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Review

Dual Role of Host Toll-Like Receptor 3 in Parasitic Diseases

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Abstract

Parasitic diseases, caused by a diverse array of parasites, remain a substantial threat to global health. Toll-like receptor 3 (TLR3) represents a pivotal element in the innate immune system, distinguished by an ability to signal via the TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway upon detecting pathogen-derived double-stranded RNA (dsRNA), exosomal RNA (exoRNA), and long non-coding RNA (lncRNA). Predominantly localized on endosomal membranes, TLR3 is extensively expressed in neurons, immune cells, fibroblasts, and epithelial cells. Upon activation, TLR3 engages adaptor molecules such as TRIF, facilitating the phosphorylation of TANK-binding kinase 1 and the subsequent activation of interferon regulatory factors. This signaling cascade triggers the production of type I interferons (IFN-α/β) and proinflammatory cytokines such as interleukin (IL)-6, IL-8, IL-12, and tumor necrosis factor-alpha, which are crucial for effective immune defense against infections. Recent findings highlight the essential role of TLR3 in parasitic infections by detecting nucleic acids from damaged cells to activate dendritic and natural killer cells. TLR3 also functions with other receptors, such as TLR2 and TLR4, to enhance cytokine production and improve parasite clearance. However, TLR3 overactivation can induce excessive, harmful inflammation and tissue damage, highlighting its dual role in balancing immune defense. This review comprehensively examines the TLR3 signaling pathway and its multifaceted role in various parasitic infections, including those caused by *Plasmodium* spp., *Leishmania* spp., *Clonorchis sinensis*, *Schistosoma japonicum*, *Trichinella spiralis*, and *Neospora caninum*.

Keywords: Toll-like receptor 3; parasitic disease; immune defense; inflammation

1. Introduction

Parasitic infections pose a substantial global health burden, affecting millions of individuals annually and causing significant morbidity and mortality, particularly among vulnerable populations such as children and pregnant women [1–4]. These infections are caused by a diverse range of pathogens, including *Plasmodium* spp., *Leishmania* spp., *Clonorchis sinensis*, *Schistosoma japonicum*, *Trichinella spiralis*, and *Neospora caninum* [5–10]. A key factor in the persistence and severity of these diseases is the ability of these parasites to evade host immune surveillance, ensuring their survival and replication within the host [11]. The host's innate and adaptive immune systems are critical for combating parasitic infections, maintaining immune homeostasis by recognizing and eliminating pathogens [12,13]. Among the pattern recognition receptors of the innate immune system, the Toll-like receptor (TLR) family plays a pivotal role in initiating immune responses upon detecting pathogen-associated molecular patterns [14,15]. TLRs activate downstream signaling pathways that lead to the production of cytokines and other inflammatory mediators essential for effective immune responses [16].

Toll-like receptor 3 (TLR3), a key member of the TLR family, uniquely signals through the TIR-domain-containing adapter-inducing interferon-β (TRIF) pathway [17]. Predominantly located on endosomal membranes, TLR3 is widely expressed in fibroblasts, epithelial cells, and various immune cells [18–24]. The intracellular region of TLR3 contains a TIR domain with two critical tyrosine residues. Upon recognition of viral double-stranded RNA (dsRNA) or activation by poly(I:C), TLR3 recruits TRIF and associated adaptor molecules, initiating downstream signaling cascades (Fig. 1) [25]. Activation of the TLR3–TRIF axis recruits TANK-binding kinase 1 (TBK1), leading to the activation and phosphorylation of interferon regulatory factors 3 and 7 (IRF3 and IRF7) [26]. Specifically, TBK1 and inhibitor of kappa B kinase epsilon (IKK-ϵ) regulate IRF3 activation. Phosphorylated IRF3 dimerizes, translocates into the nucleus, and induces the production of type I interferons (IFN-α/β) [27,28]. In parallel, downstream of TLR3-TRIF, tumor necrosis factor receptor-associated factor 6 (TRAF6) interacts with transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1)-binding protein 2 (TAB2), leading to TAK1 autophosphorylation and activation. Activated TAK1 then stimulates the IKK complex, which comprises IKK-α and

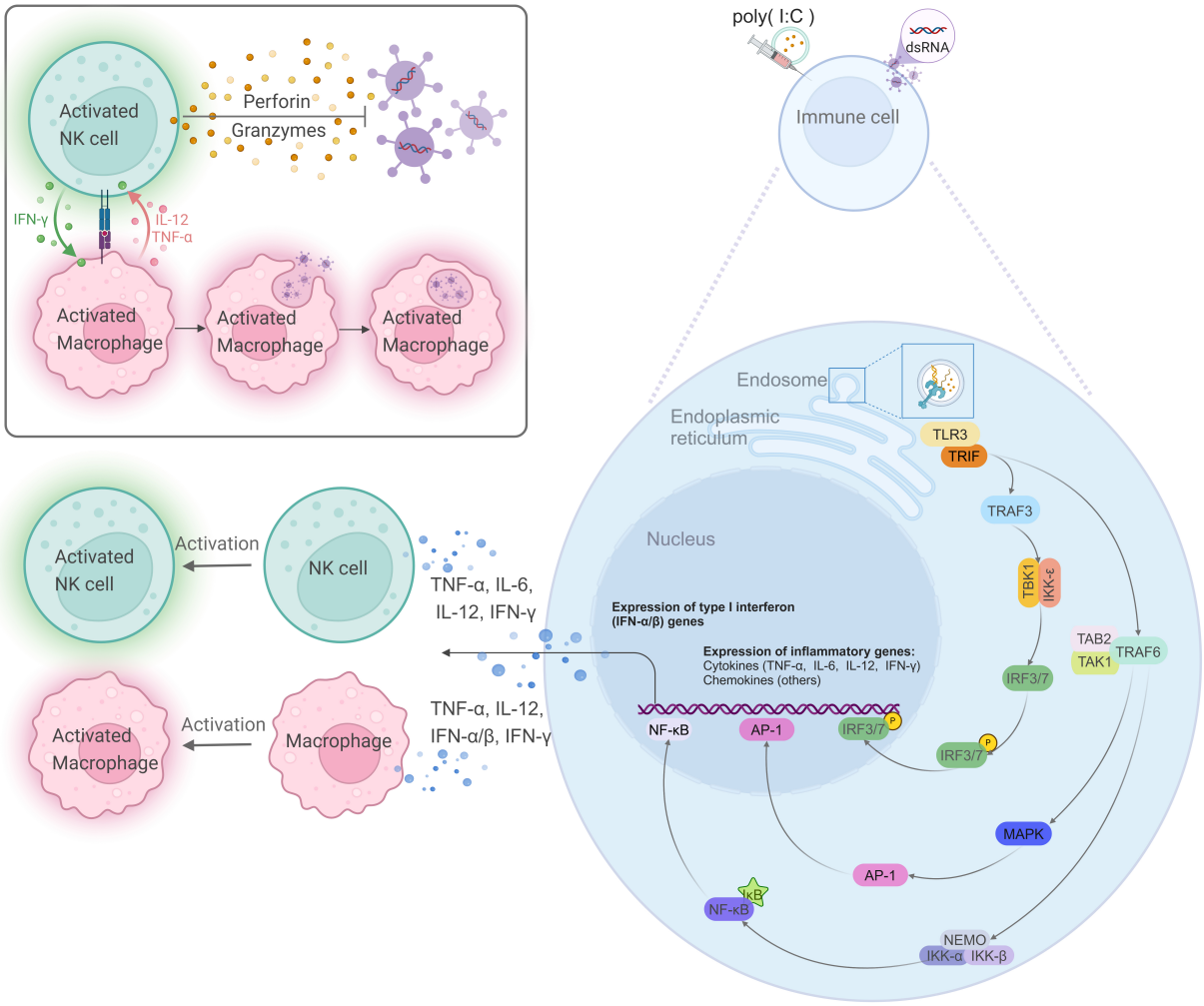

Fig. 1. The signaling pathway of TLR3 in responses to double-stranded RNA (dsRNA). TLR3, located on endosomal membranes, recognizes dsRNA or the synthetic analog poly(I:C), thereby activating the TLR3 signaling pathway. The adaptor protein TRIF is recruited, which subsequently activates TRAF3 and TRAF6. TRAF3, in conjunction with TBK1 and IKK-ϵ, promotes the phosphorylation and nuclear translocation of IRF3/IRF7, leading to the production of type I interferons (IFN-α/β). These interferons enhance immune responses, activate natural killer (NK) cell cytotoxicity, and stimulate cytokine secretion. Simultaneously, TRAF6 interacts with TAK1 and TAB2 to activate the MAPK pathway, facilitating the phosphorylation and nuclear translocation of transcription factors AP-1 and NF-κB. This cascade results in the production of pro-inflammatory cytokines, including IL-6, IL-8, IL-12, TNF-α, and IFN-γ. These cytokines play essential roles in immune cell activation, macrophage-mediated pathogen phagocytosis, and sustained NK cell functionality. Additionally, cross-regulation with other TLRs, such as TLR4 and TLR7, enhances immune responses and supports effective pathogen elimination. DsRNA, double-stranded RNA; TLR, Toll-like receptor; TRIF, TIR-domain-containing adapter-inducing interferon-β; TRAF, tumor necrosis factor receptor-associated factor; TBK1, TANK-binding kinase 1; IKK, inhibitor of kappa B kinase; IRF, interferon regulatory factors; TAK1, transforming growth factor-β (TGF-β)-activated kinase 1; TAB2, TAK1-binding protein 2; MAPK, mitogen-activated protein kinase; IL, interleukin; TNF-α, tumor necrosis factor-alpha; NF-κB, nuclear factor κB; IκB, inhibitor of NF-κB; AP-1, activator protein-1; NEMO, NF-κB essential modulator. Created with BioRender.com.

IKK-β, via nuclear factor κB (NF-κB) essential modulator (NEMO; also known as IKK-γ), thereby activating NF-κB or triggering mitogen-activated protein kinase (MAPK)-mediated activator protein-1 (AP-1) transcriptional responses [29]. As a result of TRIF-dependent signaling, phosphorylated IRF3/7, NF-κB, and AP-1 translocate to the nucleus, inducing the expression of IFN-α/β, IFN-γ, and pro-inflammatory cytokines, including interleukin (IL) -6, IL-8, IL-12, and tumor necrosis factor-alpha (TNF-α) [17,30–32]. This production of IFN-I and pro-

inflammatory cytokines following TLR3 activation is critical for host defense against pathogenic infections [33,34]. IFN-I plays a pivotal role in modulating immune responses by activating natural killer (NK) cell cytotoxicity and cytokine production via the interferon-alpha/beta receptor (IFNAR). This mechanism is particularly prominent during viral infections, where IFN-I protects NK cells from cytotoxic agents, supporting their expansion and functionality [35]. Furthermore, IFN-γ enhances macrophage phagocytic activity and pathogen clearance by regulating intracellular copper levels in phagosomes and by modulating cellular metabolism and mRNA translation to activate macrophages [36,37]. IL-12 stimulates NK cell activity and promotes IFN-γ production, while IL-6 enhances macrophage function and inflammatory responses [38,39]. TNF-α, induced through TLR3 signaling, directly activates macrophages and boosts NK cell effector functions [40]. Importantly, macrophages activated by TLR3 secrete IL-12 and TNF-α, creating a positive feedback loop that amplifies immune responses [41]. While TLR3 is essential for mediating innate immune responses and enhancing protective immunity, its activation can, under certain conditions, contribute to excessive inflammation, leading to collateral tissue damage [42,43]. This highlights the dual regulatory effects of TLR3, balancing effective immune defense with the risk of excessive inflammation. Furthermore, synergistic interactions between TLR3 and other TLRs, such as TLR2 and TLR4, can amplify immune cell activation, cytokine production, and parasite clearance [44]. It is noteworthy that TLR3 plays a critical role not only in antiviral immunity (e.g., COVID-19) but also in parasitic infections [29,44–50]. This activation results in the production of IFN-α/β and pro-inflammatory cytokines such as IL-6, IL-8, IL-12, and TNF-α, which are crucial for mounting effective immune responses against parasitic invasions [17,30–32]. Therefore, understanding the intricate signaling pathways and regulatory mechanisms of TLR3 in parasitic infections is essential for developing novel therapeutic strategies aimed at enhancing host immunity while minimizing detrimental inflammation.

The present review provides a comprehensive overview of the TLR3 signaling pathway and its critical role in various parasitic infections. It aims to identify potential targets for immunotherapy and vaccine development to improve host resistance and global health outcomes.

2. Mechanisms of TLR3 in Parasitic Infections

In parasitic infections, the timely recognition and activation of the host immune system are critical for regulating parasite proliferation and determining disease outcomes. Emerging evidence underscores the indispensable role of TLR3 in the recognition and regulation of parasitic infections [8,46,47,51,52]. TLR3 can mediate immune responses to parasitic infections through several distinct mechanisms. Parasite-derived nucleic acids are recognized by TLR3, which then activates downstream immune signaling pathways and induces a strong pro-inflammatory response [22,37,53]. This immune activation not only aids in parasite clearance but also regulates immune homeostasis [36]. The first mechanism involves TLR3 recognizing parasite-derived exoRNA released from damaged host cells, promoting cytokine secretion, and enhancing host defense, which is critical for initiating an effective immune response against parasitic infections. The second mechanism is the regulation of immune cell functions by TLR3, which involves regulating dendritic cells (DCs) and NK cells, boosting their activity, and enhancing the host's resistance to parasites. The third mechanism is the synergistic action of TLR3 with other TLRs, which amplifies immune responses by interacting with these receptors to enhance immune signaling, ultimately facilitating more effective parasite clearance. Understanding these mechanisms is essential for elucidating immune regulation in host-parasite interactions and developing related immunotherapies. These mechanisms will be further elaborated in the subsequent sections of the review.

Once exoRNA released by host cells damaged during parasitic infections is recognized by TLR3, an immune response is initiated [22,38]. Based on current experimental evidence, TLR3 may recognize parasite-derived extracellular RNA during malaria infection, thereby triggering an immune response in the host. This recognition induces the production of significant levels of pro-inflammatory cytokines, including IFN-β, IFN-γ, and TNF-α, through activation of the downstream IRF3 and NF-κB signaling pathways [46]. These cytokines, in turn, activate immune cells such as macrophages and NK cells, enhancing their cytotoxic activity and contributing to the host's control of parasitic infection [39]. Pre-stimulation of human and mouse neurons with IFN-γ enhances the activity of immunity-related GTPases, which target and disrupt the parasitophorous vacuole that shelters intracellular parasites. This disruption effectively inhibits the proliferation of *Toxoplasma gondii* [41]. Moreover, IFN-γ is a pleiotropic cytokine with diverse immunomodulatory effects; it enhances erythropoiesis, upregulates MHC-I expression, and promotes the presentation of endogenous antigens by infected host cells. These effects enhance the susceptibility of infected cells to cytotoxic T lymphocytes, aiding in the clearance of *Plasmodium yoelii* 17XNL from the host [54,55].

Another crucial role of TLR3 in parasitic infections is the modulation of host immune cell functions [36]. Activation of TLR3 by pretreatment with the agonist poly(I:C) in *Leishmania* infections promotes a T helper 1 (Th_1)-type immune response and enhances antigen presentation, thereby improving host resistance to the parasite [56]. Similar observations have been reported in *Plasmodium falciparum*-infected BALB/c mice, where poly(I:C) pretreatment ac-

tivates TLR3, enhances the Th_1 response, and induces elevated IgG antibody levels as well as IFN-γ production, effectively mitigating severe symptoms of malaria infection [57,58]. TLR3 also plays a significant role in *Schistosoma mansoni* (*S. mansoni*) infections. The recognition of *S. mansoni* eggs by host TLR3 present on DCs leads to the expression of IFN-I, induction of interferon-stimulated genes (ISGs), and phosphorylation of signal transducer and activator of transcription 1 (STAT1), ultimately resulting in NF-κB and IFN-β expression [59]. Moreover, TLR3 regulates the activity of NK cells during malaria and it seems to inhibit the activity of NK cells in the early stage of *Plasmodium* infection, which is beneficial for parasite infection [46]. The importance of NK cells in parasitic defense has been increasingly recognized, with TLR3 activation not only enhancing the cytotoxic capabilities of these cells but also modulating the functions of other immune cells via cytokine secretion [60].

TLR3 plays a crucial role in maintaining host immune homeostasis, while also enhancing immune responses through interactions with other TLRs, thereby amplifying overall immune activity [61]. During parasitic infections, cross-regulation between TLR3 and other TLRs, such as TLR2, TLR4, and TLR7, is essential for orchestrating an effective immune response. In *Schistosoma japonicum* (*S. japonicum*) infections, these TLRs contribute to the activation of T, B, NK, and $\gamma\delta$T cells, synergistically promoting IFN-γ secretion, which drives the inflammatory response [60]. In *Neospora caninum* (*N. caninum*) infections, TLR3 and TLR2 collaborate to enhance IL-12p40 production, mitigating the pathogen's threat to the host. This synergy not only boosts antigen presentation by macrophages and DCs but also significantly upregulates the production of pro-inflammatory cytokines, such as IFN-γ and IL-12p40, through co-activation of the Myeloid differentiation primary response gene 88 (MyD88) and TRIF signaling pathways. This coordinated signaling facilitates the initiation of adaptive immunity and enhances T and B cell activation and proliferation, ultimately aiding the host immune system in controlling *N. caninum* proliferation [51]. TLR3 cooperates with other TLRs, such as TLR2, TLR4, and TLR7, to mount a robust and finely tuned immune response. Recent evidence suggests that TLR3-driven responses can synergize with MyD88-dependent signals triggered by other TLRs, enhancing the production of pro-inflammatory cytokines crucial for controlling intracellular pathogens and protozoan parasites [60,61]. For instance, during *N. caninum* infections, TLR2-mediated MyD88 activation cooperates with TLR3-TRIF signaling to increase IL-12p40 production, thereby effectively orchestrating downstream IFN-γ synthesis and macrophage activation [51]. This interaction not only promotes Th_1 immune responses but also amplifies the overall magnitude of adaptive immunity, enhancing T and B cell proliferation and improving pathogen clearance.

In *S. japonicum* infections, TLR2, TLR3, TLR4, and TLR7 cooperate in a tissue-specific manner, particularly within pulmonary lymphocytes, to boost IFN-γ production from T, B, NK, and $\gamma\delta$T cells, ultimately reinforcing the protective inflammatory response [60]. Beyond these well-established synergistic roles, emerging research underscores an additional layer of complexity, whereby TLR3 can confer a form of "innate immune memory" that potentiates subsequent responses to TLR7 ligands and vice versa [61]. This crosstalk may be mediated by shared transcription factors and signaling intermediates, resulting in upregulated expression of crucial immune mediators, such as IFN-α/β, IL-6, and TNF-α, upon re-stimulation [61,62]. By facilitating reciprocal activation loops between MyD88- and TRIF-dependent pathways, TLR3 helps maintain a heightened state of readiness in innate immune cells, enabling the host to respond more rapidly and effectively to re-infection or secondary parasitic insults [61,63,64]. Furthermore, studies have shown that TLR3, TLR2, and TLR7 synergistically activate distinct signaling pathways to enhance pathogen phagocytosis and clearance by host cells [60,65]. TLR3 regulates autophagy-related genes through the TRIF pathway, while TLR2 and TLR7 release pro-inflammatory cytokines (such as IFN-β, TNF-α, and IL-6) via the MyD88 pathway. This coordinated action plays a crucial role in promoting *Trypanosoma cruzi* (*T. cruzi*) clearance, inhibiting *T. cruzi* growth, and establishing an effective immune response [65]. This integrated response, which involves the orchestrated activation of multiple TLRs, thus represents a promising target for next-generation vaccine adjuvants and immunotherapeutic interventions aimed at combating persistent or resistant parasitic infections.

Investigating the temporal dynamics of TLR3 activation and its interplay with other innate immune receptors could significantly advance our understanding of immune homeostasis in the context of persistent parasitic infections. A more profound understanding of the role of TLR may guide the development of innovative vaccine adjuvants, immune modulators, and therapeutic strategies, ultimately improving clinical outcomes for patients suffering from parasitic diseases. Through such targeted investigations, we can move closer to a paradigm in which immune-based therapies can effectively eradicate parasitic infections while minimizing adverse effects, thereby addressing a critical unmet need in global health.

3. TLR3 Signaling Pathway in Parasitic Infections

TLR3 recognizes exoRNA, long non-coding RNA (lncRNA), or poly(I:C) produced by damaged cells in response to parasitic infections (Fig. 2) to initiate immune responses [22,37,66–68]. TLR3 activates multiple transcription factors, such as IRF3, IRF7, and NF-κB, in parasitic infections [63,69–71]. There are two primary pathways downstream of TLR3 activation. In the first pathway, TLR3

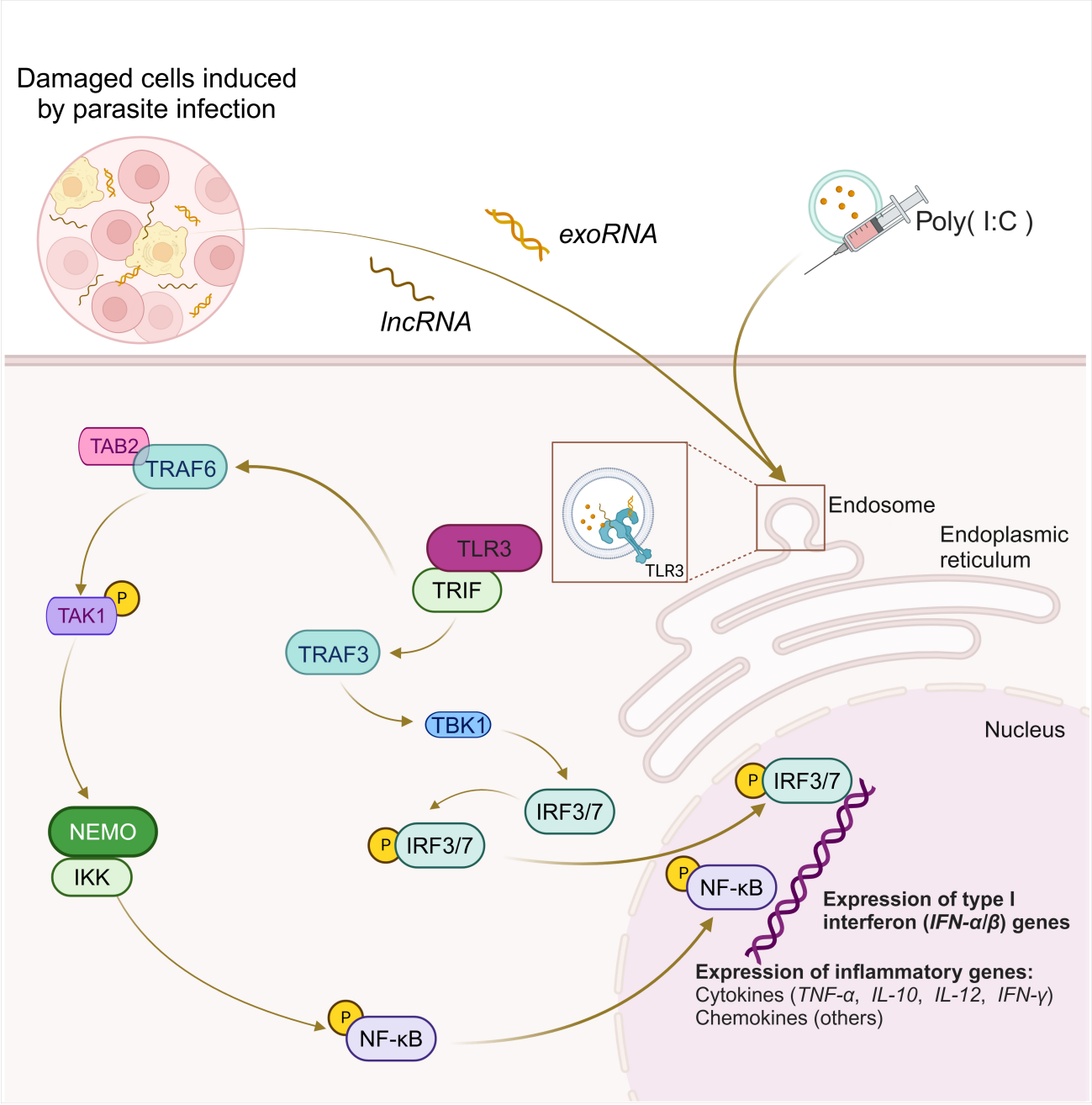

Fig. 2. Signaling pathway of TLR3 in parasite infection. TLR3 recognizes activation of exoRNA, lncRNA or poly(I:C) produced by damaged cells induced by parasite infection and generates various immune responses. Upon activation of TLR3, recruitment of TRIF occurs, which initiates signal transduction through its TIR. This activation subsequently leads to activation of the serine/threonine kinase TBK1, which then phosphorylates IRF3/IRF7. Another pathway of TLR3-TRIF is the recruitment of TAB2 via TRAF6 leading to phosphorylation and activation of TAK1 itself. Phosphorylated TAK1 stimulates IKK via NEMO, which in turn activates NF-κB to initiate IFN-γ transcription and promote IL-10 secretion. These transcription factors promote the production of pro-inflammatory signaling proteins such as TNF-α, IFN-γ and IFN-β. In general, activation of the TLR3 signaling pathway leads to the production of cytokines such as TNF-α, IFN-α/β, IFN-γ, IL-10 and IL-12. Created with BioRender.com.

activation leads to the recruitment of TRIF, which initiates signal transduction via its TIR domain. This in turn activates the serine/threonine kinase TBK1, which then phosphorylates IRF3 and IRF7 [72,73]. The phosphorylation of these transcription factors results in their nuclear translocation, ultimately inducing the transcription of IFN-α/β [74,75]. The second major TLR3-TRIF pathway involves the recruitment of TAB2 via TRAF6, resulting in the phosphorylation and activation of TAK1. Phosphorylated TAK1 stimulates the IKK complex via NEMO, which in turn acti-

vates NF-κB, promoting IFN-γ transcription and IL-10 secretion [17,76–78]. These transcription factors facilitate the production of pro-inflammatory cytokines, such as TNF-α, IFN-γ, and IFN-β [79]. Although TLR3 plays a critical role in host responses to parasitic infections, variations among different parasites may lead to diverse outcomes in infected hosts.

4. Research Progress onTLR3 and Different Parasites

4.1 Inhibitory Effect of TLR3 on the Blood Stage of Infection With Plasmodium yoelii yoelii 265 BY

Malaria is caused by *Plasmodium* species, which are transmitted to vertebrates through the bite of female *Anopheles* mosquitoes [5,80,81]. *Plasmodium* infects hundreds of millions of people with malaria each year, with the vast majority of severe malaria cases concentrated in African countries, particularly Nigeria, the Democratic Republic of the Congo, Niger, and the United Republic of Tanzania [82]. Patients with malaria usually exhibit symptoms such as fever, chills, and acute anemia. In severe cases, malaria can be fatal, causing hundreds of thousands of deaths each year, with children and pregnant women being particularly vulnerable, making it a significant health threat [80,83].

Understanding the interplay between TLR3 and immune responses is crucial for elucidating the mechanisms through which the host combats *Plasmodium* infection. Notably, TLR3 plays a key role in regulating *Plasmodium* infection [46]. In wild-type (WT) mice, activation of the TLR3-TRIF signaling axis induces the nuclear translocation of phosphorylated IRF3 and IRF7, triggering an early surge of pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-6 [72–75,79]. While these cytokines are essential for initiating immune responses, their sustained elevation results in detrimental inflammation [84]. In contrast, TLR3-knockout mice display a more balanced cytokine profile, characterized by diminished levels of pro-inflammatory mediators and increased production of the anti-inflammatory cytokine IL-10. This profile enhances parasite clearance and attenuates excessive immunopathology [85,86]. Further research indicates that, in the spleens of WT mice, TLR3 signaling appears to inhibit NK and NKT cell activity, delaying the initial immune response and allowing the parasite to establish infection [87–89]. This early activation of innate immune cells may contribute to a more rapid reduction of parasitemia in TLR3-knockout mice. During *Plasmodium yoelii yoelii* 265 BY (*P. yoelii yoelii* 265 BY) infection, TLR3-knockout mice exhibit enhanced T and B cell responses compared to WT mice. Specifically, the frequency and activation of $CD4^+$ and $CD8^+$ T cells are significantly higher in TLR3-knockout mice at the later stages of infection than in WT mice, suggesting a more robust adaptive immune response. In WT mice, TLR3 signaling inhibits the T cell response, potentially facilitating parasite survival. In contrast, in TLR3-knockout mice, the absence of TLR3 signaling in B cells leads to a higher frequency of $CD19^+$ cells and increased production of parasite-specific IgG. As depicted in Fig. 3a, after infection with *Plasmodium*, the TLR3 pathway is activated, leading to the production of IFN-γ and IL-12. This, in turn, can result in a decrease in IgG secretion by $CD19^+$ $TLR3^+$ B cells, thereby favoring parasite survival. This enhanced humoral response is likely a key factor in the improved parasite clearance observed in TLR3-knockout mice compared to WT mice. Notably, the proportion of $CD19^+$ $TLR3^+$ cells is significantly higher in the B cell population of C57 mice, potentially accounting for the delayed clearance of parasites during the erythrocytic cycle in these mice. This surge in parasite-specific antibodies was also observed to correlate with an increase in B cell numbers and enhanced parasitemia clearance. As presented in Table 1 (Ref. [8,43,44,46,47,52,90,91]), TLR3-knockout mice display an increase in total IgG, concurrent with an elevated proportion of $CD19^+$ B cells and enhanced production of parasite-specific antibodies during *P. yoelii yoelii* 265 BY infection. Moreover, IgG production is inhibited in WT mice, suggesting a role for TLR3 in regulating the adaptive immune response [46]. These findings underscore the intricate regulatory function of TLR3 in orchestrating both erythrocytic and extra-erythrocytic immune phases during *Plasmodium* infection. Overall, these data highlight the potential of strategically targeting the TLR3 pathway as a novel approach to enhance host immunity and develop innovative control measures against malaria.

4.2 Leishmania Manipulates the TLR3 Signaling Pathway to Promote Infection

Leishmaniasis is caused by *Leishmania* spp., which is transmitted to humans, mammals (such as dogs and rats), and certain reptiles (such as lizards) through the bite of a sandfly [92]. Leishmaniasis is a zoonotic parasitic disease endemic to numerous regions, including parts of North America such as the United States and Canada, posing a significant risk to human health [93]. Leishmaniasis exhibits a range of clinical manifestations, from skin lesions to potentially fatal visceral involvement [92,94].

The immune responses elicited during *Leishmania* infection are pivotal in determining disease outcomes, particularly through mechanisms such as TLR3 signaling, which shapes cytokine profiles and regulates immune cell activity [45,95]. TLR3 initiates a cascade of host immune responses by recognizing exoRNA released from damaged cells following *Leishmania* infection [22,96]. Infection with *Leishmania amazonensis* (*L. amazonensis*) disrupts the host immune response and suppresses macrophage function [97,98]. This disruption includes alterations in cytokine production, such as restricted IFN-γ expression, accompanied by increased levels of IL-10 and TGF-β and decreased levels of IFN-β [99,100]. This altered cytokine profile

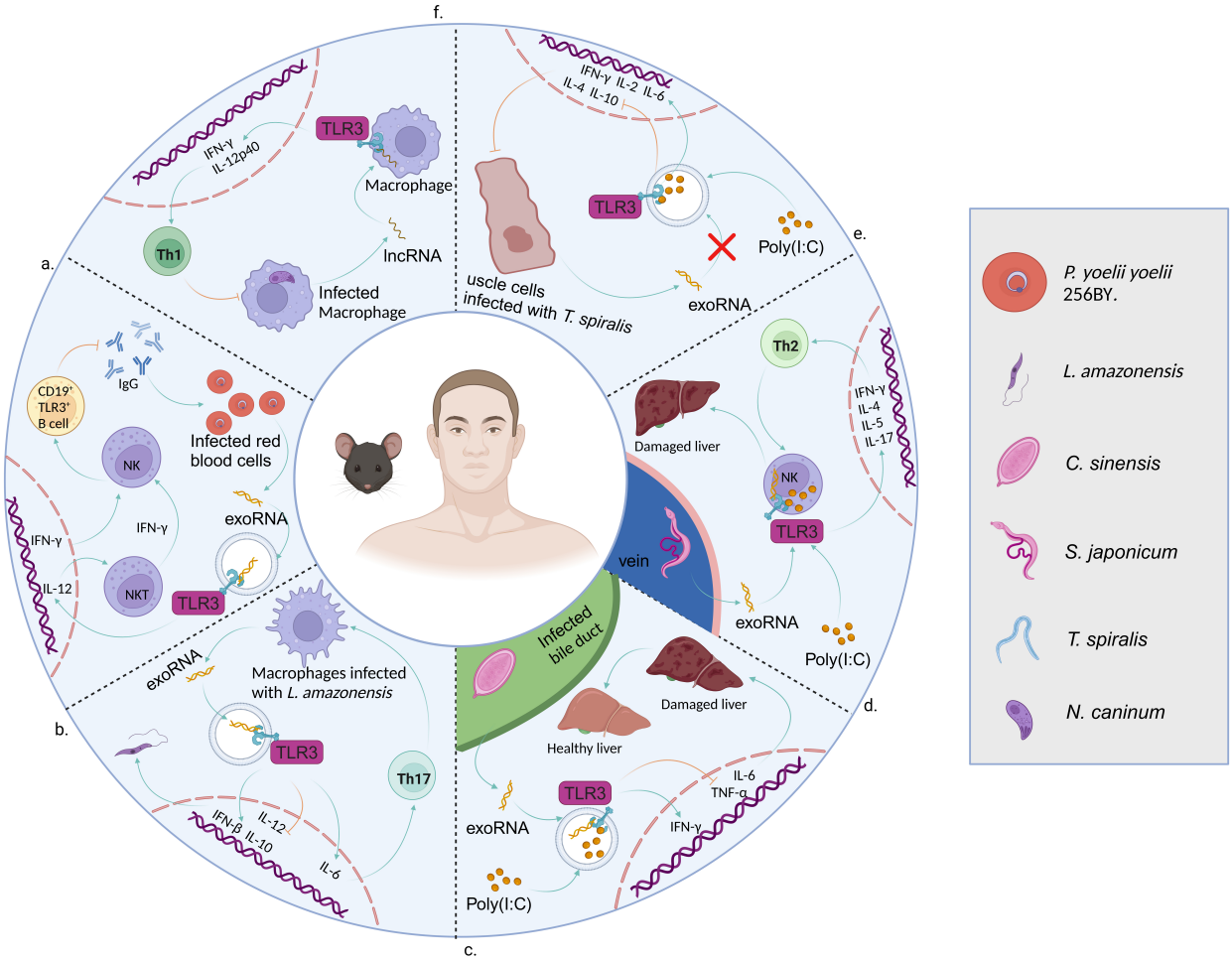

Fig. 3. TLR3-mediated immune responses in parasite infections. (a) ExoRNA released by *Plasmodium*-infected red blood cells activates TLR3, thereby promoting the transcription of cytokines such as IFN-γ and IL-12. IL-12 stimulates NKT cells to produce IFN-γ, while IFN-γ enhances the activity of $CD19^{+}$ $TLR3^{+}$ B cells through NK cells. This interaction suppresses IgG production within the host, aggravating *Plasmodium* infection and contributing to the delayed clearance of the parasite. (b) ExoRNA released by *Leishmania*-infected macrophages activates TLR3, promoting the transcription of IL-6, IFN-β, and IL-10, while suppressing the transcription of IL-12. IL-6 activates Th_{17} cells, and in synergy with other cytokines, exacerbates the progression of leishmaniasis. (c) TLR3 can be activated by exoRNA derived from *C. sinensis* residing in the host liver and bile ducts, as well as by the TLR3 agonist poly(I:C). This activation promotes the transcription of IFN-γ while inhibiting the transcription of TNF-α and IL-6, effectively alleviating liver damage caused by the parasitic infection. (d) TLR3 can be activated by exoRNA derived from *S. japonicum* residing in the host venous system, as well as by the TLR3 agonist poly(I:C). This activation promotes the transcription of cytokines such as IFN-γ, IL-4, IL-5, and IL-17, leading to NK cell expression through Th_2 cells and exacerbating liver damage caused by the parasitic infection. (e) TLR3 cannot be activated by exoRNA derived from *T. spiralis* residing in host muscle cells but can be activated by the TLR3 agonist poly(I:C). This activation promotes the transcription of IFN-γ, IL-2, and IL-6 while inhibiting the transcription of IL-4 and IL-10, thereby regulating *T. spiralis* infection to effectively reduce the parasite burden. (f) TLR3 can be activated by lncRNA derived from macrophages infected with *N. caninum*. This activation promotes the transcription of cytokines IFN-γ and IL-12p40, enhancing the specific Th_1 response, which enables the host to better control *N. caninum* infection. Created with BioRender.com.

contributes to the development of cutaneous leishmaniasis [101]. Moreover, as illustrated in Fig. 3b, activation of the TLR3-TRIF pathway during *L. amazonensis* infection enhances the production of IL-6, as well as that of other cytokines and chemokines, which promotes the polarization of T cells toward a Th_{17} phenotype. This response facilitates parasite spread and aggravates disease severity [102]. The upregulation of macrophages induced by TLR3 activation also leads to elevated IFN-β and IL-10 levels, while concurrently suppressing IL-12 expression, thus exacerbat-

Table 1. Research progress of TLR3 during different parasite infections.

Parasite	Detailed information		Reference
Plasmodium yoelii yoelii 265 BY (*P. yoelii yoelii* 265 BY)	Host:	6–8 weeks old C57BL/6jRj mice and TLR3-knockout mice	[46]
	Study Organ:	Liver and Spleen	
	Cellular and Cytokine changes:	$CD19^{+}TLR3^{+}$↑, IFN-γ↑, TNF-α↑, and IgG↓	
	Result:	Compared to WT mice, TLR3-knockout mice exhibited a significant increase in parasite-specific antibodies when infected with *P. yoelii yoelii* 265 BY. These mice demonstrated better control over the growth of *Plasmodium* and cleared the parasite earlier during infection. In WT mice infected with *P. yoelii yoelii* 265 BY, there was an elevated frequency of $CD19^{+}$ and $TLR3^{+}$ B cells, a decrease in overall IgG levels, and an increase in TNF-α and IFN-γ levels in the liver at 42 h. These changes also influenced the quantity and quality of the antibody response.	
Leishmania amazonensis (*L. amazonensis*)	Host:	6–8 weeks old C57BL/6 mice and TLR3-knockout mice	[43]
	Study Organ:	Skin	
	Cellular and Cytokine changes:	IFN-β↑, IL-10↑, and IL-12↓	
	Result:	This study concluded that *L. amazonensis* enhanced its survival within host macrophages by activating the TLR3 signalling pathway, promoting the expression of IFN-β and IL-10, while suppressing the production of IL-12, which helped to inhibit the host's immune response, thereby allowing the parasite to continue to proliferate.	
Clonorchis sinensis (*C. sinensis*)	Host:	6–8 weeks old C57BL/6 mice and TLR3-knockout mice	[47]
	Study Organ:	Liver and Bile Ducts	
	Cellular and Cytokine changes:	IFN-γ↑, IL-4↓, IL-6↓, and TNF-α↓	
	Result:	TLR3-knockout mice exhibited significantly lower body weights, higher mortality rates, and increased parasite loads compared to WT mice. The absence of TLR3 further exacerbated liver injury and inflammatory responses, leading to increased hepatic fibrosis in infected mice.	
Schistosoma japonicum (*S. japonicum*)	Host:	C57BL/6 mice	[8,90]
	Study Organ:	Liver and Spleen	
	Cellular and Cytokine changes:	IL-4↑, IL-5↑, IL-17↑, and IFN-γ↑	
	Result:	The percentage of cells producing IFN-γ, IL-4, IL-5 and IL-17 in the $TLR3^{+}$ NK cell population of infected mice was significantly increased, but the result was just the opposite in TLR3-knockout mice. TLR3 deficiency can significantly reduce the levels of aspartate aminotransferase and alanine aminotransferase, which are important indicators of liver fibrosis, reduce the number of white blood cells in peripheral blood, and restore the number of red blood cells, platelets and hemoglobin content in peripheral blood of infected mice, thus inhibiting the development of schistosomiasis. This indicates that the deletion of TLR3 reduces liver damage during infection, and there is a positive correlation between TLR3 and the severity of liver pathogenesis, that is, TLR3 is involved in the granulomatous inflammatory response during *S. japonicum* infection.	
Trichinella spiralis (*T. spiralis*)	Host:	6–8 weeks old female C57BL/6 mice with poly(I:C) treatment	[52]
	Study Organ:	Spleen	
	Cellular and Cytokine changes:	IFN-γ↑, IL-2↑, IL-6↑, IL-4↓, and IL-10↓	
	Result:	Compared to WT mice, treatment with poly(I:C) led to a significant increase in Th_1-type cytokines, including IFN-γ and IL-2, as well as Th_2-type cytokine IL-6. Conversely, there was a notable decrease in anti-inflammatory cytokines such as Th_2 cytokines IL-4 and IL-10. These changes resulted in a significant reduction in the parasite load and ultimately hindered the proliferation of *Trichinella spiralis*.	
Neospora caninum (*N. caninum*)	Host:	6–8 weeks old C57BL/6 mice, TRIF-knockout mice and TLR3-knockout mice	[44,91]
	Study Organ:	Spleen, Lung and Brain	
	Cellular and Cytokine changes:	IL-12p40↑, IFN-γ↑, and Th_1↑	
	Result:	When WT mice TLR3 recognize *N. caninum*, inducible IL-12p40 secretion promotes IFN-γ production to inhibit the *N. caninum* infection. The TLR3-TRIF pathway enhances the Th_1 immune response against the parasite, thereby improving host survival, reducing parasite load, and decreasing the inflammatory lesions of the host. This immune response effectively resists *N. caninum* infection.	

Note: activation, stimulation of secretion or increased expression ↑; inhibition of secretion or decreased expression ↓.

ing the pathogenicity of *L. amazonensis*. As presented in Table 1, TLR3 activation enhances the expression of both IFN-β and IL-10. Thus, TLR3 appears essential for the intracellular survival and proliferation of *L. amazonensis* [43]. Furthermore, the *Leishmania* RNA virus also activates the TLR3-TRIF signaling pathway, promoting the production of IFN-α/β. As a result, the expression of autophagy-related 5 is induced, which mediates the degradation of nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) and apoptosis-associated speck-like protein containing a caspase activation and recruitment domain, thereby inhibiting inflammasome activation [103,104]. This suggests that *Leishmania* parasites, through their interactions with TLR3 and other immune pathways, modulate the host immune response to enhance their survival and pathogenicity.

In conclusion, the complex immune modulation observed during *Leishmania* infection, particularly via TLR3-mediated pathways, underscores the parasite's capacity to manipulate host immune responses to support its intracellular survival and propagate disease. Further research focusing on these immune pathways could provide crucial insights into developing novel therapeutic strategies to control leishmaniasis progression and severity.

4.3 Inhibition of Inflammatory Signaling by TLR3 Regulates Hepatic Fibrosis During C. sinensis Infection

Clonorchiasis is caused by *Clonorchis sinensis* (*C. sinensis*), a liver fluke from the family Opisthorchiidae, infecting humans or mammals through the consumption of undercooked freshwater fish containing encysted metacercariae [105]. This disease is prevalent mainly in parts of China and other East Asian countries [106]. Over 15 million people are, reportedly, infected with the parasite, with more than 80% of the infections occurring in China. Consequently, it is considered one of the most widespread and detrimental food-borne parasitic diseases in China [7,107]. Infection with *C. sinensis* leads to various pathological changes such as epithelial cell proliferation, degeneration, liver inflammation, cholangitis, and bile duct obstruction. If left untreated, this long-term infection can result in bile duct fibrosis, liver cirrhosis, and even cholangiocarcinoma [108].

A recent study has highlighted the significant role of TLR3 activation in liver fibrosis associated with *C. sinensis*, emphasizing its importance as a target in modulating hepatic stellate cell activation and promoting liver regeneration [47]. Activation of TLR3 using poly(I:C) promotes the regeneration of damaged liver tissue due to *C. sinensis* infection [109]. TLR3 may potentially detect exocytotic RNA released from host cells damaged by *C. sinensis* infection [22,110]. Compared to WT mice, TLR3-knockout mice exhibit hyperactivation of pro-inflammatory pathways such as ERK, p38, AKT, and p65, along with increased expression of cytokines IL-4, IL-6, and TNF-α, and reduced expression of IFN-γ. This imbalance leads to exacerbated hepatic inflammation and fibrosis. The immune response triggered by TLR3 signaling during *C. sinensis* infection is pivotal in regulating liver pathology, impacting both the development and resolution of hepatic fibrosis. In contrast, as depicted in Fig. 3c, WT mice infected with *C. sinensis* activate the TLR3 signaling pathway, which inhibits the release of IL-6 and TNF-α, while upregulating IFN-γ expression [47]. Notably, TLR3-regulated cytokines such as TNF-α and IL-4 are significantly elevated and positively correlated with fibrosis severity [111–113]. Whereas IFN-γ promotes the gradual regression of hepatic fibrosis by inducing hepatic stellate cell apoptosis [114]. This finding underscores the crucial role of IFN-γ within the TLR3 pathway in mitigating liver fibrosis. Therefore, the role of poly(I:C) in liver disease appears to be dualistic. Specifically, treatment with poly(I:C) in C57BL/6 mice non-pathogenic liver disease is associated with the induction of primary biliary cirrhosis [115]. However, as indicated in Table 1, poly(I:C)-treated mice infected with *C. sinensis* exhibit a significantly lower degree of hepatic fibrosis than that of untreated controls, indicating effective alleviation of liver damage. These observations suggest a protective role of TLR3 in controlling liver fibrosis induced by *C. sinensis* [47].

In conclusion, TLR3 signaling plays a pivotal role in modulating the immune response and hepatic fibrosis during *C. sinensis* infection, with its activation demonstrating protective effects against liver damage. Future studies should aim to elucidate the dual role of TLR3 in liver diseases to better leverage its therapeutic potential for managing fibrosis and other liver pathologies.

4.4 The Role of TLR3 in Modulating Immune Responses and Liver Pathogenesis During Schistosoma japonicum Infection

Schistosoma japonicum is a dioecious zoonotic parasite in the family Schistosomatidae, causing schistosomiasis in 78 tropical and subtropical countries, particularly where medical resources are limited, and thus posing a major threat to human health and economic development [116–118]. The cercariae of *S. japonicum* are released into freshwater environments by their intermediate host, the Oncomelania snail, contaminating water sources. The end hosts are vertebrates, including humans, who become infected with schistosomiasis through exposure to this contaminated water [119]. The damage caused by *S. japonicum* to the host, particularly from parasitized eggs, can be severe and varies in magnitude [120,121]. Schistosomiasis represents a significant public health challenge, causing chronic inflammation and organ damage that leads to genitourinary and intestinal complications. This, in turn, severely impairs the quality of life, especially in affected populations [122].

Upon *S. japonicum* infection, the host initiates a variety of immune responses, with NK cells playing a crucial role. These cells, integral to the innate immune system, re-

spond rapidly to pathogens through cytotoxic mechanisms and cytokine secretion [123]. Recent studies suggest that TLR3 detects exoRNA released from damaged host cells during *S. japonicum* infection [53,124]. In experimental models, *S. japonicum*-infected mice showed increased secretion of IFN-γ and IL-4, as illustrated in Fig. 3d [122]. *In vitro* experiments confirmed these findings, revealing that murine spleen cells pre-stimulated with poly(I:C) and co-cultured with *S. japonicum* produced significantly higher IL-4 levels. Additionally, *S. japonicum*-infected mice exhibited a higher proportion of $TLR3^{+}$ NK cells in the spleen compared to uninfected controls, along with increased expression of IL-4, IL-5, and IL-17. In contrast, TLR3-deficient mice showed a marked reduction in these cytokines, underscoring TLR3's role in activating splenic NK cells during infection [90]. Moreover, TLR3-mediated immune responses were found to vary across tissues due to organ-specific factors [8,90]. Notably, TLR3 deficiency in infected mice led to reduced levels of aspartate aminotransferase and alanine aminotransferase, lower peripheral leukocyte counts, and normalized erythrocyte, platelet, and hemoglobin levels, as summarized in Table 1. These results suggest that TLR3 is positively associated with liver pathology severity, and its absence helps alleviate liver injury during infection [8].

4.5 TLR3 Agonist Poly(I:C) Immunomodulates Trichinella spiralis Infection

Trichinellosis *is caused by Trichinella spiralis* (*T. spiralis*), which belongs to the nematode order of the phylum Aschelminthes [125]. The life cycle of this species consists of three distinct phases: the myxo-larval, adult, and neonatal larval stages, all of which occur within a common host organism [126]. Poor dietary habits, such as consumption of raw or undercooked pork or wild game contaminated with trichinella larvae, can lead to *T. spiralis* infections in a wide range of mammals, including humans and pigs [127]. During the acute phase of infection, individuals commonly exhibit symptoms such as increased body temperature; these symptoms can persist for multiple weeks and potentially result in organ dysfunction [128]. In certain cases, the mortality rate of *T. spiralis* infection may soar up to 30% [129]. As of 2023, the health of people living in the African continent continues to be threatened by *T. spiralis* [130].

Building on the understanding of immune regulation induced by *T. spiralis*, current research is delving into the underlying molecular mechanisms through which the parasite evades the immune system, aiming to identify novel molecular targets for therapeutic intervention against *T. spiralis*. This pathogen modulates the host immune response by regulating the expression of TLRs, thereby influencing cytokine expression at various stages of infection [131]. TLR agonists have a wide range of therapeutic applications, including their use in signal therapy to accelerate and enhance vaccine-specific immune responses [132]. TLR3, as a commonly used vaccine adjuvant, plays an important role in host resistance to pathogen infection [133]. Although *T. spiralis* infection induces the release of exoRNA from damaged host cells, this exoRNA either fails to be recognized by TLR3 or the parasite successfully evades the host immune response [22,53,134]. Notably, the administration of poly(I:C) results in consistently elevated TLR3 expression and significantly increased levels of serum IFN-γ, IL-2, and IL-6 in C57BL/6 female mice compared to the control group, accompanied by significantly reduced IL-10 and IL-4 levels (Fig. 3e and Table 1). These findings suggest that TLR3-targeted therapy may be effective in reducing worm burden by modulating cytokine levels in *T. spiralis*-infected mice. Notably, poly(I:C) proved more effective at blocking the immune evasion strategy of *T. spiralis* compared to agonists targeting TLR4, TLR8, and TLR9 [52]. As *T. spiralis* is suggested to successfully escape the host TLR3-mediated immune response under natural circumstances, poly(I:C) represents a promising therapeutic approach with great potential in controlling *T. spiralis* infections.

4.6 The Role of TLR3-TRIF Pathway in Modulating Immune Responses Against Neospora caninum Infection

Neosporosis is caused by the protozoan parasite *N. caninum*, belonging to the phylum Apicomplexa. It primarily infects intermediate hosts like pigs, sheep, horses, cattle, and rabbits via oral or transplacental transmission, in addition to parasitizing definitive hosts such as dogs and other canids [135]. It is globally distributed and represents a major etiological agent of abortion in pregnant cattle, leading to considerable economic losses in the livestock industry [136]. Although *N. caninum* has not yet been classified as a zoonotic pathogen, environmental studies have highlighted its potential to pose a significant risk to human health, warranting further investigation [137,138].

The recognition of *N. caninum* by host immune receptors, particularly TLR3, highlights the critical interplay between innate immune sensing and the subsequent adaptive immune responses, which are essential for controlling infection and mitigating pathogenic effects. TLR3 may recognize lncRNAs produced by host cells in response to *N. caninum* infection [139,140]. This recognition triggers the production of various cytokines and chemokines, including IL-12 and IFN-γ, which further promote immune cell activation and inflammatory responses. Compared to WT mice, TLR3-knockout mice exhibit reduced IL-12p40 secretion, increased parasite burden, and decreased survival rates following *N. caninum* infection [44]. Upon recognition of *N. caninum* by TLR3, the inducible secretion of IL-12p40 promotes IFN-γ production, thereby inhibiting infection in mice. Further research involving experiments in WT mice, TLR3-knockout mice, and TLR3-knockout mice supplemented with IL-12p40 demonstrated that IL-12p40 exerts paracrine effects on infected activated macrophages

to control parasite proliferation. Moreover, the TLR3-TRIF signaling pathway induces ERK phosphorylation, facilitating the recognition of *N. caninum* and triggering IL-12p40 production. This mechanism plays a crucial role in controlling *N. caninum* proliferation in C57BL/6 mice [51]. These findings suggest that the TLR3 pathway promotes the production of IL-12p40 and IFN-γ and enhances specific Th_1 responses (Fig. 3f and Table 1), potentially enabling the host to better regulate the effects of *N. caninum* infection [44,91]. Therefore, understanding the detailed mechanisms through which the TLR3-TRIF pathway initiates Th_1 responses could provide novel insights for developing targeted therapeutic strategies aimed at mitigating the impact of *N. caninum* infection in livestock, with potential implications for safeguarding public health.

5. Conclusions

TLR3 plays a complex role in parasitic infections, contributing to both protective immunity and immune-mediated pathologies through a delicate balance. It recognizes parasite-derived nucleic acids, such as exoRNA and lncRNA, and regulates immune cells like macrophages and NK cells to enhance host defenses. However, its activation can also lead to excessive inflammation, resulting in tissue damage, fibrosis, and exacerbating parasitic diseases. The interplay between TLR3 and other TLRs amplifies immune responses, highlighting its critical role in both innate and adaptive immunity.

In various parasitic infections, TLR3's effects are host-dependent. For example, during *Plasmodium* infection, TLR3 triggers the production of pro-inflammatory cytokines essential for parasite clearance, but excessive activation can cause tissue damage. In *C. sinensis* infections, TLR3 activation is protective, reducing liver fibrosis and injury by modulating inflammatory and anti-inflammatory cytokines. In contrast, in *S. japonicum* infections, TLR3 exacerbates granulomatous inflammation and liver pathology, with its deficiency mitigating these effects. Similarly, in *L. amazonensis* infections, TLR3 skews the immune response towards a Th_{17} phenotype, promoting parasite survival and disease progression. In *T. spiralis* infections, TLR3 activation enhances Th_1 responses, helping to limit parasite burdens. In *N. caninum* infections, TLR3-mediated production of IL-12p40 and IFN-γ drives robust Th_1 immunity, enhancing parasite clearance and reducing inflammation.

These findings highlight TLR3's multifaceted roles in parasitic infections, acting both as a defender against pathogens and a contributor to immune-mediated damage. Understanding its dual functions is key to unraveling host-parasite interactions and positions TLR3 as a promising therapeutic target. Targeting TLR3 in parasitic infections holds potential for improving immune defense while minimizing harmful inflammation. Future research should focus on deciphering the precise mechanisms through which TLR3 mediates its diverse roles in different parasitic diseases. Developing specific TLR3 agonists or antagonists tailored to the infection type may offer innovative approaches to disease management. Additionally, understanding the cross-regulation between TLR3 and other immune pathways could pave the way for strategies to fine-tune immune responses. Insights from these studies may contribute to advancing vaccines, immunotherapies, and targeted treatments, ultimately improving patient outcomes and reducing the global burden of parasitic diseases.

Abbreviations

C. sinensis, Clonorchis sinensis; DCs, dendritic cells; dsRNA, double-stranded RNA; exoRNA, exosomal RNA; IFN-α/β, type I interferons; IKK, inhibitor of kappa B kinase; IL, interleukin; IRF, interferon regulatory factors; ISGs, interferon-stimulated genes; *L. amazonensis*, *Leishmania amazonensis*; lncRNA, long non-coding RNA; MAPKs, mitogen-activated protein kinases; *N. caninum*, *Neospora caninum*; NEMO, NF-κB essential modulator; NF-κB, nuclear factor κB; NK, natural killer; *P. yoelii yoelii* 265 BY, *Plasmodium yoelii yoelii* 265 BY; *S. japonicum*, *Schistosoma japonicum*; TAB2, TAK1-binding protein 2; TAK1, TGF-β-activated kinase 1; TBK1, TANK-binding kinase 1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-alpha; TLR, Toll-like receptor; TRAF6, tumor necrosis factor receptor-associated factor 6; TRIF, TIR-domain-containing adapter-inducing interferon-β; *T. spiralis*, *Trichinella spiralis*.

Author Contributions

YY, QL, YZ, NJ, and QC designed and wrote the manuscript. YY, QL, YZ, NJ, and QC were involved in original draft preparation; YY, QL, YZ, NJ, and QC participated in reviewing and editing. YZ and NJ contributed to the design of the figures. QC finalized the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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