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Passage of parasites across the blood-brain barrier

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Abbreviations: ALCAM, activated leukocyte cell adhesion molecule; BBB, blood-brain barrier; CSF, cerebrospinal fluid; CNS, central nervous system; CVOs, circumventricular organs; CXCL10, C-X-C motif chemokine 10; GBP, galactose-binding protein; HAT, human African trypanosomiasis; HFF, human foreskin fibroblast; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; LCMV, lymphocytic choriomeningitis virus; MBP, mannose-binding protein; MHC, major histocompatibility complex; MIC2, micronemal protein 2; MMP, matrix metalloprotease; MyD88, myeloid differentiation primary response gene (88); ND, not defined; NO, nitric oxide; PAR2, protease-activated receptor-2; PfEMP-1, *Plasmodium falciparum* erythrocyte membrane protein 1; RAG, recombination activating gene; TLR, Toll-like receptor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; WBCs, white blood cells

The blood-brain barrier (BBB) is a structural and functional barrier that protects the central nervous system (CNS) from invasion by blood-borne pathogens including parasites. However, some intracellular and extracellular parasites can traverse the BBB during the course of infection and cause neurological disturbances and/or damage which are at times fatal. The means by which parasites cross the BBB and how the immune system controls the parasites within the brain are still unclear. In this review we present the current understanding of the processes utilized by two human neuropathogenic parasites, *Trypanosoma brucei* spp and *Toxoplasma gondii,* to go across the BBB and consequences of CNS invasion. We also describe briefly other parasites that can invade the brain and how they interact with or circumvent the BBB. The roles played by parasite-derived and host-derived molecules during parasitic and white blood cell invasion of the brain are discussed.

Introduction

The spread of a pathogen to the brain during an infection is in general considered as a rare but serious complication of the disease. However, certain parasites have a propensity to infiltrate into the central nervous system (CNS), which may provide a so-called immune-privileged site and therefore be of advantage for survival of the invading microbe. For such parasite-host interactions certain sets of parasite-derived molecules may facilitate invasion of the parasites into the tissues, while host-derived immune response molecules are produced with the aim to inhibit their spread. A number of mechanisms have also evolved by which the immune response against a parasite may be dampened. For instance, the Th1 immune response, which is directed against intracellular pathogens, can be inhibited during infections with certain microbes in which the Th2 response, which is directed against extracellular pathogens, instead is promoted; the two arms of the immune response being mutually inhibitory.[1]

Recent reviews have been focused on bacterial invasion across the BBB, but also covered broader aspects by which various microbes spread to the nervous system.[2-4] In this review we will describe the mechanisms by which one extracellular parasite, *Trypanosoma brucei* (*T. b.*) may pass across the blood-brain barrier (BBB) to enter the brain parenchyma, since this event is considered to be of crucial importance for therapeutic considerations. In order to disclose any distinguishing features in the passage of this parasite, comparisons will be made other parasites and in particular with *Toxoplasma gondii* that can be both extra- and intra-cellular, but predominantly intracellular.

The two human pathogenic trypanosome subspecies *T. b. gambiense* and *T. b. rhodesiense* invariably cause fatal meningoencephalitis if the infections are left untreated, while the *Toxoplasma gondii* parasites can remain dormant for long periods of time in cysts within neurons and astrocytes, but can be reactivated if the host is immunocompromised and result in encephalitis that also is lethal if not treated.[5,6] Before reviewing mechanisms for neuroinvasion by the pathogens, certain properties of the BBB that the parasites have to overcome to be able to enter into the brain parenchyma will be high-lighted.

In order to maintain constancy of the CNS internal environment, which is vital for neuronal function, the passage of molecules across blood vessels in the CNS is restricted and tightly regulated compared with other tissues. This is attributed to the BBB[7,8] (**Fig. 1A**), which has been described in detail by reviews referred to above. Here we will only highlight certain features of relevance for an understanding of passage of the parasites, which are the focus of this review. The cerebral endothelial cells are bound together with tight junctions, which provide a structural barrier that prevents the diffusion of molecules between the endothelial cells into the brain parenchyma, i.e., through the paracellular pathway. The cerebral endothelial cells have low levels

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of pinocytotic activity or transcytosis and form a functional barrier by selectively transporting only specific molecules into the brain parenchyma.[8,9] The endothelial basement membrane enwraps pericytes, which among other things are important for regulating transcytosis across the BBB.[10] At the level of capillaries, where exchange of metabolites across the BBB mainly occurs, one basement membrane separates endothelial cells and astrocytes, whereas at the level of post-capillary venules, where infiltration of white blood cells (WBCs) into the brain parenchyma occurs during inflammation, two basement membranes separate the endothelial cells and the abutting astrocytic endfeet, namely the endothelial and the parenchymal basement membranes.[11,12] The latter basement membrane is also referred to as the astrocytic basement membrane because it is produced principally by astrocytes and deposited at their endfeet.[13] The laminin isotype composition of these two basement membranes plays a role in infiltration of WBCs into the brain parenchyma. The endothelial basement membrane containing laminin α4 is permissive to WBC penetration, while the one with laminin α5, which in contrast to laminin α4 has a patchy distribution, is not. Penetration of WBCs across the parencyhmal basement membrane, which contains laminin α1 and α2, requires focal activation of the matrix metalloproteases (MMP) 2 and 9. These proteases cleave the dystroglycan receptors, which anchor the astrocytic end-feet to this basement membrane.[11] Before activation of the MMPs occur, infiltrating WBCs are trapped between the two basement membranes.[14]

The endothelial cells of the leptomeningeal vessels are also linked together by tight junctions, but in spite of this they are more permeable to proteins than the cerebral vessels and they are not equipped with an astrocyte-derived parenchymal basement membrane.[15] Of relevance for spread of parasites to the brain also is the choroid plexus, which has fenestrations in the endothelial cells of the vessels that permit passage of proteins from the blood into the stroma. Further passage into the cerebrospinal fluid (CSF) is, however, prevented by the choroid plexus epithelial cells, which are linked to each other by tight junctions. Similarly, the vessels of the circumventricular organs (CVOs), which are secretory or sensory organs distributed along the walls of the third and fourth cerebral ventricles, are fenestrated to provide direct contact between nervous tissue elements and the blood.

These differences in the permeability of the vessels within these three territories, i.e., the brain parenchyma, leptomeninges and the choroid plexus/CVOs, play a role in the targeting of different parasites to the brain.

Parasite-Derived Factors that Promote BBB Crossing by Parasites

In order to enter into an organism or a cell, several parasites produce and secrete proteases to facilitate their passage across the skin, epithelial cells layers or plasma membranes.[16-19] The question has therefore arisen as to whether parasites in the bloodstream could secrete proteases that would also facilitate their passage across the BBB (**Box 1**).

Box 1. Suggested roles of parasite-derived factors in *Trypanosoma brucei* spp and *Toxoplasma gondii* crossing of the BBB.
Trypanosoma brucei spp cross the BBB as extracellular parasites. *T. brucei*-derived cysteine proteases (i.e., brucipain) may interact with host endothelial cell G protein-coupled receptors (i.e., protease-activated receptor-2, PAR2). It has been suggested that this results in an increase in BBB permeability which promote parasite crossing of the BBB.[31-35] The extracellular form of *Toxoplasma gondii*'s adhesin MIC2 interacts with host ICAM-1 to initiate the free parasite to cross epithelial barriers made up of human foreskin fibroblast (HFF) cell monolayers.[20,21] In order to cross the BBB as an intracellular parasite *Toxoplasma gondii* secreted cyclophilin 18 interacts with the chemokine receptor CCR5 and attracts WBCs to the site of infection.[36,37] *Toxoplasma gondii* derived proteases process and shed parasite-derived proteins necessary for the penetration into the host cell. Once the parasite has invaded the immune cells (e.g., $CD11b^+$ monocytes or dendritic cells) it increases their motility and migratory activities from blood vessels to deliver parasites into the brain extravascular space in a manner that is dependent on CD11b integrin function.[38-41]

In vitro studies have shown the capabilities of free *Toxoplasma gondii* parasites to cross epithelial barriers made up of human foreskin fibroblast (HFF) cell monolayers.[20,21] The *Toxoplasma gondii* adhesin micronemal protein 2 (MIC2) interaction with intercellular adhesion molecule 1 (ICAM-1) initiates this process.[21] Proteases and kinases that are released from *Toxoplasma gondii*'s apical secretory organelles rhoptries, micronemes and dense granules, in particular, serine- and cysteine-proteases play an important role in the parasite invasion of host cells by processing and shedding parasite-derived proteins that execute the penetration into the host cell (reviewed by Li et al.).[22] In this way the parasite can invade almost any nucleated cell in the body of the host including endothelial cells.[23-25] Although *Toxoplasma gondii* parasites infect endothelial cells and modulate the transcriptome of these cells, almost none of the free parasites migrate across an in vitro co-culture (brain endothelial cells and astrocytes) model of the BBB in the absence of leukocytes.[24] In addition, in an in vivo study very few *Toxoplasma gondii* tachyzoites injected into the tail vein of mice were observed in the brain.[26] Thus, although *Toxoplasma gondii* can invade endothelial cells, its ability to cross the BBB as extracellular parasites in vivo is not clear.

Similarly, there are several molecules that are expressed on and released from the external surface of *Trypanosoma brucei* spp, which might promote their passage across endothelial cells. Trypanosomes express phosphatases on their external surface and can release cysteine- and metallo-proteases.[27-30] A few of these proteases have been described to play a role in parasite penetration across cerebral endothelial cells in in vitro models of the BBB.[31-34] For instance, in such in vitro models of human BBB, RNA interference against the cysteine proteases cathepsin L (brucipain) resulted in reduced passage of *T. b. brucei*[31] similar to the effects of an irreversible inhibitor of cathepsin-L like proteases on passage of a *T. b. rhodesiense* strain.[32] Data from Grab and coworkers have also indicated that *T. b. brucei* transmigrate across a BBB in vitro model via the parasite-derived cysteine proteases or parasite-induced activation of endothelial cell G protein-coupled receptors (i.e., protease-activated receptor-2,

PAR2).[34,35] These studies therefore indicate a role for parasite-derived proteases, specifically brucipain, in the migration of trypanosomes across the BBB. The route for the passage taken by the parasite for crossing the BBB in vitro models is not clear, since both a paracellular and a transcellular route have been indicated.[29,32,33]

Since most studies suggest that *Toxoplasma gondii* most likely invade the CNS as an intracellular parasite, research activities have tried to elucidate how parasite derived molecules play a role in attracting and increasing the migration of infected cells. A molecule secreted by *Toxoplasma gondii,* cyclophilin 18, interacts with the chemokine receptor CCR5 and this results in the production of nitric oxide (NO), interleukin 12 (IL-12), and tumor necrosis factor α (TNFα) as well as attraction of macrophages to the site of infection to increase the chances of parasite-leukocyte interaction.[36,37] Once the parasite has invaded the

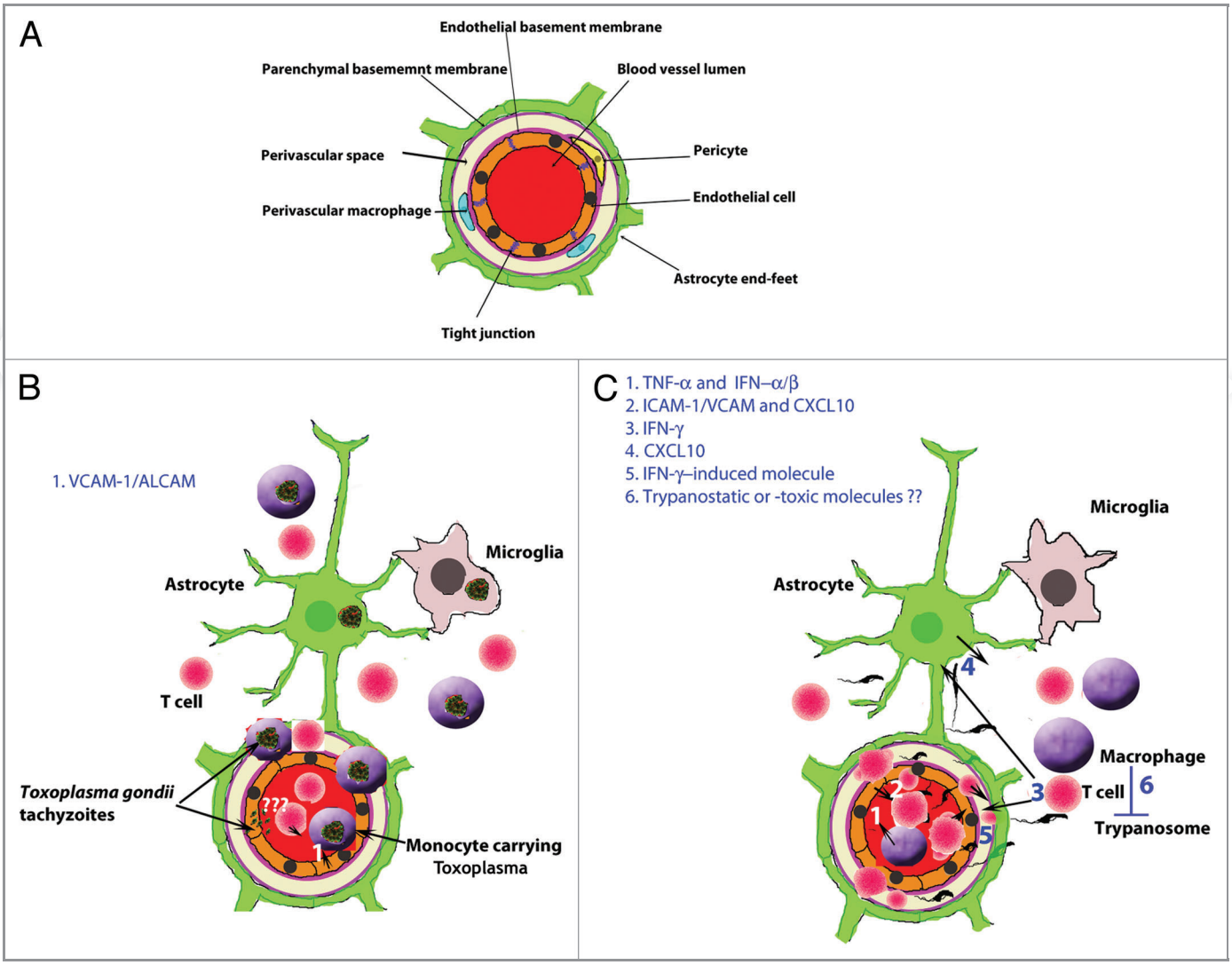

Figure 1. Crossing of the blood-brain barrier (BBB) by parasites associated with WBCs. (A) Illustration of a cerebral post-capillary vessel showing the BBB, consisting of a complex of cerebral endothelial cells and their tight junctions, basement membranes and pericytes as well as astrocytic end-feet. Note the perivascular space that is noticeable during inflammation. (B) *Toxoplasma gondii* crossing the BBB. (1) Induction of vascular cell adhesion molecule 1 (VCAM-1) and adhesion molecules activated leukocyte cell adhesion molecule (ALCAM) in the brain during infection might aid the monocytes infected *Toxoplasma gondii* tachyzoites to cross the BBB. The infection cause an increased motility of the monocytes which may facilitate their migration into the brain. *Toxoplasma gondii* can invade endothelial cells, however, its ability to cross the BBB as extracellular parasites in vivo is not clear. (C) The extracellular parasite *Trypanosoma brucei* spp and T cells cross the endothelial cell layer, the endothelial basement membrane and the parenchymal to invade the brain parenchyma. (1) TNFα and IFNα/β are released upon TLR9/MyD88-mediated activation of the innate immune response. (2) TNFα induces ICAM/VCAM on cerebral endothelial cells which allow attachment of T cells. IFNα/β induces a limited release of CXCL10 by endothelial cells and/or astrocytes, which is enough for penetration of T cells accompanied by some trypanosomes into the perivascular space. (3) Trypanosome-derived antigens taken up and expressed by macrophages could then be recognized by sensitized T cells to induce IFNγ, which augment the process through (4) induction of CXCL10 production by astrocytes and (5) molecules that open the parenchymal basement membrane for spread of both T cells and trypanosomes into the brain parenchyma. (6) Once inside the brain the parasites are most likely controlled by macrophages or microglia which produce trypanotoxic or static molecules.

immune cells it increases their motility and migratory activities via a G_i-protein coupled receptor signaling pathway.[38-40] How the parasite activates the G_i-protein coupled receptor signaling pathway is still not known. *Toxoplasma gondii*-infected dendritic or monocytic CD11b$^+$ cells, migrate from blood vessels to deliver parasites into the brain extravascular space of rodents (**Fig. 1B**) in a manner which is dependent on CD11b integrin function.[41]

At the level of the blood-CSF barrier, Toxoplasma parasites can, in immunosuppressed humans[42] as well as in experimental models,[43] localize to the choroid plexus, which may serve as an point of entrance for the parasites to the CSF similar to what is described during infections with the lymphocytic choriomeningitis virus (LCMV).[44] In experimental rodent models, *T. b. brucei* also crosses the fenestrated vessels in the stroma of the choroid plexus (**Fig. 2**) and CVOs very early after infection accompanied by WBCs and induction of cytokines including TNFα.[45,46] TNFα can disrupt the choroid plexus epithelial barrier,[47] and trypanosomes may appear early during infection in the CSF when trypanotoxic drugs that do not pass across the BBB are still effective as seen in a primate model of the disease.[48] Although trypanosomes may cross damaged choroid plexus epithelial cells into the CSF, they do not seem to enter the brain parenchyma through the ependymal cell layer. Neither are there signs of accumulation of Toxoplasma parasites or Toxoplasma-infected cells around the ventricles.[43] Instead there are perivascular accumulations of WBCs and parasites around the intracerebral vessels, and this is most prominent within the white matter of the trypanosome-infected brain.

Both Toxoplasma parasites and African trypanosomes can cross the leptomeningeal vessels, and in trypanosome infections WBC infiltration in the leptomeninges precede inflammatory changes in the brain parenchyma.[49] Since both trypanosomes and WBCs can pass into the CSF before they have infiltrated the brain parenchyma, the correlation between numbers of WBCs in the CSF and severity of the disease in human African trypanosomiasis (HAT) patients is still under debate for therapeutic considerations, i.e., the use of drugs that cross the BBB or not.

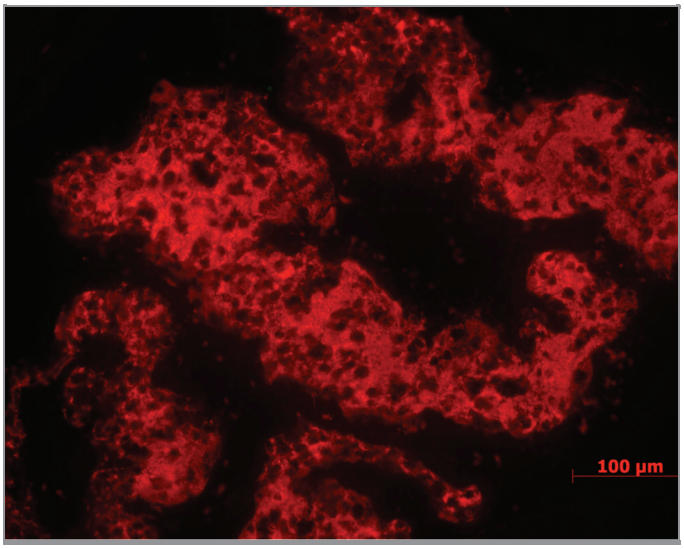

Figure 2. Large accumulation of *T. b. brucei* (red) in the choroid plexus following intra-peritoneal injection in a rodent model. Choroid plexus loaded with trypanosomes is seen already one week after the infection and before trypanosome crossing of the BBB, of which timing and prevalence is dependent on the rodent strain.

Host-Derived Factors that Promote Crossing of the BBB by Parasites Associated with WBCs

Although the in vitro studies have shown that free-living Toxoplasma parasites and African trypanosomes by themselves can cross epithelial or endothelial cell layers, it is not clear to what extent such phenomena contributes to the neuroinvasion in vivo, in which host-derived mechanisms also may contribute to or even prevail in the process. As described in detail in a recent review,[50] the Toxoplasma parasite can infect monocytes and dendritic cells and be carried within such cells across the BBB (a "Trojan horse mechanism," **Figure 1B**). The extracellular trypanosomes may on the other hand follow T cells that pave their way into the brain by focal and transient openings of the BBB (**Box 2**).[51]

During toxoplasmosis and trypanosomiasis, both in humans and experimental animal models, there is expression of host derived molecules such as adhesion molecules, chemokines, cytokines, metalloproteases, which play a role in the traversal of WBCs across the BBB and thereby also in the neuroinvasion of parasites.[24,52-54]

In line with this hypothesis, it was observed that infection with *Toxoplasma gondii* resulted in an upregulation of the adhesion molecules activated leukocyte cell adhesion molecule (ALCAM), ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) in the CNS of C57BL/6 and BALB/c mice (both haplotype H-2^d).[54] However, C57BL/6 mice that expressed more VCAM-1 and ALCAM had more inflammatory cells and *Toxoplasma gondii* parasites in the CNS than BALB/c mice,[54] suggesting an important role of these adhesion molecules in the differential CNS invasion by the parasite. A higher expression of interferon (IFN) -γ in C57BL/6 mice compared with BALB/c mice was most likely an important factor for the induction of the higher expression of VCAM-1 in the brains of the former mice;[54]

Box 2. Suggested roles of host-derived factors in *Trypanosoma brucei* spp and *Toxoplasma gondii* crossing of the BBB.
T. b. brucei cross the BBB into the brain parenchyma in a multi-step passage that appear to be similar to that of T cells during inflammation. Results obtained using animal models of African trypanosomiasis including genetic modified rodents indicate an important role of host-derived molecules in T cell and parasite penetration across the BBB. These molecules include the cytokines IFNα/β, IFNγ and TNFα, the chemokine CXCL10 and possibly the adhesion molecules i.e., ICAM-1.[51,57,63] The possible role of IFNγ and CXCL10 in the neuropathogenesis of the disease has been further corroborated with a clinical study in HAT patients and analysis of CSF of patients with HAT.[63,65] The Toxoplasma parasite most likely cross the BBB inside leukocytes.[41,50] Host-derived molecules such as ALCAM, ICAM-1, VCAM-1 and IFNγ, which facilitate the passage of leukocytes across the BBB, have also implicated in the migration of *Toxoplasma gondii* infested CD11b$^+$ monocytes/dendritic cells to deliver parasites into the brain parenchyma.[54,55]

since *Toxoplasma gondii*-infected IFNγ-deficient mice had less VCAM-1 than wild-type mice, but treatment of these mutant mice with recombinant IFNγ restored the expression of VCAM-1 in cerebral vessels.[55]

The role played by host factors in African trypanosome neuroinvasion is further emphasized by the observation that in two major histocompatibility complex (MHC)-matched (haplotype H-2^b) C57BL/6 and SV-129/Ev mice, an isolate of *T. b. brucei* crosses extensively the BBB in one strain of the mice (C57BL/6), but not in the other (129Sv/Ev), although the levels of parasites in the blood are even higher in the latter mouse strain.[56]

We have observed that African trypanosomes enter the brain in two phases, namely first across the fenestrated vessels in the choroid plexus and CVOs as well as through leptomeningeal vessels, and then in a multi-step passage across the BBB. The role played by molecules released by the immune response for the multi-step passage of trypanosomes across the BBB has been studied systematically using a series of gene knockout C57BL/6 mice. Based on the following observations the passage of *T. b. brucei* across the BBB into the brain parenchyma appears to similar to that of WBCs during inflammation. Mice deficient of TNFα had reduced numbers of both parasites and T cells in the brain parenchyma compared with wild type mice.[57] Such mice also had a reduced expression of adhesion molecules, e.g., ICAM-1 on the cerebral endothelial cells, indicating that TNFα could facilitate T cell and parasite penetration by increasing expression of adhesion molecules.[58-61] Furthermore, we have found that mice deficient of IFNγ, its receptor or recombination activating gene (RAG) had higher parasitemia than wild type mice, while the parasites as well as T cells accumulated in the perivascular space like cuffs.[51] The parasites passed the endothelial cell layer and its basement membrane but were trapped between this and the parenchymal basement membranes, which can be transiently opened for passage of T cells by activation of MMP-2 and -9.[62]

Mice deficient of the IFNγ inducible chemokine CXCL10 or its receptor CXCR3 were found to have less parasites in the brain parenchyma albeit similar parasitemia levels compared with wild type mice.[63] CXCL10 was induced during the infection and expressed on cerebral endothelial cells and most prominently on astrocytes. This indicates that astrocytes by expressing CXCL10 could play a role by increasing the trafficking of both T cells and trypanosomes across the BBB or their retention in the brain parenchyma. However, cuffing of trypanosomes and T cells around cerebral vessels was not seen in these mice, which suggests that different IFNγ-regulated genes are involved in attraction or retention of T cells and trypanosomes on one hand and opening the parenchymal basement membrane for their passage on the other.

Interestingly, IFNα/β also plays a role in the neuroinvasion of T cells and trypanosomes, since IFNα/β receptor knockout mice show both less infiltration into the brain parenchyma as well as reduced levels of CXCL10. IFNα/β has been suggested to initiate a series of events that are amplified when IFNγ is induced following antigen-T cell recognition in the brain during infections with LCMV.[44] The following sequence of events for *T. b. brucei* crossing the BBB could therefore be suggested: The innate immune response molecules TNFα and IFNα/β are released upon activation of macrophages after stimulation of toll-like receptor (TLR) 9 by trypanosomal CpG-DNA.[57] TNFα induces ICAM/VCAM on cerebral endothelial cells which allow attachment of T cells. IFNα/β induces a limited release of CXCL10, which is enough for penetration of T cells accompanied by some trypanosomes into the perivascular space. Trypanosome-derived antigens taken up and expressed by macrophages could then be recognized by sensitized T cells to cause IFNγ release to augment the process; induce more CXCL10 in astrocytes and open the parenchymal basement membrane for more spread of both T cells and trypanosomes into the brain parenchyma (**Fig. 1C**).

It is not clear why the T cells and trypanosomes have a predilection for invasion of the white matter and hypothalamic areas, but cytokines released into the CSF from the infected choroid plexus and CVOs could diffuse between ependymal cells and then permeate through the relatively wide extracellular spaces of the white matter, and nearby hypothalamic nuclei, respectively. Inflammatory cytokines in these areas could increase the immune response to augment T cells and trypanosome passage across the post-capillary venules.[64]

The possible role of IFNγ and CXCL10 in the neuropathogenesis of the disease has been further corroborated with a clinical study in HAT patients.[65] Patients with higher plasma titers of IFNγ had increased frequency of progression to and severity of the meningoencephalitic stage of HAT than those with lower titers of the cytokine.[65] Moreover, CXCL10, which may be a biologically meaningful marker for inflammatory processes within the brain parenchyma since it is induced in astrocytes, was expressed more in the CSF of patients with late stage HAT in comparison to early stage HAT patients caused by either *T. b. gambiense* or *T. b. rhodesiense*.[63,66-68]

From these studies it is apparent that immune response molecules and reaction to them play a crucial role for the brain invasion of both *Toxoplasma gondii* and *T. b. brucei* (**Table 1**). Infections with intracellular pathogens, like *Toxoplasma gondii,* activate mainly the Th1 arm of the immune response, whereas infections with extracellular pathogens including helminthes elicit Th2 cell responses.[69-71] It is therefore paradoxical that infections of C57BL/6 mice with *T. b. brucei* elicit mainly a Th1 response in the host resulting in elevated levels of pro-inflammatory cytokines such as IFNγ and TNFα.[72-76] Since these cytokines facilitate the infiltration of WBCs across the BBB in to the brain, the immune response promotes parasite dissemination into the brain in contrast to their traditional one in parasite control.[77-79]

Parasite Survival and Death in the Brain Parenchyma

As described in the previous section it is apparent that immune response derived molecules can facilitate the passage of WBCs and parasites across the barriers provided by the BBB. These molecules could therefore serve a dual function since they also provide an immunological barrier against further replication and spread of the parasites within the brain parenchyma. The immunological

Table 1. Interaction of selected blood-borne parasites with the blood-brain barrier (BBB)

Parasite	Intracellular or extracellular parasite	Name/Nature of disease caused after entering the CNS	Crossing of the blood-brain barrier	Molecules important for interaction/crossing of the BBB		References
				Parasite-derived molecules	Host derived-molecules	
Toxoplasma gondii	Predominantly intracellular	Toxoplasmic encephalitis	Crosses the BBB inside monocytes	MIC2	ALCAM, ICAM-1, VCAM-1, IFNγ,	21, 54, 55
Trypanosoma brucei spp	Extracellular	Stage 2 or late stage HAT, meningoencephalitis	Crosses the BBB	Brucipain	CXCL10, IFNα/β, IFNγ, PAR2, TNFα,	34, 35, 51, 57, 63
Trypanosoma cruzi	Intracellular.	Meningoencephalitis	Crosses infrequently the BBB inside WBCs	ND	ND	87, 88
Plasmodium falciparum	Intracellular	Cerebral malaria	Do not cross the BBB. Infected red blood cells adhere to endothelial cells and sequester	PfEMP-1	ICAM-1	125–129
Acanthamoeba spp	Extracellular	Granulomatous amoebic encephalitis, Acanthamoeba amoebic encephalitis	Crosses the BBB	MBP, Serine proteases	ND	130, 131
Balamuthia mandrillaris	Extracellular	Granulomatous amoebic encephalitis, Balamuthia amoebic encephalitis	Crosses the BBB.	GBP, Metalloproteases	ND	95, 97–99, 132, 133
Toxocara canis	Extracellular	Neurotoxocariasis, cerebral toxocariasis	Crosses the BBB	ND	ND	101, 134
Taenia solium	Extracellular larvae	Neurocysticercosis	Lodge in cerebral vessels and form cysts	ND	ND	102, 104, 105
Schistosoma spp	Extracellular helminths	Cerebral schistosomiasis or neuroschistosomiasis	Parasite or its eggs lodge in vessels to elicit an immune reaction	ND	ND	107-109

ALCAM, activated leukocyte cell adhesion molecule; BBB, blood-brain barrier; CNS, central nervous system; CXCL10, C-X-C motif chemokine 10; GBP, galactose-binding protein; HAT, human African trypanosomiasis; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; MIC2, micronemal protein 2; MBP, mannose-binding protein; ND, not defined; PAR2, protease-activated receptor-2; PfEMP-1, *Plasmodium falciparum* erythrocyte membrane protein 1; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; WBCs, white blood cells.

control of a pathogen within the immune-privileged brain presents a high order of complexity that is not well understood[50] and beyond the scope of the present review. Only a few observations of relevance for the accumulation of parasites in the brain as a result of processes regulating both their spread into and control within the parenchyma will be pointed out.

In studies aiming at defining the role of host factors as determinants of parasite neuroinvasion or control of parasites it is often difficult to separate between these two different events, i.e., opening of the BBB for passage of parasites and control of their replication within the parenchyma. From studies on *T. b. brucei* infections in C57BL/6 mice data indicate that while TNFα and IFNα/β derived from the innate immune response promote the initiation of brain invasion of T cells and trypanosomes, they do not contribute to control of parasite growth in the brain.[57] Although the induction of TNFα and IFNα/β and the control of parasite growth in the brain is dependent on TLR9-myeloid differentiation primary response gene (88) (MyD88)-mediated signaling, the effector molecules for the control of parasite growth are distinct from those promoting invasion, but their nature is still not clear.[57]

Once *Toxoplasma gondii* tachyzoites enter the brain parenchyma inside monocytes/dendritic cells they are transmitted to astrocytes, microglia and neurons. The rapidly replicating tachyzoites transform in to the very slowly replicating bradyzoites, which form cysts and persist as a chronic latent infection in the immunocompetent host. The importance of the immune response also in the control of growth of this parasite in the brain is demonstrated by the reactivation of the infection in an immunodeficient host, which results in encephalitis that can be fatal if not treated.[5,6,80,81] IL-12 and IFNγ play an important role in the control of *Toxoplasma gondii* within the CNS and a number of effector molecules produced by different cells such as macrophages, microglia and astrocytes have been proposed.[82-84] In addition, although infections with *Toxoplasma gondii* elicit a prominent Th1 immune response, a balancing Th2 immune response within the CNS has been observed in mice on a resistant BALBc background. IL-33, which is a recently described cytokine that amplifies the Th2 response, plays an essential role in controlling *Toxoplasma gondii* within the brain and limiting immune mediated neuropathology.[85] The effector molecules for the control of parasites in these mice, which is independent of TNFα and IFNγ, are not clear; a CD40-CD40L signaling, which increase autophagocytosis, has been pointed out as one possible mechanism for the parasite growth control.[85]

BBB Interactions with other Parasites

Several other parasites, besides *Toxoplasma gondii* and *Trypanosoma brucei* spp, affect the CNS resulting in devastating or lethal

consequences to the host, with or without crossing the BBB as will be briefly described for comparisons (**Table 1**).

In contrast to the African trypanosomes, *Trypanosoma cruzi,* which is prevalent in Latin America, replicates intra-cellularly. Infrequently, and mainly in children less than 2 y old, the parasites can spread to the brain and form nests in astrocytes at an acute stage of the disease. In immunosuppressed patients with chronic disease the infection in the brain can be reactivated showing necrosis and large nodular lesions with numerous parasites in astrocytes.[86] The mechanisms for spread of the parasites to the brain are not clear, but probably involve dissemination of infected WBCs through the BBB.[87,88]

The endothelial cells and their tight junctions present the first impediments parasites encounter when they cross the BBB. In addition, they play an important role in the neuropathogenesis of infections with the parasite *Plasmodium falciparum,* which does not enter the brain.[89] *P. falciparum* infested erythrocytes attach to the activated cerebral vessel endothelial cells via the *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1), thus, are sequestered in the CNS and cause microcirculatory and neurological dysfunctions (cerebral malaria) without crossing the BBB. However, during cerebral malaria there is disruption of the BBB integrity and function.[90,91] In experimental models of cerebral malaria there is induction of pro-inflammatory cytokines such as IFNγ and IL-12, which contribute to the neuropathology of the disease.[92] It is hypothesized that cerebral malaria could be a result of various factors such as pro-inflammatory immune mediated pathology, mechanical damage by sequestered infected erythrocytes, platelets or microparticles, or a combination of both factors i.e., immune pathology and mechanical damage.[93]

Acanthamoeba invade the brain to cause granulomatous encephalitis mainly in immune compromised individuals. In vitro studies suggest that its passage across the BBB is facilitated by extracellular serine proteases which degrade the tight junction proteins resulting in increased permeability of the BBB.[94] *Balamuthia mandrillaris* also invades the CNS to cause encephalitis. Within the CNS the parasites are usually found clustered around blood vessels in localized areas of the brain, but they have also been found in the CSF of a patient who died of Balamuthia encephalitis.[95,96] Using in vitro models the crossing of the human BBB by Balamuthia seems to be aided by a galactose-binding protein (GBP), induction of host cytokines and parasite metalloproteases.[97,98] Balamuthia surface GBP can bind to endothelial cell galactose-containing glycoproteins and laminin, which possibly leads to attachment of the parasite to the BBB and later release of parasite proteases which degrade the tight junction proteins and basement membranes to aid its passage across the BBB.[95,97,99,100]

Toxocara canis larvae have been found in the choroid plexus and adjacent brain areas after oral administration of embryonated eggs. The mechanisms of invasion of the larvae into the brain parenchyma are not clear, but the presence of larvae is not correlated with enhanced BBB permeability.[101]

Larvae of the pork tapeworm, *Taenia solium* can spread in the bloodstream and upon reaching small blood vessels in the brain, they lodge and start to develop into cysts. When the larvae die, after 3–5 y, an inflammatory reaction ensues and neurocysticercosis may develop, which results in neurological symptoms including epilepsy and intracranial hypertension.[102] Patients with symptomatic neurocysticercosis have increased expression of pro-inflammatory cytokines and adhesion molecules, TNFα, IFNγ, IL-1β and ICAM-1.[103] In a murine model of neurocysticercosis breakdown of the BBB and blood-cerebrospinal fluid barrier was observed and found to be associated with leukocyte migration into the CNS.[104] Recently, extensive astrogliosis, neuronal damage, rapid angiogenesis and disruption of BBB, which allowed an influx of WBCs into brain lesions, were observed in a porcine model of neurocysticercosis.[105]

Neuroschistosomiasis is a severe clinical outcome associated with infection with the human pathogenic subspecies of Schistosoma, i.e., *S. mansoni, S. hematobium* and *S. japonicum*. Schistosoma eggs may spread to the CNS, through the arterial system after crossing previously developed pulmonary shunts or anastomosis or through retrograde venous flow. They are deposited in cerebral vessels and secrete antigens such as glycans and glycoproteins that elicit a Th2 immune response leading to granuloma formation.[106-108] Adult worms can also migrate via vessels to reach meninges and the choroid plexus where they may shed massive amounts of eggs into the CNS.[107-109]

Olfactory Route

One way to circumvent the BBB is to invade the brain via the olfactory route, i.e., from the olfactory epithelia in the nasal cavity along the olfactory nerve into the CSF and brain. Although infrequent, certain free-living parasites found in water can infect humans along this route of neuroinvasion. The most prominent example is *Naegleria fowleri*, which can thrive in warm lakes as well as in untreated swimming pools, resort spas and hot springs.[110]

After inhalation, the amoeba can attach to the olfactory epithelium possibly via a Nfa1 protein expressed in their food pockets.[111,112] They may then move along the spaces between the unmyelinated nerve fibers of the fila olfactoria and traverse the cribriform plate to reach the CSF and olfactory bulbs.[113] Through further release of proteases, the parasites digest the olfactory bulb and spread into the brain parenchyma to cause a granulomatous meningoencephalitis.[114] Since it was first described in 1965, cases of infection by this amoeba have been observed around the world and the infections are almost invariably fatal.[110]

Consequences of Parasite Invasion of the Brain

In general, infection of the CNS by a parasite is considered as a serious complication of the disease. Several parasitic infections of the brain are lethal if left untreated, (e.g., Balamuthia, African trypanosomes), while others can be controlled by the immune response to remain as a chronic or persistent infection (e.g., *Toxoplasma gondii, Trypanosoma cruzi*) or be cleared over time (e.g., *Taenia solium* larvae, the rat lungworm *A. cantonensis)*, in spite of the fact that the brain provides an immunoprivileged site. In addition to life-threatening conditions, parasitic infections of the brain can cause disturbances of the brain function. For

instance, they are a common cause of seizures and epilepsy (*Taenia solium* larvae, *P. falciparum*), disruption of the sleep pattern (African trypanosomes) and behavior or cognitive disturbances (*P. falciparum*).[64,102,115]

By being inside the brain, parasites may have an advantage because of the less efficient immune responses in the brain and also be protected behind the BBB from circulating antibodies. Thereby, Toxoplasma parasites may remain in the brain for the life span of an infected rodent. To facilitate the spread of the parasite to its definite host, the cat, it has been suggested that persistent Toxoplasma infections in rodents may change the rodents' behavior to show reduced avoidance of the predator cats.[116,117] It has also been suggested that African trypanosomes may hide in the brain, behind the BBB, between relapses in sub-optimally treated individuals.[118-121] In contrast to toxoplasmosis, there are no obvious changes in the behavior of the host caused be this parasite that could be associated with an increased rate of transmission. However, persistence over long periods of time in a host animal would favor the chances of spread of the parasite within populations, since it is transmitted by tsetse flies, the bite of which is a relatively rare event.

Conclusions

Both intracellular and extracellular parasites that invade the brain can result in devastating or lethal consequences to the host. These parasites pose a significant threat to human health, mostly in low-income countries. There are gaps in knowledge in terms of the interplay between the parasite-derived molecules and host-derived molecules and the weight of their roles in parasite traversal of the BBB into the brain parenchyma. Parasite derived molecules, including adhesins and proteases, promote cell penetration of several parasites, and several studies indicate that they play an important role also in the traversal of *Toxoplasma gondii* and *Trypanosoma brucei* spp across in vitro models of the BBB. The role of these parasite derived molecules in migration of parasites across the BBB in an in vivo setting warrant to be evaluated, because they might present novel drug targets to reduce neuropathology in these parasitic infections. For instance, molecules on the surface of parasites, which play a role in parasite interaction with the BBB, such as MIC2 for *Toxoplasma gondii*, PfEMP-1 for *Plasmodium falciparum*, are plausible targets for anti-parasitic vaccine development.[122-124] In in vivo settings host derived immune response molecules are, however, crucial in the migration of these parasites into the brain parenchyma. The immune response molecules that promote passage of the parasites across the BBB may be distinct from those that inhibit their growth within the brain. The immune response can therefore have the dual and partly paradoxical function to on one hand reduce parasite growth in the brain, but on the other promote their brain invasion. Further research on the role of host derived molecules and the immune system on the invasion of the CNS and control of the parasites inside the CNS would not only further the knowledge of the neuropathology of parasitic diseases, but could provide a platform for drug discovery to reduce CNS invasion and ameliorate immune mediated pathology in these parasitic CNS infections.

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