Toll-like Receptor 2 in Pro- and Anti-Inflammatory Processes

Subjects: Immunology

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While a certain level of inflammation is critical for humans to survive infection and injury, a prolonged inflammatory response can have fatal consequences. Pattern recognition Toll-like receptors (TLRs) are key players in the initiation of an inflammatory process. TLR2 is one of the most studied pattern recognition receptors (PRRs) and is known to form heterodimers with either TLR1, TLR4, TLR6, and TLR10, allowing it to recognize a wide range of pathogens.

Toll-like receptor 2 dimerization homodimerization heterodimerization

1. Introduction

Over the past few decades, a great deal of knowledge has been gained about human innate and adaptive immunity and its key players, including the pattern recognition receptors (PRRs). These germline-encoded receptors can rapidly identify the specific molecular structures on the surface of pathogens, so-called pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs), linking non-specific immunity to specific immunity [1][2]. To date, two distinct classes of PRRs have been described: the membrane-bound receptors, including Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and the cytoplasmic proteins, such as nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG)-I-like receptors, absent in melanoma 2 (AIM2)-like receptors (ALRs), and DNA or RNA sensors, such as cyclic GMP-AMP synthase (cGAS) [3][4][5]. TLRs are type I transmembrane proteins with an extracellular domain containing leucine-rich repeats that facilitate recognition of PAMPs. They also have a transmembrane domain and an intracellular toll-interleukin-1 receptor (TIR) domain needed for downstream signaling [6]. So far, ten receptors (TLR1-10) have been identified in the human body, which can be divided into cell surface receptors such as TLR1, TLR2, TLR4-6, TLR10, and intracellular receptors including TLR3, and TLR7-9 [7][8]. TLRs are widely distributed on cells of the immune system, such as monocytes, as well as on non-immune cells, such as endothelial or epithelial cells [9]. Upon PAMP or DAMP recognition, homo- or heterodimerization of TLRs is triggered, leading to an intracellular signaling cascade that in most cases results in a pro-inflammatory response [10]. A prominent example of homodimerization is TLR4, which is induced after exposure to lipopolysaccharide (LPS) isolated from the outer membrane of Gram-negative bacteria such as *Escherichia coli*, whereas TLR2 is known to form heterodimers with either TLR1 or TLR6, depending on the ligand [11][12]. In addition to heterodimer formation, TLR2 can function as a single receptor and in a homodimer, albeit the latter is still under debate [12]. Although TLRs, especially TLR2, have been extensively studied, their role in health and disease is still

very much in the spotlight, as evidenced by the large number of studies on TLRs and SARS-CoV-2 infection, for example [13][14][15].

2. TLR2 Ligands and Signaling

TLRs, which are the mammalian orthologues of the *Drosophila melanogaster* Toll receptor originally discovered in 1985, are well conserved and primarily associated with pattern recognition [12][16][17]. TLR2, along with TLR4, is one of the most studied pattern recognition receptors, and unlike certain other receptors in this family, TLR2 is known to form various heterodimers with TLR1, TLR4, TLR6, and TLR10 [18][19][20]. In recent years, a growing number of studies have shown that TLR2 may be the most versatile TLR, as this receptor recognizes a broad repertoire of ligands from a variety of pathogen sources and interacts with a large number of other receptors [12][21].

TLR2/1 heterodimers can sense triacylated lipopeptides (LPs) from Gram-negative bacteria or mycoplasma, such as lipoarabinomannans and lipomannans, whereas TLR2/TLR6 heterodimers recognize diacylated LPs, including lipoteichoic acid (LTA) from Gram-positive bacteria and mycoplasma [12][22][23][24]. Depending on the ligand, low-endotoxic atypical LPS can induce TLR2/TLR4 heterodimerization, and the TLR2/TLR10 heterodimer has been found to participate in *Helicobacter pylori* LPS recognition [25][26]. Additional co-receptors, such as clusters of differentiation 14 (CD14), have been described that bring CD14 and TLR2 and TLR1 into physical proximity by binding LPs to induce signaling [27]. Interestingly, the mRNA expression of TLR2, but not TLR1, TLR4, and TLR6, was strongly induced in alveolar macrophages by prolonged LPS treatment (24 h) [28]. Besides heterodimerization, some evidence also points to the existence of TLR2 homodimerization, but this is still controversially discussed [12][29]. Commonly used TLR2 ligands for in vitro and in vivo studies are synthetic di- and triacylated LPs such as Pam2CSK4, Pam3CSK4, isolated from *Escherichia coli*, and FSL-1, which represents a pathogen-associated molecular pattern of the LP secluded from *Mycoplasma fermentans* or *Mycoplasma salivarium* [12][30][31]. Moreover, endogenous ligands, danger signals for TLR2, have been identified, including heat shock proteins, human β-defensin-3, high mobility group box 1 protein (HMGB1), and hyaluronan fragments [32][33][34][35]. Other ligands of TLR2 that play a major role in neurodegenerative disorders are amyloid-β (Aβ) and α-synuclein (αSyn) [36][37]. Therefore, in addition to PAMPs, endogenous TLR2 activation by host-derived danger signals is a viable factor in the pathogenesis of inflammation and related diseases.

Ligand-induced dimerization is the starting point for TLR2 signal transduction. Dimerization brings the TIR domains of the cytoplasmic tails into close proximity, providing a platform for signaling by TIR domain-containing adaptor molecules [12]. TLR2 primarily relies on the myeloid differentiation factor 88 (MyD88) and the Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP) adaptors for signaling [38]. The MyD88-dependent pathway involves death-domain interactions mediating intracellular signaling in a stepwise manner. Specifically, MyD88 recruitment is indirect and mediated by TIRAP [39]. Active MyD88 then sequentially triggers the phosphorylation of interleukin-1 receptor-associated kinase 4 (IRAK4), IRAK1, and IRAK2 [40]. The IRAK complex engages tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), which undergoes K63-linked autoubiquitination and ubiquitinates nuclear factor kappa B (NF-κB) essential modulator (NEMO). The complex of transforming growth factor-β-activated kinase-1 (TAK1), TAK1-binding protein 2 (TAB2), and TAB3 is then activated. Next, TAK1

phosphorylates IkappaB kinase alpha (IKKα) and IKKβ, and the IKKs phosphorylate IκB, are marked for degradation, which ultimately leads to the production of pro-inflammatory cytokines via NF-κB and activating protein-1 (AP-1), and activation of mitogen-activated protein kinase (MAPK), modulating cell proliferation and survival (**Figure 1**) [6][41]. Interestingly, the interaction of TIRAP with IRAK1 and IRAK4 can lead to the degradation of TIRAP following its phosphorylation and ubiquitination, resulting in the inhibition of TLR2 signaling [42].

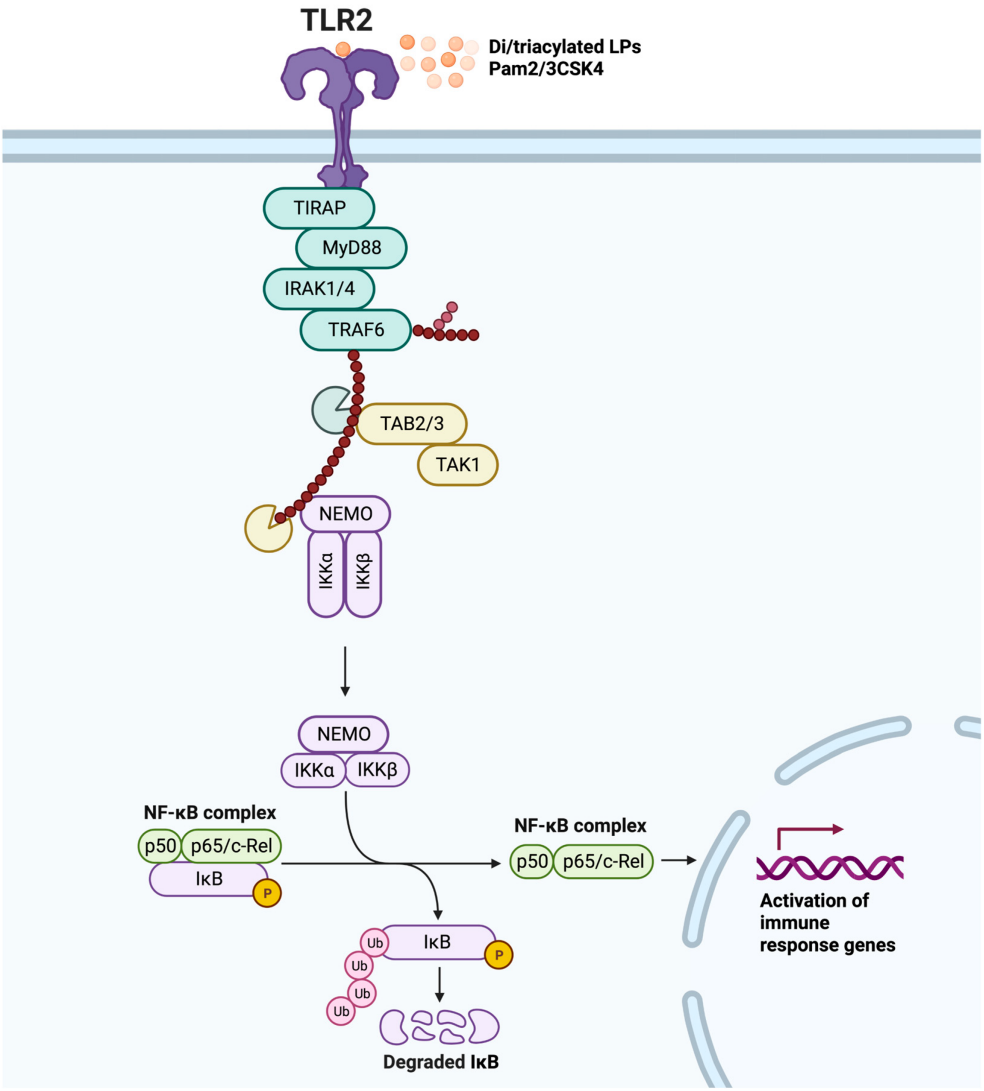

Figure 1. TLR2 MyD88-dependent signaling pathway. Dimerization is triggered by ligand binding (diacylated lipopeptides (LPs) or triacylated LPs, and synthetic Pam2CSK4 or Pam3CSK4), resulting in a signaling cascade that begins with Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP) binding to TLR2, which then leads to the recruitment of MyD88. Following phosphorylation of interleukin-1 receptor-associated kinase (IRAK) 4, IRAK1, and IRAK2, TNF receptor-associated factor 6 (TRAF6) undergoes K63-linked autoubiquitination and ubiquitinates nuclear factor kappa B (NF-κB) essential modulator (NEMO). The complex of transforming growth factor-β-activated kinase-1 (TAK1), TAK1-binding protein 2 (TAB2), and TAB3 complex is then activated to phosphorylate IkappaB kinase alpha (IKKα) and IKKβ, and the IKKs phosphorylate IκB, marking it for degradation and releasing the NF-κB complex (consisting of p50 and p65/c-Rel). This ultimately leads to the activation of immune response genes, including the production of pro-inflammatory cytokines via the transcription factor NF-κB.

3. Dimerization and Additional Co-Receptors of TLR2

3.1. Homodimerization

The existence of TLR2 homodimers has been mentioned in a number of publications in recent years, however, the function of this homodimer is still controversial [12][43][44][45]. In vitro studies such as those of de Groot et al. suggest that TLR2 is functional as a homodimer, although it may require co-receptors to reach an active state. In particular, they were able to show that TLR2 signaling was reduced in the TLR1- and TLR6-deficient reporter systems, but was still evident in response to *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* [46]. In a different investigation, another research group concluded that LTA-activated TLR2 via the TLR2 homodimer is likely to be less potent than that of LPs via the TLR2 heterodimer, which is limited to the induction of IRAK-M [47]. Su et al. identified diprovocim-1 as an effective inducer not only for the formation of TLR2/TLR1 heterodimers, but also for the formation of TLR2 homodimers in vitro [48]. Contrary studies show that the proline-proline-glutamic acid 18 (PPE18) protein of *Mycobacterium tuberculosis* induces TLR2 homodimerization, which triggers anti-inflammatory type responses that cause increased activation of the mammalian p38 MAPK [49]. Furthermore, by generating a CRISPR/Cas9-mediated knock-out of endogenous TLR6 in JE6-1 TLR2/6 reporter cells, it was recently shown that TLR2 homodimers are expressed on the cell surface. However, these reporter cells did not respond to any of the bacterial TLR2 agonists tested, nor could they be detected by diprovocim-1 induction. Activation of reporter cells occurred only in cells expressing TLR2/1 heterodimers [50]. Taken together, the recent results suggest that the function of a TLR2 homodimer is strongly dependent on ligands and co-receptors yet to be discovered. To address these unanswered questions, novel methods and strategies could help to further elucidate potential functions of the TLR2 homodimer.

3.2. TLR2 Heterodimers

The ability of TLR2 to dimerize not only with itself but also with a variety of TLRs, greatly expands the spectrum of detectable pathogens. Ozinsky et al. were among the first to discover that TLR2 relies on heterodimerization with either TLR1 or TLR6 to initiate adequate cell activation and a pro-inflammatory response [18][21]. Structural studies of the heterodimers have supported the importance of ligand binding to stabilize TLR2/1 and TLR2/6 dimerization for downstream signaling [51][52]. However, since the heterodimerization of TLR2 with TLR1 or TLR6 has already been extensively studied, researchers will focus on insights into other TLR2 heterodimerizations. There is accumulating evidence that TLR10 is capable of forming functional heterodimers with TLR2 [20][53]. This is plausible because in mammals, TLR10 is a member of the TLR1 subfamily and shares numerous paralogous genes with TLR1, 2, and 6 [54][55]. To assess whether the TLR2/10 heterodimer induces downstream signaling, Pachathundikandi et al. examined the mRNA expression levels of pro-inflammatory cytokines upon exposure to *Helicobacter pylori* or LPS and found a significant upregulation of interleukin-1β (IL-1β) in TLR2/10-transfected HEK293 cells [56]. In another study, they silenced TLR10 in the human colon adenocarcinoma cell line HT-29 and in monocytic THP-1 cells, which led to increased viability of *Listeria monocytogenes*, and they unveiled that the heterodimer of TLR2/TLR10 was the one behind the activation of NF-κB [57]. Nagashima et al. further confirmed this by using NC1-N87 gastric cells incubated with *Helicobacter pylori* and concluded that the TLR2/TLR10

heterodimer upregulates NF-κB activation to a greater extent than other TLR2 heterodimers [26]. A recent research report indicated that TLR10 regulates TLR2-induced cytokine production in monocytes isolated from Parkinson's disease patients [58]. However, the specific ligand(s) and function of the TLR2/10 heterodimer have not been fully elucidated. Interestingly, a report from 2014 suggested that the hemoglobin-induced TLR2/4 heterodimer mediates inflammatory injury in intracerebral hemorrhage in in vivo and in vitro models [19]. Furthermore, an in vitro study by Muniz-Bongers et al. showed that in HEK293, matrix metalloproteinase 2 (MMP2) binds to both TLR2 and TLR4 for signaling, suggesting that TLR2 and TLR4 may form a heterodimer and consequently trigger a MyD88-dependent signaling cascade [59]. The existence of functional TLR2/4 heterodimers was further confirmed by Francisco et al. who showed that low-endotoxic atypical LPS isolated from *Ochrobactrum intermedium* is a potent TLR2/TLR4-inducing agonist, which they additionally confirmed by molecular docking analysis and fluorescence resonance energy transfer [25]. Nevertheless, the detailed mechanism of these divergent TLR2 heterodimers is still in question, and additional research and specific ligands are needed to substantiate these findings.

3.3. Other Co-Receptors Supporting TLR2

Additional co-receptors, called accessory receptors, are often required to augment TLR2 ligand delivery, pattern recognition, and other functions (see **Figure 2**) [12][21][60]. Prominent adaptors include CD14 and CD36, which are glycoproteins that are expressed primarily on monocytes and macrophages and that promote TLR2-dependent inflammation [61][62][63][64][65]. By performing immunoprecipitation and sugar inhibition assays, the physical interaction of ArtinM, a TLR2 agonist, with TLR2 and CD14 was observed to be a prerequisite for ArtinM-induced M1 macrophage activation [66]. Another study demonstrated that treatment of the LPS-incubated human microglia with anti-CD36 regulated the inflammatory cytokine levels in the brains of newborn mice and resulted in a significant decrease in TLR2 expression levels, while TLR4 expression was not altered [67]. In addition to CD14 and CD36, the hyaluronan receptor CD44 was found to be significantly upregulated in THP-1 wild-type versus TLR2 knock-out cells using quantitative mass spectrometry [68]. A number of reports in the last few years have indicated an interaction between TLR2 and CD44 [69][70][71][72]. Another interesting group of TLR2 co-receptors are the heterodimeric integrin receptors, which are critical for facilitating cell–cell and cell–extracellular matrix adhesion during inflammation [73]. They are composed of an α and a β subunit, which allows them to recognize a variety of different ligands that are relevant to cell adhesion and migration [74]. Numerous research articles report that β1, β2, as well as β3, directly or indirectly interact with TLR2 to initiate signaling cascades that culminate in cytokine secretion [21][68]. An in vitro study from 2019 demonstrated that α- 1- acid glycoprotein potentiated TLR2-dependent β2-integrin-mediated cell adhesion of neutrophils [75]. On the other hand, De Baros et al. showed that Pam3CSK4 increased α3β1 integrin levels, which was inhibited by silencing TLR2. However, *Paracoccidioides brasiliensis* infection led to an increase in TLR2 and in parallel, α3β1 integrin levels were downregulated in human lung epithelial cells [76]. These results once again emphasize that TLR2 modulation is ligand- and cell-type dependent.

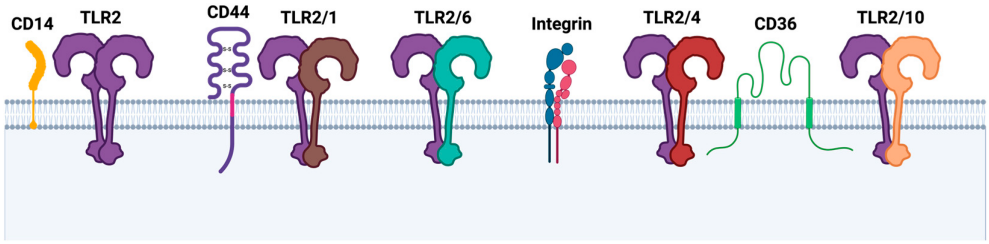

Figure 2. TLR2 homo- and heterodimers and additional co-receptors. Upon ligand binding, dimerization is initiated, often requiring additional co-receptors such as cluster of differentiation 14 (CD14), CD44 receptor, integrin receptors, or CD36.

3.4. Optogenetics, an Innovative Approach to Study TLR Dimerization and Signaling

Conventional techniques to further identify and characterize dimerization and signaling mechanisms, such as pharmacological control including ligand exposure, knock-out models, or biochemical assays, may not always be the most appropriate method. For example, models based on TLR2 knock-outs emphasize the importance of TLR2 but do not provide insight into the detailed signaling mechanism or interactions with other co-receptors. However, new experimental models, such as optogenetics, are emerging that do not rely on ligand binding to activate cellular receptors. Optogenetics was first introduced by Deisseroth in 2006 in the field of neuroscience, where light-sensitive ion channels were being utilized to remotely control action potentials and thereby neuronal networks [77]. In short, this biological technology uses genetic engineering to combine an effector protein with a light-sensitive protein domain of microbial, fungal, or plant photoreceptors to precisely control the activity of specific cells with light [78]. To enable the activation and inactivation of signaling pathways, a variety of optically controlled receptors have been developed in recent years, including G protein-coupled receptors (GPCRs) or receptor tyrosine kinases (RTKs) [79][80][81][82]. Grusch et al. have used the light–oxygen–voltage (LOV) sensing domain to induce RTK dimerization by light [80]. In a variety of eukaryotic and prokaryotic proteins, LOV domains bind a flavin chromophore to function as blue light sensors. In order to use these LOV domains for optogenetic approaches, they were isolated from different organisms, including *Arabidopsis thaliana* or *Chlamydomonas reinhardtii* [83][84]. The research group has established light-inducible TLR4 cell models using human pancreatic adenocarcinoma and endothelial cell lines [85][86]. For this purpose, the LOV domain, isolated from the yellow-green alga *Vaucheria frigida aureochrome 1*, was C-terminally fused to the full-length TLR4. This innovative system allows precise on/off switching under temporal and spatial control, which may be an interesting approach to elucidate TLR2 homodimerization and signaling.

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