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. The infection is mostly acquired through the oral route by ingestion of *Toxoplasma* tissue cysts or oocysts from undercooked or raw food or water. 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. 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 testes. 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. 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. 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. 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.

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. Latent infection is thought to be asymptomatic but latent infection has been associated with manipulation of the host’s behavior and development of mental disorders including depression and schizophrenia.

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, retinocochoroiditis and encephalitis in immunocompromised individuals. 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, 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. 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. In humans type II strains of *T. gondii* were found in about 80% of patient samples. Recent reports support the association of atypical strains of *T. gondii* with more severe disease presentation in humans. In this regard the development and recurrence of ocular toxoplasmosis appear to be dependent on the *Toxoplasma* genotype in patient cohorts in Europe (Shohab 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 rheoptery (ROP) kinases, i.e., ROP16, ROP18 and the ROP5 pseudokinases that the parasite secretes into the host cell. ROP16 is a secreted protein kinase that leads to activation of the transcription factor STAT3.
and STAT6 in host cells that in turn downregulate the host immune responses. Type II strains of T. gondii show a defect in the kinase ROP16 and therefore fail to suppress immune responses. The downregulation of STAT3 and STAT6 activation after type II strain infection enhances the host’s ability to mount a protective Th1 immune response characterized by the production of IL12 and effective control of parasite replication. 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. 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.

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 choroidal plexus, and the blood-brain barrier (BBB) (Fig. 1). The arachnoid epithelium separates the subarachnoid cerebrospinal fluid from the basolateral site (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. 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 choroidal epithelium 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.
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 bloodstream 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 \( \alpha_4 \beta_7 \)) 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
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. 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 toxoplasmonic encephalitis (TE). A CD4 T-cell count of <200/μl renders a seropositive patient susceptible to reactivation and the onset of TE. As a primary response to infection with T. gondii, macrophages, granulocytes and dendritic cells secrete proinflammatory cytokines, i.e., IL-12, the most important inducer of IFN-γ synthesis. A proper IFN-γ production in turn is inevitable for successful host resistance against infection with the parasite. Activated antigen-presenting cells together with IFN-γ support the proliferation of CD4+ and CD8+ T cells that are subsequently recruited to the brain. CD8+ T cells are essential in resistance due to their cytotoxic action as they lyse Toxoplasma infected cells during the active phase of infection. CD4+ and CD8+ T cells contribute to resistance and activate CD8+ T cells by secretion of cytokines. During acute TE, monocytes, CD4+ and CD8+ T cells migrate into the CNS and activate resident microglia cells. Nevertheless, glial cell activation might be observed before parasite invasion of the CNS due to systemic levels of proinflammatory cytokines during acute infection. The movement of infiltrating cells was associated with an infection-induced reticular system of fibers. Thus, the inflamed brain appears to induce specialized structures that guide the migration of T cells in this immune-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. Upon infection, astroglia and microglia secrete IL-1, IL-6, GM-CSF or IL-10 and TNF, respectively. During TE a microglial upregulation of adhesion molecules like LFA-1 and Mac-1 was observed. 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. 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. The production of IL-10 in T. gondii-infected brains favors parasite survival and therefore rather aids chronicity of the infection. 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. 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. 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. 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. In low doses brain DCs induced significantly higher T cell proliferative responses compared with normal splenic DCs although this effect was reversed in experiments where higher doses of DCs were used. 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. IFN-γ stimulation of astrocytes inhibits parasite growth through the production of reactive oxygen intermediates, the activation of indolamine-2,3-dioxygenase and the action of small GTPases. 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. In mice which lack the signal-derived MCP-1 can mediate the migration of monocytes across the BBB producers of the chemotactic cytokines IP-10 and MCP-1 while 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. It was shown in mice with TE that astrocytes are the main producers of the chemokine IP10 and MCP-1 while activated microglia and leukocytes infiltrating across the BBB also secrete chemokines. Chemokine secretion is in turn reactivated microglia and leukocytes infiltrating across the BBB.

In summary, T. gondii interferes with 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.

**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. Several 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 cell, while transcellular migration is characterized by uptake of microorganisms by endothelial cells of the BBB or direct infection by pathogens to invade the CNS. In vitro experiments with Toxoplasma brucei point to a paracellular migration across cells in a human BBB model while Cryptococcus neoformans, Candida albicans, Escherichia coli, S. pneumoniae and West Nile virus cross the endothelial barrier in a transcellular way. For N. meningitidis both ways of migration seem to be possible.

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

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**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             | Toxoplasma brucei          | Cryptococcus neoformans      |
| Streptococcus pneumonia           | enteroviruses             | Echinococcus granulosus   | Entamoeba histolytica       | Aspergillus spp              |
| Listeria monocytogenes            | herpes viruses            | Toxocara canis            | Balanomastix mandibularis  |                              |
| Mycobacterium tuberculosis        | rabies virus              | Trichinella spiralis      | Plasmodium falciportii*    |                              |
| Treponema pallidum                | JC virus                  |                           |                            |                              |
| Brucella abortus                  | West Nile virus           |                           |                            |                              |
| Staphylococcus aureus             |                           |                           |                            |                              |
| Borrelia burgdorferi             |                           |                           |                            |                              |

*P. falciportii does not cross the BBB and remains physiologically outside the BBB but symptoms are present in the CNS.*
proinflammatory responses of infected host cells.108-110 Host cells may present a safe 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.111-113 In case of Listeria monocyctogenes 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, axonal uptake and transport of bacteria via the trigeminal nerve and transcellular ways of migration through an endothelial barrier have been shown.114-116 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.117,118

Dissemination and Neuroinvasion of T. gondii

Reactivated toxoplasmosis in mice is typically localized in the frontal and parietal cortices, and sites of reactivation are found perivascularly thereby supporting the idea of parasite dissemination from the bloodstream into the CNS.119 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.120-122

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 parasite crosses before disseminating in the host. Extracellular tachyzoites were shown to actively overcome cell monolayers and migrate into deeper cell layers.123,124 As T. gondii lacks cilia or flagella it relies on a type of migration called gliding motility.125 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.126-128 Upon infection micronemal proteins (MICs) are excreted 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.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 occurs by 12 h post-infection.131 The upregulation of CD44 and ICAM-1 on the surface of T. gondii-infected human monocytes leads to a better adherence of infected cells to immobilized hyaluronan 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 chemotaxicant 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.134-137

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. Courert et al.7 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, Peyers’ patches, and lymph nodes. A few days later blood leukocytes harboring T. gondii are mainly CD11c+ /CD11b- . Seven days after intragastric 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.138 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+ /CD11b+ cells in the migrated fraction was 13-fold higher compared with the percentage in the starting population. Also, infection rates in the migrated CD45+ /CD11b+ fraction showed a 5-fold increase compared with the same population before migration; infection rates of infected CD45+ /CD11b+ cells were 18-fold higher than those of CD45+ /CD11b- cells. Interestingly, not only infected but also uninfected CD45+ /CD11b+ cells showed enhanced migratory capacities through the BBB model.139 CD11b+ /CD11c+ mouse dendritic cells were preferably infected among all CD11c+, CD11b+ 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.140

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-1+/CD68- ) while type II strains are more...
often associated with activated macrophages (CD68+/Gr-1+). While type II tachyzoites, dendritic cells adopt 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. While infected macrophages increased their migration rate 6-fold, other leukocytes did not show a modified migratory phenotype upon infection. 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. Type I strain tachyzoites in turn are capable of migrating longer distances on host-cell monolayers as extra-cellular parasites. This strain dependent characteristic is 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. 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. Although both strains show bias to infection of CD11c+ cells, type II strains appear more often in intracellular compartments than type I strains do. When mice were infected 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. 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 intra-cellularly located parasites appeared to outperform the capacities of extracellular parasites in reaching peripheral sites of the host and thereby mediated a more widespread distribution.

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 studies 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. 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. Only in some cases knockout parasites have been analyzed in more detail to study for example tissue dissemination. Parasite mutants with specific effects during their sexual 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 infection, replication or egress; in most cases the underlying mechanism has been well described. While these mutants allow the dissection of the respective molecular pathways 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/antibodies 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. 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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