Zhou et al. (2005)

(Continued)

Table 1 | Continued

Ligand	Origin	TLRS	Ligand delivery	Reference
Unknown	Yellow fever	TLR2/?	Unknown	Querec et al. (2006)
Unknown	Varicella zoster	TLR2/?	CD14	Wang et al. (2005)
Unknown	Respiratory syncytial	TLR2/TLR6	Unknown	Klouwenberg et al. (2009)

Observation: The question marks "?" presented in the table imply that the co TLR, required for TLR2 ligand recognition, is still undefined.

**Synthetic PGs does not induce TLR2 signaling, and TLR2 activation promoted by the natural ones was attributed to lipopeptide contamination by some authors (Travassos et al., 2004; Zähringer et al., 2008). Nevertheless, PG extracted from mutant Staphylococcus strain lacking lipopeptides still activated TLR2 and NOD2 (Müller-Anstett et al., 2010).*

***Zymosan activation through TLR2 was also attributed to contamination by other authors (Ikeda et al., 2008).*

****Dectin-1 recognizes β-glucans from histoplasma, but these molecules are normally shielded by α-glucans in this pathogen (Rappleye et al., 2007).*

*****Intact GPI are recognized mainly by TLR2/TLR1, but exclusion of its sn-2 fatty-acid portion changes the ligand heterodimer to TLR2/TLR6 (Gowda, 2007).*

******The purity of this preparation is controversial (Vanlandschoot et al., 2005).*

macrophages and improving the response against this pathogen. RP105 has an ectodomain related to the TLRs, but no intracellular moiety (Blumenthal et al., 2009). Further research is needed to define if the accessory mechanisms involved with triacyl LPs are complementary, non-concomitant, or overlapping.

So far, only the ganglioside GD1a has been shown to potentially have an accessory function in recognition of non-acetylated TLR2 ligands. It binds the β subunit of type IIb heat-labile enterotoxin of *Escherichia coli*, enabling this ligand to induce TLR2/TLR1 signaling within lipid rafts. GD1a does not appear to interact with triacyl molecules (Liang et al., 2007b). Since bacterial porins, which have been shown to be TLR2 ligands (Massari et al., 2002; Liu et al., 2008), are also oligomeric pore forming proteins that bind to the same dimer, there is a possibility that GD1a may also affect or enhance their signaling, but there is no experimental evidence supporting this hypothesis (Massari et al., 2006).

In regards to innate immune recognition of whole bacteria by TLRs, phagocytosis is an important step, forming phagosomes that could recruit TLRs and form different receptor complexes. The soluble molecule mannose binding lectin (MBL) was found to bind *Staphylococcus aureus* through membrane LTA and to synergize with TLR2/6, drastically increasing inflammatory responses upon complex internalization (Ip et al., 2008). The same complex is likely to occur with peptidoglycan, lipoarabinomannan, and lipophosphoglycan, since they were described to bind to MBL (Ip et al., 2009). CD36 may possibly maintain its ligand delivery role inside the phagosomes, because it is required for phagocytosis of *S. aureus* (Stuart et al., 2005). Lack of integrin α3β1 impairs release of IL-6 after *Borrelia burgdorferi* phagocytosis, due to weak activation of endosomal TLR2 (Marre et al., 2010). In addition, the β3 integrin was reported to facilitate host cell invasion by several bacterial pathogens and could also be linked to TLR2 triggering inside phagosomes (Gerold et al., 2008).

The only non-TLR molecule found to physically interact with TLR2 and induce cross-talk signaling was Dectin-1, the main receptor for β-glucans found on most fungi. Dectin-1 dependent signaling synergizes with both TLR2 and TLR4 for induction of tumor necrosis factor-α (TNF-α) in human primary peripheral blood mononuclear cells (PBMCs), when all three receptors are engaged and stimulated via their respective ligands (Ferwerda et al., 2008).

Finally, and of potential clinical importance, the responses induced by transmembrane TLR2 signaling has recently been found to be modulated by the presence of soluble TLR2 (Raby et al., 2009), in human plasma, milk, and amniotic fluid (Dulay et al., 2009). It is unclear what role this phenomenon may play in response to pathogens and defense against infections, but it could be postulated that varying levels of soluble TLR2 may positively or negatively modulate such responses.

TLR2 INTRACELLULAR SIGNALING NETWORK

Following ligand stimulation, TLR2 heterodimers generally initiate a MyD88-dependent intracellular signaling pathway, common to all TLRs except TLR3. This pathway induces nuclear translocation of nuclear factor-B (NF-B) to modulate gene transcription and consequent inflammatory cytokine production (**Figure 1**). The cascade also triggers serine/threonine-specific protein kinases (MAPKs) that can influence both transcription of inflammatory genes and mRNA stability of those transcripts, by activation protein 1 (AP-1) induction (Watters et al., 2007).

Although the general signaling pathway is not unique, the phosphorylation and ubiquitination processes crucial for the cascade are not completely elucidated, especially the feedback loops. For example, IL-1 receptor associated kinase 1/4 (IRAK 1/4) were found to phosphorylate, ubiquitinate, and increase degradation of TIR domain containing adaptor protein (TIRAP also termed MyD88 associated ligand, MAL), indicating a possible down-regulation mechanism for TLR2 and TLR4 activation, in addition to their role in activating these pathways (Dunne et al., 2010). Sub-activating doses of TLR2 ligands may tolerize dendritic cells for TNF-α production, by a mechanism that involves disruption of signal transduction at the IRAK1 level (Albrecht et al., 2008). Bruton's tyrosine kinase (Btk) and PI3 Kinase are likewise able to modulate TLR2 production of cytokines stimulated by LTA, but their place in the cascade is not clear (Liljeroos et al., 2007).

Since TLRs, nucleotide binding oligomerization domains (NODs), and Dectin-1 can induce NF-B translocation and MAPK p38 activation (O'Neill, 2008), intracellular cross talk for cytokine production synergy is likely to occur. In this context, Dectin-1 can synergize with TLR2 and TLR4 through an NF-B non-canonical pathway and augment cytokine expression induced by the cited TLRs (Gringhuis et al., 2009). Human PBMCs stimulated with heat

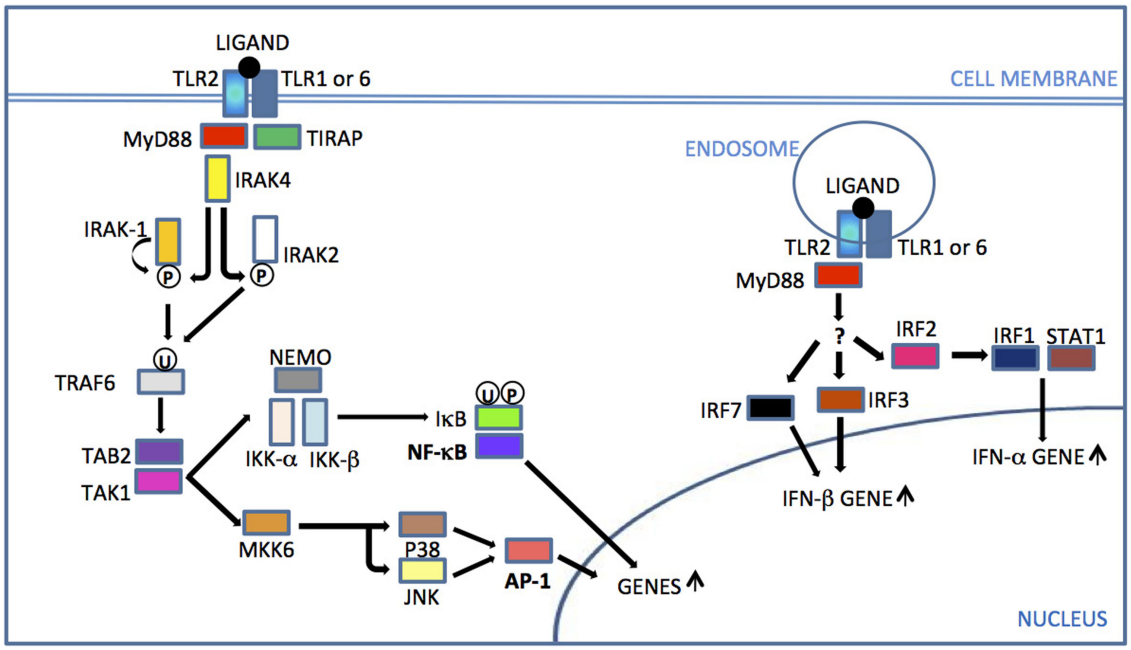

FIGURE 1 | TLR2 signaling. After ligand recognition and consequent TLR2 dimer rearrangement, the TIR domain of TIRAP binds the TIR domain of TLR2 and recruits the adaptor protein MyD88. IRAKs are then recruited and IRAK 4 phosphorylates (P) IRAK1, which then initiates auto-phosphorylation. Phosphorylated IRAK1 dissociates from the complex and activates TRAF6. Since IRAK1 is rapidly degraded, IRAK2 also activates TRAF 6 in latter responses. Ubiquitinated (U) TRAF6 triggers the activation sequence TAB2 – TAK1 – IKK complex. IκB phosphorylation and ubiquitination by the IKK complex leads to its degradation and release of NF-κB translocation to the nucleus for gene up-regulation. TAK1 also activates MKK6 for subsequent JNK and p38 activation, leading to AP-1 activation that triggers gene transcription of cytokines and accessory molecules. Internalized receptor complex triggered by a viral ligand can activate by an unknown pathway IRF7/3 to IFN-β gene up-regulation or IRF2/IRF1/STAT1 for IFN-α gene up-regulation (Underhill et al., 1999; Watters et al., 2007; Liljeroos et al., 2008; Barbalat et al., 2009; Dietrich et al., 2010; Dunne et al., 2010). MyD88, myeloid differentiation primary-response gene 88; TIRAP, TIR adaptor protein; IRAK, interleukin-1 receptor associated kinase; TRAF, TNF receptor associated factor; TAK, transforming growth factor beta-activated kinase 1; TAB, TAK1-binding protein; MKK/JNK/P38, MAP kinases, NEMO/IKKs, kinase complex; NF-κB, nuclear factor-κB; IκB, kinase complex; AP, activator protein; IRF, interferon regulatory factor, STAT, signal transducer and activator of transcription 1.

killed *Listeria monocytogenes* (recognized through TLR2), plus a TLR7/8 ligand, demonstrated synergistic up-regulation of IFN-γ production and, to a minor extent, IFN-α production (Ghosh et al., 2007). Although with a different TLR2 ligand (Pam3CSK4), the opposite outcome of IFN-α was reported with human dendritic cells. In this case, TLR2 activation restrained the type I IFN (IFN-α/β) amplification loop used by TLR4 and TLR7/8 ligands (Wenink et al., 2009). The controversy can be partially explained by the fact that TLR2 depletes early IFN-α/β release induced by TLR9/TLR7, due to transient degradation of IRAK 1, but not later induction of type I IFN (Liu et al., 2012). The urokinase-type plasminogen activator receptor was recently described as important for optimal MAPK p38 activation and consequent inflammation induced by lipopeptides recognized by TLR2 (Liu et al., 2011). Mutations of the NOD2 gene results in defective release of Interleukin-10 (IL-10) from PBMC stimulated with TLR2 ligands, suggesting another avenue of cross-signaling (Netea et al., 2004a).

Type I interferon (IFN-β/α) production was recently found to be induced through TLR2 engagement. It was then necessary to postulate an additional signaling pathway to account for this phenomenon, as type I IFN synthesis requires activation of IFN regulatory factors (IRF), but not NF-B or AP-1, traditionally seen with TLR2 signaling. The stimulation occurs in the endosomal environment, which requires microbial or ligand endocytosis. *In vitro* stimulation of phagocytes with vaccinia virus (VV) and *Lactobacillus acidophilus* induced IFN-β production, while LTA from *S. aureus* stimulated IFN-α production in murine macrophages (Liljeroos et al., 2008; Dietrich et al., 2010; Weiss et al., 2010). It is possible that *L. acidophilus* also stimulates IFN-α due to LTA presence. Surprisingly, bacteria but not viruses induced TLR2-dependent production of IFN-β in dendritic cells, suggesting cell specificity related to the type of microbe. Although not yet elucidated, the newly discovered pathway was described as MyD88-dependent and requires IRF1/7 for IFN-β and IRF1/2 for IFN-α release (**Figure 1**). Activators of transcription 1 (STAT1), STAT 3, PI3, and Btk were also reported as part of the signaling cascade required for IFN-α release induced by LTA. TRIF adapter is not required for TLR2 activation of interferon production, as it is for TLR4 and TLR3 (Barbalat et al., 2009).

The intracellular cross-talk scenarios are essential for understanding host–microbe interactions, since most invaders have multiple molecules recognized by multiple innate immune receptors. Investigators have still not been able to relate most of what has been learned about intracellular regulation of pathogens with infection outcomes in the host, and this must be the focus for future studies.

INFECTIOUS DISEASES AND THE ROLE OF TLR2

In order to assess the role for TLR2 in immune protection or pathogenesis of infections, a number of techniques have been developed. The vast majority of researchers have used inbred mice as the *in vivo* model, limiting individual gene variability and allowing for examination of knockout or transgenic mice. However, limiting genetic variability also limits immune response variability. In addition, another important consideration in interpreting results is the phenotypic divergence between mice and humans, including the level of TLR2 expression and which cells express TLR2. Comparison of murine and human TLR2 sequences has revealed higher correlation between intracellular domains (84%) than between extracellular domains (65%; Grabiec et al., 2004), the latter being involved with ligand recognition. Regarding cellular expression, one example of the divergence between mice and humans is the fact that murine T lymphocytes express TLR2 in a constitutive manner while human T cells do not (Rehli, 2002). These discrepancies may contribute to the differential pathology and immune response observed in mouse models of infectious diseases as compared to humans. In addition, there is evidence of associations between human TLR2 polymorphisms with disease course and susceptibility, but other factors, such as ethnicity, location, environmental factors, and exposure to infectious agents contribute to the conflicting results regarding these associations (Corr and O'Neill, 2009). Specific descriptions of TLR2 polymorphisms are included in the following sections. To our knowledge, it is unclear whether TLR1 or TLR6 can activate host immune response in the absence of TLR2 involvement. Nevertheless, we cannot assume that TLR1 or TLR6 polymorphisms that lead to alteration in receptor function are impacting TLR2 recognition and activation. There is evidence that TLR1 and TLR6 polymorphism do exist in humans that affect responses to infectious diseases (especially mycobacteria; Kesh et al., 2005; Bhide et al., 2009; Shey et al., 2010). However, for sake of clarity, this review will not address TLR1 or TLR6 polymorphisms and will only focus on TLR2 polymorphisms.

In vitro models are mostly based on the use of murine cells, human cells, or cell lines derived from both species, including dendritic cells, macrophages, and human PBMCs. The use of human PBMC is not free of criticism as well, since these cells might not replicate the responses of tissue resident cells in a specific infected organ (von Herrath and Nepom, 2005).

All models have discrepancies from true biological responses, so the conclusions based on these models need to be examined closely to insure that there is no over-interpretation. We shall examine the role of TLR2 in infections by pathogen type: viruses, fungi, protozoan/helminthes, and bacteria.

VIRUSES

Viruses are biological organisms that only replicate inside host cells. Cell adhesion and entrance usually occurs without specific PAMP recognition. In fact, almost all viral PAMPs are nucleic acid-based, which are not exposed until after host cell entry, and TLRs that recognize these PAMPs are almost exclusively intracellular. For this reason, host immune recognition of viruses relies mainly on a complex combination of endosomal TLRs and cytosolic non-TLR receptors, activated by viral nucleic acids uncommon to the host (Thompson and Iwasaki, 2008). Type I interferon (IFN) seems to be a key innate immune factor against viruses since IFN α/β receptor knockout mice are extremely vulnerable to multiple viral infections (Müller et al., 1994). For some types of viruses, type II IFN (IFN-γ) is also essential to assure viral clearance (Zhang et al., 2008). Type I IFN, mainly produced by dendritic cells, can prime natural killer (NK) cells, essential for early infection control (Szomolanyi-Tsuda et al., 2006), and induce maturation of T helper 1 (Th1) cells (Joffre et al., 2009). The production of neutralizing antibodies and activation of cytotoxic T lymphocytes (CTL) are likewise important for a specific and effective antiviral immune response (Koyama et al., 2008). However, despite these observations, there is mounting evidence of TLR2 involvement in responses to viral infections.

IFN-β production by murine monocytes can be triggered by TLR2 following stimulation with virus particles like VV or murine Cytomegalovirus (CMV; Barbalat et al., 2009). TLR2 is also involved in NK cell response, as demonstrated by impaired NK cell activity and increased murine CMV load in TLR2 knockout mice (Szomolanyi-Tsuda et al., 2006). In humans, malfunction of TLR2 caused by homozygosis for R753Q polymorphism contributes to CMV infection after liver transplantation (Kang et al., 2012). VV was recently shown to directly stimulate NK cells via the TLR2–MyD88 signaling pathway (Martinez et al., 2010), in addition to directly promoting CD8 T cell survival, allowing cloning expansion and memory cell establishment in mice (Quigley et al., 2009). TLR2/TLR6 were identified as important murine receptors to control murine respiratory syncytial virus (RSV; Murawski et al., 2009). Based on these studies, TLR2 seems to have an overall protective role in VV, CMV, and RSV infections.

Lack of functional viral Hemagglutinin impairs TLR2 response to measles virus, resulting in diminished IL-6 secretion by murine monocytes and measles receptor CD150 (Bieback et al., 2002). Varicella zoster virus (VZV) virulent strain induces IL-6 production by human monocytes through TLR2 and CD14, but blocks TLR2 mediated production of IL-12 in human dendritic cells to evade the Th1 driven immune response. The attenuated Varicella strain used for the current vaccine can not block IL-12 production, which suggests that Th1 driven immune responses are important for protection against VZV. However, the mechanisms of TLR2 blockade or IL-12 inhibition have not been clarified (Wang et al., 2005; Gutzeit et al., 2010). dUTPase from Epstein–Barr Virus also induces IL-6 production through TLR2 in TLR2 over-expressing HEK293 cells, but CD14 does not act as the co-receptor (Ariza et al., 2009). Yellow fever-attenuated virus, used as the current Yellow Fever vaccine, is capable of activating multiple TLRs and induces a balanced Th1/Th2 response in murine dendritic cells. However, in TLR2 knockout mice, the Th1 responses are considerably intensified while IL-6 and IL-12 production is decreased (Querec et al., 2006). Although hepatitis B virus capsid particles was also found to prime human THP-1 macrophages for production of TNF-α, IL-6, and IL-12p40 via TLR2 (Cooper et al., 2005), the lack of purity of this preparation makes these results controversial (Vanlandschoot et al., 2005).

Hepatitis C virus (HCV) can be recognized by the host by the TLR2/TLR6 heterodimer by recognition of the HCV core and NS3 proteins, along with recognition of viral genome by TLR3, 7, and 8 (Chang et al., 2007; Moriyama et al., 2007). HCV TLR2 recognition

activates human monocytes and macrophages to secrete mainly IL-10 and TNF-α, but inhibits macrophage-dependent dendritic cell differentiation and function (Chang et al., 2007). Accordingly, patients with chronic hepatitis were also found to have increased expression of TLR2 in PBMC, correlated with augmented circulating TNF-α and hepatic necroinflammatory activity (Riordan et al., 2006; Wang et al., 2010). Activation of PBMCs from chronic HCV patients induced by TLR2/TLR4 ligands resulted in decreased IL-6 production when compared to healthy subjects, probably caused by TLR2-induced tolerance (Chung et al., 2011). Divergent results demonstrated that the TLR2 polymorphism R753Q impairs TLR2 recognition of HCV core and NS3 proteins and increases the risk of allograft failure after liver transplantation for chronic hepatitis C patients with this mutation (Brown et al., 2010). This is an example of the contrasting roles TLR2 may play in infectious processes in humans.

The ability of viruses to stimulate cells can differ from species or viral type, but also according to the murine strain, organ, or cell type infected. TLR2/TLR9 double-knockout mice infected intravaginallly with herpes simplex (HSV) 2 had significant higher viral loads in the brain than single knockouts or wild-type mice. Viral loads in the vaginal mucosa or liver, on the other hand, did not differ between groups of mice. The observations lead to a synergistic protective role for both TLRs in the brain, benefic for encephalitis prevention, but not effective for general decrease of HSV2 viral loads (Sorensen et al., 2008). TLR2/TLR9 were shown to have a more prominent protective role for HSV1, as TLR2/TLR9 double-knockout mice all died after intranasal infection with HSV1 EK strain, as compared to 90% survival of infected wild-type mice or TLR2 knockout mice and 40% survival of infected TLR9 knockout mice. Another experiment pointed out a deleterious role for TLR2 in mice infected with HSV1 KOS strain, in which TLR2 knockout mice were more resistance to infection as compared to WT mice. Nevertheless, these apparently contradictory results were observed using different HSV1 strains and viral loads, inoculated through different routes (Krug et al., 2004; Lima et al., 2010). More work is obviously needed to truly dissect the dual property of TLR2 to be involved in both HSV disease protection and disease induction. TLR2 may also be involved in inflammation related to morbidity and mortality caused by lymphocytic choriomeningitis virus (LCMV); TLR2 is essential for induced monocyte chemotactic protein 1 (MCP-1), RANTES, and TNF-α, in mouse central nervous system glial cells (Zhou et al., 2008; Lee et al., 2012).

The common immune response measured by most studies when examining TLR2 function has been increase in IL-6 and TNF-α production during acute processes, while IL-10 was consistently found in chronic infections. IL-6 secreted by dendritic cells drives Th2/Th17 T cell differentiation (Wenink et al., 2009). Considering that type I IFN is released upon virus stimulation and constrains Th17 differentiation in mice (Guo et al., 2008), IL-6 in the context of viral infection most likely drives Th2 responses. When the Th1 phenotype is dominant, TNF-α act as an enhancer of IFN-γ killing through activation of cellular immune responses. In contrast, when Th2 or Th0 is dominant, TNF-α causes tissue damage (Hernandez-Pando and Rook, 1994; Rizzardi et al., 1998). In this context, TLR2 activation may improve viral clearance when the Th1 response is fully functional and dominant, during the initial stage of infection. TLR2 can also promote Th2 responses, which are important for adequate antibody production and protect the host by inhibition of exacerbated Th1 response.

To our knowledge, none of the viral particles were tested for TLR2 induction of regulatory T (T_{reg}) cells or Th17 cell function or activation, which could help to elucidate outcomes of TLR2 receptor activation and reveal new information regarding the Th1/Th2 bias studied so far. It is clear that TLR2 function and its role in viral immunity are co-dependent on other PRRs and the subsequent adaptive immune response. Therefore, isolated analyses can be insufficient to determine the true role of TLR2 in each infection type.

In relation to recognition, the examples of viruses mentioned above are variable in relation to species, genetic material and disease outcomes, but all viruses assumed to be recognized by TLR2 are enveloped virus. Some viruses do not have their TLR2 ligands defined. TLR2/6 was the only TLR2 heterodimer described for viral ligands, but the heterodimer needed for TLR2 recognition of many other viral ligands has not been discerned. The involvement of the TLR2/6 heterodimer is consistent with the cytokine profile described above, since the same heterodimer has been found to drive IL-10 production in dendritic cells (Depaolo et al., 2008). Studies on TLR2 accessory molecules involved with viral recognition has also been minimal and only revealed a role for CD14.

FUNGI

As opposed to viruses, pathogenic fungi are facultative intracellular or extracellular eukaryotic organisms and therefore do not depend on the host cell to replicate. Some fungal species are dimorphic and change between different forms, for example, yeast or conidia to hyphae, and consequently modify the way they are recognized by the host. In addition, cell wall composition varies among species and serotypes, which can also change the way these cells are processed by the immune system (McKenzie et al., 2010). Fungal infections remain generally localized when controlled by a regular immune response, but systemic dissemination more often occurs when the host is immunocompromised, has its physical barriers disrupted or has its microbiota altered (Chai et al., 2009a). Dendritic cells usually trigger adaptive immune response against fungal invasion, while direct clearance is performed by neutrophils, monocytes, and macrophages. All of these cells express dectin-1, TLR2, and TLR4, receptors associated with fungal recognition (Hohl et al., 2006). Most yeast can be phagocytized by macrophages through Dectin-1 receptor recognition, whereas TLR2 helps initiate the concomitant inflammatory state (Zak and Aderem, 2009). The two receptors, when stimulated, mutually synergize their cytokine and immune responses to promote a consistent pathogen clearance (Zak and Aderem, 2009). In contrast, phagocytosis of hyphae is believed to occur without independent PRR recognition and leads to Th2/Treg cells bias (Romani, 2004).

The role of TLR2 in response to one of the most common fungi involved in human disease, *Candida albicans*, is unclear and results have been somewhat contradictory. The TLR2 ligand phospholipomannan is well defined and present in hyphae and yeast forms (Li et al., 2009), while the outcomes triggered by it are not quite clearly understood. Human keratinocytes stimulated with

phospholipomannan produce IL-6 and IL-8, necessary for activation and recruitment of neutrophils and macrophages *in situ* (Li et al., 2009). Studies with TLR2 knockout mice showed both resistance (Netea et al., 2004b) or susceptibility to primary or secondary systemic *C. albicans* infection (Gil et al., 2005; Hise et al., 2009), while TLR2 knockout macrophages showed impaired fungal clearance (Blasi et al., 2005), with both impairment or enhancement of pro-inflammatory cytokine production (especially TNF-α; Blasi et al., 2005; Gil and Gozalbo, 2006). The absence of TLR2 also decreased chemotaxis rate of murine neutrophils, together with decreased fungal killing mechanisms and survival of these cells (Tessarolli et al., 2009). TLR2 is probably not directly involved with humoral response after secondary *C. albicans* systemic infection, since this parameter was not altered in TLR2 knockout mice (Villamón et al., 2004). On the other hand, Dectin-1 and TLR2 were directly related with protection against oral candidiasis through an effect on IL-1 β release, but only when both receptors are engaged (Hise et al., 2009). Other factors can influence TLR2 mediated effects and contribute to fluctuations in cytokine levels in candidiasis, for example high concentrations of vitamin D3 in mice can decrease TLR2 surface expression (Khoo et al., 2011).

Similar to *C. albicans*, *Aspergillus fumigatus* recognition varies with morphology. Both conidium and hyphae are recognized by TLR2 (Chai et al., 2009b), but hyphae are not recognized by TLR4 and result in IL-10 production through TLR2 activation (Netea et al., 2003). Murine neutrophils, on the other hand, have increased fungicidal activity and release pro-inflammatory cytokines when activated by TLR2. It has been shown that TLR2 is essential for protection in immunocompromised mice but not immunocompetent mice (Chignard et al., 2007).

Paracoccidioides brasiliensis is recognized by TLR2, and pulmonary infection of TLR2 knockout mice leads to Th17 skewed immunity and increased (Loures et al., 2009) or similar (Calich et al., 2008) lung inflammation as compared to wild-type mice. Even so, fungal burden is either diminished or the same as wild-type mice (Calich et al., 2008; Loures et al., 2009), with equal mortality rates demonstrating that overall outcomes are not necessarily affected by TLR2 signaling.

Cryptococcal recognition by TLR2 occurs through the polysaccharide glucuronoxylomannan, and the level of NF-κB activation differs based on polysaccharide effective diameters of the varying cryptococcal species (Fonseca et al., 2010). Although TLR2 was found to be important for control of *Cryptococcus neoformans* murine infection (Yauch et al., 2004), this is still quite controversial (Nakamura et al., 2006). TLR2 was also shown to play a major role in protection against *Penicillium marneffei*, due to stimulation of murine bone marrow-derived dendritic cells to produce IL-12p40 upon fungal recognition (Nakamura et al., 2008). *Histoplasma capsulatum* is recognized by mice TLR2 through the cell wall protein Yps3p, resulting in activation of NF-κB (Aravalli et al., 2008). Regardless, TLR2 knockout mice had no alteration in inflammatory cytokine production induced by this pathogen (Lin et al., 2010).

Generation of a dominant T_H1-cell response is required for most protective immune responses to fungi (Romani, 2004). The infection models mentioned above did not evaluate fungal morphology during the course of infection, which can account for the varied immune responses and survival rates described. Other TLRs and Dectin-1 expression were also not measured in parallel, and these parameters are able to alter the profile of TLR2 responses. The shielding of β-glucans can impair Dectin-1 recognition and consequent loss of synergy with TLR2, which allows for a preferential induction of an anti-inflammatory response when stimulated by fungal particles (Netea et al., 2008). In addition, it has been shown that different murine strains have different dectin-1 isoforms, which may impact on TLR2 function (Heinsbroek et al., 2008). However, it is safe to say that the absence of TLR2 influences macrophage and neutrophil anti-fungal activity, mainly through an effect on TNF-α production. This cytokine is important for induction of fungicidal activity (Chignard et al., 2007). The relevance of this effect varies according to the infectious microenvironment and with Dectin-1 function. When TLR2 responses were found to be detrimental to the host, it was due to an overwhelming suppression of the early inflammatory response and consequent increased fungal burden. Since almost all fungi are recognized to some extent by TLR2 and are recognized by TLR4 as well, it would be meaningful to evaluate the synergism between these two TLRs in the context of fungal infections, as bacterial ligands have been shown to synergistically induce IL-10 when both TLRs are engaged (Hirata et al., 2008). To date, TLR2 polymorphisms have not been shown to be related to susceptibility or protection to fungal infections, but it is also true that these studies are scarce in the literature.

PROTOZOAN/HELMINTHS

Protozoa are a group of intracellular or extracellular eukaryotic organisms that can cause human disease and depending on its life cycle, may mainly cause chronic infections (Sacks and Sher, 2002). TLR2 is activated by glycosylphosphatidylinositols (GPIs) present on some of these protozoa. The level of the inflammatory response induced is directly linked to GPI lipid and carbohydrate content (Almeida and Gazzinelli, 2001). *P. falciparum*, one of the plasmodia that cause malaria, can trigger TNF-α and IL-6 production in murine macrophages by means of TLR2/TLR1 or TLR2/TLR6 activation with GPI. This GPI is only recognized in merozoites, the erythrocyte infective form of the protozoan (Wong-Baeza et al., 2010; Zhu et al., 2011). GPI can also modulate internalization of malaria-parasitized erythrocytes. Still, when inside the erythrocyte, the parasite does not allow for display of its TLR ligands to murine and human macrophages, resulting in a non-inflammatory phagocytosis of these erythrocytes and delayed cytokine responses (Erdman et al., 2009). No TLR2 polymorphisms are related with *P. falciparum* infections (Greene et al., 2009). However, the presence of human heterozygotes for a TIRAP polymorphism (TIRAP S180L) has been related to protection of malaria. This adaptor protein mediates TLR2 and TLR4 signaling whereas its polymorphic variant severely decreases IL-6 production triggered by these TLRs, suggesting that a normal TLR2 response would be detrimental to the infected human host (Khor et al., 2007).

Toxoplasma gondii GPIs from the highly dividing tachyzoite form, also trigger TLR2 for TNF-α and MCP-1 production. TLR2 knockout mice have increased susceptibility to infection caused by high doses of *T. gondii* (Mun et al., 2003). However, the use of

lower doses leads to an increase parasite burden only in double TLR2/4 knockout mice (Debierre-Grockiego et al., 2007), suggesting a protective role for TLR2 in synergy with TLR4. Strong IL-12 induction through TLR11 is protective and part of the murine immune response, but since this gene is not functional in humans, other TLRs can have a different role in this host (Yarovinsky et al., 2005). A human embryonic intestinal epithelial cell line recognizes the parasite through TLR2, resulting in production of IL-8 and other chemokines important for neutrophil and phagocyte recruitment (Ju et al., 2009). TLR2 mediated signaling by GPIs from *T. cruzi* infective trypomastigotes results in IL-12, TNF-α, and nitric oxide production by murine macrophages (Campos et al., 2004). The *T. cruzi* protein 52 (Tc52) can induce IL-6 and IL-8 in a TLR2-dependent manner (Wong-Baeza et al., 2010). TLR2 stimulation leads to IL-12 and TNF-α production in *T. cruzi* infections, in addition to cooperating with TLR9 to enhance this production. *T. gondii* infection of TLR2/TLR9 double-knockout mice had increased susceptibility to *T. cruzi* infection. The higher parasite burden of double knockouts was related to low IL-12 and IFN-γ levels (Bafica et al., 2006). Surprisingly *T. cruzi* IL-10 modulation of murine bone marrow-derived dendritic cells was found to be independent of TLR2 (Poncini et al., 2010). An interesting cooperation between TLR2 and the bradykinin receptor in *T. cruzi* murine subcutaneous infection has been reported, where TLR2 induces leak of plasma that leads to a kininogen accumulation. This molecule is degraded by *T. cruzi* proteases to kinins recognizable by the bradykinin receptor, with consequent induction of IL-12 production by murine dendritic cells (Monteiro et al., 2006).

Entamoeba and *Leishmania* are protozoa genera that have lipopeptidophosphoglycans (LPPG) and lipophosphoglycans (LPG), respectively, which have been identified as TLR2 ligands. *Entamoeba* LPPG, also recognized by TLR4, leads to TNF-α, IL-12, IL-10, and nitric oxide release in phagocytes (Wong-Baeza et al., 2010). It also stimulates murine NK Cells for production of IFN-γ through TLR2, which is directly related with protection from amebic liver abscess (Lotter et al., 2009). Membrane LPG from *Leishmania* up-regulates the same cytokine milieu as LPPG in J774 murine macrophage cell line (Kavoosi et al., 2010). However, *Leishmania brasiliensis* infection of TLR2 knockout mice presented higher levels of IFN-γ and resistance to infection *in vivo* when compared to wild-type mice, while DCs from knockout mice had up-regulated IL-12 secretion *in vitro* (Vargas-Inchaustegui et al., 2009). This is likely associated with a diminished Th2 environment that may be normally induced by TLR2 stimulation, as this has been shown to be associated with increased protection from leishmaniasis.

Human parasitic helminths are complex eukaryotic organisms that mostly live asymptomatically inside the host, with infection usually associated with tolerogenic responses (Maizels and Yazdanbakhsh, 2003). TLR2 is known to be activated by lysophosphatidylserine of two genera of this group: *Schistosoma* and *Ascaris*. There is no information regarding the relevance of TLR2 in *Ascaris* infection. *S. mansoni* eggs fraction containing lysophosphatidylserine activate DCs via TLR2 to induce a Th2 response and regulatory T-cell development (van der Kleij et al., 2002). Conversely, *S. mansoni* infection of MyD88$^{-/-}$ mice had a normal Th2 response while other research has shown that SEA induces a Th2 bias in a TLR2 independent manner. It is likely that the SEA used in the latter experiments lacked lysophosphatidylserine to explain such contradictory results (Kane et al., 2008).

As expected, the effect of TLR2 mediated stimulation is dependent on the cellular environment in which activation occurs. Parasite clearance is related to early IFN-γ synthesis by NK cells, which, in turn, is mostly induced by IL-12 produced by dendritic cells (Campos et al., 2004; Patel et al., 2007). TLR2 ligands derived from parasites induce IFN-γ directly in NK cells and IL-12 in dendritic cells, but production of the latter is more efficient with concomitant TLR4 or TLR9 stimulation. Nevertheless, lack of TLR2 does not increase parasite burden or decrease Th1 responses, suggesting a redundant role in early infection. TNF-α induced via TLR2, on the other hand, may be involved with pathology seen with these infections, when induced at later time points during the course of disease. This may explain why TLR2 knockout mice or human TLR2 polymorphism can lead to an attenuated or resolved infection. Another possibility is that TLR2-driven Th2 responses are involved with a more severe disease state, as commonly seen in leishmaniasis (Deak et al., 2010). It is likely that a defective early IFN-γ response allows for TLR2-induced Th2 skewing and consequent suppression of IL-12 production. Parasites can infect cells and replicate inside them without TLR recognition, whereas the infected cell is frequently phagocytized in a non-inflammatory process, which may allow for delayed recognition and TLR2 mediated responses to these pathogens. Curiously, TLR2 mediated regulation of IL-10 during parasitic infections has only been to demonstrated for schistosomiasis, showing that the Th2 skewing outcome was more relevant than the alteration of the Th1/Th2 profiles in TLR2 context in this disease.

BACTERIA

Bacteria are prokaryotic unicellular organisms with varying strategies for energy production, survival, infectivity, and self-protection. Bacterial cells are limited by a common phospholipid bilayer membrane with inserted functional proteins, covered by a peptidoglycan cell wall. Some species have an outer membrane while others have a capsule or are able to sporulate, which alters the way they are recognized by the host (Silhavy et al., 2010). Lipoproteins, important TLR2 ligands, are produced by all bacteria. Due to the high number of bacterial pathogenic species, they are analyzed in the present review by their genera and Gram staining groups. The genera to be explored are the ones that include the main human pathogens.

Gram-positive bacteria

The Gram-positive bacterium cell wall contains a thick peptidoglycan layer, combined with teichoic acids and extracellular proteins. Lipoteichoic acid (LTA), as well as lipoproteins and peptidoglycan, can differentially activate TLR2 dependent on the bacteria of origin (Ryu et al., 2009; Müller-Anstett et al., 2010). The pathogenic bacteria considered here are from the genera *Corynebacterium*, *Nocardia*, *Bacillus*, *Listeria*, *Staphylococcus*, *Clostridium*, *Enterococcus*, *Streptococus*, *Mycobacterium*, and *Mycoplasma*. The last two genera do not stain as Gram-positive because they have different cell wall structure, but are regularly grouped with Gram-positive bacteria due to the genetic background (Silhavy et al., 2010). So far,

all, Gram-positive bacteria activate TLR2 to some extent. Murine phagocytes with impaired TLR2 function, either by using blocking antibodies or gene knockouts, when exposed to the above bacteria or their cell wall components have diminished or absent production of TNF-α or/and IL-6, as opposed to normal cells (Takeuchi et al., 1999, 2000; Torres et al., 2004; Bafica et al., 2005; Leendertse et al., 2008; Love et al., 2010).

Various infection models have helped to characterize some functions of TLR2 in recognition of Gram-positive bacteria. Respiratory infection models of TLR2 knockout mice with *Mycoplasma* and *Mycobacterium* showed increased bacterial burden, tissue damage, and death. This potentially protective role for TLR2 in mycobacterial infection was confirmed in humans, where TLR2 polymorphisms that decrease TLR2 expression were found to predispose people to tuberculosis (Yim et al., 2006) and non-tuberculous mycobacterial lung disease (Yim et al., 2008). Conversely, protection from respiratory infection with *Streptococcus pneumoniae* only requires TLR2 when the TLR4 ligand pneumolysin is not expressed, indicating redundancy in recognition and protective responses to these bacteria (Dessing et al., 2008). Interestingly, middle ear infections (Han et al., 2009) and meningitis (Letiembre et al., 2005) caused by *Streptococcus* are exacerbated when TLR2 is absent, which may indicate that pneumolysin may be differentially expressed depending on the environment and strain variant. Intraperitoneal inoculation of *Enterococcus* (Leendertse et al., 2008), *Listeria* (Torres et al., 2004), and *Staphylococcus* (Mullaly and Kubes, 2006) caused similar disease and inflammatory states in TLR2 knockout as compared to wild-type mice, while, in contrast, intravenous inoculation of these TLR2 KO mice with *Listeria* (Torres et al., 2004) or *Staphylococcus* (Takeuchi et al., 2000) resulted in death and bacterial burden as compared to wild-type mice. This suggests that the presence of TLR2, for these organisms at least, triggers an immune response that prevents dissemination. However, once dissemination occurs, TLR2 stimulation is no longer occurs or is protective. Regardless of strain variations, the route of infection seems quite important in regards to protection induced by TLR2 toward Gram-positive bacterial infections, at least in mice.

Human polymorphism studies found no relationship between TLR2 gene polymorphism R753Q and serious pneumococcal (Moens et al., 2007; Yuan et al., 2008), streptococcal (Liadaki et al., 2011), staphylococcal infection (Moore et al., 2004), or altered cytokine patterns in Gram-positive septic patients (Woehrle et al., 2008)' even though this polymorphism prevents TLR2 from responding to LTA. However, one functional allele is enough to compensate for this deficiency, since heterozygous subjects respond to infections the same way as the ones without the polymorphism (von Aulock et al., 2004). A TLR2-16933AA promoter human polymorphism has been associated with increased prevalence of Gram-positive bacterial sepsis but not an increase in true shock or mortality (Sutherland et al., 2005). Accordingly, blood monocytes from septic patients had higher TLR2 and CD14 expression than healthy individuals, but mortality was associated with down-regulation of the same receptors and consequent cytokine induction (Schaaf et al., 2009).

These studies demonstrates that TLR2 is important, if not essential, for control of Gram-positive infections in general, but its absence can be compensated by activation of other receptors by some genera.

Gram-negative bacteria

The Gram-negative bacterium cell wall contains a thin peptidoglycan layer with pore forming proteins, covered by an extra layer of lipopolysaccharides (LPS). However, unlike Gram-positive bacteria, they do not produce the TLR2 ligand lipoteichoic acid. LPS is an important TLR ligand present in all Gram-negative bacteria, with its molecular composition varying among the genera. These variation leads to different receptor activation and subsequent inflammation (Munford and Varley, 2006).

Campylobacter, *Bordetella*, *Shigella*, *Escherichia*, *Haemophilus*, *Salmonella*, *Neisseria*, *Klebsiella*, and *Leptospira* produce the typical LPS, a hexaacylated form capable of activate inflammation through TLR4 (Munford and Varley, 2006). All of the above genera can stimulate cells via TLR2. *Escherichia*, *Haemophilus*, *Salmonella*, *Neisseria*, *Klebsiella*, and *Leptospira* have all been examined in animal models of infection to determine the role of TLR2 in protection or pathology. In this context, TLR2 was not essential for resolution of infection for these bacteria, while TLR4 played a much greater role (Lorenz et al., 2005; Spiller et al., 2007; Sjölinder et al., 2008; Fedele et al., 2010; Moranta et al., 2010; Pore et al., 2010; Seibert et al., 2010). Nevertheless, TLR2 knockout mice had higher bacterial burdens during the course of infections with *Klebsiella* and *Salmonella*, but with mortality or antibody responses were not altered as compared to wild-type mice (Spiller et al., 2007; Seibert et al., 2010). TLR2/TLR4 double-knockout mice were even more susceptible to infection with *Leptospira* and *Klebsiella*, as compared to TLR4 single knockout mice, demonstrating an important role for TLR2 recognition in control of these infection and a potential synergistic function with TLR4, demonstrating another potential redundancy of immune system activation (Spiller et al., 2007; Chassin et al., 2009). Regarding animal models of sepsis, *Escherichia and Salmonella* trigger excessive inflammation and subsequent mice death via TLR4 and TLR2. IFN-γ induced by TLR4 stimulation increases TLR2 up-regulation and affects the immunopathology, a probable reason why TLR4/TLR2 double-knockout mice all survived infection with these organisms after antibiotic therapy as opposed to single knockouts or wild-type mice, where antibiotics could not rescue these animals (Spiller et al., 2008). This demonstrates a pathologic effect of the inflammatory response induced by bacteria through these TLRs.

The under-acylated forms of LPS are weak inducers of inflammation, some of them capable of competing with typical LPS for TLR4 and therefore acting as anti-inflammatory agents (Munford and Varley, 2006). Gram-negative bacteria that produce these forms of LPS generally evade TLR4-driven immune response and the host relies on other receptors to recognize and react to the threat. *Porphyromonas* and *Coxiella* infection resolution are partially dependent on TLR4, but pro-inflammatory cytokine production is dependent on TLR2. The establishment of *Porphyromonas* chronic infection and inflammation appears to be affected by TLR2, where the absence or presence of TLR2 has been associated with both deleterious and protective effects (Shin et al., 2010). *Chlamydia* murine infections have TLR2 dependent immune pathology, although TLR2 human polymorphisms have

not been associated with the disease (Karimi et al., 2009). It has also been shown that TLR2 mediates morbidity and mortality in murine models of infection with *Burkholderia* species, as TLR2 knockout mice have decreased pathology and increased survival as compared to wild-type mice (Wiersinga et al., 2007). TLR2 can mediate protection as well, i.e., in murine infection models of *Legionella*, *Francisella*, *Citrobacter*, and *Borrelia*. The resolution of these infections or consequent inflammation are TLR4 independent, while lack of TLR2 appears to be associated with higher bacterial burden (Archer and Roy, 2006; Abplanalp et al., 2009; Dickinson et al., 2010), tissue damage (Gibson et al., 2008), or decreased survival (Fuse et al., 2007; Gibson et al., 2008; Abplanalp et al., 2009; Dickinson et al., 2010). TLR2 mice orally infected with *Yersinia* develop a gut barrier defect and diminished intestinal clearance, demonstrating a role for TLR2 in full protection from this infection, but this may not just be specific for this bowel pathogen (Dessein et al., 2009).

Overall, the role of TLR2 in Gram-negative infections seems to be directly related with the dominant PRR activated by the bacterium. Often, at least in animal models, an excessive bacterial burden increases TLR2 sensitivity and its role in pathology. It is important to note that infection models often use attenuated or heat killed bacteria, which can change the predominant roles of participating PRRs. Accordingly, heat killed *Treponema* signals through TLR2, as opposed to live bacteria which suppresses activation by this receptor (Shin et al., 2010).

Bartonella quintana, *Helicobacter pylori*, *Moraxella catarrhalis*, *Pasteurella multocida*, *Rickettsia akari*, and *Vibrio vulnificus* are also recognized by TLR2 with subsequent induction of many inflammation related cytokines or chemokines: TNF-α, IL-6, IL-10 (phagocytes), or IL-8 (mucosal epithelial cells), depending on which cells were examined (Slevogt et al., 2007; Matera et al., 2008; Hildebrand et al., 2009; Peek et al., 2010; Lee et al., 2010; Quevedo-Diaz et al., 2010). Surprisingly, no relationship to disease has been studied or confirmed (Oliveira et al., 2008).

CONCLUSION

As discussed, there are a large variety of microbial pathogens in various phyla that express components that are recognized by TLR2. These molecules then trigger various innate immune responses that are involved with protection from these organisms and are also involved with inflammatory sequelae that are associated with disease caused by these microbes. The outcomes of ligand recognition were shown to be dependent on the recognition dimer (TLR2/TLR1 or TLR2/TLR6), and co-receptors. It is important to remember, however, that the innate immune system does not recognize microbial TLR2 ligands in a vacuum, and many of these pathogens express ligands recognized by other PRRs, i.e., LPS and TLR4, RNA and TLR3, CpG DNA motifs and TLR9, etc. Therefore, the responses to these organisms are complex and not easily predicted. It needs to be mentioned, though it is beyond the scope of this review, that many investigators have taken advantage of the ability of some of these microbial derived molecules to stimulate cells via TLR2, or other TLRs, to utilize this ability in at the development of vaccine adjuvants (Wetzler, 2010; Duthie et al., 2011).

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