Chapter

TLR Signaling on Protozoan and Helminthic Parasite Infection

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Abstract

Toll-like receptors (TLRs), a major component of innate immune system, are expressed as membrane or cytosolic receptors on neutrophils, monocytes, macrophages, dendritic cells (DCs), B lymphocytes, Th1, Th2, and regulatory T lymphocytes. It recognizes pathogen-associated molecular patterns (PAMPs) and Toll-interleukin1 (IL-1) receptor (TIR) of various invading pathogens. Downstream signaling of TLRs activates NF-κB, which acts as a transcription factor of pro-inflammatory cytokines, chemokines, and costimulatory molecules. A balance between pro- and anti-inflammatory cytokine protects host body from infectious agents and also induces the healing process. Some of parasitic infections by protozoans and helminths such as Malaria, Leishmaniasis, Trypanosomiasis, Toxoplasmosis, Amoebiasis, Filariasis, Schistosomiasis, Ascariasis, Taeniasis, and Fasciolosis are the leading cause of death and economic loss in both developing and developed nations. Frequent exposure to parasites, immigration, refugee resettlement, increasing immunodeficiency, climate change, drug resistance, lack of vaccination, etc. are the major cause of emerging and re-emerging of the above-stated diseases. However, TLR activation by parasites could stimulate antigen presenting cells and ultimately clear the pathogens by phagocytosis. So, a better understanding of host-parasite interaction in relation to TLR signaling pathway will improve the controlling method of these pathogens in immunotherapy.

Keywords: Toll-like receptors, pathogen-associated molecular patterns, protozoan parasite, helminth infection

1. Introduction

Increasing cases of parasitic infections (due to protozoans and helminths) and high rate of mortality are the greatest problem of today's world. Some of these diseases such as Malaria, Filariasis, Trypanosomiasis, Leishmaniasis, Toxoplasmosis, Amoebiasis, Ascariasis, Schistosomiasis, and Taeniasis affect over half a billion people worldwide and cause economic loss in both developing and developed countries [1]. Overpopulations, migration of people into large urban areas, and unhygienic environment are the main reasons for making these diseases epidemic [2]. However, the tragedy is that only 5% of total health expenditure was given for research work on parasitic diseases [3]. Currently, there is no effective vaccine available for these major problems. So, a better understanding of pathogenesis during infection, resistance mechanism of pathogens, host protective immune response initiation, and progression is needed for developing effective vaccines or therapeutic interventions [4].

Among the two types of vertebrate immune system, innate immunity provides the first line of defense against parasites. Previous studies stated innate immunity as nonspecific response, and it induces the acquired immunity (slower and specific response) by providing pathogens to T and B cells [5]. However, recent evidence proved that innate immune system also had a great degree of specificity and can provide host defense against invading parasites. This is because of the presence of five classes of pattern recognition receptors: TLRs (Toll-like receptors), C-type lectin receptors, NOD-like receptors (nucleotide-binding oligomerization domain leucine-rich repeat-containing receptors), RIG-I (retinoic acid inducible gene I protein) helicase receptors, and cytosolic dsDNA sensors [6, 7]. Among them, TLRs form a bridge between innate and adaptive immunity and play a very important role in parasite eradication. TLRs recognize specific pathogen-associated molecular patterns (PAMPs) in pathogens and initiate opsonization, phagocytosis, pro-inflammatory and anti-inflammatory response, and apoptosis [7, 8].

2. Cells expressing TLRs

TLRs, a major component of innate immunity, are Type-1 transmembrane glycoproteins present in both vertebrates and invertebrates [9]. Toll-like receptors are named due to their similarity with Drosophila Toll protein (Toll) [10]. All TLRs have a highly variable extracellular domain containing leucine-rich repeat (LRR) domain for ligand binding and intracellular TIR homology domain [11]. Toll-like receptors and interleukin-1 receptor together form "Interleukin-1 receptor/Toll-like receptor" superfamily whose all members have a common Toll-IL-1 receptor (TIR) domain [12]. Till date, 10 humans and 12 mice functional TLRs were identified. Although humans and mice have similar TLR1–9, TLR10 is nonfunctional in mice and TLR11–13 are lost in humans [13]. TLR1, TLR2, TLR4, TLR5, and TLR6 recognize extracellular PAMPs, which are expressed on cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are expressed within endoplasmic reticulum (ER), endosomes, lysosomes, and endolysosomes and identify nucleic acids [14]. The presence of TLRs on specific intracellular vesicles restricts their activation by self-nucleic acids released by apoptotic cells [15]. TLR11 (a relative of TLR5) and TLR13 are expressed in intracellular vesicles [16], but cognate PAMP of TLR13 has not been identified yet [17]. **Table 1** shows the distribution of various TLRs in different cells.

TLRs can be classified on the basis of their recognized ligands—TLR1/TLR2 heterodimer (triacylated lipopeptides), TLR2/TLR6 heterodimer (diacylated lipopeptides), TLR4 (lipopolysaccharide), TLR3 (double-stranded RNA), TLR5

Cells	Expressing TLRs
Neutrophils	TLR 1, 2, 4, 5, 6, 7, 8
Monocytes/macrophages	TLR 1, 2, 4, 5, 6, 7, 8
Myeloid dendritic cells	TLR 2, 3, 4, 7, 8
Plasmacytoid dendritic cells (PDCs)	TLR 1, 6, 7, 9
B lymphocytes	TLR 1, 3, 6, 7, 9, 10
T lymphocytes (Th1/Th2)	TLR 2, 3, 5, 9
T lymphocytes (regulatory)	TLR 2, 5, 8
Peripheral blood mononuclear cell (PBMC)	TLR 2, 4, 5, 7, 8, 9

Table 1.
Different Toll-like receptors expressed by immune cells [7, 16].

(flagellin), TLR 7/8 (single-stranded RNA), and TLR9 (unmethylated CpG motif) [18, 19]. These ligands for TLRs are of bacterial, viral, protozoan, fungal, and helminth membrane bound or endogenously released molecules such as hyaluronic acid, fibrinogen, fibronectin, b-defensins, heparan sulfate proteoglycans, heat shock proteins, nucleic acids, and synthetically derived molecules [20].

3. TLR signaling pathway

TLRs present on dendritic cells (DCs) [both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs)], neutrophils, macrophages, natural killer (NK), and natural killer T (NKT) cells induce dendritic cell maturation, MHC molecule upregulation, and costimulatory molecule production (CD40, CD80, and CD86) [21, 22]. The cytokines released by TLR signaling ultimately activate Th1 cells (via IL-12 from DCs) and Th2 cells (via IL-4 from B cell) [21, 23].

Toll-interleukin-1 receptor (TIR) domain is responsible for transducing the signal from TLRs to their adaptor proteins. The C-terminus of all TLRs, IL-1 and IL-18 and adaptor proteins of TLRs have this TIR domain. Six adaptor proteins involved in TLR signaling are MyD88 (myeloid differentiation factor 88), TIRAP (Toll-IL-1 receptor domain-containing adaptor protein) and MAL (MyD88 adapter-like), TRIF (TIR domain-containing adaptor inducing interferon-β) and TICAM-1, TRAM (TRIF-related adaptor protein) and TICAM-2, SARM (sterile-α and HEAT/Armadillo motifs-containing protein) and MyD88-5, and BCAP (B Cell Adaptor for PI3K) [24]. TLR signaling occurs via two separate pathways: MyD88 (myeloid differentiation primary response protein)-dependent pathway and MyD88-independent pathway. MyD88-dependent pathway stimulates all TLRs except TLR-3, which gets stimulated by MyD88-independent pathway. However, in case of TLR4, both MyD88-dependent and independent pathways operate [25]. MyD88 (an adaptor molecule) activates IRAK-4 (interleukin-1 receptor-associated kinase-4) alone or in combination with TIRAP (Toll-IL-1 receptor domain-containing adaptor protein) or MAL (MyD88

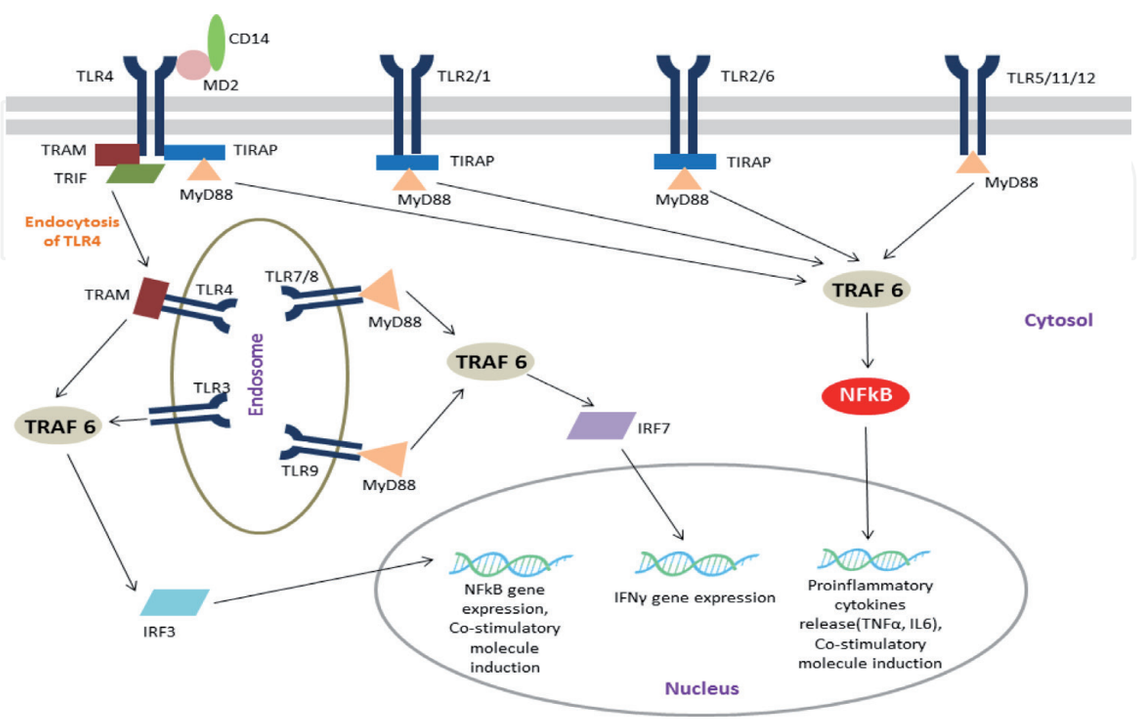

Figure 1.
TLR signaling pathway.

adapter-like). Then, IRAK-4 phosphorylates IRAK-1 [26] which in turn phosphorylates IRAK-2. IRAK-2 ubiquitinates TRAF6 (tumor necrosis factor receptor-associated factor 6) and induces two signaling pathways: (1) AP-1 (activator protein 1) activation via MAK 4/7 (mitogen-activated protein kinase) phosphorylation and (2) TAK1 (transforming growth factor-β-activated kinase 1) activation ultimately leads to MAPK (mitogen-activated protein kinase) and IKK complex [27] stimulation and nuclear factor κB (NF-κB) translocation inside the nucleus via degradation of its inhibitor. Both AP-1 and NF-κB induce the expression of pro-inflammatory cytokines and chemokines. A different MyD88-dependent pathway stimulates TLR 7, 8, and 9, which acts as a ligand for viral nucleic acids. MyD88-associated IRAK1 (interleukin-1 receptor-associated kinase-1) phosphorylates IRF7 (interferon-regulatory factor-7), which regulates Type I interferon expression [28]. TLR signaling through MyD88-independent pathway occurs via two adaptor molecules—TRIF (Toll-IL-1 receptor domain-containing adaptor inducing interferon-β) and TRAM (TRIF-related adaptor molecules) (**Figure 1**). This induces Type 1 interferon by IRF-3 (interferon-regulatory factor-3), NF-κB activation, and expression of co-stimulatory molecules [29].

4. Protozoan infections

Different protozoan (Plasmodium, Leishmania, Trypanosoma, Toxoplasma, and Entamoeba) PAMPs induced pathogenic reactions through TLR signaling pathway.

4.1 Malaria

Malaria, one of the most life-threatening diseases of human history, has infected about 219 million people over 90 countries with around 1 million deaths per year. Plasmodium, an intracellular protozoan parasite, is the causative agent of malaria. It is transmitted by infected female Anopheles mosquito biting, and four species of *Plasmodium* are responsible for human malarial infection. Among *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale,* and *Plasmodium malariae*, *P. falciparum* is the deadliest. Recently, another species named *Plasmodium knowlesi* has been found to infect humans [30]. In the early presymptomatic stage, a very low level of plasmodium can induce inflammatory response [31]. The innate immune genes such as TLRs, PRRs, and inflammatory cytokines are already upregulated, and these lead to elevate the level of TNF, IFN, and IL-12 from plasmodium-infected peripheral blood mononuclear cells (PBMCs) up to 48 h of infection [32, 33]. These inflammatory responses are associated with the pathophysiological condition and clinical symptoms of malaria including anemia, cerebral malaria, and ultimate death [34]. Cerebral malaria is caused due to overexpression and binding of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1), vascular cellular adhesion molecule 1 (VCAM-1), endothelial/leukocyte adhesion molecule (ELAM-1), and CD36 [35] on brain endothelial cell receptors. Thus, inflammatory response leads to sequestration of infected red blood cells in host brain [36]. Furthermore, TNF and IFN suppress hematopoiesis and lead to anemia during malarial infection [37]. The potential immunomodulators of the malarial parasites are: (1) plasmodial glycosylphosphatidylinositol (GPI) anchors, (2) hemozoin, and (3) plasmodial DNA. All of these three molecules are referred as "malaria toxin" released during schizogony and cause inflammation and symptoms of malaria [38, 39].

Homodimer of TLR4 and heterodimer of TLR1/TLR2 and TLR4/TLR6 can bind to GPIs released during erythrocytic phase of *P. falciparum* infection [40]. GPI induces TLR-mediated proinflammatory cytokines (TNFα and IL-1) [41] and

nitric oxide [42] release from macrophages. It also induces cerebral malaria at later course of infection [43]. Plasmodium 2-Cys peroxiredoxin also acts as a TLR4 ligand in monocyte and mast cells and causes cytokine production [44]. Hemozoin is released during each life cycle of *P. falciparum* infection and makes a complex with plasmodial DNA. This complex acts as a TLR9 ligand and leads to the production of proinflammatory cytokines (TNFα and IL-1β) [45]. Hemozoin DNA complex induces cerebral malaria by caspase 1-mediated inflammasome (NLRP3) formation by TLR9 in case of *P. chabaudi* infection [46] but is absent in *P. berghei* spoprozoite infection [47]. Although in case of both mice and humans, Plasmodium infection renders no TLR stimulation in dendritic cells. The infant exposed to TLR-mediated cytokine profiles (IL-10) is associated with higher risk of *P. falciparum* maternal infection during delivery [48]. RNA of *P. chabaudi* acts as a ligand for TLR7 and induces IFNγ, IL-10, IL-12, and TNF release at 24 h of infection [49]. In case of *P. vivax* infection, TLR5 and TLR7 hinder parasitic growth, but TLR9 is associated with high inflammation and cytokine production [50]. The 19 kDa C-terminal fragment of merozoite surface protein 1 (MSp1) in *P. vivax* acts as a ligand for TLR5 [51]. *P. yoelii* infection in peritoneal macrophages enhances TLR and parasite-specific immune response [52] (**Figure 2**). Other than Th1 response, malaria parasite-derived molecules also induce Th2 response via IL-4-inducing factor (released by PI3K-Akt-NF-κB signaling) in DC [53].

4.2 Leishmaniasis

Leishmaniasis is one of the deadliest parasitic infections with an estimation of 200,000–400,000 worldwide infections each year. A protozoan parasite is the causative agent of this disease, which is transmitted to humans by the biting of female Phlebotomus sandfly. The pathology of this infection and causative parasitic species includes cutaneous (i.e., *L. major*, *L. mexicana*, and *L. guyanensis*), mucocutaneous (i.e., *L. amazonensis* and *L. braziliensis*), or visceral leishmaniasis (*L. donovani* and *L. chagasi*) [54]. Several reports indicate that few Leishmania-derived molecules could interact with innate immune receptors (TLRs) of host and result in inflammatory

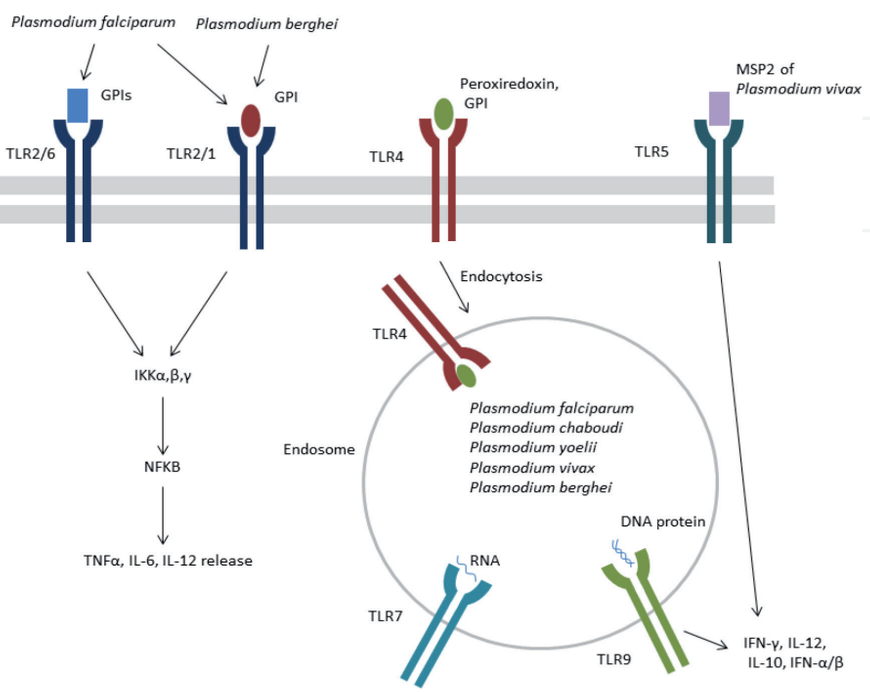

Figure 2.
TLR signaling during Plasmodium infection.

response. This inflammation effectively deprives parasites from the host by inducing efficient adaptive responses.

Lipophosphoglycan (LPG) occurs as a surface protein of *L. major*, *L. mexicana*, *L. aethiopica*, and *L. tropica* and acts as a major ligand for TLR-mediated host immune response. LPG's secreted form is structurally similar to membrane bound form with differences in sugar types of glycan and in number of phosphorylated oligosaccharide repeats. Membrane bound LPG induces ROS production and Th2 cell differentiation, whereas soluble LPG causes Th1-promoting cytokine production [55]. Inside NK cells, LPG of *L. tropica* induces TNFα, IFNγ, nitric oxide (NO), and reactive oxygen species (Th1 response) release via TLR2 upregulation and stimulation [56, 57]. TLR2 can also induce immune response by altering TLR9 expression [58]. However, in case of *L. braziliensis* and *L. amazonensis*, parasite could decrease IL-12 production, increase IL-10 production by TLR2-mediated p38 MAPK inhibition in macrophages, and thus increase pathogenesis. TLR2/TLR4 dimerization induces the expression of SOCS-1 and SOCS-3 (suppressor of cytokine signaling protein) by LPG [59]. A protein structurally related to silent information regulator 2 (SIR2) family could activate B lymphocytes, major histocompatibility complex (MHC) II, CD40 and CD86 (costimulatory molecules) overexpression, DC maturation, and TNFα and IL12 secretion through TLR2 [60]. HO-1 (heme oxygenase-1) mediated inhibition of TLR2, 4, 5, and 9 (but not TLR3) association with their adaptor proteins resulted in downregulation of TNFα and IL-12 production in *L. chagasi* and *L. donovani* infection [61]. This inflammatory imbalance occurs due to MAPKp38 phosphorylation inhibition and ERK 1/2 phosphorylation activation in macrophages. In addition, *L. donovani*, *L. mexicana* (expressed p8 proteoglycolipid complex), and *L. major* suppressed TLR4 activation by releasing TGFβ that activates A20, a complex deubiquitinating enzyme, through SRC homology region-2 domain containing phosphatase-1 (SHP-1) and IRAK inactivation [62]. Proteoglycolipid complex (P8), host-derived Apolipoprotein E (ApoE), and four glycolipids of *L. pifanoi* amastigote were the ligands of TLR4 and control the parasite [55]. P8 activates TLR4 of parasitophorous vacuole, which induces IL1 and TNFα production and aids in phagocytosis of *L. pifanoi*. At early stage of infection, neutrophil-derived serine protease and elastase results in parasite death, but at later stage, bone marrow derived macrophages (M2b macrophage) phagocytose neutrophil and helps in *L. major* replication by Th2-type response [63]. *L. panamensis* infection results in TNF α production through TLR-1, TLR-2, TLR-3, and TLR-4 pathway in human primary macrophages [64], metacyclic promastigote of *L. mexicana* induce phosphorylation of MAP kinases (ERK, p38, and JNK) through TLR4 and MΦ(bone marrow-derived macrophages), iNOS, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), NO, and arginase-1 are act as the inflammatory response mediators [65]. Leishmania parasites grow inside the phagolysosome of the host cells, which reflect that endosomally localized TLRs are also involved in pathogenesis [66]. In case of *L. donovani* infection, TLR7 activates IRF-5 and induces Th1 responses of host [67]. Cytosine-phosphate-guanosine motifs in DNA of *L. major* induce TLR9-mediated NK cell activation and IL12 production from bone marrow-derived DC [68, 69]. Recent reports show that viral RNA present in *L. guyanensis* (LRV1-Lg), *L. major* (LRV2-Lmj) [70], and *L. aethiopica* (LRV2-Lae) serves as a ligand for TLR3 [71]. TLR3 produces NO and TNFα during *L. donovani* infection and mediates leishmanicidal activity [72] (**Figure 3**).

4.3 Trypanosomiasis

The protozoan parasites of the genus *Trypanosoma* cause a group of disease in several vertebrates, called trypanosomiasis or trypanosomosis. In humans,

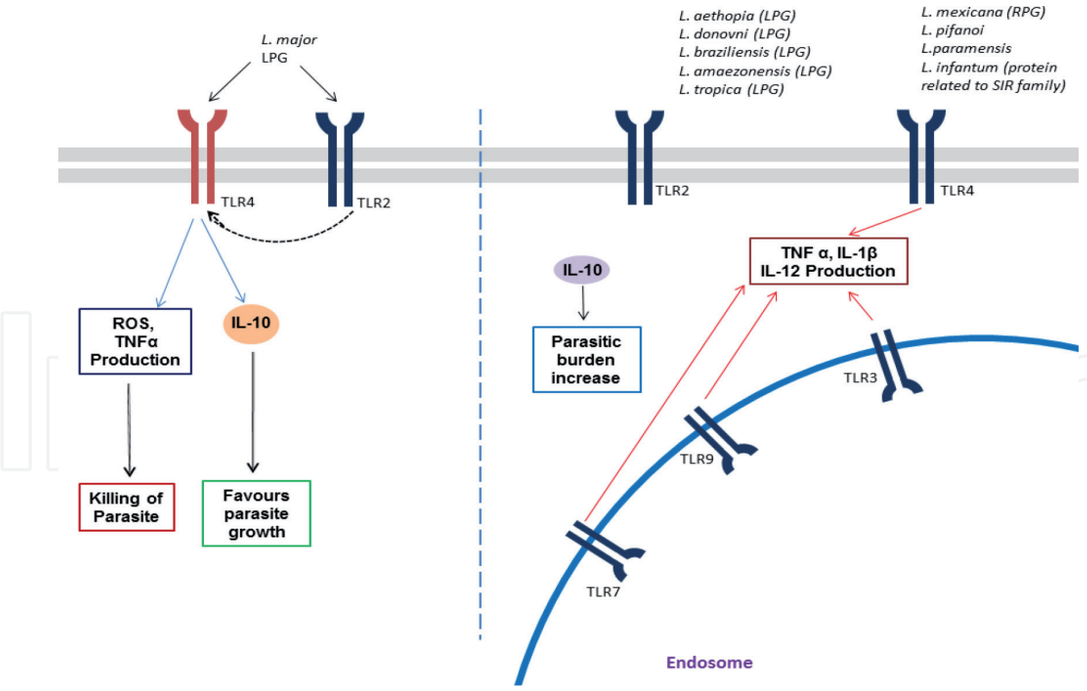

Figure 3.
TLR signaling induced by different Leishmania ligands.

Trypanosoma brucei gambiense and *Trypanosoma brucei rhodesiense* cause African trypanosomiasis or sleeping sickness (transmitted by tsetse fly), and *Trypanosoma cruzi* causes American trypanosomiasis or chagas disease (blood feeding Triatominae bugs) [73]. All of these parasites cause millions of death per year in both sub-Saharan African and Latin American countries. The disease remains asymptomatic for several years and ultimately affects the central nervous system, heart, and GI tract [74].

TLR receptor plays an important role in internalization of the parasite through phagocytosis and induces immune response for parasite eradication from cells [75]. GPI anchored mucin-like glycoproteins (tGPI-mucin contains unsaturated alkyl-acylglycerol) of the *T. cruzi* trypomastigote membrane activates MAPK (by phosphorylation) and IkB (inhibitor of NF-κB), which triggers TLR2-mediated cytokine production by macrophages [76]. A TLR2-TLR6 and CD14 complex recognize the free GPI (glycoinositophospholipids containing ceramide) from *T. cruzi* parasite (epimastigote) [77]. Tc25, a *T. cruzi* derived protein, induces TLR2-mediated pro-inflammatory cytokine release from host cells [78]. However, role of GPI anchors VSGs of *T. brucei* Trypomastigotes in specific TLR-mediated macrophage activation and proinflammatory cytokine (TNFα, IL-6, and NO) production have not been elucidated yet [79]. *T. cruzi* and *T. brucei* genomic DNA (contains unmethylated CpG motifs) have TLR9-mediated TNFα and IFNα/β stimulation and penetration of T cells in brain parenchyma [80, 81] (**Figure 4**).

4.4 Toxoplasmosis

Toxoplasma gondii, an obligate intracellular apicomplexan parasite, is a leading cause of food borne disease in a wide range of worm-blooded animals worldwide [82]. *T. gondii* causes asymptomatic toxoplasmosis in healthy adults and produces severe toxoplasmic encephalitis in immune compromised people [83]. Moreover, it causes congenital toxoplasmosis in fetus leading to death and abortion [84]. Inside its intermediate host humans, mice, etc., *T. gondii* proliferates asexually to form tachyzoite and bradyzoite stages [85].

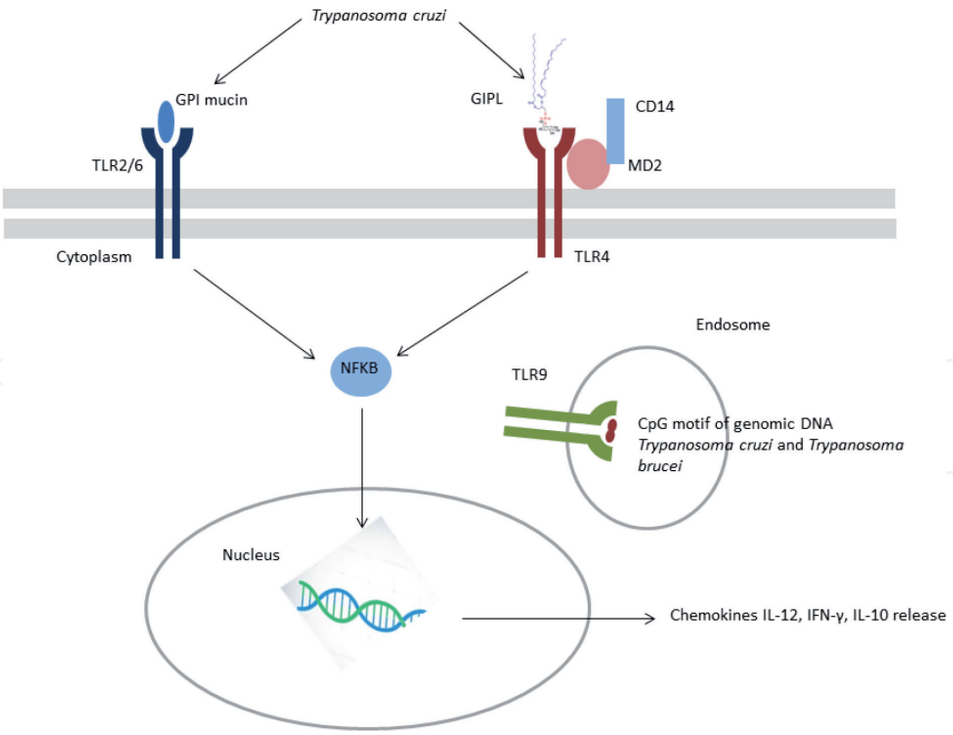

Figure 4.
Trypanosoma PAMPs and TLR signaling.

TLR11 and TLR12 recognize *T. gondii* profiling (TgPRF) and induce IL12 and IFNα production in conventional dendritic cells (cDCs), macrophages, and plasmacytoid dendritic cells (pDCs). This IFNα induces IFNγ production from NK

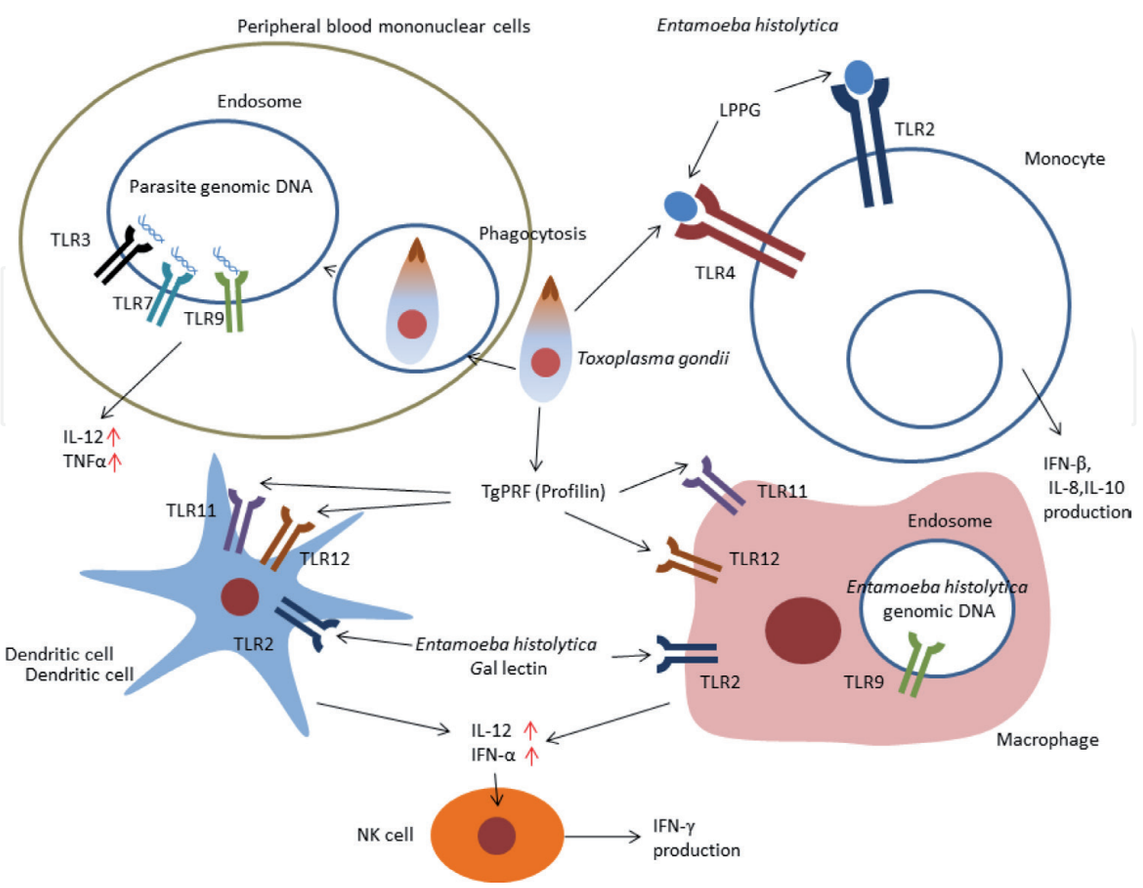

Figure 5.
Toxoplasma and Entamoeba induced TLR signaling pathway.

cells. *T. gondii* infection also induces IFNβ production in inflammatory monocytes (IMs) and TLR4-mediated phagocytic uptake of the parasite [86]. Endosomal TLRs (TLR3, TLR7, and TLR9) stimulate IL12 production in human PBMCs in response to DNA and mRNA of *T. gondii* tachyzoites when the cells were primed with IFNγ [87]. GPIs present in parasite membrane aggravate TLR2- and TLR4-mediated TNFα production in inflammatory response [88]. In some cases, tachyzoites differentiate into bradyzoites inside the central nervous system and cause neurological and behavioral abnormalities [89]. TLR2 signaling pathway makes chronic inflammation in different central nervous system cell types [85] (**Figure 5**).

4.5 Amoebiasis

Entamoeba histolytica is a protozoan parasite, which causes amebiasis in humans. It is one of the deadliest diseases after malaria and causes almost 40,000–100,000 deaths per year in underdeveloped countries [90]. The clinical symptoms include diarrhea, dysentery, pain in lower abdomen, and liver abscess, which occur due to invasion of amoeba in host lung, heart, brain, skin, genital, etc. [91]. The lipophosphopeptidoglycan (LPPG) present on the surface of *E. histolytica* induces TLR2- and TLR4-mediated NF-κB activation and cytokine (IL-8, IL-10, IL-12p40, and TNFα) release from human monocytes [92]. The Gal/GalNAc lectin (Gal-lectin), a surface molecule of *E. histolytica,* upregulates cytokines and TLR2 genes via NF-κB and MAP kinase activation in macrophages and dendritic cells [93]. TLR9 recognizes *E. histolytica* genomic DNA and helps in TNFα production in macrophages [94] (**Figure 5**).

5. Helminth infections

Although several studies were conducted on TLR signaling in response to intracellular parasites, only a few examination reflects the interaction of helminths with TLRs.

5.1 Filariasis

Lymphatic filariasis (commonly called elephantiasis), caused by three species of nematode parasites, *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*, is a major health problem in tropical countries. During initial stage, infection remains asymptomatic. Acute condition displays local inflammation of skin, lymph nodes, and lymphatic vessels, which ultimately leads to edema in chronic condition [95]. Wolbachia, an intracellular symbiotic bacterium of filarial nematode, is the major mediator of inflammatory response in case of lymphatic filariasis and onchocerciasis [2]. WSP protein in outer membrane of *Wolbachia* sp. induces TLR2- and TLR4-mediated inflammation in macrophages and DCs [96].

In case of chronic infection, filarial nematode downregulates host immune response via TLR4-mediated T cell apoptosis [97]. Live microfilariae of *B. malayi* can downregulate mRNA and protein expression of TLR1, TLR2, TLR4, and TLR9 and activate TLR2 upon antigen stimulation on B cells and monocytes [98]. In DCs, live microfilariae and microfilarial antigen (MF Ag) diminish IL-12, IFNα, and cytokine production via inhibition of NF-κB complex formation [99]. Microfilariae infective stage (L3) of *B. malayi* also shows partial inhibition of Langerhans cells (LCs) that lead to CD4+ T cell proliferation [100]. Circulating B cells (called Breg) express TLR2 and TLR4 and maintain a worm favorable condition via induction of Treg, IL-10, and filarial-specific IgG. However, Breg-mediated response causes

asymptomatic infection in initial stages but leads to secondary infection by bacteria and virus in filarial patients [92]. A phosphocholine-containing glycoprotein (ES-62) of *Acanthocheilonema viteae* (rodent filarial nematode) inhibits B and T lymphocyte activation. The secretory ES-62 inhibits TLR4-mediated IL-12 and TNFα production [101] (**Figure 6**).

5.2 Schistosomiasis

Schistosomiasis is a worldwide distributed parasitic disease caused by a flatworm, Schistosoma. It accounts for 260 million infected people in tropical and sub-tropical regions (Africa, South America, the Middle East, East Asia, and the Philippines) [102]. *S. mansoni*, *S. intercalatum*, *S. haematobium*, *S. japonicum,* and *S. mekongi* are the five species of schistosomes that cause disease in humans. *S. mansoni*, *S. japonicum,* and *S. intercalatum* are responsible for intestinal schistosomiasis, while *S. haematobium* causes urinary schistosomiasis and is most important in terms of public health [102]. Fresh water snail of the genus *Bulinus* (*S. haematobium*), *Biomphalaria* (*S. mansoni*), and *Oncomelania* (*S. japonicum*) acts as an intermediate host of Schistosoma parasites [103].

S. japonicum eggs are deposited in the liver, lung, and intestinal wall of host, which induce granulomatous inflammation and progressive fibrosis. Th cells, natural killer (NK) cells, NKT cells, myeloid-derived suppressor cells (MDSCs), and macrophages are mainly involved in fight against *S. japonicum* and its eggs [104]. Expressions of TLR1, TLR3, TLR7, TLR8, and NF-κB are greatly repressed at the initial stage of schistosomiasis. TLR3 modulates Th2 response in lung in *S. mansoni* infection and in NK cells during *S. japonica* infection [105]. *S. mansoni* is known to attenuate Th1 responses (decrease IFNγ, TNFα, IL-12, and NO) but to promote Th2 immune responses (increase IL-10 and TGFβ) [106]. Although TLR4 protects the host from Schistosoma infection, TLR2 favors the parasite growth [107]. Both SEA (soluble egg antigen) and ES products of *S. mansoni* act as a strong inducer of Th2 response [108]. It induces transcription of markers CD40 and CD86 and cytokines IFNβ, TNFα, and IL-12-p40 in mouse myeloid DCs [109]. Glycans present in *S. mansoni* induce Treg by TLR2-mediated DC differentiation and IL-10 secretion [110]. Schistosoma egg product LFNP III also stimulates IL-10 production

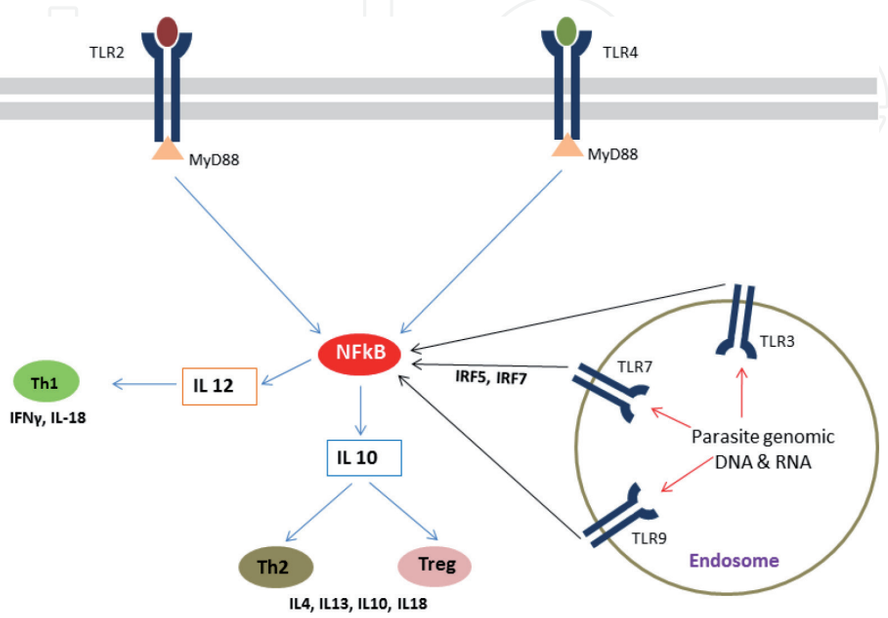

Figure 6.
TLR signaling pathway induced by Helminth pathogens.

from TLR2 and promotes Treg activation [111]. An immunomodulatory peptide, SJMHE1 of *S. japonicum*, induces TLR2-mediated Treg activation. The lysophosphatidylserine and glycolipids [112] of scistosome also activate TLR2 in DCs [113] (**Figure 6**).

5.3 Taeniasis

The pork tapeworm (*Taenia solium*) is a cestoda parasite transmitted to humans by feeding cystic larvae infected pork. Here, pig acts as an intermediate host, which swallows *T. solium* egg containing human stool and develops larva inside their body [114]. The cysticercosis cyst causes neurocysticercosis (NCC) in the nervous system, and adult taenia produces intestinal taeniasis in humans. Both are endemic in Latin America, sub-Saharan Africa, India, vast parts of China, and South East Asia [115].

TLR4 and TLR2 play an important role in developing murine NCC caused by *Mesocestoides corti* [116]. The carbohydrate of *T. crassiceps* induces TLR4- and TLR2-mediated cytokine release (IL-6 and IL-4) [117]. However, molecules derived from *T. sodium* did not induce TLR2- or TLR4-mediated cytokine release in human lymphocytes [118]. Both *T. solium* and *T. crassiceps* express several glycolipids (GSL-1) and phospholipids that may act as PAMPs. *T. crassiceps* expresses lysophosphatidylcholine [119], also present on Schistosome, and triggers TLR2 response. Although the mechanism of these molecules inducing TLR signaling has not yet been evaluated, the host may use a similar pathway of this parasite recognition [120] (**Figure 6**).

5.4 Ascariasis

Phospholipids from schistosomes and *Ascaris* worm trigger TLR2, and lysophosphatidylserine can activate DCs to induce Th2 and IL-10-producing Treg [121].

5.5 Fasciolosis

F. hepatica tegumental antigens (FhTeg), *F. hepatica* ES, and ES-derived enzymes (thioredoxin peroxidase 2-Cys peroxiredoxin, fatty acid-binding protein) inhibit TLR4- and TLR3-mediated inflammatory response and facilitate parasite survival inside the host [122]. The protease activity of *F. hepatica* Cathepsin L1 (FheCL1) causes endosomal degradation of TLR3 and downregulates IL-1 production [123].

6. Conclusion

In conclusion, induction of TLR signaling pathway by infectious pathogen recognition provides a better understanding of innate immune defense mechanism against this disease. Immunotherapy emerges as a promising therapeutic approach for parasitic infection treatment over the past few years. Although no effective drugs have emerged, vaccine adjuvants yield promising results due to induction of cellular immunity via TLR. Large scales of clinical studies were conducted for developing potent and well-tolerated adjuvants. The protozoan and helminth parasites can cause activation (to a small degree) and negative regulation (to a larger degree) of TLRs resulting in increasing or decreasing parasite burden [103]. TLR agonists or antagonists are small molecule mimics, natural ligands used for treating Type I allergy, cancer, and infectious diseases. MF59 (Novartis) and AS04 (GSK) are some examples of TLR4 agonist licensed for human use [124]. GLA (TLR4 ligand) and

3M-052 (TLR7/8) ligands are now in clinical trial. Recently, RTS,S/AS01, a recombinant chimeric protein (c-terminal of circumsporozoite antigen fused with HPB antigen, and "ASO1" refers to the adjuvant formulation MPL and QS21, a natural glucoside), is used for treating Malaria [125]. Several new drugs have been chemically synthesized for better understanding of the interaction of TLRs with their ligands. The knowledge from these studies will provide a greater opportunity for developing plant-derived new therapeutic drugs. So, major efforts are required for targeting TLRs in pathological conditions.

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Conflict of interest

The authors declare no conflict of interest.

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