Parasitology

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Abbreviations: BA: biogenic amine, BBB: blood–brain barrier, BCSFB: blood–cerebrospinal fluid barrier, CSF: cerebrospinal fluid, CSFB: cerebrospinal fluid barrier, CNS: central nervous system, CM: cerebral malaria, DHEA: dehydroepiandrosterone, DA: dopamine, DC: dendritic Cell, EFG: epidermal growth factor, ELAM-1: endothelial-leucocyte adhesion molecule 1, FSH: follicle stimulating hormone, Fizz-1: found in inflammatory zone-1, GABA: gamma-aminobutyric acid, GAPDH: glyceraldehyde-3-phosphate dehydrogenase, GST: glutathione S-transferase, HO-1: haeme oxygenase 1, HRPE: human retinal pigment epithelial, ICAM-1: intercellular adhesion molecule 1, IFN: interferon, IL: interleukin, IP-10: IFN-γ-inducible protein 10, IPSE: interleukin-4-inducing principle from *Schistosoma mansoni* eggs, LDL: low-density lipoprotein, LT-α: lymphotoxin-alpha, MHC: major histocompatibility complex, MMP: matrix metalloproteinases, NC: neurocysticercosis, NK: natural killer, NO: nitric oxide, PAF: platelet-activating factor, PGD: prostaglandin, RBC: red blood cell, TGFβ: transforming growth factor-beta, TLR: toll-like receptor, TNF: tumour necrosis factor, Tregs: T regulatory cells, VCAM-1: vascular cell adhesion protein 1, VWF: Von Willebrand factor, CDA-1: (Human) cell division autoantigen-1.

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Understanding host–parasite relationship: the immune central nervous system microenvironment and its effect on brain infections

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Abstract

The central nervous system (CNS) has been recognized as an immunologically specialized microenvironment, where immune surveillance takes a distinctive character, and where delicate neuronal networks are sustained by anti-inflammatory factors that maintain local homeostasis. However, when a foreign agent such as a parasite establishes in the CNS, a set of immune defences is mounted and several immune molecules are released to promote an array of responses, which ultimately would control the infection and associated damage. Instead, a host–parasite relationship is established, in the context of which a close biochemical coevolution and communication at all organization levels between two complex organisms have developed. The ability of the parasite to establish in its host is associated with several evasion mechanisms to the immune response and its capacity for exploiting host-derived molecules. In this context, the CNS is deeply involved in modulating immune functions, either protective or pathogenic, and possibly in parasitic activity as well, *via* interactions with evolutionarily conserved molecules such as growth factors, neuropeptides and hormones. This review presents available evidence on some examples of CNS parasitic infections inducing different morbi-mortality grades in low- or middle-income countries, to illustrate how the CNS microenvironment affect pathogen establishment, growth, survival and reproduction in immunocompetent hosts. A better understanding of the influence of the CNS microenvironment on neuroinfections may provide relevant insights into the mechanisms underlying these pathologies.

Introduction

Several pathogens are capable of entering the human central nervous system (CNS). Particularly in resource-limited settings, protozoan and helminth parasites can infiltrate the CNS and/or other organs or tissues. Pathogens taking the CNS as its primary target of infection (i.e. exhibit neurotropism) require a successful dissemination from an entry point (respiratory or intestinal) to the CNS, either crossing or disrupting the blood–brain barrier (BBB) or the blood–cerebrospinal fluid barrier (BCSFB), evading both peripheral and CNS immune system responses. The mechanical barriers in the CNS (BBB and BCSFB) are characterized by a selective permeability to macromolecules and hydrophilic molecules. These properties are due to tight junctions, which are prominent in the BBB. Parasites crossing these barriers are contended by the local immune response.

A trophic or coevolution relationship between pathogens and hosts is very plausible. Extensive studies on various parasite species, along with recent data on parasitic genome/transcriptome and proteome, have singled out molecules and strategies that parasites developed to deal with the CNS specialized immune response (Perry, 2014). While complex, the host–parasite relationship seems to be prone to a 'fine-tuned balance' (because of its low metabolic and proliferative activity) that permit 'transient silent' neurological symptoms after the initial invasion, then leading to a chronic infectious process, a fragile quasi-commensal relationship (Adamo, 2013) that ultimately can translate into significant morbidity and mortality.

Host factors such as hormones, neuropeptides, cytokines and chemokines may be significant parasite exploitation targets since they can be used to favour parasite growth. In this review, we will compile available evidence highlighting how four parasites (protozoan and helminths) can exploit components of the CNS microenvironment to establish, survive and/or growth therein.

Although parasitic agents such as Amoebozoa (*Acanthamoeba* spp., *Balamuthia* spp., *Entamoeba histolytica*, etc.), fungi (*Blastomyces dermatitidis*, *Coccidioides* spp., *Cryptococcus* spp., etc.), worms (*Angiostrongylus cantonensis*, *Lagochilascaris minor*, *Strongyloides stercoralis*, *Toxocara* spp.) and flagellates (*Trypanosoma* spp.) can effectively infiltrate and infect the CNS, we will focus on four key parasitic agents (*Toxoplasma gondii*, *Taenia solium*, *Plasmodium falciparum* and *Schistosoma* spp.) that are known to attack CNS and cause

high worldwide morbidity and mortality (John *et al.* 2015) to illustrate this complex host–parasite relationship.

Life cycle

Toxoplasma gondii

Toxoplasma gondii (phylum Apicomplexan) is an obligate intracellular parasite, infecting over one-third of the world population. The parasite life cycle is complex, consisting of two stages, the sexual one, which occurs in felines (the definite host), and the asexual one, which can befall in any homeotherm animal (the intermediate host). Felines become infected by ingesting meat containing oocysts; in most cases, the infection is asymptomatic. After 7–15 days, felines release oocysts in feces.

Humans and other intermediate hosts become infected by ingesting oocysts (containing infective sporozoites). Parasites invade the gastrointestinal epithelium and differentiate into tachyzoites. The sustained tachyzoite replication and dissemination through blood or lymphatic stream to muscles, heart, brain, retina, testes and other organs lead to tissue damage and the lysis of infected cells (through endodyogeny), which correlates with the acute phase of the infection. In the presence of a vigorous cell-mediated immunity, parasite replication is contained and tachyzoites turn into bradyzoites within parasitic vacuoles (dormant intracellular cysts) (Mercier and Cesbron-Delauw, 2015).

Taenia solium

Taenia solium is a platyhelminth whose life cycle requires two hosts. The adult tapeworm lives in the small intestine of humans (definite host); there, gravid proglottids and infective eggs are released with feces into the environment. Several mammals, but particularly pigs (intermediate host) become infected by ingesting *T. solium* eggs. Eggs hatch in the intestinal tract to release oncospheres, which traverse the intestinal wall and disseminate through the bloodstream to several tissues (muscle, heart, brain and retina). In those tissues, oncospheres evolve into metacestodes (cysticerci), which cause neurocysticercosis (Del Brutto, 2014).

Plasmodium falciparum

Plasmodium life cycle starts when an anopheles mosquito bites a vertebrate host and inoculates sporozoites. Parasites disseminate through the bloodstream and reach the liver (asexual cycle) were they actively replicate (schizonts).

When hepatocytes are lysed, merozoites are released from the schizont into the bloodstream. In each replication cycle, a few amount of asexual parasites progress to sexual stages (female or male gametocytes). The sexual stage is the only form transmitted to the mosquito vector. The next target are red blood cells (RBC), in which several stages occur (ring trophozoites and new merozoites), completing the erythrocytic cycle. The destruction of RBC is associated with febrile peaks (Meibalan and Marti, 2017).

Schistosoma *spp.*

Schistosoma spp. are digenetic blood trematodes, causative agents of schistosomiasis. The main species infecting humans are *Schistosoma haematobium*, *S. japonicum* and *S. mansoni*. *Schistosoma* life cycle begins when eggs are released with feces or urine, and less frequently with sputum by the human infected host (definitive host). In water, miracidia are released from hatched eggs. In this environment, miracidia penetrate a specific kind of snail (first intermediate host) were they turn into sporocysts (successive generations) and migrate to hepatic and pancreatic tissues in the snail, producing cercariae.

Most cercariae die within the first 24 h, but some of them are released from the snail and either penetrate the human skin, evolving into schistosomula, or adopting a cyst form (metacercariae) to infect a second intermediate host (crustacean or mammals that eat contaminated aquatic vegetation). Schistosomula migrate to several tissues and finally located in the veins. The specific venule location seems to depend on species: *S. japonicum* is frequently found in the superior mesenteric (drains in the small intestine), *S. mansoni* in the inferior mesenteric and hemorrhoidal plexus (drains in the large intestine), while *S. haematobium* is frequently lodged at the venous plexus of the bladder and rectal venules. Female worms deposit fertilized eggs in the small venules of the portal and perivesical system. *Schistosoma mansoni* and *S. japonicum* eggs can move to the intestine lumen, while *S. haematobium* eggs move into the bladder and ureters. Finally, they are released in feces or urine (Colley *et al.* 2014).

How do parasites reach the CNS?

To enter the CNS, parasites must evade the host immune response. The bloodstream (which is used as a vehicle by both extracellular and intracellular parasites) plays an important role in parasite dissemination. Then, parasites need to cross the mechanical barriers (BBB or BCSFB) (Kristensson *et al.* 2013) that protect the CNS.

The CNS is a highly specialized microenvironment, often considered as an immune-privileged site due to brain topography [widely reviewed and discussed by (Ousman and Kubes, 2012; Ransohoff and Engelhardt, 2012)]. It is noteworthy that blood vessels in the leptomeninges are more permeable than those in the brain parenchyma; nevertheless, there exist regions lacking such barriers (choroid plexus, brain circumventricular organs and peripheral nerve root ganglia). Additionally, the immune response in the meninges is stronger than that in the brain parenchyma (Galea *et al.* 2007).

Parasites profit these characteristics of host CNS in their invasion strategies. Apicomplexan parasites, *Toxoplasma* spp. and *Plasmodium* spp., possess particular mechanisms.

During active or acute infection by *Toxoplasma*, tachyzoites and sporozoites attach and invade host cells. Tachyzoites exhibit a high metabolic rate and a tremendous demand for nutrients. Tachyzoites live intracellularly in parasitophorous vacuoles, which are particularly resistant to lysosome fusion, avoiding parasite degradation in monocytes, spreading by the bloodstream and gaining access to tissues through infected monocytes (Trojan horse mechanism); additionally, tachyzoites may directly breach intercellular junctions and transmigrate between endothelial cells (transcytosis) after egressing from infected leucocytes (Barragan and Sibley, 2003; Tardieux and Ménard, 2008; Lambert and Barragan, 2010; Gregg *et al.* 2013). The actin-myosin machinery takes part in this invasive process, following the expulsion of microneme and rhoptry proteins from the apical complex. *Toxoplasma gondii* can invade any nucleated host cell. After invading neurons, its replication drops markedly, but bradyzoites persist in a 'quiescent state' during the host lifespan.

In the case of *Plasmodium*, although the entry mechanism is not fully understood, the parasite is able to modify host erythrocytes. When carried into red cells, mature parasites express proteins to attach endothelial cells of brain vessels, inducing erythrocyte sequestration. In fact, while infected erythrocytes may not enter brain tissue, uninfected erythrocytes can spontaneously bind them, forming a rosette and leading to blood flow obstruction, hypo-perfusion and hypo-oxygenation; in turn, these may contribute to BBB breakdown and vascular leakage (Ueno and Lodoen, 2015; Pal *et al.* 2016). The parasites use both mechanisms to evade splenic clearance and obtain nutrients from the host.

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For neurocysticercosis, once the eggs hatch in the small intestine of infected humans, the hooked oncospheres into the gut are released. Thereafter, oncospheres penetrate the epithelium of the intestine and migrate to various tissues, including CNS through BBB (through a not fully understood mechanism). However, in a murine model, BBB disruption was a consequence of the inflammatory response to parasites (Alvarez and Teale, 2007). It has also been suggested the oncospheres can penetrate the brain through those regions lacking the BBB. At the CNS, oncospheres can locate and transform into the larvae stage or cysticerci, in brain parenchyma, in the subarachnoid space, or in the ventricles, the last two being the ones that most compromise human health.

For *Schistosoma*, schistosomula enter the vascular system after infiltrating the skin; then, they can spread to lung or mesenteric vessels. Eggs can reach the CNS by embolization through the Batson's plexus. Several proteins surrounding the parasite induce granuloma formation and necrosis in the vascular walls (Scrimgeour and Gajdusek, 1985).

Experimental and human immunopathology

Toxoplasma gondii *infection*

In the CNS, *T. gondii* infection may lead to severe complications, especially in immunosuppressed patients. The disease is becoming a global health issue since 30–50% of human population is infected (Flegr *et al.* 2014).

Parasites reach the immunologically protected CNS through a 'Trojan horse mechanism,' entering monocytic cells, dendritic cells (DCs) and neutrophils (Flegr *et al.* 2014). Macrophages, natural killer (NK) cells and lymphocytes have also been observed to carry tachyzoites into the CNS (Persson *et al.* 2009; Lambert and Barragan, 2010; Unno *et al.* 2010; Lachenmaier *et al.* 2011; Lambert *et al.* 2011; John *et al.* 2015). Once inside the CNS, parasites disperse and can invade astrocytes, microglia and neurons, forming cysts and establishing a latent infection in immunocompetent hosts. A combination of several pathways may be utilized.

Brain infection: experimental studies. Transmigration of infected leucocytes across the BBB and cerebrospinal fluid barrier (CSFB) has been shown to be due to a regulation of cell migratory properties by *Toxoplasma* and may account by both the paracellular or transcellular pathways (Trojan horse) to traverse the epithelial layer or penetrate immune cells (particularly monocytes), An upregulation in the expression of adhesion molecules, particularly intercellular adhesion molecule 1 (ICAM-1), which interacts with parasite adhesin MIC2 (Barragan *et al.* 2005), may also be involved. For instance, infected monocytic cells upregulate CD44 and ICAM-1 expression to adhere and extravasate cells (Unno *et al.* 2010).

It has been observed that both human and murine DCs infected by *Toxoplasma* tachyzoites exhibit a dramatic change in their phenotype; in fact, they become 'hypermigratory' cells characterized by rapid cytoskeletal changes (Lambert *et al.* 2011). The requirement of a live tachyzoite for these changes (Lambert and Barragan, 2010) may indicate a tightly regulated control of this hypermotility that has being proposed to be promoted by the expression of functional $GABA_A$ receptors and gamma-aminobutyric acid (GABA) secretion (Fuks *et al.* 2012). GABAergic signalling seems to modulate parasite dissemination; in fact, pre-treatment of infected DCs with GABAergic inhibitors (a mouse model of toxoplasmosis) reduced parasite dissemination (Fuks *et al.* 2012).

Other observed phenotypic CD changes are a redistribution of the CD11c and CD18 integrins (Weidner *et al.* 2013) and selective chemotaxis given by an upregulation of CCR7 expression and the regulation of CCR5 (Fuks *et al.* 2012; Weidner *et al.* 2013); parasitized neutrophils and lymphocytes expressing CD11b can be found in the brain, although the amount of these cells seems to be very small, being DCs the largest population of CD11b + cells in the CNS (Courret *et al.* 2006).

Also in infected macrophages phenotypic changes have being observed, i.e. they exhibit an increased expression of MT1-MMP and ADAM10 matrix metalloproteinases (MMPs), as well as the $\alpha v\beta 3$ integrin (Seipel *et al.* 2010); additionally, the secretion of a multi-protein complex containing MMP9 suggests its possible cleavage to the CD44 integrin (Schuindt *et al.* 2012). All these changes of infected macrophages may help in their brain migration, nevertheless, further reports regarding the interaction of macrophages, MMPs and integrins expressed in brain endothelial cells during toxoplasmosis are needed.

NK cells have been proposed also as parasite reservoirs since they lack intracellular killing pathways and especially, considering that mature CD11b + high NK cells can cross brain barriers to performing CNS immunosurveillance. Thus, infected NK cells have been proposed to reach the CNS and disseminate the parasite *in situ* (Persson *et al.* 2009; Ransohoff and Engelhardt, 2012). A recent report demonstrated that CD11b + leucocytes, either expressing CD11c or not, participate in *T. gondii* intracellular transport through the BBB (Lachenmaier *et al.* 2011).

During CNS invasion, tachyzoites invade astrocytes, microglial cells and neurons, forming cysts. Parasite-release mechanisms are not known, but it is likely that the inflammatory response against the infection promotes the lysing of infected cells, and thus tachyzoite spread. Parasites are dispersed throughout the brain, but they locate especially in the cerebral cortex, hippocampus, basal ganglia and amygdala (Melzer *et al.* 2010). Astrocytes and microglia become parasitized, although protection mechanisms help minimize parasite load; particularly interferon (IFN)γ, alone or in combination with TNFα, interleukin (IL)1 and IL6, inhibits *T. gondii* replication. This mechanism does not seem to be mediated by nitric oxide production (Halonen *et al.* 1998).

Brain infection: human studies. *Toxoplasma* is able to form cysts in CNS target cells (astrocytes and microglial cells). As shown in a microarray analysis of fibroblasts infected by the type-II strain, a significant change in the abundance of transcripts, particularly those associated with the immune response, were observed in 1% of the genome within the first 2 h (Blader *et al.* 2001). These findings suggest that host cells activate some kind of 'alarm signal' even before CNS invasion. In another similar study on human fibroblasts, an autoantigen [human cell division autoantigen-1 (CDA-1)] was found to be crucial for bradyzoite development, since its overexpression in CDA1 slowed parasite growth (Radke *et al.* 2006).

Copious evidence links human infection by *Toxoplasma* with an increased incidence of schizophrenia (Cetinkaya *et al.* 2007; Dickerson *et al.* 2007; Hinze-Selch *et al.* 2007; Mortensen *et al.* 2007; Lindgren *et al.* 2017) and neurodegenerative diseases (Coccaro *et al.* 2016). In fact, increased anti-*T.gondii* IgG antibody levels have been reported in patients with first-onset schizophrenia (Wang *et al.* 2006; Torrey *et al.* 2007) and with behavioural changes (aggression/impulsivity traits) in chronically infected subjects (Flegr *et al.* 1996, 2003; Havlícek *et al.* 2001). More recently, susceptibility genes for congenital toxoplasmosis were identified in a cohort of infected children, being all target genes expressed in the brain; effects of the infection on neurodevelopment and on plasticity of the neural, immune and endocrine networks have also been described, identifying associations between parasite–brain interactions and epilepsy, movement disorders, Alzheimer dementia and cancer (Ngô *et al.* 2017).

Factors involved in host infection. *Toxoplasma gondii* virulence seems to be associated with genetic factors, such as strain type

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(being type-II the most prevalent in immunosuppressed patients) and rhoptry type. Additionally, the parasite possesses two genes encoding for tyrosine hydroxylase (a rate-limiting molecule for dopamine synthesis). It has been demonstrated *in vivo* and *in vitro* that toxoplasma cysts inside neurons can express tyrosine hydroxylase and dopamine (DA); actually, DA release is increased in infected cells (Gregg *et al.* 2013). This important neurotransmitter interferes with locomotion, cognition, memory and mood, and may directly influence the host's behaviour (Lachenmaier *et al.* 2011). Interestingly, DA can also modulate the adaptive human immune response (Lambert and Barragan, 2010). Indeed, DA may regulate T cell activation and differentiation (Lambert *et al.* 2011), and T regulatory cells (Tregs) are able of synthesizing and storing DA (Persson *et al.* 2009).

On the other hand, it has been demonstrated that *T. gondii* influences the expression of the transforming growth factor beta (TGFβ), an important immune modulator. In fact, soluble *T. gondii* extract can upregulate TGFβ1 and TGFβ2 mRNA levels, favouring the secretion of both molecules in human retinal pigment epithelial (HRPE) cells. Similarly, TGFβ can affect HRPE, enhancing *T. gondii* replication (Nagineni *et al.* 2002; Unno *et al.* 2010). Despite these shreds of evidence, many questions remain unanswered. Other studies to evaluate how the key host cell–parasite relationship acts during *Toxoplasma* infection are needed to clarify the mechanisms of immune response evasion of this parasite.

Plasmodium falciparum infection

Cerebral malaria (CM) is a potentially life-threatening disease caused by the intracellular protozoon *P. falciparum*, which induces a severe and diffuse encephalopathy. About 212 million new cases were reported worldwide in 2015. The African region accounted for 90% of cases, followed by South-East Asia and Eastern Mediterranean regions (Malaria, 2017). CM due to sequestration of infected erythrocytes is characterized by a high mortality and post-recovery neurocognitive disorders in children, leading to metabolic disturbances, neuroinflammation and alterations in the human immune response (Wassmer *et al.* 2003). The specific mechanism of brain injury is poorly understood, but current evidence is compiled below.

Brain infection: experimental studies. Sequestration of the brain microvasculature by *Plasmodium* seems to be the main pathogenic factor, promoting several tissue changes in the parasite's vicinity. In the acute phase of infection, CM involves an increase in circulating levels of cytokines and chemokines such as IL1β, IL6, IL17 and TNFα (Wu *et al.* 2010; Keswani *et al.* 2016), associated with leucocyte accumulation and a breakdown of the BBB, as well as oxidative stress (NO), endothelial cell activation (expression of ICAM-1, VCAM-1, P-selectin and E-selectin) and endothelial cell apoptosis. Platelet binding to endothelial cells probably involves the tumour necrosis factor receptor superfamily member 5 (CD40), which is upregulated in brain endothelial cells after TNFα stimulation (Piguet *et al.* 2001).

It was recently demonstrated that the uptake of parasite-derived vesicles by astrocytes and microglia induce these cells to produce and release IFNγ, lL-12 and the inducible protein 10 (IP-10) (Shrivastava *et al.* 2017). In correlation to the proinflammatory response during CM, there is an anti-inflammatory response characterized by the presence of Tregs and immunomodulatory cytokines like TGFβ and IL10 (Wu *et al.* 2010; Keswani *et al.* 2016). In malaria-infected pregnant mice, parasitaemia was closely associated with increased IL17 levels and lower levels of IL10 and TGFβ. In malaria-infected BALB/c mice, increased TGFβ levels were associated with the resolution of infection (Omer *et al.* 2003). These observations suggest that the parasite induces immunological changes to favour its establishment.

Brain infection: human studies. In humans, *Plasmodium* infection has been demonstrated to alter brain endothelial cells and platelets, inducing the production of chemokines, cytokines and other signalling molecules. In fact, CM patients show a high proportion of platelet-filled vessels, which induce cytoadhesion of *Plasmodium*-infected erythrocytes to microvascular endothelial cells through the Platelet glycoprotein 4 (CD36) (Wassmer *et al.* 2003). In addition, sequestration of infected erythrocytes in the brain microvasculature also participates in BBB disruption. An interesting study in an *in vitro* CM model using microarray technology demonstrated that platelets alter the gene expression profile in human brain endothelial cells, favouring the expression of chemokines, cytokines and other signalling molecules that promote platelet adhesion to the brain microvasculature. In CM, platelet activation is induced by the platelet-activating factor (PAF), an inflammation mediator, which seems to orchestrate several inflammatory processes, including leucocyte recruitment and the increase of vascular permeability, all processes mediated by the PAF receptor. This receptor is also crucial for the cascade of events leading to changes in vascular permeability, T cell accumulation and activation in blood vessels, and apoptosis of leucocytes and endothelial cells. Besides PAF, adhesion molecules like ICAM-1, E-selectin, CXCR3, LT-α, ELAM-1 (endothelial-leucocyte adhesion molecule 1) and VCAM-1 are crucial in CM development, since they have been found in cerebral microvascular endothelial cells from patients who died from CM (Armah *et al.* 2005; Togbe *et al.* 2008; Almelli *et al.* 2014; Madkhali *et al.* 2014; Van Den Ham *et al.* 2015). Cytokines like TNFα may also be involved in pathology and ICAM-1 overexpression (Clark *et al.* 1989; Gimenez *et al.* 2003; Armah *et al.* 2005), as well as in leucocyte chemotaxis and activation through CCL18, CXCL10, CCL2 and CCL5 (Barbier *et al.* 2011).

On the other hand, several immune alterations accompany CM; the marked sequestration of parasitized erythrocytes results in endothelial activation of the capillary and post-capillary venules, reducing the vascular lumen and leading to mechanical obstruction. This process induces prostaglandin (PGD) synthesis; PGD2, the major brain prostanoid produced, is involved in the regulation of sleep and pain responses. *In vitro* studies in a human astrocyte cell line with PGD2 significantly increased the expression levels of haeme oxygenase 1 (HO-1) mRNA (Kuesap and Na-Bangchang, 2010). The expression of HO and TGFB2 genes in a paediatric population in Angola was related to specific risk factors for CM (Sambo *et al.* 2010). Higher TGFβ levels were also associated with severe/complicated malaria (Lourembam *et al.* 2013). These data suggest that CM modifies the expression of several host proteins, and these alterations may favour the parasite.

Factors involved in host infection. The balance between pro- and anti-inflammatory responses, as well as the specific pharmacologic treatment, determines the outcome of the disease and leads to parasite elimination or persistence in the CNS. Under these conditions, the parasite has developed mechanisms to persist within the host, taking advantage of its location by exploiting hormones and other host-produced molecules. As reported in various *in vitro* studies, hormones like cortisol, estradiol, progesterone and even insulin increase the number of gametocytes, while treatment with 16-α bromoepiandrosterone decreased division rates (Maswoswe *et al.* 1985; Lingnau *et al.* 1993). While no further *in vitro* observations have been reported, pregnant infected women showed higher cortisol levels (Vleugels *et al.* 1989; Bayoumi *et al.* 2009). Besides, uncomplicated malaria

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patients showed higher steroid [cortisol, dehydroepiandrosterone (DHEA)] levels correlating with parasitaemia in a Brazilian study (Libonati *et al.* 2006). These data suggest that the parasite can exploit host-produced hormones to survive.

In view of these findings, it seems that *Plasmodium* exploits host's immune, vascular, endocrine and nervous system to establish an effective infection. This complex interaction may require extensive use of massive genomic and transcriptomic platforms to be understood, aiming to design diagnosis, treatment and control strategies.

Taenia solium infection

In its larval stage, *T. solium* can infect pigs and humans and when parasite establishes in the CNS causes neurocysticercosis (NC). The mechanisms that mediate cysticercus establishment in the CNS are not well known. It has been proposed that *T. solium* oncospheres enter the CNS and may establish in different locations (Sciutto *et al.* 2000). In this regard, it should be noted that in India cysticerci establish predominantly in skeletal muscle, while neurocysticercosis is more prevalent in Latin America (Sciutto *et al.* 2000; White, 2000). It is evident that cysticerci exhibit different tissue tropism in America than in Asia or Africa. The evidence also suggests that the parasite can take advantage of the CNS local immune response, and probably drive host sexual hormones to promote its own growth and survival.

Brain infection: experimental studies. A model of neurocysticercosis in rodents uses *Mesocestides corti* as the challenge agent instead of *T. solium*. In spite of its limitations, this model allowed researchers to describe some of the main mechanisms of CNS infection. *M. corti* metacestodes are intracranially injected. Initially, metacestodes are found in the leptomeningeal space, and then they bind and traverse the arachnoid–pia complex to penetrate the parenchyma. The number of immune cells infiltrating the CNS and surrounding the parasites in the first weeks after infection is low, considering the size of the parasite. It has been demonstrated that the parasite exhibits structural changes in surface molecules to evade the immune response. In addition, asymptomatic individuals show viable encysted parasites with little or no evidence of surrounding inflammation; early granulomas also show little inflammatory infiltrate. With respect to the immune response, a Th1 (IL2, IL12, IFNγ and TNFα) is initially observed, later switched to a Th2 response (IL4 and -10). Infection by *T. solium* downregulates APC maturation and the expression of MHC-II in infiltrating myeloid cells; furthermore, infiltrating macrophages express markers associated with an alternatively activated phenotype [Fizz-1 (found in inflammatory zone-1) and Arginase-1] (Alvarez *et al.* 2010).

In addition, an experimental encephalitis model of in mice using brain inoculation of *Taenia crassiceps* cysticerci has been reported. This work demonstrated that susceptible BALB/c mice show severe neuroinflammation, characterized by infiltration of polymorphonuclear cells associated to oedema, perivasculitis, and meningitis, in clear contrast with non-susceptible C57BL/6 mice. In BALB/c mice, polymorphonuclear cells predominated in the inflammatory cell infiltrate, while mononuclear cells predominated in C57BL/6 mice. These findings point out marked differences in the immune response according to susceptibility in mouse strains (Matos-Silva *et al.* 2012).

Histopathological findings in a *T. solium* neurocysticercosis model in rats showed inflammatory infiltrates surrounding the cysts. These infiltrates were composed of eosinophils, neutrophils, macrophages, microglia, plasmocytes and lymphocytes. In the case of ventricular cysts, infiltrate was less abundant than that surrounding parenchymal ones. These findings suggest that cysticerci location is determinant in the host–parasite relationship, strongly influencing the immune response (Verastegui *et al.* 2015).

With respect to other neurocysticercosis models [extensively reviewed by (Arora *et al.* 2017)], induced infection in pigs seems to be the most natural model. Immunopathological studies in infected pigs reported astrogliosis, neuronal degeneration and altered BBB permeability. BBB disruption allowed an influx of peripheral blood immune cells like eosinophils, macrophages, CD3 + T cells, B lymphocytes and plasma cells into the lesion (Sikasunge *et al.* 2009). In pigs, the granulomatous reaction is characterized by an abundance of eosinophils, the relative paucity of plasma cells, the presence of lymphocytes and macrophages, and a discrete deposition of collagen (Alvarez *et al.* 2002). With respect to the host–parasite relationship, it is likely that cysticerci controlled the immune response to survive during infection. Furthermore, other studies have demonstrated an exacerbated immune response after anti-parasite treatment (Guerra-Giraldez *et al.* 2013; Mahanty *et al.* 2015; Cangalaya *et al.* 2016).

Brain infection: human studies. The human immune response against cysticerci is closely associated with the parasite stage and location. When cysticerci lodge in the subarachnoid space of the base or in the ventricles (extra-parenchymal location) they induce a severe clinical picture (hydrocephalus, intracranial hypertension and/or vasculitis) and the patient exhibits increased cerebrospinal fluid (CSF) IL5, IL6 and IL10 levels. In contrast, lower inflammatory cytokine levels are observed when cysticerci lodge in the subarachnoid sulci or in the parenchyma (Chavarría *et al.* 2005). Additionally, parenchymal parasites are frequently damaged, with low CSF inflammation and mild or moderate clinical symptomatology (Chavarría *et al.* 2005).

Cysticerci can be found in three main stages: (a) vesicular, when they are viable; (b) colloidal, partially damaged cysticerci; and (c) calcified when they are dead. Vesicular extraparenchymal parasites are associated with a strong inflammatory response (Chavarría *et al.* 2005), with increased CSF L1β, IL5, IL6 and IL10 levels (Sáenz *et al.* 2012). Additionally, vesicular parasites are associated with the presence of regulatory T cells in CSF (Adalid-Peralta *et al.* 2012), probably induced by excretion/secretion parasite products (Adalid-Peralta *et al.* 2013). The parasite entices a low inflammatory response by releasing immunomodulatory factors that induce alternatively activated monocytes. These macrophages could also mediate neuroinflammation control (Gundra *et al.* 2011). A plausible hypothesis is that during NC, viable parasites drive the immune system to a suppressive environment that favoured their survival, evading the host immune response (Vignali *et al.* 2008; Arce-Sillas *et al.* 2016). *In vitro* studies have shown that, in the presence of cysticerci, monocyte-derived dendritic cells acquire a tolerogenic phenotype, promoting Treg proliferation (Adalid-Peralta *et al.* 2013). NC patients exhibit higher levels of IL10, a Treg-secreted immunomodulatory cytokine (Arce-Sillas *et al.* 2016).

Factors involved in host infection. *Taenia solium* and *T. crassiceps* cysticerci can modulate the host immunoendocrine system to favour their own survival (Table 1). Sexual dimorphism has been reported in a mouse model of *T. crassiceps* infection, being female mice more permissive to parasite growth than males (Larralde *et al.* 1989). In concordance, gonadectomy equalizes parasite susceptibility between sexes (Huerta *et al.* 1992). In addition, 17β-estradiol administration increases parasite numbers in infected males (Terrazas *et al.* 1994). Most interestingly, cysticercosis lead to feminization of male hosts, since the parasite increases oestrogen synthesis (200 times the normal values) and reduces testosterone production (90%) (Larralde *et al.* 1995).

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Table 1. Parasite products that modulate the host immune–endocrine system.

Parasite	Biological components	Effect on the host–parasite interactions	Commentary	References
Taenia solium	Human			
	Secretion and excretion products	Induce regulatory T cells (Tregs)	Cysticerci drive dendritic cells to induce Tregs to evade immune response	Adalid-Peralta *et al.* (2012, 2013)
	Cysts	Reduce dehydroepiandrosterone (DHEA) levels. Reduce testosterone levels	Cysts may modify host hormone levels	Cárdenas *et al.* (2012)
	Animal models			
	TGF*β*-like receptor	Probably binds host TGF*β*	Cysticerci seem to use host TGFβ to promote their growth and survival	Adalid-Peralta *et al.* (2017)
	Cysts	Lead to the feminization of male hosts	The parasite modulates the host immunoendocrine system to favour parasite survival	Morales *et al.* (2002), Peña *et al.* (2007)
Plasmodium spp.	Human			
	Parasitaemia	Induces TGF*β* release and activation	Parasites promote an immunosuppressive microenvironment	Omer *et al.* (2003)
	Parasitaemia	Higher steroid (cortisol, dehydroepiandrosterone) levels	Modulates host endocrine molecules	Omer *et al.* (2003)
	Parasitized erythrocytes	Induce prostaglandin (PGD) secretion. Increase haeme oxygenase and TGFB2 expression	Probably favours parasitaemia	Kuesap and Na-Bangchang (2010), Sambo *et al.* (2010)
	Animal model			
	Parasitaemia	Induces endothelial activation and chemokine expression. ICAM-1, VCAM-1, P-selectin, and E-selectin	Promotes attachment of infected erythrocytes to endothelial cells of brain vessels	El-Assaad *et al.* (2013)
	Parasite vesicles	Dynamic transfer of vesicles from the parasite to astrocytes and microglia	Drive neuroinflammation	Shrivastava *et al.* (2017)
Toxoplasma gondii	Human			
	Cyst, genes encoding for tyrosine hydroxylase	Increase DA release in infected cells. DA interferes with locomotion, cognition, memory, mood, and may directly influence the host's behaviour	*Toxoplasma gondii* exerts a direct effect on neuronal functions; it also induces activation of glial cells, particularly astrocytes, which could be associated with schizophrenia and other neurological diseases	Basu and Dasgupta (2000), Cosentino *et al.* (2007), Golcu *et al.* (2014), Pacheco *et al.* (2009), Prandovszky *et al.* (2011)
	Toxoplasma extract	Induces *in vitro* secretion of TGFβ1 and TGFβ2 in human retinal pigment epithelial cells	May enhance *T. gondii* replication in the host	Nagineni *et al.* (2002)
	Animal model			
	Tachyzoites	Infect several cells (dendritic cells, astrocytes, and neurons). In dendritic cells, it promotes a 'hypermigratory' phenotype	Promotes parasite dissemination	Lambert and Barragan (2010), Lambert *et al.* (2011)
	Parasitaemia	Modify monocyte adhesion and transvasation	The Trojan horse mechanism of infection promotes parasite dissemination	Barragan *et al.* (2005)
Schistosoma spp.	Human			
	Parasitaemia (granulomatous mass)	Induces a strong Th2 response, with high IL4, IL5, IL6, CCL3 and IL13 levels	Favours parasite persistence	Ferrari *et al.* (2008), Rezende *et al.* (1993)
	Biogenic amines synthetized by the flatworm	Control parasite muscle contraction and movement	Favours parasite establishment and regulates metabolic activity.	El-Shehabi and Ribeiro (2010), Hamdan and Ribeiro (1999), Nishimura *et al.* (2007), Pax *et al.*

(*Continued*)

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Table 1. (*Continued.*)

Parasite	Biological components	Effect on the host–parasite interactions	Commentary	References
			Favours miracidium transformation into sporocyst	(1984), Ribeiro *et al.* (2005), Taft *et al.* (2010), Taman and Ribeiro (2009)
	Animal models			
	TGFβ receptor, epidermal growth factor (EFG) receptor, and insulin receptor (in adult parasites)	Favour parasite development and survival into the host	These receptors may induce immunomodulatory molecules in the tegument of the adult parasite, which favours immune evasion	Dissous *et al.* (2006), Shi and Massagué (2003), Wilson (2012)
	Egg shell antigens (*S. japonicum*)	*In vivo* and *In vitro* Treg induction	Promotes immune suppression in the host	Sun *et al.* (2012), Zhou *et al.* (2015)

Several reports on *T. solium* infections have described endocrine alterations in pig hosts (Morales *et al.* 2002; Peña *et al.* 2007). A significant reduction in testosterone levels was found in NC pigs with respect to healthy animals, with no differences in other hormones (Peña *et al.* 2007). Previously, it was reported that castration and pregnancy increased cysticercosis prevalence and parasite load in rural pigs (Morales *et al.* 2002). While these observations show a marked endocrine modification in the host, several *in vitro* studies have reported that *T. solium* is able to process progesterone and other corticosteroids and sex steroids as metabolites (Valdez *et al.* 2014). Progesterone is also important for inducing scolex evagination, possibly by binding a specific receptor (Escobedo *et al.* 2010). On the other hand, it has been reported that human neurocysticercosis triggers changes in the endocrine status; patients showed lower DHEA levels, as well as lower 17β-estradiol and testosterone levels, particularly in males. All patients with clinically severe presentation (hydrocephalus and subarachnoid parasites) had lower progesterone and androstenedione levels, particularly females. Significant correlations between estradiol and IL10 in males and between DHEA and IL1β and androstenedione and IL17 in females were also observed. These findings are relevant to human pathology not only because human brain cells are able to produce progesterone and other neurosteroids, but also because these hormones can exert immunomodulatory effects (Tan *et al.* 2015) which would favour parasite development and persistence.

Additionally, TGFβ, another Treg-produced cytokine, is augmented in patients unresponsive to cysticidal treatment, suggesting it could play a role in parasite persistence (Adalid-Peralta *et al.* 2017). Considering that both *T. solium* and *T. crassiceps* cysticerci express a TGFβ-like receptor that probably binds TGFβ, it its feasible that through this strategy the parasite may modulate its own physiological processes, favouring growth and survival, as it has been observed (Adalid-Peralta *et al.* 2017).

Schistosoma spp. infection

About 218 million people required preventive treatment for schistosomiasis, and 66·5 million were treated for the infection in 2015; over 90% of human cases are caused by *S. mansoni* (schistosomiasis, 2017).

Besides mesenteric veins, worm pairs can reside in ectopic sites, being CNS the most severe location. Both the brain and the spinal cord can be affected (Ross *et al.* 2012). *Schistosoma japonica*, *S. haematobium* and *S. mansoni* have been reported as the most frequent species infecting the brain, causing neuroschistosomiasis (Ferrari and Moreira, 2011).

Schistosoma eggs can get trapped in the spinal cord, brain, cerebellum, leptomeninges and choroid plexus, either from *in situ* deposition after aberrant adult worm migration to sites close to the CNS or by blood-mediated dissemination (Ferrari and Moreira, 2011). Eggs are complex structures, able to secrete immunogenic substances that elicit a strong inflammatory response, resulting in the granuloma, fibrosis and a destructive disease, seriously compromising the CNS integrity.

Brain infection: experimental models. Both parasite stages (adult and egg) can establish particular host–parasite relationships. It is well known that adult worms express tegumental receptors to several host-derived growth factors, exploiting them for their own development. Indeed, growth factor receptors and signalling pathways for the TGFβ family, epidermal growth factor (EFG) and insulin were conserved among several helminth parasites, including *Schistosoma* spp. Each of these receptors and signalling pathways controls several processes in cellular and organismic function [revised in (Livneh *et al.* 1985; Rajaram *et al.* 1997; Shi and Massagué, 2003)]. Their expression in *Schistosoma* spp. favors the parasite development and survival into the host [thoroughly reviewed and discussed by Dissous (Dissous *et al.* 2006). However, the relevance of such host-derived molecules in neuroschistosomiasis has not been demonstrated, being parasite eggs the major causative agents of the strong neuroinflammatory response. Nevertheless, adult worms that migrate to the CNS could exploit host-derived growth factors to modulate their metabolism and differentiation and survive for years in the brain. It is important to consider that several virulence factors and immunomodulatory molecules are released or tegument-expressed by adult mature worms or by eggs (Wilson, 2012); therefore, it is likely that a long permanence of worms or eggs in host tissues, including brain, may be due to its ability to evade the immune response, including the induction of Th2 cells (Fairfax *et al.* 2012); an increase in Treg levels is observed once the parasite has established and deposited eggs, causing the immune suppression that characterizes chronic schistosomiasis (Sun *et al.* 2012).

A wholly different scenario is the deposition of eggs in the CNS since eggs not only can induce strong inflammatory and cellular immune responses but also mechanically disrupt the spinal cord, causing neurological dysfunction.

Schistosoma eggs are particularly interesting, being mature structures that actively secrete proteins. Two major egg-secreted glycoproteins, IPSE/alpha-1 and Omega, are very immunogenic and strong inducers of IL4 production by basophils and therefore of the characteristic Th2 response (Schramm *et al.* 2007; Everts *et al.* 2009) that ultimately will be responsible for granuloma formation.

Brain infection: human studies. Neurological symptoms in neuroschistosomiasis, due to the cellular inflammatory response to

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Schistosoma eggs, range from a minimal inflammatory reaction (with no neurological manifestations) to a severe reaction resulting in a space-occupying granulomatous mass and nervous tissue necrosis. The granulomatous response is suspected to confer protection to eggs from the host immune response, by sequestering soluble egg antigens (Ferrari *et al.* 2008). It is well known that an early and transient Th1 immune response is established after egg deposition, switching to a strong and sustained Th2 specific response, characterized by high IL4, IL5, IL6, CCL3 and IL13 levels (Sousa-Pereira *et al.* 2006; Ferrari *et al.* 2008). Additionally, high IL10 levels are observed, which may protect the host from the detrimental inflammatory response in the brain. Immune complexes containing schistosomal antigens have been found in cerebral spinal fluid from patients; although the relevance of these immune complexes in the pathogenesis of the disease is still unknown, they could be involved in the genesis of the immune-mediated vascular lesions and/or in the down-modulation of granuloma formation (Rezende *et al.* 1993).

Factors involved in host infection. Several proteins are secreted by the larval stage (miracidium) within the eggshell. This latter structure has also an important interaction with the host immune response. The eggshell composition was recently elucidated by proteome analysis of free host-attached proteins from purified *Schistosoma* eggshells (Dewalick *et al.* 2014). Approximately 45 structural and non-structural proteins were identified, which seem to be involved in energy metabolism, protein folding and stress response, and protein synthesis, or to be part of the cytoskeleton or of the membrane and nuclear structures. Besides the potential immunogenic properties of some eggshell proteins [such as GST (glutathione S-transferase) and GAPDH], the membrane low-density lipoprotein receptor may have an important role in exploiting host factors, since eggs could take low-density lipoprotein (LDL) from the host, considering that the genome of this parasite shows no metabolic pathways for lipid synthesis (Berriman *et al.* 2009; Consortium, 2009; Dewalick *et al.* 2011; 2014).

The Von Willebrand factor (VWF) and other host plasma proteins involved in healing and blood clotting (fibrinogen and fibronectin) were found attached to eggs; they seem to promote egg binding to the endothelium, initiating and facilitating egg extravasation to their final destination, mainly the intestinal wall (Long *et al.* 1980; Dewalick *et al.* 2014). The potential role of these attached proteins in the capacity of *Schistosoma* eggs to reach the brain has not been studied. Other relevant eggshell-attached proteins are apolipoprotein-IV and apolipoprotein E, which could bind LDL through the LDL-receptor-like protein. The importance of this receptor and its host ligands has not been studied, although LDL binding could help the parasite to mask antigens, avoiding recognition by the immune system (Everts *et al.* 2009; Dewalick *et al.* 2011; 2014).

Biogenic amines (BAs) such as catecholamines, serotonin and histamine have been reported to play an important role in controlling parasite muscle contraction and movement (Ribeiro *et al.* 2005) which ultimately would favour parasite establishment; for example, serotonin is myoexcitatory in all flatworm species and can be synthetized by the parasites (Hamdan and Ribeiro, 1999). Additionally, both dopamine and histamine have a function in the flatworm nervous system (Nishimura *et al.* 2007; El-Shehabi and Ribeiro, 2010). Dopamine has important neuromuscular activities, either excitatory or inhibitory, depending on the flatworm species. In *S. mansoni*, dopamine causes body wall-muscle relaxation (Pax *et al.* 1984), possibly through a receptor associated with neuromuscular structures (Taman and Ribeiro, 2009). In addition to motor effects, BAs have been shown to regulate metabolic activity in several flatworms (Ribeiro *et al.* 2005). In addition, recent *in vitro* evidence indicates that serotonin and dopamine are both involved in *S. mansoni* miracidia transformation into sporocysts (Taft *et al.* 2010), suggesting a role in parasite development.

Concluding remarks

As shown in this review, each parasite infecting the CNS has developed unique strategies to infect its host, survive within it and reach its niche. The evasion of the immune response stands out among these strategies, either by disarming some specific responses like in antibody degradation/cellular apoptosis, or by exerting a strong immunomodulation, e.g. switching an inflammatory environment to an anti-inflammatory milieu, or replacing the effective Th1 response by an ineffective Th2 one.

While several works describe general pathogenic mechanisms in parasitic diseases, there is still little information focusing on how parasites exploit host molecules for successfully establishing in it. Being the CNS a tightly regulated microenvironment, parasites have evolved and developed strategies to make use of growth factors, host proteins, and hormones, to favour their establishment. The specific nature of the host molecules used depends on the intrinsic requirements of the infective parasite, especially on whether they are intracellular or extracellular parasites, and on their metabolic demands. However, and despite these differences, their shared need for host molecules could also provide general approaches to cope with them.

A neuroscience-oriented research of CNS parasites could provide a deeper understanding on how parasites induce cognitive and behavioural disorders in humans. These findings could facilitate the design of new therapeutic strategies, including novel drugs or vaccines that may block some of these targets to inhibit parasite establishment in the CNS, impacting parasite survival and improving the outcome of the disease.

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