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Toxoplasma gondii and the blood-brain barrier

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Infection with the protozoan parasite *Toxoplasma gondii* is characterized by asymptomatic latent infection in the central nervous system and skeletal muscle tissue in the majority of immunocompentent individuals. Life-threatening reactivation of the infection in immunocompromized patients originates from rupture of Toxoplasma cysts in the brain. While major progress has been made in our understanding of the immunopathogenesis of infection the mechanism(s) of neuroinvasion of the parasite remains poorly understood. The present review presents the current understanding of blood-brain barrier (patho)physiology and the interaction of *Toxoplasma gondii* with cells of the blood-brain barrier.

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The protozoan parasite *Toxoplasma gondii* can infect a variety of warm-blooded hosts including humans although the sexual life cycle only occurs in members of the feline family.[1] The infection is mostly acquired through the oral route by ingestion of Toxoplasma tissue cysts or oocysts from undercooked or raw food or water.[2-4] Within a short period of time the tachyzoite form of the parasite actively crosses the gastrointestinal barrier by penetrating enterocytic cells in the small intestine and entering submucosal tissue.[5,6] Intracellular tachyzoites form a parasitophorous vacuole that ruptures following multiple cycles of replication. From there tachyzoites disseminate throughout the body and reach immunologically protected sites including brain, retina and fetus.[7-9] In vitro studies revealed that tachyzoites can invade astrocytes, microglia and neurons of the mouse brain with subsequent formation of tissue cysts within these cells.[10] Latent infection with *T. gondii* involves an elaborate interplay between the parasite and the host in which the parasite ensures its survival and proliferation but avoids fatal damage to the host at the same time.[11] It has been hypothesized that during the latent phase of infection tissue cysts containing bradyzoites are controlled by the intact immune system, and only in the case of immune suppression, i.e., AIDS, bradyzoites released convert to tachyzoites and reactivated toxoplasmosis takes a lethal course if left untreated.[12] Alternatively, cyst rupture and re-formation of cysts may be a constant process even in immunocompetent individuals, and the immune system's role may be limited to the control of the tachyzoite form of the parasite.

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After passage of the blood-brain barrier (BBB) bradyzoite-filled tissue cysts develop which are predominantly found in neuronal cells in the cerebral cortex, the hippocampus, basal ganglia, and amygdala.[13,14] Latent infection is thought to be asymptomatic but latent infection has been associated with manipulation of the hosts' behavior and development of mental disorders including depression and schizophrenia.[15-18]

While major progress has been made in our understanding of the interplay between the parasite and the host immune system our knowledge regarding the fascinating ability of the parasite to cross biological barriers, i.e., the BBB, remains surprisingly poor. Importantly, the most severe forms of the disease occur as a result of the parasite accessing sites protected by barriers, including congenital toxoplasmosis,[19] retinochoroiditis[20] and encephalitis in immunocompromised individuals.[21] A detailed understanding of the mechanisms of BBB passage and establishment of latency in the brain however may allow to develop innovative strategies to prevent invasion of the central-nervous system by the parasite and subsequent disease. While the passage of biological barriers driven by the motility of the parasite has recently been reviewed,[5] this review focuses on the interaction of the parasite with the BBB.

T. gondii Strain-Specific Differences in Virulence

Differences in susceptibility to infection with *T. gondii* of different hosts have been attributed primarily to the route of infection, host genetic background, and Toxoplasma strain type. The *T. gondii* population structure consists of three major clonal lineages (types I–III), which differ in their virulence and their geographical occurrence.[22-24] As few as one parasite of a type I strain may cause lethal infection in mice but does not cause lethal infection in rats; type II and III strains are mildly virulent and establish latent or chronic-progressive infections in the mouse.[25,26] In humans type II strains of *T. gondii* were found in about 80% of patient samples.[27,28] Recent reports support the association of atypical strains of *T. gondii* with more severe disease presentation in humans.[24] In this regard the development and recurrence of ocular toxoplasmosis appear to be dependent on the Toxoplasma genotype in patient cohorts in Europe (Shobab et al., manuscript in preparation) and the US (M. Grigg, personal communication).

The differences in virulence of *T. gondii* strains are mainly caused by the expression of polymorphic rhoptry (ROP) kinases, i.e., ROP16, ROP18 and the ROP5 pseudokinases that the parasite secretes into the host cell.[29-34] ROP16 is a secreted protein kinase that leads to activation of the transcription factors STAT3

and STAT6 in host cells that in turn downregulate the host innate immune responses.[32,35] Type II strains of *T. gondii* show a defect in the kinase ROP16 and therefore fail to suppress immune responses.[36] The downregulation of STAT3 and STAT6 activation after type II strain infection enhances the hosts' ability to mount a protective Th1 immune response characterized by the production of IL12 and effective control of parasite replication.[37,38] Type I ROP18 inactivates host GTPases of the IRG family that accumulate on the parasitophorous vacuole membrane in infected cells and contribute to rupture of the vacuolar membrane.[39,40] Recently, the host endoplasmic reticulum-bound transcription factor ATF6β was identified as the host cell target for ROP18. ROP18-induced degradation of ATF6β in dendritic cells resulted in defective $CD8^+$-T cell defenses against the parasites.[41]

While the contribution of individual factors of virulence in the parasite and the host have been investigated in detail in mice as outlined above, limited information is available from other rodent species and in particularly from humans. Differences in the presence of absence of specific host factors (i.e., IRG family members, NO), in addition to the mostly asymptomatic nature of human infection are limiting the access to controlled human studies and add to the complexity in translating results from mouse models to the human patient.

Blood-Brain Barrier

The central nervous system (CNS) contains three main barrier sites, the arachnoid epithelium, the epithelium of the choroid plexus, and the blood-brain barrier (**Fig. 1**).[42] The arachnoid epithelium separates the subarachnoid cerebrospinal fluid from potentially harmful blood-born molecules that might pass from bloods vessels in the dura mater. Leukocytes or pathogens may also enter the CNS at the choroid plexus where the cerebrospinal fluid (CSF) is produced. But in contrary to the fenestrated blood capillaries of the choroid plexus the choroid plexus epithelium possesses tight junctions. The blood-CSF barriers protect the meningeal spaces as several meningitis eliciting pathogens including *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Streptococcus agalactiae* use the blood-CSF interface as an entry site.[43] The third barrier in the CNS is the blood-brain barrier (BBB). Highly specialized microvascular endothelial cells build a functional and structural barrier that is characterized by low permeability, low pinocytotic activity, lacking fenestrations, and high transendothelial resistance (**Fig. 2**). Surrounding cells like pericytes, microglia and astrocytes interact with endothelial cells of the BBB and support the maintenance of barrier functions through the release of soluble agents including transforming growth factor-β (TGFβ), glial-derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF) and angiopoetin 1.[42,44-50] Additionally, hydrocortisone and intracellular cAMP elevating agents like adrenomedullin decrease paracellular permeability and strengthen the endothelial barrier.[46,48,51] In contrast to these factors impairment of BBB function may be caused by inflammation or CNS injuries mediated by cytokines (IL-1, IL-6, TNF), reactive oxygen species (ROS), nitric oxide (NO), vasoactive mediators (bradykinin, histamine, serotonin), phospholipase A2, arachidonic acid, prostaglandins or leukotrienes.[42,46,52] Interendothelial tight junction and adherence junction proteins [members of the claudin family, occludin, junctional adhesion molecules (JAMs), platelet-endothelial cell adhesion molecule (PECAM) and vascular endothelial cadherin (VE-cadherin)] together with several intracellular components seal the spaces between endothelial cells and separate the apical from the basolateral site[44,53-55] (**Fig. 3**). The presence of tight junctions and adherence junctions restricts the paracellular flux of hydrophilic molecules and prevents the migration of cells through the endothelial barrier. Nevertheless, there are several pathways for molecular trafficking through the BBB. The lipid membranes of the endothelium for example allow the diffusion of lipid-soluble agents, while specific receptors (insulin receptor, transferrin receptor) carry their ligands across the endothelium through receptor-mediated endocytosis and transcytosis.[42] Transport proteins (including carriers for glucose, amino acids, purine

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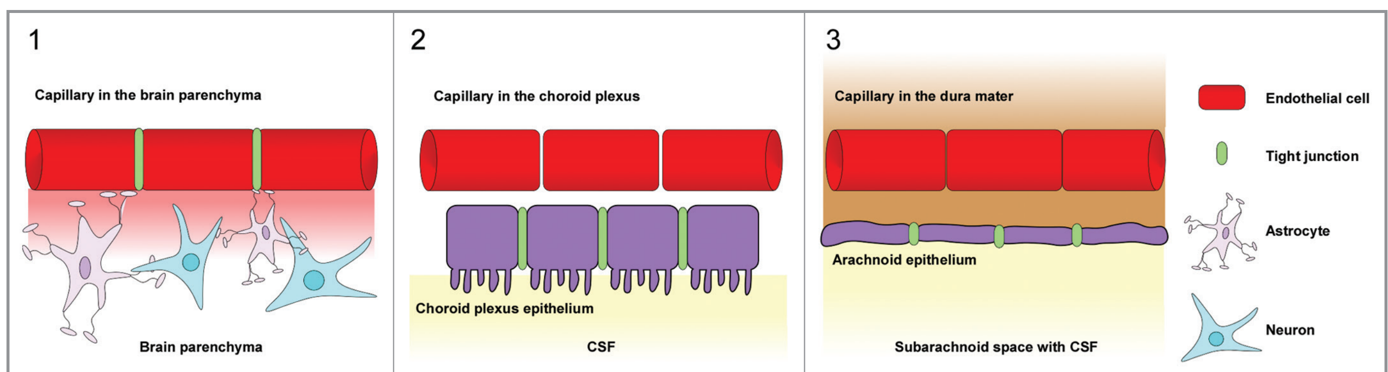

Figure 1. Barrier sites in the CNS. The CNS contains three main barrier sites: (1) The blood-brain barrier which is formed by specialized brain capillary endothelial cells, (2) the barrier between the blood and the cerebrospinal fluid that exists at the choroid plexus epithelial cells and (3) the arachnoid epithelium presenting the middle layer of the meninges. While the endothelial cells of the BBB restrict the migration of potentially harmful blood-born agents to the central-nervous tissue, the choroid plexus epithelium and the arachnoid epithelium protect the cerebrospinal fluid. Tight junctions between endothelial and epithelial cells seal the intercellular spaces and minimize paracellular pathways.

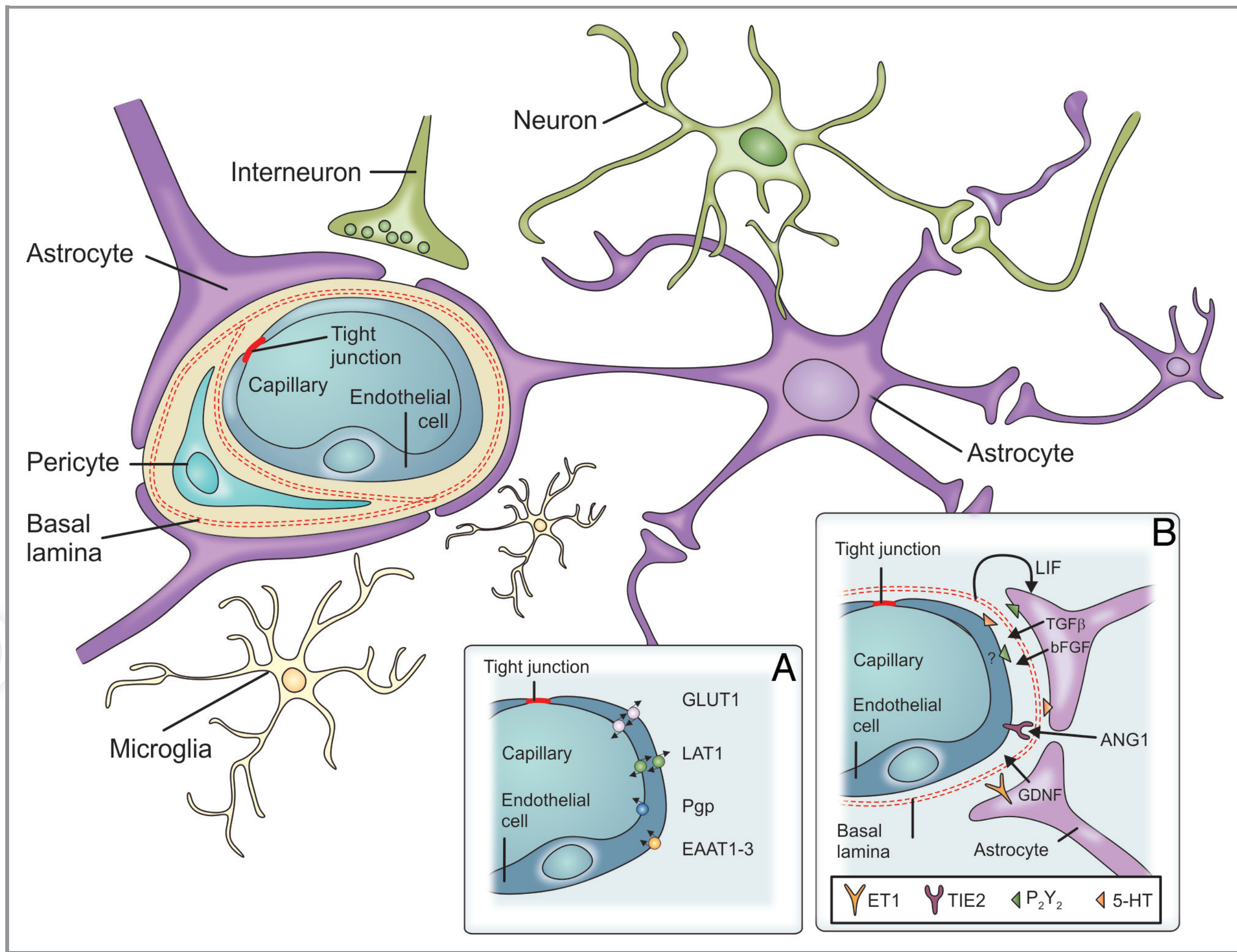

Figure 2. Components of the blood-brain barrier. The blood-brain barrier consists of specialized capillary endothelial cells that are lined by the basal lamina, astrocytic endfeet, pericytes and microglial cells. (A) Among several other transporters and receptors brain endothelial cells express excitatory amino acid transporters (EAAT1–3), glucose transporter 1 (GLUT1), L-system for large neutral amino acids (LAT1) and P-glycoprotein (Pgp). (B) Surrounding cells intensely interact with endothelial cells and release soluble agents in order to support the maintenance of BBB functions [5-HT (5-hydroxytryptamine [serotonin]), angiopoetin 1 (ANG1), basic fibroblast growth factor (bFGF), endothelin 1 (ET1), glial cell line-derived neurotrophic factor (GDNF), leukemia inhibitory factor (LIF), purinergic receptor (P2Y2), transforming growth factor-β, endothelium-specific receptor tyrosine kinase 2 (TIE2)] (from ref. 42, with permission).

bases and nucleosides) in turn provide the brain with nutrients and other substances while the transport protein P-glycoprotein acts as an efflux pump that can actively transport lipophilic drugs out of endothelial cells.[42,56]

In the course of inflammation circulating leukocytes leave the blood stream and migrate across the endothelial barrier into inflamed tissue. Transendothelial migration of leukocytes follows a defined sequence of adhesion and extravasation steps which result in the crossing of the endothelial barrier, the basal lamina and the extracellular matrix.[57-59] Circulating leukocytes interact with endothelial cells mediated by members of the selectin family and their corresponding ligands on both endothelial cells and leukocytes. Endothelial cells express selectins such as E- and P-selectin, while P-selectin glycoprotein ligand 1 (PSGL-1) is one of the corresponding ligands on leukocytes.[57,60,61] Chemokines on the luminal surface of activated endothelial cells induce changes in affinity and valency of leukocyte integrins. Activated integrins (VLA-4, LFA-1, Mac-1 and α4β7) then bind to endothelial adhesion molecules (VCAM-1, ICAM-1, ICAM-2 and MAdCAM-1) that function as integrin ligands and induce a stronger adherence to the endothelium.[57,62] Leukocyte extravasation can involve a paracellular or a transcellular route, possibly due to variable cell signaling.[57,63]

The immunologically privileged state of the CNS paraphrases the fact that certain foreign antigens circumvent the systemic immunological recognition in order to avoid impairment of neuronal tissue by cytotoxic cells.[64] Nevertheless, microglia, macrophages and other perivascularly located cells may circulate from the blood to the brain parenchyma to fulfill routine surveillance.[65,66]

Immunopathogenesis of Cerebral Toxoplasmosis

Immunosuppression of the host as in the case of immunosuppression caused by AIDS and transplantation may lead to the

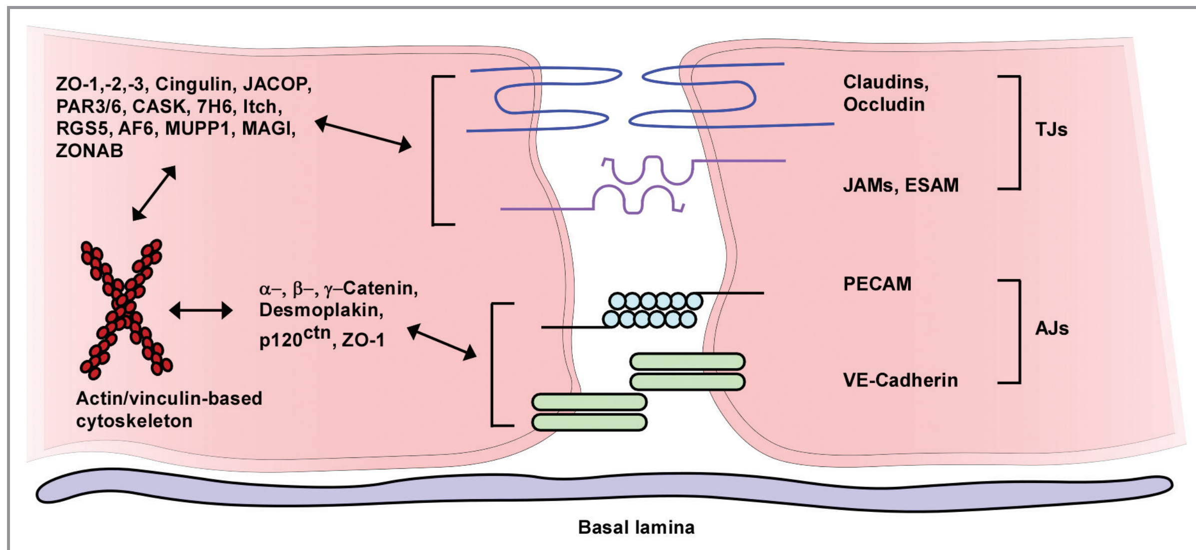

Figure 3. Assembly of endothelial tight junctions. Transmembranous molecules like claudins, occludin, junctional adhesion molecules (JAMs) and endothelial selective adhesion molecule (ESAM) are important tight junction components. On the cytoplasmic site these proteins are connected to adaptor and regulatory/signaling proteins [zonula occludens-1, -2 and -3 (ZO-1–3), cingulin, junction-associated coiled-coil protein (JACOP), the partitioning defective proteins 3 and 6 (PAR3/6), Ca^{2+}-dependent serine protein kinase (CASK), tight junction-associated protein 7H6, Itch (E3 ubiquitin protein ligase), regulator of G-protein signaling 5 (RGS5), afadin (AF6), multi-PDZ-protein 1 (MUPP1), MAGI (membrane-associated guanylate kinase with inverted orientation of protein-protein interaction domains), ZO-1-associated nucleic acid-binding protein (ZONAB)], which link the membranous components to the actin/vinculin-based cytoskeleton. Vascular endothelial cadherin (VE-cadherin) and the platelet-endothelial cell adhesion molecule (PECAM) are components of endothelial adherens junctions and interact via homophilic bindings. Catenins, desmoplakin and p120 catenin ($p120^{ctn}$) connect the adherence junction proteins with the cytoskeleton (modified from ref. 55, with permission).

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uncontrolled release of parasites during rupture of tissue cysts in the brain of latently infected individuals. Subsequently, released bradyzoites converting into rapidly proliferating tachyzoites may cause reactivated toxoplasmosis and lethal encephalitis if left untreated.[12,13] In seropositive AIDS patients cerebral toxoplasmosis is among the most frequent CNS pathologies and as many as one third of all *T. gondii*-infected HIV-positive patients not treated with antiretroviral therapy may develop toxoplasmic encephalitis (TE).[67,68] A CD4 T-cell count of $< 200/\mu l$ renders a seropositive patient susceptible to reactivation and the onset of TE.[69]

As a primary response to infection with *T. gondii,* macrophages, granulocytes and dendritic cells secret proinflammatory cytokines, i.e., IL-12, the most important inducer of IFN-γ synthesis.[70] A proper IFN-γ production in turn is inevitable for successful host resistance against infection with the parasite.[71] Activated antigen-presenting cells together with IFN-γ support the proliferation of $CD4^+$- and $CD8^+$-T cells that are subsequently recruited to the brain.[72] $CD8^+$-T cells are essential in resistance due to their cytotoxic action as they lyse Toxoplasma infected cells during the active phase of infection.[73] $CD4^+$-T cells and astrocytes also contribute to resistance and activate $CD8^+$-T cells by secretion of cytokines.[74,75] During acute TE, monocytes, $CD4^+$- and $CD8^+$-T cells migrate into the CNS and activate resident microglia cells.[76-78] Nevertheless, glial cell activation might be observed before parasite invasion of the CNS due to systemic levels of pro-inflammatory cytokines during acute infection.

The movement of infiltrating cells was associated with an infection-induced reticular system of fibers.[79] Thus, the inflamed brain appears to induce specialized structures that guide the migration of T cells in this immuno-privileged environment whereas pre-existing scaffolds for guidance of lymphocyte migration exist in other tissues. Astrocytes and microglial cells become activated by IFN-γ and are major effector cells in the control of parasite replication.[78] Upon infection, astroglia and microglia secrete IL-1, IL-6, GM-CSF or IL-10 and TNF, respectively.[10] During TE a microglial upregulation of adhesion molecules like LFA-1 and Mac-1 was observed.[80] As there is also a prominent upregulation of the cell adhesion molecule ICAM-1 on cerebral endothelia and choroid plexus epithelium during acute and chronic TE, this may support the infiltration of circulating leukocytes.[80] Although the cell adhesion molecule VCAM-1 has been shown to mediate control of infection with *T. gondii*, other adhesion molecules may compensate for the leukocytic homing functions of VCAM-1.[81] The production of IL-10 in *T. gondii*-infected brains favors parasite survival and therefore rather aids chronicity of the infection.[82,83]

While DCs cannot be detected in the brain parenchyma of healthy hosts, brains of chronically infected mice show a 50- to 100-fold expansion of DCs upon brain infection. The marked increase might be explained by the development of DCs from infiltrating blood monocytes, the recruitment of meningeal DCs, the proliferation and differentiation of perivascular macrophages or the development of brain DCs from intracerebral progenitors or resident microglia. These brain-derived DCs resemble a myeloid subset of mouse DCs and are related to macrophages/microglia.[84] The recruitment of DCs to the CNS seems to be dependent on the signaling through multiple chemokine receptors and possible changes in the affinity of the leukocyte integrin

LFA-1.[85] Based on their strong expression of costimulatory molecules and the ability to process and present antigen to naive T cells in vitro brain DCs are supposed to be important inducers of T cell responses in TE.[85] As brain DCs also show a high level of IL-12 production ex vivo they might be important for maintaining IFN-γ production by T cells in the brain.[84] In low doses brain DCs induced significantly higher T cell proliferative responses compared with normal spleen DCs although this effect was reversed in experiments where higher doses of DCs were used.[84] The presence of IFN-γ is an important requirement for the immune system to control acute and chronic infections with *T. gondii*. IFN-γ mediates a variety of host anti-Toxoplasma immune mechanisms. Along with neurons, astrocytes are the most frequent host cells harboring cysts in the brain.[10,14,86] IFN-γ stimulation of astrocytes inhibits parasite growth through the production of reactive oxygen intermediates, the activation of indolamin-2,3-dioxygenase and the action of small GTPases.[87-90] Small GTPases of the IRG family are found in mice but not in humans. Mice lacking nitric oxide (NO) production develop severe necrotizing lesions and uncontrolled tachyzoite replication in the CNS during chronic infection.[91,92] Experiments with TNF-, lymphotoxin-α- and TNF/lymphotoxin-α-deficient mice revealed that TNF receptor type I-mediated immune reactions influence NO production and are crucial for the survival of mice with TE.[93]

It was shown in mice with TE that astrocytes are the main producers of the chemotactic cytokines IP-10 and MCP-1 while activated microglia and leukocytes infiltrating across the BBB also secrete chemokines.[94] Chemokine secretion is in turn responsible for an enhanced neuroinvasion of leukocytes as astrocyte derived MCP-1 can mediate the migration of monocytes across an in vitro model of the BBB.[95] In mice which lack the signal-transducing receptor gp130, astrocytes possess a crucial role in maintaining immunoregulatory functions during CNS infections with *T. gondii* by containing inflammatory lesions, supporting parasite control and preventing lethal necrotizing TE.[96] Microglial cell activation is dependent on the interaction of CD200 on blood vessel endothelial cells and CD200R on microglia during infection with *T. gondii*.[97]

In summary, *T. gondii* interferes with multiple arms of the innate immune system to ensure an environment suitable for sustained parasite growth in the absence of severe pathology. *T. gondii* is remarkably able to control its own fate via modulation of many of the intricate pathways described above that the host uses to try to kill it.[98]

Neuroinvasion by Pathogenic Microorganisms

Several human pathogens gain entry to the CNS by crossing the endothelium of cerebral microvessels or by crossing the epithelium of the choroid plexus. Additionally, the uptake and transport of pathogens may occur via unprotected axon endings in the periphery or along olfactory neurons that allow pathogens to reach the CNS.[99,100] Selected important pathogens are listed in **Table 1**.

Whereas extracellular bacteria typically cause severe acute meningitis (i.e., *S. pneumoniae* and *N. meningitidis*), encephalitis is often less severe and typically caused by intracellular pathogens (i.e., viruses and protozoa). Another group of organisms causes brain abscesses (i.e., *E. histolytica, Candida* spp and *Aspergillus* spp). It is tempting to speculate that the route of entry and the immune response elicited by these pathogens impacts the clinical outcome of CNS disease.

Beside the anatomical localization of CNS entry, the mechanisms of neuroinvasion differ among pathogens. Crossing the cells of the blood-brain barrier can occur paracellularly, transcellularly or inside infected leukocytes (Trojan horse mechanism). In paracellular migration, pathogens must pass the tight junction proteins connecting neighboring cells while transcellular migration is characterized by uptake of microorganisms by endothelial cells of the BBB or direct infection by pathogens to invade the CNS.[99] In vitro experiments with *Trypanosoma brucei*[101] and *Borrelia burgdorferi*[102] point to a paracellular migration across cells in a human BBB model while *Cryptococcus neoformans*,[103] *Candida albicans*,[104] *Escherichia coli*,[105] *S. pneumoniae*[106] and West Nile virus[107] cross the endothelial barrier in a transcellular way. For *N. meningitidis* both ways of migration seem to be possible.[108,109]

In addition to paracellular and transcellular neuroinvasion there exists a way of intracellular pathogen trafficking in which host leukocytes are used as vehicles for transport purposes. Infection with certain pathogens subverts host signaling cascades and affects

Table 1. Selected important pathogens that cross the BBB

Bacteria	Viruses	Helminths	Protozoa	Fungi
Neisseria meningitidis	human immunodeficiency virus	*Schistosoma mansoni*	*Toxoplasma gondii*	*Candida albicans*
Escherichia coli	tick-borne encephalitis virus	*Taenia solium*	*Trypanosoma brucei*	*Cryptococcus neoformans*
Streptococcus pneumoniae	enteroviruses	*Echinococcus granulosus*	*Entamoeba histolytica*	*Aspergillus* spp
Listeria monocytogenes	herpes viruses	*Toxocara canis*	*Balamuthia mandrillaris*	
Mycobacterium tuberculosis	rabies virus	*Trichinella spiralis*	*(Plasmodium falciparum)**	
Treponema pallidum	JC virus			
Bacillus anthracis	West Nile virus			
Staphylococcus aureus	measles virus			
Borrelia burgdorferi				

**P. falciparum* does not cross the BBB and remains physiologically outside the BBB but symptoms are present in the CNS

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proinflammatory responses of infected host cells.[38,110,111] Host cells may present a save shelter for intracellular pathogens. Through intracellular migration the pathogen can evade microbicidal effectors and clearance by the host immune response, while the downregulation of proinflammatory responses in the host supports survival of host and pathogen.[112-114] In case of *Listeria monocytogenes* several ways of bacterial migration have been described. Ly6C-positive monocyte populations are exploited by *L. monocytogenes* as "Trojan horses" for their passage across the BBB; in addition, an axonal uptake and transport of bacteria via the trigeminal nerve and transcellular ways of migration through an endothelial barrier have been shown.[115-118] The infection of endothelial BBB cells with human immunodeficiency virus in turn impairs BBB functions and facilitates the migration of potentially infected monocytes into the brain.[119,120]

Dissemination and Neuroinvasion of *T. gondii*

Reactivated toxoplasmosis in mice is typically localized in the frontal and parietal cortex, and sites of reactivation are found perivascularly thereby supporting the idea of parasite dissemination from the bloodstream into the CNS.[13] Tachyzoites of *T. gondii* are sensitive to several arms of the humoral immune responses of the host. First, sera containing antibodies directed against Toxoplasma mediate parasite lysis by activation of the complement system while *T. gondii*-specific IgM blocks host cell invasion by tachyzoites. For this reason the intracellular habitat of the parasite poses important survival and dissemination advantages.[121-123]

Parasite- and host cell-specific factors of invasion and dissemination. After the ingestion of cyst-containing material the epithelium of the small intestine is the first cellular barrier the parasite crosses before disseminating in the host. Extracellular tachyzoites were shown to actively overcome cell monolayers and migrate into deeper cell layers.[5,124] As *T. gondii* lacks cilia or flagella it relies on a type of migration called gliding motility.[125,126] The invasion of host cells is an active process and no contribution of the host cell is required. The penetration itself is mediated by the secretion of distinct parasite proteins into the host cells.[127,128] Upon infection micronemal proteins (MICs) are exocytosed from the apical site of the parasite and are secreted into the host cell.[129] A micronemal protein called MIC2 is displayed on the apical surface of the parasite and appears to bind the host cell adhesion molecule ICAM-1. Before paracellular migration across cell layers parasites seem to localize near intercellular junctions while maintaining cell barrier integrity.[128,130] Toxoplasma infection can induce modulations in the expression of different cell adhesion molecules and cytokines in host cells. Upon infection with *T. gondii* tachyzoites, brain endothelial cells upregulate ICAM-1 expression as soon as 2 h post-infection while the secretion of the chemokine MCP-1 occurrs by 12 h post-infection.[131] The upregulation of CD44 and ICAM-1 on the surface of *T. gondii*-infected human monocytic cells leads to a better adherence of infected cells to immobilized hyaluron compared with uninfected cells. Thereby *T. gondii*-infected monocytes of the circulating blood might improve their capacities to bind to extracellular matrix and favor their extravasation into deeper tissues.[132] When monolayers of human HeLa epithelial cells and fibroblasts were infected with *T. gondii* an increase in the secretion of the proinflammatory and chemoattractant cytokines IL-8, GRO-α and MCP-1 was observed.[133] Human retinal pigment epithelial cells respond to infection with *T. gondii* with the secretion of IL-1, IL-6, GM-CSF and ICAM-1 while infected BUVEC cells upregulate the expression of the chemokines GRO-α, IL-8, IP-10, MCP-1, RANTES and GM-CSF.[134,135]

Thus, proinflammatory chemokine secretion and upregulation of adhesion molecules or immunomodulatory molecules appears to be an important host cell response to infection with *T. gondii* and could favor the entry of Toxoplasma infected leukocytes into the CNS.

Intracellular vs. extracellular invasion of the CNS. Courret et al.[6] showed that during the early phase of infection and dissemination *T. gondii* tachyzoites are frequently associated with $CD11c^+$ and $CD11b^+$ leukocytes of the lamina propria, Peyer's patches, and lymph nodes. A few days later blood leukocytes harboring *T. gondii* are mainly $CD11c^-/CD11b^+$. Seven days after intragastrical delivery of Toxoplasma cysts into mice an increased number of $CD11b^+$ and $CD11c^+$ cells could be detected in the brain so that these two leukocyte subsets accounted for about 60% of the total cells that had migrated from the blood to the brain by this time point. Fifteen days after oral infection parasites were found in the brain in both $CD11c^+/CD11b^{+/-}$ and $CD11c^-/CD11b^+$ leukocyte populations. In other experiments it was shown that in the brains of 7- or 9-d parasitized mice the majority of parasites could be found in leukocytes that must have infiltrated the brain earlier before.[6] We used an in vitro co-culture model of the BBB to investigate the migratory capacities of infected and uninfected antigen presenting cells. Blood mononuclear cells from rats were infected with *T. gondii* tachyzoites. After migration through an in vitro model of the BBB the percentage of infected $CD45^+/CD11bc^+$ cells in the migrated fraction was 13-fold higher compared with the percentage in the starting population. Also, infection rates in the migrated $CD45^+/CD11bc^+$ fraction showed a 5-fold increase compared with the same population before migration; infection rates of infected $CD45^+/CD11bc^+$ cells were 18-fold higher than those of $CD45^+/CD11bc^-$ cells. Interestingly, not only infected but also uninfected $CD45^+/CD11bc^+$ cells showed enhanced migratory capacities through the BBB model.[131] $CD11b^+/CD11c^+$ mouse dendritic cells were preferably infected among all $CD11b^+$, $CD11c^+$ and double positive cells. Nevertheless, infected $CD11b^+/CD11c^-$ cells—most likely monocytic cells—dominated the infected antigen presenting cell population after migration through an in vitro BBB model. Interestingly, $CD11b^+/CD11c^-$ cells showed an increased overall migration potential compared with other PBMC subpopulations.[131]

Parasite-Dependent Effects on Host Cell Motility and Parasite Dissemination

Interestingly type I and type II strains differ in their ability to recruit cells to the site of infections. Type I strains preferentially attract neutrophils ($Gr\text{-}1^+/CD68^-$) while type II strains are more

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often associated with activated macrophages ($CD68^+$/$Gr\text{-}1^+$).[136] *T. gondii* also seems to alter host cell motility to promote its own dissemination. DCs were challenged with live parasites and allowed to migrate in a transwell system. In response to active invasion by *T. gondii* tachyzoites, dendritic cells adopted a state of hypermotility that enabled them to cross biological barriers at higher frequencies than uninfected DCs. According to the dose dependent modulation of cell motility the absolute number of migrating cells also increased with higher MOI.[137] While infected macrophages increased their migration rate 6–20-fold, other leukocytes did not show a modified migratory phenotype upon infection.[138] The subversion of host cell properties is furthermore a genotype specific matter as infections with type II strains lead to higher host cell migration rates than infections with type I or type III strains do.[139] Type I strain tachyzoites in turn are capable of migrating longer distances on host-cell monolayers as extracellular parasites.[5] This strain dependent characteristic is possibly one feature that allows tachyzoites of the type I strain a quicker proliferation in the infected host and thereby mediates the pronounced virulence in mice.[140] Despite the fact that type II strains only show a moderate expansion and less pronounced extracellular migration type II tachyzoites are nevertheless successful in establishing latent infections; thus, these parasite may exploit alternative (intracellular) habitats for effective dissemination.[121] Although both strains show bias to infection of $CD11c^+$ compared with $CD11c^-$ cells, type II strains appear more often in intracellular compartments than type I strains do. When mice were co-inoculated with free type I and type II tachyzoites this resulted in a strong domination of type I parasites referring to the total parasite load in the spleen. While in case of type I strain parasites were found mainly extracellular the type II population showed an even distribution between intracellular and extracellular compartments.[139] Unno et al. used green and red fluorescent parasites of the type II PLK strain to establish an intracellular and an extracellular form of the parasite. Following injection into mice at the same time the majority of tachyzoites found in tissues corresponded to the tachyzoite form that had been administered inside host cells. The dissemination of intracellularly located parasites appeared to outperform the capacities of extracellular parasites in reaching peripheral sites of the host and thereby mediated a more widespread distribution.[141]

In conclusion, monocytes and dendritic cells are the most important candidates for the transport of *T. gondii* from the periphery to the immunologically privileged sites of the brain. Intracellular neuroinvasion represents the starting point for establishment of latent infection characterized by cyst formation.

Genetic Tools and In Vivo Imaging to Study the Immunopathogenesis of Infection with *T. gondii*

While the key host molecules involved in the immune response to *T. gondii* have been identified and analyzed with the help of gene knockout mice, knowledge on critical parasite molecules that specifically modulate the host's immune system is still embryonic. This might be in part because of a lack of communication between researchers focusing on basic parasite cell biology, who perform most of their assays in vitro and researchers, who work in vivo, focusing on the host's immune response.

In recent years the adaptation of several reverse and forward genetic tools established *T. gondii* as an attractive model system for apicomplexan parasites and general molecular biology.[142] However, these techniques are not frequently employed for the study of host-pathogen interactions and most of the times, the only in vivo experiments performed to study the function of a gene of interest are virulence studies (survival experiments), without a detailed analysis of the immune response.[143,144] Only in some cases knockout parasites have been analyzed in more detail to study for example tissue dissemination.[145] Parasite mutants with specific effects during their asexual life cycle could be useful tools to study the immunopathogenesis, i.e., if combined with in vivo imaging. Over the years several conditional parasite mutants have been generated with specific defects during invasion,[143-147] replication[148,149] or egress;[150,151] in most cases the underlying mechanism has been well described. While these mutants allow the dissection of the respective molecular pathway in vitro, they can also be used for studies of immunopathogenesis in vivo.

Various imaging techniques, including bioluminescent imaging, confocal and multiphoton microscopy have been applied to study the immunopathogenesis of infection with *T. gondii*. The ability to manipulate parasites to express fluorescent/bioluminescent markers or model antigens/enzymes combined with the development of reporter mice that allow the detection of distinct immune populations have been crucial to the success of many of these studies. These approaches have permitted the visualization of parasites and immune cells in real-time and provided new insights into the nature of host-pathogen interactions. In this regard, fluorescent tagged parasites and host cells allowed dynamic imaging of *T. gondii* interactions with—among others—T cells, neutrophils and astrocytes.[79,152-154] The use of the combinations of conditional knockout parasites with in vivo imaging will certainly increase to give novel insights into host-parasite interactions.

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