Journal of Molecular Immunology

Review Article OMICS International

Host-oriented Inherent Measures and Eukaryotic Parasite Countermeasures

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Abstract

The recognition and elimination of eukaryotic parasites appear to be a hardwired prerequisite for host survival. However, eukaryotic parasites, such as *Toxoplasma gondii, Leishmania* sp., *Trypanosoma cruzi, Giardia* sp., and *Schistosoma* sp. employ the innate system of the host for their growth, replication, and continuation of their life cycle. So far, however, there has been little discussion about the interaction of the eukaryotic parasites and the innate immune system. Driven by this need, this review provides an overview of the host-oriented inherent measures and eukaryotic parasite countermeasures for evading host defences. Additionally, this review discusses control of parasite and its evasion strategy at innate and adaptive arms of the immune system. Taken together, this information could be exploited to discover novel therapies, vaccine strategies and prophylactic intervention points for broad-spectrum host-oriented inherent measures and eukaryotic parasite counter-measures, and to understand the parasitic disease progression and the infection consequence.

Keywords: Eukaryotic parasites; Innate immune system; Therapeutic and prophylactic intervention

Fighting / Evasion at the Front Lines (First and Second Defense Lines)

The role of the innate immune response in parasitic infections is to confront infections by producing non-specific immune responses. In addition to the physical barriers, such as skin and mucous membranes, which represent the first defense line, the innate immunity consists of cellular and humoral defense mechanisms (second defense line). The humoral molecules of innate immunity include fibronectin, complement, Tumor necrosis factor (TNF)-α, lysozyme, C-type lectins, lactoferin, and tranferin. Examples of the cellular branch include phagocytes, natural killer (NK) cells, γδ T-cells, and natural killer T (NKT) cells.

NK cells play a pivotal role in the immune response controlling *Plasmodium* infection. Moreover, NK cells contribute to the control of parasitemia via Th1 cytokines in the erythrocytic phase [1-3]. Filtjens et al. demonstrated that Ly49E expression has a transitory role in the immune control of *Plasmodium* pathogenesis [4].

Breaching the first defense line

The skin membrane barrier is one of the most important parts of innate immunity and first line of defense against invading organisms. The skin consists of thick epidermis (i.e. stratified squamous epithelial cells) and dermis. The thick outer layer acts as a physical barrier to the infection. Furthermore, the presence of fatty acids and sweat can trap and kill the small attackers. Though these strong anatomical barriers, the parasites use different ways to invade the skin and the mucosal membranes. They either actively insult the skin as in the case of cercariae of *Schistosoma* using serine and cysteine proteases or passively invade the skin (i.e. injected directly into the bloodstream, such as *Plasmodium* sporozoites, *Brugia* and *wuchereria* L3 larva or migrate from vector bite, for example, L3 of *Onchocerca* volvulus and trypomastigote of *Trypanosoma cruzi* [5]. Biting mosquito salivary glands have a lot of different soluble components, such as platelet aggregation inhibitors, anticoagulants (thrombin), and antihistamines. These components provide *Plasmodium* sporozoite survival and facilitate their inoculation [6,7]. The mucosal membranes can protect non-specifically against invaders by two effector mechanisms: luminal defense mechanism (for example, antimicrobial peptides, mucous, acidic pH, peristalsis and microbiota) and epithelial defense mechanism: single or multiple layers of cells depending upon the location and the animal species, tight junction between the cells, and Toll-like receptors (TLRs) on the cell surface and within the cytosol, and cytosolic nucleotide binding oligormerization domain (NOD) [8].

Most of the parasitic infections (eggs, oocysts, larvae, and metacercariae) occur through oral route. Apicomplexan parasites can actively deal with the first defense line by gliding motility. Other parasites invade by the bite of certain type of flies, and then spread through phagocytosis as in *Leishmania* and *Trypanosoma cruzi*. The newly emerged juvenile of trematodes can actively penetrate the intestinal mucosa through the secretion of Cathepsin B during invasion/migration processes. Some parasites reside in the intestine for the rest of their life as *Giardia*, which avoid peristalsis by attachment/re-attachment mechanisms [9]. However, cestodes move up- stream in a snake-like motion to avoid peristalsis.

Another Chance (Second Defense Line): Waves of the Inflammatory Response

First Wave of the Inflammatory Response

Toll-like receptors (TLRs) are most important primary innate immune receptors [10]. Thirteen mammalian TLRs have been

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Received February 02, 2017; **Accepted** February 03, 2017; **Published** February 09, 2017

Citation: El-Ashram S, Al Nasr I, Hu M, Suo X (2017) Host-oriented Inherent Measures and Eukaryotic Parasite Countermeasures. J Mol Immunol 2:106.

described; 10 and 13 TLRs are present in humans, and mice respectively [11]. The role of TLR was first shown in tissue lesions in the context of *T. gondii* and *Plasmodium berghei* infections [12,13]. For examples, TLRs play an important role in adaptive/innate immune responses against helminth infections [14-16]. The first wave of immunological falls after evasion of the first line is the early inflammatory response in which TLRs employ a crucial role as the initiator of the innate immunity. TLRs are an emerging family of innate receptors that belong to pattern recognition receptors (PRRs). Immune and nonimmune cells use TLRs to trigger the innate immune response and to orchestrate adaptive immunity. Tabulated below, a brief summary of pathogen-associated molecular patterns (PAMPs) of protozoan parasite [17]. PAMPs of protozoan parasite (Table 1) [18].

It has been shown that TLR signalling pathway plays a pivotal role in host resistance and pathogenesis during protozoan infection (Table 2). Roles of TLR signalling pathway during protozoan infection [18].

Several recent studies have reported that TLR11, TLR12 (tachyzoite-derived profilin-like protein detection) and the diverse IFN γ-inducible mouse GTPase (IRG) proteins are species-specific while TLR7 and TLR9 (parasite RNA and DNA detection) are widely distributed in different animal species [19-21]. Importantly, TLR11 expression is induced in neurons and glial cells in the immune response to *T. gondii* infection [22].

TLRs, in particular, TLR 2, TLR 3, TLR 4 and TLR 9, have been demonstrated to play an important role in leishmaniasis [23] via upregulating the pro-inflammatory responses in *Leishmania*-infected macrophages. TLR 2 played a protective role in leishmaniasis, and in addition both TLR 2 and TLR 3 were contributed to phagocytosis of *L. donovani* promastigotes [24,25]. Hosein et al. demonstrated that Th17 cytokines played an important pathological and protective role in *L. infantum* experimentally infected dogs [26]. Evasion of the innate signature; TLRs-PAMPS by protozoan parasites, for example, *T. gondii* enhances the production of IL-10, which exerts its anti-inflammatory signal. The expression of amastigote of *Leishmania mexicana* – specific cysteine peptidase suppresses the production of IL-12 by macrophages. The dendritic cells (DCs) become unresponsive to lipopolysaccharides (LPS), and unable to activate T cells in the presence of malaria hemozoin, which is a TLR9 agonist [17]. The down-regulation of TLR signaling pathway by these organisms leads to the long-term persistence in their hosts. Helminths and TLRs: Helminths (worms) include roundworms (nematode) and flatworms (trematode and cestode). The interfering with TLR expression and function may contribute to infection outcome as illustrated in the (Table 3). TLR activation and regulation of by two systemic helminth infections [18].

Second Wave of the Inflammatory Response

A second amplification wave of the inflammatory response comes

PAMP	Parasite	Expression stage	Structure	TLR
GPI anchors	*L. major*	Promastigotes	LPG	TLR2
	L. donovani			
	T. cruzi	Trypomastigotes	Contains unsaturated alkylacylglycerol	TLR2
		Epimastigotes	GIPLs containing ceramide	TLR4
	T. brucei	Trypomastigotes	GPI anchors of VSGs	ND
	P. falciparum	Merozites	GIPLs and GPI anchors of the MSP	TLR2
	T. gondii	Tachyzoites	GIPLs and GPI anchors	TLR2
Genomic DNA	*T. brucei*	All stages	Contains unmethylated CpG motifs	TLR9
	T. cruzi	All stages	Contains unmethylated CpG motifs	TLR9
Haemozoin	*P. falciparum*	Merozoites	β-Haematin crystal made from haemin	TLR9
PFTG	*T. gondii*	Tachyzoites	Profilin-like protein	TLR1

Table 1: GIPL, glycoinositolphospholipid; GPI, glycosylphosphatidylinositol; *L. donovani, Leishmania donovani; L. major, Leishmania major*; LPG, lipophosphoglycan; MSP, merozoite surface antigen; ND, not determined; *P. falciparum, Plasmodium falciparum*; PFTG, profilin-like protein; *T. brucei, Trypanosoma brucei; T. cruzi, Trypanosoma cruzi; T. gondii, Toxoplasma gondii*; TLR, Toll-like receptor; VSGs, variant surface glycoproteins.

Parasite	Knockout	Phenotype
L. major	*Myd88*$^{-/-}$	TH2 phenotype and increased susceptibility
	Tlr4 mutant	No major effects on immune response
	Myd88$^{-/-}$	Decreased pro-inflammatory cytokines and increased susceptibility
	Tlr1$^{-/-}$, *Tlr2*$^{-/-}$, *Tlr4*$^{-/-}$, *Tlr6*$^{-/-}$ *or Cd14*$^{-/-}$	Normal cytokine responses, parasitaemia and survival
	Tlr2$^{-/-}$ *and Tlr4*$^{-/-}$ *or Tlr9*$^{-/-}$	Impaired IL-12 and IFNγ production and increased susceptibility
T. cruzi	*Myd88*$^{-/-}$	Impaired pro-inflammatory cytokines and increased susceptibility
	Tlr2$^{-/-}$	Increased IL-12 and IFNγ, and unaffected parasitaemia and survival
	Tlr4$^{-/-}$, *Tlr6*$^{-/-}$*or Cd14*$^{-/-}$	Normal cytokine responses, parasitaemia and survival
	Tlr9$^{-/-}$	Impaired IL-12 and IFNγ production, increased parasitaemia and accelerated mortality
	Tlr2$^{-/-}$ *and Tlr9*$^{-/-}$	More pronounced effects than just *Tlr9*$^{-/-}$mice
P. berghei	*Myd88*$^{-/-}$	Impaired pro-inflammatory cytokines and decreased pathology
	Tlr2$^{-/-}$, *Tlr4*$^{-/-}$ *or Tlr6–/*	Normal cytokine responses, parasitaemia and pathology
T. gondii	*Myd88*$^{-/-}$	Impaired IL-12 and IFNγ production, and increased susceptibility
	Tlr2$^{-/-}$	High-dose inocula—increased susceptibility to infection; low or intermediate dose—normal cytokine responses, parasitaemia and survival
	Tlr4$^{-/-}$	Normal cytokine responses, parasitaemia and survival
	Tlr11$^{-/-}$	Impaired production of IL-12 and IFNγ, and increased susceptibility

Table 2: IFN, interferon; IL, interleukin; *L. major, Leishmania major*; Myd88, myeloid differentiation primary-response gene 88; P. berghei, *Plasmodium berghei; T. brucei, Trypanosoma brucei; T. cruzi, Trypanosoma cruzi; T. gondii, Toxoplasma gondii*; TH, T helper; Tlr, Toll-like receptor.

	Filarial infections				Schistosome infections			
	Murine models		Human infections		Murine models		Human infections	
	in vitro	*in vivo*	*in vitro*	*ex vivo*	*in vitro*	*in vivo*	*in vitro*	*ex vivo*
Direct Activation of TLR by parasite products	+	+	+	ND	+	+	+	ND
Alteration of TLR expression on APCs	+	ND	+	+	ND	ND	ND	ND
Inhibition of signaling through TLR	+	+	+	+	+	+	+	+
ND=Not Determined								

Table 3: In addition to TLRs, the alternative and lectin pathway play an important role. The mediator like C5a of this pathway starts to recruit neutrophils and eosinophils to the site of inciting agents to amplify the inflammatory event. Macrophage has many receptors such as mannose-fucose receptors, complement receptors (CR3 for C3bi), Toll-like receptors, etc. Some parasites as we will mention to start to gain access to the intracellular milieu via these receptors as *Leishmania* and *Trypanosoma cruzi*.

from the secretion of mediators released by activated macrophages and epithelial cells interleukin (IL)-1, IL-6 and TNF-α. These mediators exacerbate the acute inflammatory responses, which starts locally (by increasing vascular permeability, recruitment of leukocytes, and coagulation) and spreads systemically causing fever and the production of acute phase protein by the liver.

Recently published article by Atmaca et al. detected that high levels of acute phase proteins (APP) in *T. gondii* infected-mice were closely linked to brain lesions and tissue cysts. Briefly, APP is a potentially good marker for *T. gondii* infection based on correlation values detected its level in serum, tissue cysts' number and inflammatory score in the brain. This suggests a strong link may exist between acute phase proteins and *T. gondii* infection [27].

The Parasite and the Host are Under Stress

The infective agents, which are transmitted through vectors as in the case of *Plasmodium, Trypanosoma*, *Filaria* come from different environments (i.e. cold-blooded animal vectors) and try to gain access into other environments (i.e. worm-blooded vertebrates), consequently, both the parasite and the host become stressed. The epithelial cells upregulate the heat-shock proteins (highly conserved). Furthermore, the cytolytic activity of the innate cells and γδ T-cells after engagement the heat-shock protein through their NKG2D receptor is augmented [28]. We hypothetically think they can kill the parasites by the same manner: NK or γδ T cells can be activated by IL-12 and TNF-α from macrophage to release IFN-γ or can cause direct lysis of infected cells after enhancement by IFN-α from activated macrophage [29].

Heat shock protein 90 (Hsp90) has been implicated to play a pivotal role in life cycle and growth of *Leishmania*, *Giardia*, *Toxoplasma* and *Plasmodium* [30-33]. Hsp90 is critical for growth and survival of *E. histolytica* and its attendance in regulation of phagocytosis and encystation [34-35]. Hsp90 inhibition has been led to the death of *Entamoeba* trophozoites [35].

Establishment of a beachhead after infection

Intracellular parasites evolved several strategies to evade the host immune attack in a sylvatic host environment before, during, and after entry into the host cell (i.e. they circumvent to complement attack, oxidative, and non-oxidative killing respectively).

Other evasion strategies of *Leishmania* spp aganist immune defense are δ-amastins. As a consequence of δ-amastins, *Leishmania* promastigotes set up a secure niche within mammalian host macrophages [36].

Before entry to the safe paradise

Protozoan parasites evade complement pathways employing different strategies. The major obstacle, which faces the obligate intracellular parasites, is the complement attack by lectin and alternative pathways. For examplas, *Plasmodium* sp, *Giardia intestinalis, T. cruzi and Leishmania* sp have shown an efficient activation of a lectin pathway [37-41]. The activation of the complement by the parasite surface (non-self surface) leads to the production of a cascade of mediators such as C4b and C3b that bind to CR1 (CD35) receptors on erythrocytes, neutrophils, monocytes, macrophages, eosinophils, follicular dendritic cells, T-cells and B-cells. Additionally, C3bi is the ligand for CR3 (CD11b/18) and CR4 (CD11c/18) on the surface of monocytes, macrophages, natural killers and some T-cells [42]. These complement mediators bind to different ligands on the parasite surfaces and enhancing their internalization. Internalization can be occurred by plasma fibronectin (FN) which has a receptor on *Trypanosoma cruzi* [43]. Leishmanolysin (gp63) of *Leishmania* spp. has fibrinonectin-like properties fascilitating parasite internalization by binding fibrinonectin receptor on macrophage [44].

The parasite can evade the complement-mediated killing pathway by different mechanisms:

Inhibiting complement activation: *Trypanosoma brucei rhodesiense* can avoid complement attack by their thick outer coat as they prevent C5b-9 MAC complex to be inserted on the trypomastigote surface [43]. The trypomastigotes and tachyzoites of American's trypanosomes, *T. cruzi* and *T. gondii* respectively prevent complement cascade activation. C3 convertase (C3bBb or C4b2b) can be inhibited by gp87-93 DAF-like molecule of *Trypanosoma cruzi* in a way similar to decay-accelerating factor of mammals [45]. In addition to single variant surface glycoprotein, which is expressed by African trypanosome *T. brucei;* this provides slacking of the complement system [46,47]. The single variant surface glycoprotein that covers on the parasite surface acts as a physical barrier to the host immune system [47-49].

The tachyzoites (the dividing form) of *T.* gondii causes C3 conversion to C3bi, therefore, limiting the C3 to attach to the parasite surface [50,51]. It is also worth reporting that *T. cruzi*-induced microvesicle release early in infection from blood cells, leading to the complement C3 convertase stabilization and inhibition [52]. Gp58/68 is an important glycoprotein for trypomastigotes. It enables the parasite to escape complement lysis by the alternative pathway [53]. *L. major* promastigotes releases the MAC (C5b-9) and during complement activation, MAC (C5b- 9) is deposited to escape host complement system [54].

T. cruzi membrane contains special structures, mucin-like molecules on its surface declining the host protective immunity. It is attached to the terminal β-galactosyl and sialic acid residues, which are transferred from host glycoconjugates [55-57].

Preventing membrane-attack complex (C5b-9 MAC) lysis: Lipophosphoglycan (LPG), a surface glucoconjugate of *Leishmania donovani* and *Leishmania major* promastigote, is very long; therefore, it prevents C5b-9 MAC insertion [58].

Circumventing during entry

Intracellular parasites try to acquire access to the intracellular

paradise in a way to avoid the receptors associated with the respiratory burst receptors, thus circumventing the oxidative killing mechanisms of the phagocytes. They sort the receptors to select the best for their survival and ignore the old proverb "All roads lead to Rome."

Mannose-fucose receptor (MFR) on macrophage binds to LPG, and CR1 binds to C3b, LPG, and gp63. Furthermore, β1 integrins on macrophage bind to Leishmanial ligands such as gp63, fibronectin, and laminin and collagen. Gaining access to the intracellular milieu via the complement receptors as in the case of the leishmanial promastigote which activates the complement on its surface, but it inhibits the final lytic product to attach to its surface facilitating its entry to the macrophage. Additionally, it lives happily inside the phagolysosome as it degrades the killing cascade of lysosomal enzymes by gp63. It was also reported that *Trypansoma cruzi* gp83 (trans-sialidase-like molecule) could bind to laminin γ-1 receptor on mammalian cells [59]. Apicomplexans such as *Toxoplasma*, *Cryptosporidium, Eimeria, Isospora, Sarcocystis, Babesia, Theileria, Cyclospora* and *Plasmodium* have a crescent-shaped body and exhibit a peculiar type of locomotion to invade the cells actively by gliding motility. The myosin motor complex is attached to the inner membrane complex. The inner membrane complex is in close association with the microtubules. The adhesin molecules secreted by micronemes bind to the Aldolases that in turn link to the actin cytoskeleton. Following actin filament polymerization, it starts to translocate the myosin motor complex posteriorly propelling the parasite forward [60,61]. The membrane-bound vacuole (parasitophorous vacuole) which wraps the tachyzoites of *T. gondii* devoids of plasma membrane receptors, therefore both vacuolar acidification and a fusigenic signal (i.e. to fuse with the lysosome) don't occur [50].

Proline racemase (PRAC) enzymes, potent host B-cell mitogens, released by *T. cruzi* lead to the generation of a non-specific B-cell proliferation, which results in producing non-specific antibodies; therefore, having an influence on the parasite persistence in the host cells [62-65].

T. cruzi inhibits production of IL-12 owing to the impairment of host dendritic cell functions [66]. *T. cruzi* mucin-like molecules are important driving factors of the immune system impairment and the invasion of the host. Moreover, infective trypomastigote is protected from host attack mediated by complement factor B and anti-galactosyl antibodies by sialylated mucins, which form a surface coat [67-69].

Recrudescence and intracellular survival of intracellular parasites after the entry of the host cell

Leishmania major Gp63, a surface protease, evades the host cell after entry by inhibiting oxidative respiratory burst. In addition to that, it prevents the chemotatctic events of monocytes and neutrophils [70]. Lysosome fusion is inhibited by LPG, and lysosomal enzymes are hindered by gp63 [71-73].

In the literature, most *Leishmania* species activate the complement pathway. For examples, *L. Enrietti, L. Braziliensis,* and *L.major* enhance the alternative complement pathway; however, *L. donovani* appears to stimulate the classical pathway [74-76]. Nevertheless, *L. Braziliensis, L. Mexicana, L. Major and their* promastigotes activate the lectin pathway by binding to mannan-binding lectin [77-80].

A glycosylphosphatidylinositol (GPI) anchor of leishmanial promastigote contains lipophosphoglycan (LPG) and gp63, which inhibit the action of a non-oxidative killing pathway of the macrophage [50]. The active form, trypomastigote of *T. cruzi,* invades the host cell within a membrane-bound vacuole, and destroys the vacuole by its membrane-forming protein to escape into the cytoplasm avoiding the non-oxidative killing by hydrolysases [45]. In a similar context, *T. cruzi* -infected macrophage results in the anti-inflammatory cytokine secretion, for example IL-10 and TGF-ß which favors parasite dissemination. Additionally, *T. cruzi* interferes with dendritic cell antigen presenting function and suppresses $CD4^+$ T cell responses via host sialic acid-binding Ig-like lectin receptors [81].

Parasitophorous vacuole: Parasitophorous vacuoles (PV), which formed within the host cells are the residence and development niche of apicomplexan parasites. They inhibit the fusion of acidic organelles from the different exo- and endocytic pathways [82-84]. After their active entry into the host cells, *T. gondii* and *N. caninum* tachyzoites, *Encephalitozoon cuniculi* spores, *T. cruzi* and *L. amazonensis* amastigotes hide inside the PV and escape killing by humoral immune response [82,85,86].

Wilson et al. showed that LYST/Beige plays an important role at the innate level. They also illustrated that increased expression of LYST/Beige functions to protect the host cells via restricting *Leishmania* amastigote growth because of struggling PV expansion [87].

Macrophage (Double-Edged Sword)

Macrophage is a double-edged tool as it is considered one of the safe milieus to many intracellular organisms, such as *Leishmania*, *Trypanosoma cruzi* and *T. gondii*. The best solution for the parasites is to live within macrophages at peace with the host perhaps by being cryptic. However, once "woken," the macrophage has a number of oxidative and non-oxidative killing mechanisms. Oxidative stress (OS) occurs when there is an imbalance between pro-oxidant-antioxidant levels and is induced by reactive nitrogen species (RNS) and highly reactive oxygen species (ROS) [88,89]. *T. gondii* expresses antioxidant enzymes, such as catalases and peroxidases to protect itself against ROS activity [90,91]. Increased OS and OS-related neuropathology in *T.gondii*-infected mice was determinated by Dincel and Atmaca (2015) [92]. In general, therefore, it seems that oxidative killing mechanisms against *T. gondii* were activated by microglia/macrophages, other glial cells and neurons. Microglia/macrophages might be responsible for both recurrent and systemic *T. gondii* infections. Tachyzoite- and bradyzoite- hidden mechanisms in the cells act as a "Trojan horse" [93-95]. Therefore, macrophages provide a framework for both in the occurrence and prevention of disease.

Macrophages and neutrophils kill the nematode, *Strongyloides stercoralis* larvae owing to the activation of IL-4Rα [96]. Overall, intestinal helminth and its larva macrophage killing mechanisms were controlled by type 2 immune cell responses [97-99].

Apoptosis

Programmed cell death also called apoptosis involved in immune response to infections by modulating *T. gondii* proliferation [100,101]. Dincel and Atmaca (2015) demonstrated that *T. gondii* and other soluble factors trigger apoptosis employing both instrinsic and extrinsic pathways. *T. gondii*-mediated apoptosis might associate with the pathogenesis of neurodegeneration and neuropathology [102]. Furthermore, the binding of *Plasmodium* sporozoites also induced Kupffer cells apoptosis [103].

Non-Specific and Specific Ways that Lead to Macrophage Activation

Parasite products and cytokine-mediators from different cell types such as γδ T cells after parasite insulting can secrete IFN-γ to

activate resting macrophages. Moreover, IFN-γ is produced from NK cells after parasite activation or after induction by IL-12 and TNF-α that are secreted from other activated macrophages. On the other side, $CD4^+$ T-cells and $CD8^+$ T-cells produce IFN-γ after antigen processing, presenting and naïve T-cells activation by professional antigen presenting cells [104].

Nitric Oxide Synthase (NOS) Toxic Pathway and Parasitic Evasion: Non-Oxidative Killing Mechanism

Activated macrophage synthesizes nitric oxide (NO) from L-arginine under the influence of inducible nitric oxide synthase (iNOS/NOS-2). Nitric oxide and L-ornithine can be produced from L-arginine through hydroxylation and oxidation or hydrolysis in corresponding order. L-ornithine is the precursor for the parasite growth factors such as L-glutamine, L-proline, and putrescine (Figure 1). The nitric oxide toxicity is associated with the production of the reactive hydroxyl group.

NO triggers the development of tissue cysts in *T. Gondii* and *Neospora caninum* by inhibiting parasite replication. A decrease in NO production might cause tissue cyst reactivation [105-110]. NO dependent mechanisms are responsible for the killing of *N. caninum* tachyzoites inside macrophages [111]. eNOS, iNOS and nNOS derived NO, produced by microglia/macrophages, astrocytes and neurons contributes to the development of tissue cysts, and protective immunity [110].

NO derived from nNOS is effective in the elimination of *Giardia lamblia* infections in mice [112]. NO inhibition causes excystation and encystation of *G. lamblia* cysts, thereby establishing and continuing the infection process in the small intestine [113]. *Giardia* has evolved strategies to escape NO-mediated host defenses. For example, epithelial NO production was depleted because of consuming arginine by *Giardia* [113, 114].

IFN-gamma- and TNF-alpha-mediated activation of NO, which is potent microbicidal agent, importantly derived from inducible nitric oxide synthase in murine macrophages shows a major leishmanicidal effect [115, 116].

T. gondii survives in the activated macrophages, and avoids nitric oxide-killing mechanism. A possible explanation for this might be that a *T. gondii* patatin-like protein (TgPL1), protects from *T. gondii* nitric oxide degradation in the activated macrophages [82,117].

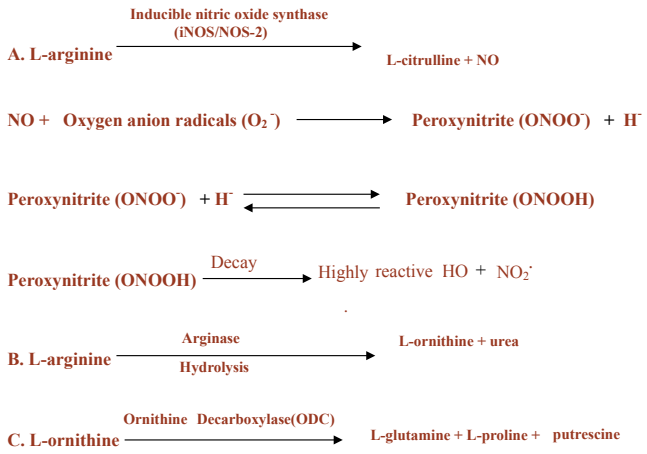

Figure 1: Different metabolic pathways to generate NO and factors for parasite growth [115,118].

Parasites evade the ready-made armory of immune system by avoiding NO harmful effect by depletion of L-arginine through activation of Arginase.

It was reported that NO synthesis (parasite death)/Arginase activation (parasite survival) influenced by the cytokines secreted from the T-helper type 1 (Th1)/T-helper type 2 (Th2) respectively [118]. Cruzipain (major cysteine proteinase) of *Trypanosoma cruzi*, an intracellular parasitic protozoon, favors Th2 arm of immunity; therefore, evade NOS pathway. Furthermore, cruzipain regulates parasite survival and differentiation through arginase activation [119]. Arginase induction during *Leishmania major* infection leads to promastigote–amastigote transformation and amastigote replication within the phagolysosome of macrophage [120].

Having considered what is meant by the inducible nitric oxide synthase (NOS2) and the macrophage-secreted NO, we will now move on to briefly shed the light on IFN-γ-inducible IRG proteins, which destroy *T. gondii* tachyzoites by rupturing of the parasitophorous vacuole (PV) [21,121,122]. Pseudokinase (ROP5) and kinase (ROP18) are secreted by certain *T. gondii* strains resulting in the formation of ROP5/ROP18 kinase complex, which phosphorylates and inactivates IRG proteins. However, some strains of mice are ROP5/ROP18 kinase complex-resistant [21,123].

Oxidants and Anti-Oxidants

The host innate immune cells such as macrophages, eosinophils, neutrophils, and platelets release reactive oxygen species (ROS) that can kill the adult schistosome. Schistosome, other helminths and protozoa developed countermeasures to avoid oygen-mediated killing. They produce antioxidant enzymes, e.g. superoxide dismutase (SOD) which is responsible for the dismutation of the superoxide anion to hydrogen peroxide (H_2O_2), Catalase and Glutathione-peroxidase (GPX) which detoxify the hydrogen peroxide, and glutathione-S-transferase (GST) and peroxidoxin which eliminate the hydrogen peroxide. The anti-oxidants avert the toxic action of the secreted ROS [124,125]. They infectivity differences between non-zoonotic (*Trypanosoma brucei brucei*) and zoonotic ones (*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*) are due to the absence/presence of serum resistance associated gene (SRA) respectively. Serum lysis, high-density lipoprotein lytic factor called "TLF1," can prevent *Trypanosoma brucei brucei* to infect the human host. TLF1, which uptakes via its ligand {haptoprotein (HPr)} on the parasite surface leads to phagosome formation. Following phagolysosome formation, the acidity enhances the peroxidase activity and eventually cell lysis [126]. We hypothesize that there is a virulence factor which may be the product of RSA gene. It may decrease the acidification of the phagolysosomal vesicle, and deactivate the oxidative killing of the human infective subspecies such as *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense.*

Helminths Deal With the Complement Attack as Well

Schistosomes live within a harsh environment within a blood circulation. They are exposed to immunological falls of killing effectors such as the complement cascade, which can be activated by three pathways (classical "adaptive," alternative and lectin pathways) [127]. To circumvent the complement attack, they possess a plethora of parasite regulatory proteins as illustrated in the (Table 4).

The production of IL-10, IL-6, and TNF-α from monocyte is enhanced by glycolipids of female schistosome egg [128]. The oncosphere larva of *Echinococcus granulosus* (hydatid disease) penetrates the intestinal wall, and migrates to liver and lung where

Protein	Type of Protein	Affected Pathway	Regulatory Function
Parasite C3 surface receptor	Membrane bound	All pathways	Binds and inactivate C3
DAF-like molecule	Membrane bound	All pathways	Accelerates the C3 convertase (C3bBb and C4b2a) dissociation
Parasite C2 receptor	Membrane bound	Lectin and Classical pathway	Interferes with C3 convertase
C1q-binding protein	Membrane bound	Classical pathways	Prevents complement activation through binding to C1q
Surface antibody bound through Fc	Membrane bound	Classical pathways	Docking site becomes unavailable to bind to C1q
C8-C9-binding protein	Membrane bound	All pathways	Acts like CD59

Table 4: Schistosomal components that regulate complement system [42,127].

transformation occurs to hydatid cyst. The latter consists of outer layer and inner laminated layer lined with germinal epithelium. The germinal layers give rise to the daughter cyst "brood capsules," which contains protoscolices "hydatid sands." The hydatid cyst wall acts as a barrier against the immunologically hostile milieu. The acquisition of host myo-Inositol hexakisphosphate (IP_6) at the surface of the hydatid cyst wall inhibits C3 convertase factor I, which cleaves C3ba and C4b [129]. The hydatid disease is divided into two stages:

Precystic stage (establishment phase): This can occur after egg infection, and oncoshpere migration in the intermediate host (i.e. primary infection) or protoscolex migration after cyst infection in the definitive host (i.e. secondary infection). In these two cases oncospheres and protoscoleces undergo transformation into the cyst stage. Protoscoleces (PSCs) can trigger alternative complement pathway and lead to inflammatory responses.

Cystic stage (inert phase): the laminated layer of the hydatid cyst is acellular, mechanically resistant, permeable for a macromolecule, and carbohydrate rich (galactose and N-acetyl galactosamine). It is lined with parasite living syncytial germinal layer. Although the hydatid cyst wall (HCW) is rich in carbohydrate, the lectin pathway can't be activated. The reason could be low affinity of binding between the mannose binding lectin and hydatid cyst wall sugar or poor recruitment of inflammatory cells. HCW can capture the host H factor that binds to C3b leading to blocking C3 convertase (C3bBb). The same mechanism has been reported for *Taenia taeniformis* (Rat tape worm), where the membrane associated inhibitor molecules can block the final lytic pathway of the complement [130].

Parasitic helminths "Masters of the immunoregulation"

Helminthic parasites have evolved to be protected from host immune systems. Parasitic helminths have an inherent ability to elicit Th2-dominated immune response characterized by Th2 cytokines, robust immunoglobulin E (IgE), eosinophil, and mast cell responses [131]. Many species of parasitic helminths and helminth-derived molecules are instrumental in the shaping of the immune response of the host by creating regulatory environment [132]. Th2 cytokines and chemokines are most important and increased after *T. spiralis* infection in mesenteric lymph node [133]. Moreover, TLR4 and TLR9 are overexpressed during *T. spiralis*-infected mice in small intestine and muscle tissue [134]. Elevated levels of regulatory T cells (Tregs), regulatory B cells (Bregs), alternatively activated macrophages (AAMs), IL-10 and transforming growth factor (TGF) -ß have been observed after infection with parasitic helminths [135-138]. In a similar context, the adoptive transfer of intestinal DCs from *Heligmosomoides polygyrus bakeri*-infected mouse to naïve one provides protection from colitis [139]. Further, *Fasciola hepatica* total extract (TE) endorses CpG-ODN (CpG)-activated DCs to diminish exacerbated immune response in collagen-induced arthritis (CIA) [140], and human DCs primed with soluble products (SPs) of *Trichuris suis* induce a T helper 2 (Th2) response and suppress TLR-induced Th1 and Th17 responses [141]. Furthermore, it has been demonstrated that dinitrobenzene sulfonic acid (DNBS)-induced colitis was reduced in mice by using in vitro IL-4 -derived alternatively activated macrophages (AAMs) from *Hymenolepis diminuta*-infected mice [142]. A significant analysis and discussion on the rule of helminths and their products that could dampen the inflammatory and autoimmune disorders were presented by [139,143-149].

Trichinella spiralis paramyosin (Ts-Pmy) is exhibited on the outer membrane of both larvae and adults *[150]*. Ts-Pmy is linked to complement components C8 and C9, which have a considerable impact on of the membrane attack complex (MAC) and the complement activation cascade. Ts-Pmy inhibits the formation of MAC via interfering with the complement component C9, thus evading the attack of the host complement system *[151]*.

Further humoral molecules of innate immune system

Lectins are carbohydrate binding proteins; host galectins and C-type lectins are associated with a variety of immune processes, such as cell adhesion and T cell polarisation *[152]*. Collectins are C-type lectins (C-TLs) or $Ca2^+$ dependent lectins include mannan-binding lectin (MBL), surfactant protein A and D (SP-A and SP-D). They consist of an N-terminal collagenous domain and C-terminal carbohydrate-recognition domain (CRD). They differ from Ficolins (L-ficolin, M-ficolin, and H-ficolin), which contain a fibrinogen-like domain instead of CRD. Collectins are found in mucosal surfaces and on the blood. MBL and Ficolin are PRRs and recognize PAMPs. They can launch the lectin pathway. SP-A and SP-D can opsonize, agglutinate, and neutralize the bacteria and viruses [153]. The majority of collectins and ficolins are homomultimeric to increase the avidity of binding with their ligands. Other examples of C-type lectins (C-TLs) include:

Mucosal addressin cell adhesion molecule (MAdCAM) is a ligand for L-selectin.

Macrophage mannose receptor, DEC-205 and galactose-GalNAc receptor bind to glycan ligand and facilitate endocytosis.

NK cell receptors are integeral membrane proteins that include Ly-49, NKRP-1, and CD94. They prevent lysis of the target after engagement of MHC class I molecule.

CD23 receptor that engages IgE on haematopoeitc cells.

T. cruzi is compelled evade the cytolytic effects of the complement system. At this point, L-Ficolin binding to *Trypanosoma cruzi* calreticulin (TcCRT) undertakes the influential task. TcCRT can bind C1 and mannan-binding lectin/ficolins inhibiting the prominrnt lectin complement and classical pathway activation. This clearly shows that the role of TcCRT/ *T. cruzi* evasion strategy to inhibit an important innate immune response pathway [154, 155].

Parasites evade the CTLs

Helminths also secrete C-type lectins as a way to evade the host C-type lectins. CTLs of nematodes compete for L-selectin ligand

(MAdCAM), which is upregulated during the inflammatory response inhibiting the extravasation of the leukocytes. Schistomal CTLs play a crucial role in molecular mimicry; the parasite covers its surface by C-type lectins [152].

Eosinophil-mediated parasite killing

Eosinophils are non-specific killer polymorphic granulocytes. It was reported that the innate immune response was efficient to eliminate the parasite [156]. Eosinophil-mediated parasite killing can result in parasite clearance. Eosinophil production, recruitment, and activation can occur by different ways in incompatible hosts as can be seen from (Figure 2).

IL-5, constitutive production by eosinophils, plays an important role in the immune system, such as eosinophil differentiation from the bone marrow and critical for healing and recruiting of the eosinophils following nematode infection [157]. Increased expression of IL-5 leads to the reduction of *N. brasiliensis* worm recovery from the lungs and strongly advocates that eosinophils play a key role in the augmentation of immunity against *N. brasiliensis* infection and protection against its migrating larvae [158].

Eosinophils are important immune cells for *T. spiralis* larvae survival. IL-10-secreting DCs, CD4+ T cells and IL-10 control the activation of macrophages and neutrophils in the context of *T. spiralis* larvae tissue invasion [159-161].

Owing to host measure and the parasite counter-measure to reach a state of equilibrium (adaptation/long persistence/chronicity), the innate immune response is inefficient to get rid of infected parasite larvae in susceptible hosts. Specific molecules are required to increase the avidity (i.e. the overall binding strength) of binding between the eosinophils and the parasite surface either directly (eosinophil Fc-specific ab-Ag complexes) or indirectly (classical pathway complement activation). Augmentation of the eosinophil's production can occur by specific IL-5 (i.e. $CD4^+$ Th2) [162]. All of host mediators can act synergistically to clear the parasite larvae before their ability to evade the immune responses [156]. Eosinophils bind to either IgE or IgG through Fc receptor and to the epitope on the parasite surface via Fab. CR3 receptor binds to C3bi, which coats the parasite surface. This high avidity of binding leads to eosinophil degranulation on the parasite surface (Figure 3).

Linking innate and adaptive immune response

Apart from antigen processing and presentation by antigen presenting cells such as macrophages, dentritic cells and B cells, mediators are released from mast cells either as a response to anaphylatoxins (C3a, C4a and C5a) or through IgE-dependent degranulation [163,164]. C5a, eosinophil chemotact factor (released from mast), and IL-5 enhance eosinophil production and recruitment to the parasite surface. IgE, IgG, and complement can mediate eosinophil killing by releasing toxic granules. IgE can lead to functional changes in macrophage and mediate macrophage-killing mechanism. Moreover, neutrophils can mediate killing through respiratory burst or Ab (IgG) mediated degranulation and liberation of toxic granules [165].

Neutrophil extracellular traps (NETs) and their microbicidal molecules are strategies exploited by neutrophils to kill *T. gondii*

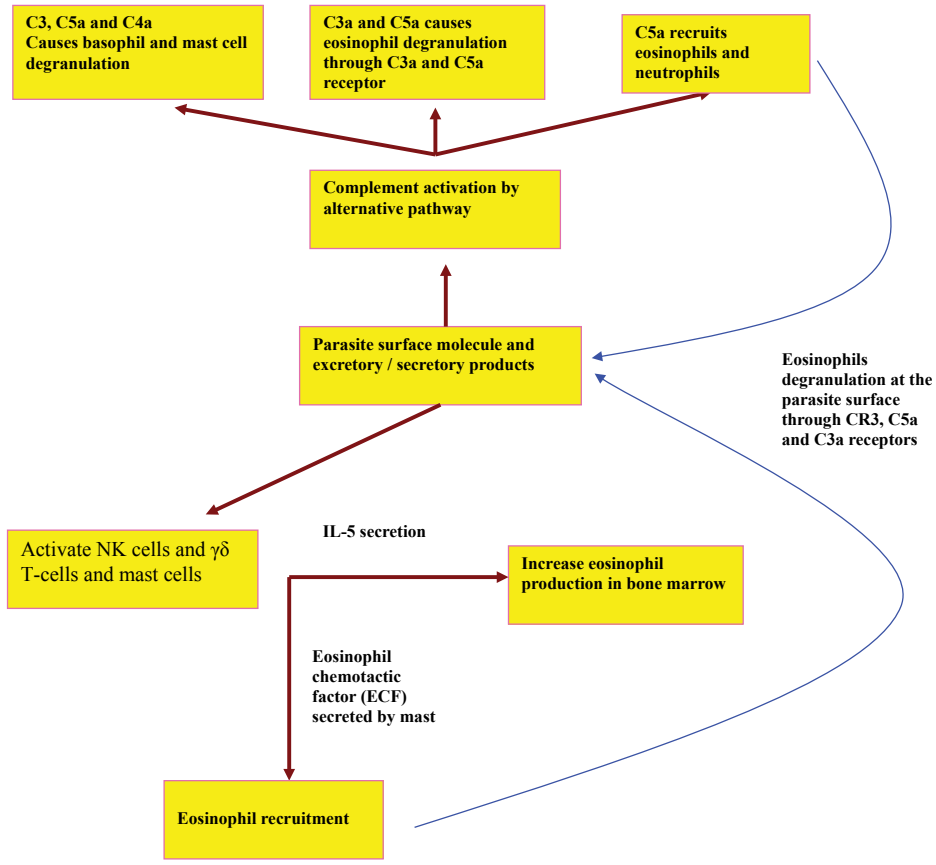

Figure 2: Different mechanisms involved in eosinophil production, recruitment, and degranulation at the parasite surface in aberrant host [11,156,162-164].

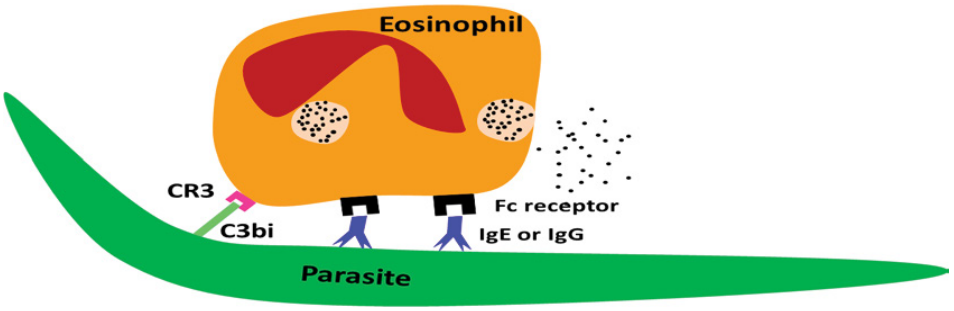

Figure 3: High avidity binding between the eosinophil and the parasite leads to parasite death after eosinophil degranulation.

tachyzoites and *L. donovani* and *Leishmania amazonensis* promastigotes [166-168].

Myeloperoxidase is a heme protein synthesized during myeloid differentiation and most abundantly expressed in neutrophils and to a lesser extent activated macrophages during the primary immune response. It has a considerable impact on larval killing, such as *S. stercoralis*. Neutrophils, macrophages and complement also killed the adult worms [96,169-172]. Importantly, NETs as well play a role in the control of the extracellular parasite, for example, *S. stercoralis* [172].

Cercarial dermatitis (swimmer's itch/hunter's itch) as an example of linking innate and acquired immunity

Three genera of non-human schistosomes (cattle, rodent and avian schistosomes) can cause cercaial dermatitis namely, *Ornithobilharzia, Gigatobilherzia and Trichobilharzi* [173]. *Trichobilharzia* can be categorized into visceral and nasal species according to the migratory route [174]. *Trichobilharzia regenti* is a neurotropic metazoan parasite (nasal species) that infects the avian host. Following skin penetration, the cercariae undergo transformation to schistosomula. The secretion of cathepsin B-like cysteine peptidases by schistosomula results in myelin basic protein degradation. The immature stage migrates through the nervous tissue of the brain. Adult stage resides in the nasal tissue of the duck in- and out-sides of the blood vessels. Cercarial dermatitis represents an allergic reaction (type I hypersensitivity reaction/ an immediate hypersensitivity) during cercarial penetration in the primed or unprimed incompatible animal host. Moreover, the late phase inflammatory reaction is due to the persistence of dead cercariae in the skin. In immunologically naïve animal, histamine is released from mast cells in IgE independent manner, and cause vascular permeability, and oedema after cercarial penetration. However, in immunologically primed animal, histamine and IL-4 secretions are elevated in IgE-dependent way from mast cell (i.e. through tertiary event). Additionally, the late phase response is due to leukocytes and $CD4^+$ T cell recruitment to the site of penetration. Dendritic cells and monocytes have H2 receptor (H2R) for histamine binding leading to IL-12 release inhibition and IL-10 enhancement. This can be bias the immune response toward Th2, IgG1 and IgE class switching [175].

Concluding remarks and perspectives

This review provides an overview of the host-oriented inherent measures and eukaryotic parasite countermeasures, and the foundation of the molecular pathways of these interactions. A reasonable approach to exploit this information could be to discover new therapeutic and prophylactic intervention points for broad-spectrum host –oriented measures and parasite counter- measures, and to determine the infection outcome.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This research was supported by the National Key Basic Research Program (973) of China (2015CB150300), the Special Fund for Agro-scientific Research in the Public Interest (201303042), and the Open Project of the State Key Laboratory of Veterinary Etiological Biology (SKLVEB2011KFKT001).

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