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Conceptual Paper

Toxoplasma gondii: A Journey into the Brain

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Toxoplasma gondii is one of the most widespread zoonotic parasites in the world. It is an obligate intracellular protozoan that can infect all warm-blooded animals including humans as intermediate hosts and cats are its definitive host [1]. *T. gondii* infects humans via ingestion of undercooked meat containing tissue cysts, or food and water contaminated with sporulated oocysts or via vertical transmission from mother to baby [2].

T. gondii can establish a life-long, latent infection in tissues such as muscles, the central nervous system and eye with the brain as the major affected organ [3]. Within a short period of time following infection, the tachyzoite actively crosses the first cellular barrier by penetrating enterocytes [4,5]. Intracellular tachyzoites form a parasitophorous vacuole that ruptures following replication leading to dissemination of tachyzoites throughout the body including some protected sites such as brain, retina and fetus [6,7].

Several pathogens can cross the blood-brain barrier (BBB) such as bacteria e.g. *Neisseria meningitides*, *Listeria monocytogenes* and *Escherichia coli*, viruses e.g. human immunodeficiency virus, rabies virus and tick-borne encephalitis virus, helminths e.g. *Trichinella spiralis*, *Echinococcus granulosus* and *Taenia solium*, protozoa e.g. *Toxoplasma gondii*, *Trypanosoma brucei* and *Entamoeba histolytica* and fungi e.g. *Candida albicans*, *Aspergillus* spp. and *Cryptococcus neoformans* [8].

The BBB is a selective barrier that can exclude large peptides and proteins and only allow free diffusion of gaseous molecules like oxygen and carbon dioxide and immune cells [9,10].

T. gondii has developed three mechanisms for crossing the BBB: paracellular entry, transcellular entry and 'Trojan horse' mechanism.

Paracellular entry: *T. gondii* migrates directly through the tight junction proteins that connect neighboring cells of the endothelial cell layer. *T. gondii* is able to propel itself by its gliding motility using actin-myosin motors [11]. Some studies verified this mechanism of entry such as those by Barragan and Sibley [12] and Tardieux and MeÂnard [13]. They showed that *Toxoplasma* is able to cross polarized cell monolayers and extracellular matrix, which mimic the BBB.

Transcellular entry: Uptake of *Toxoplasma* by endothelial cells of the BBB followed by replication, then lyses of the host cells [14,15]. Moreover, tachyzoites are able to adhere to CNS endothelial cells, invade, replicate, then released into the CNS parenchyma [15]. In support of this mechanism, early CNS infection where no infected infiltrating immune cells are yet detected [16].

'Trojan horse' mechanism: Infected immune cells can cross the BBB, bringing the intracellular parasite into the brain parenchyma. Courret., *et al*. [5] and Lambert., *et al*. [17] found that intravenous inoculation of mice with *Toxoplasma* infected macrophages or dendritic cells led to a rapid appearance of parasites in the CNS more than if free parasites were inoculated. Once infected, dendritic cells develop a state of hypermotility. Interestingly, not only infected but also uninfected cells showed greater migratory abilities through the BBB with a 5-fold increase in the infection rates in the migrated cells [17,18].

Courret., *et al*. [5] showed that seven days after oral infection of *Toxoplasma* cysts in mice, an increased number of infected leukocytes could be detected in the brain and it was the same leukocyte subset that was detected earlier in the lamina propria, Peyer's patches, and lymph nodes. These infected immune cells represent about 60% of the total cells that had migrated from the blood to the brain.

The invasion of host cells is an active process mediated by the secretion of distinct molecules of parasite origin into the host cells [19]. Upon infection micronemal proteins (MICs) are secreted from the apical complex of the parasite into the host cell which bind to the host intracellular adhesion molecule (ICAM)-1 [19-21]. Interestingly, it was found that expression of ICAM-1 on the surface of *T. gondii*-infected monocytes in the circulating blood leads to a better adherence of infected cells to extracellular matrix and favor their leakage into deeper tissues [22].

Besides, *Toxoplasma* infection can modulate the expression of different pro-inflammatory and chemoattractant cytokines in host cells e.g. monocyte chemoattractant protein-1 (MCP-1), interleukin (IL-8) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Thus, pro-inflammatory cytokines together with cell adhesion molecules appear to be in favor of the entry of *Toxoplasma* infected leukocytes into the CNS [8,18]. After crossing the BBB, *Toxoplasma* invades both astrocytes and neurons. Astrocytes can clear the parasites while neurons couldn't clear all, leaving neurons as source for persistent infection [23].

Host cell invasion by *T. gondii* is an efficient rapid multistep process which is critical for the survival and dissemination of the parasite. That is why *Toxoplasma* is one of the most successful parasites.

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Volume 1 Issue 3 March 2018