

Review articles

Toxoplasma gondii and the host cells[1]

Henryka Długońska

Department of Immunoparasitology, Faculty of Biology and Environmental Protection, University of Lodz, Banacha 12/16, 90-237 Łódź, Poland

Corresponding author: Henryka Długońska; e-mail: hdlugo@biol.uni.lodz.pl

ABSTRACT. The protozoan *Toxoplasma gondii*, described by Nicolle and Manceaux in 1908, is a ubiquitous and cosmopolitan parasite that infects a wide range of mammal and bird species with high prevalence. The biological success of *T. gondii* is associated with the formation of a specific relationship between the parasite and host cells leading to the establishment of a latent, chronic infection. During primary infection, acquired mostly by the oral route, the quickly multiplying tachyzoites disseminate through the body crossing several structural-functional barriers as blood-brain or blood-retina, then they transform into dormant bradyzoites which, enclosed in tissue cysts, occupy preferentially the brain, skeletal muscle and eye. Although *T. gondii* is able to infect all kinds of nucleated cells, it uses strictly defined host cells, dependent on the life-cycle phase and infection stage. The article discusses selected aspects of the parasite passing *via* the host body barriers as well as particular role of dendritic cells and skeletal muscle cells, used by the parasite as an very effective vehicle to disseminate throughout the host body or the site of long-term *T. gondii* persistence, respectively.

Key words: *Toxoplasma gondii*, host barriers, dendritic and muscle cells

Introduction

The protozoan *Toxoplasma gondii* is believed to be one of the most successful parasites on earth. Its biological success could be expressed by its cosmopolitan occurrence, a very wide host range (almost all species of endothermic animals and humans), an ability to infect all nucleated cells of an individual host and high infection prevalence achieving in several local populations nearly 100%. The parasite is estimated to infect over one billion people worldwide, although there is a wide geographic variation in the prevalence of latent *T. gondii* infection Once infected, people and other hosts generally retain a chronic infection that in the light of current knowledge is usually asymptomatic but may lead to a variety of pathologies [2].

Toxoplasma gondii, described in 1908 by Nicolle and Manceaux in the dessert rodent *Ctenodactylus gundii* and by Splendore in the laboratory rabbit, first seemed to be a relatively mild parasite in contrast to *Plasmodium,* which had been described almost 30 years before [3]. Extensive research on *T. gondii* and toxoplasmosis has significantly modified this opinion and has thrown new light on the sophisticated relation between this obligatory intracellular parasite and host cells.

Although *Toxoplasma gondii* is essentially able to infect all kinds of nucleated cells of its hosts, it uses preferentially a defined one, depending on the developmental stage and the infection phase. For instance, sexual *T. gondii* reproduction occurs only in enterocytes of a definitive parasite host (family Felidae members), whereas in the brain and skeletal muscle cells the conversion of tachyzoites to bradyzoites takes place starting the chronic phase of toxoplasmosis and long-term persistence of the parasite, usually until the host's death. Long-lasting persistence in rodent brains associated with behavioural changes in the hosts favour the parasite's transmission to definitive host to complete life cycle [4,5]. Secondly, the presence of

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bradyzoites in the muscles of many farm animals enables the wide transmission to carnivores and omnivores [6,7].

Biological barriers restrict partially the distribution of *T. gondii* in the host

How does *T. gondii* move and disseminate throughout the host body? The parasite is not equipped with any specific surface locomotory organelles as cilia or flagella but it is able to move very intensively using an actomyosin motor complex. Håkansson et al. [8] distinguished three major types of *T. gondii* motility: circular or helical gliding (which leads to forward parasite movement) and twirling. Dissemination of the parasite from the primary infection site (mainly gut epithelium) to secondary tissues occurs *via* intracellular and extracellular mechanisms. *Toxoplasma* can flow freely in host fluids, migrate on cell layers (endothelium, epithelium), cross them (paracellular route) or use motile host cells as vehicles (intracellular route) to achieve distant or hardly accessible organs [9,10].

The most serious forms of toxoplasmosis are due to crossing many biological barriers of the infected host and entering immunoprivileged organs. The immune privilege concept was formulated in the 1940s by Peter Medawar, who stated that the brain and anterior chamber of the eye, due to the absence of lymphatics or blood vessels, are classical immune privilege sites, free from anti-allotransplant reaction and inflammatory response [11]. In general, this immune phenomenon is thought to be a homeostasis mechanism and a kind of evolutionary adaptation to protect very important biological functions of certain organs (tissues). The term immune privilege has been extended to placenta, foetus and testicles and many other tissues. For instance, it develops *de novo* in accepted vascularized grafts [12] or even in several separate compartments of blood vessels during arteriosclerosis [13].

Crossing the blood-brain, blood-eye or placenta (maternal-foetal) barriers by *T. gondii* tachyzoites initiates the development of infection leading to neurotoxoplasmosis, ocular toxoplasmosis (toxoplasmic retinochoroiditis) and congenital toxoplasmosis, respectively [14].

Brain. The blood-brain barrier (BBB) is essential for the brain to maintain homeostasis and a favourable environment for neurons and other cells to carry out their normal functions. The BBB relies on very tight junctions between capillary endothelial cells that line the inner walls of cerebral blood vessels and separate brain blood vessels and parenchyma. This barrier characterized by an extremely high electrical resistance of at least 1000 Ωcm^{-2} is a unique feature of brain capillaries. Additionally, the blood-cerebrospinal fluid barrier (B-CSF) is composed of tight junctions between epithelial cells in choroid plexus epithelium and arachnoid epithelium, thus cerebrospinal fluid is doubly protected. The barrier function of BBB endothelial cells is additionally supported by surrounding cells like pericytes, astrocytes and microglia which secrete anti-inflammatory cytokines (like TGF-β). However, pro-inflammatory cytokines (like IL-1, TNF) as well as mediators of anaphylaxis (like histamine) and several drugs damage the BBB [15]. Collectively, despite a variety of cooperative and protective barrier mechanisms of the BBB, several microorganisms including protozoan parasite *Toxoplasma gondii* are able to cross it. It was found that extracellular tachyzoites can pass polarized cell monolayers *in vitro* and *in vivo*. The passage involves *T. gondii* gliding motility and interaction of the parasite's MIC2 antigen with host cell surface adhesion molecule ICAM-1 (intercellular adhesion molecule) [16]. The process is referred as paracellular transmigration. The tachyzoites of *T. gondii* genotype I (RH, BK, etc.), highly virulent to mice, enter the bloodstream as free cells or paracellularly, whereas those of genotype II (ME49, DX etc., cyst forming and low virulent to mice) – mainly by intracellular transmigration [17], changing the phenotype of vehicle cells from adhesive to hypermigratory as described in the next section concerning dendritic cells.

After crossing the barrier, *T. gondii* tachyzoites transform into bradyzoites, which enclose in tissue cysts distributed throughout the brain. A strictly selective tropism of *T. gondii* was not observed [4] although the systematic mapping has recently revealed that some brain regions exhibited consistently higher cysts density than others. These included the olfactory bulb, the entorhinal, somatosensory, motor and orbital, frontal association and visual cortices, and, particularly important, the hippocampus and the amygdala, which are involved in defence behaviours control and emotion processing [18]. A confocal microscope study performed on a mouse model revealed that cysts occur almost exclusively in neurons throughout chronic infection [19].

Using *in vivo* bioluminescence imaging it was found that recrudescence of toxoplasmosis in immunocompromised mice was characterised by a multifocal distribution located primarily in the frontal and parietal cortex and more commonly in the gray matter than in the white matter. Reactivation foci were found perivascularly, confirming that passage would occur preferentially in the peripheral microvasculature [20].

Eye. The eye is a specialized sense organ whose internal compartments are separated from blood and lymphatic circulation by the blood-aqueous (BAB) and the blood-retinal (BRB) barriers. The BAB consists of three components: tight intercellular junctions of the endothelial cells (in the blood vessels of the ciliary body), non pigmented epithelial cells of the ciliary body and posterior iridial epithelium cells. These layers have tight junctions of the „leaky" type. The BRB is a binary element composed of the inner barrier, formed by tight junctions between endothelial cells of the retinal vessels, and the outer barrier, which is supported by tight junctions between retinal pigment epithelium cells that separate the choroidal fluid from the retinal layers [21,22]. The retina is the primary site of toxoplasma infection in the eye and it is where infection lesions are mainly located. Tachyzoites of *T. gondii* get into the eyeball *via* a restrictive blood-retinal barrier, using both the paracellular route (mediated by the actin-myosin parasite motor and the interaction of the parasite adhesion molecule MIC2 and host ICAM-1) or the intracellular route (inside dendritic cells) [23,24]. In an *ex vivo* migration assay performed by Furtado et al. [25] on human posterior eyecups, tachyzoites were found primarily in retinal nerve fiber layer, 8 hours after experimental infection. After entering the retina, they can navigate multiple tissue layers. Interestingly, they preferentially infect glial cells (as compared to neurons), which are located throughout the retina.

Placenta. The placenta in humans and other mammals is a chimeric organ composed of two anatomical interfaces between the mother and the foetus: the main one is the villous region, where maternal blood bathes syncytiotrofoblast (multinuclear layer) and the second – maternal decidua, where mononuclear, extravillous trophoblasts anchor the villous tree to the uterus. Using atomic force microscopy, it was demonstrated on the murine experimental model that the multinuclear syncytiotrophoblasts have a greater elastic modulus than mononuclear trophoblasts and, due to the unusually dense actin structure, are resistant to physical deformation as well as to infections [26]. The syncytial actin cytoskeleton is a general element of the placenta discrimining the pathogens entry. Tachyzoites of *T. gondii* preferentially colonise extravillous trophoblasts [27].

Similarly to *T. gondii*, its narrow relative, *Neospora caninum,* crosses the placenta using both intracellular and paracellular transmigration mechanism [28].

Dendritic cells in *T. gondii* infection

Dendritic cells (DCs) play a key function in adaptive immunity of mammalian species. DCs are located in those tissues that are in contact with the external environment, such as the skin and the inner lining of the respiratory, alimentary and genitourinary tracts. They are referred to as professional antigen-presenting cells (APCs), able to induce a primary immune response in naïve T lymphocytes, maintain B cell function and establish the immunological memory. To perform antigen presentation, DCs process an antigen intracellularly and then expose antigenic epitopes on the cell surface, in the context of MHC molecules. The cells migrate to the local lymph nodes and there specific, naïve T lymphocytes recognize the presented epitopes with the contribution of co-stimulatory molecules. The parasite's antigens could be delivered into the host cell by *T. gondii* invasion or phagocytosis. Dendritic cells are an important source of IL-12 during *T. gondii* infection, and they are also specialized for high-level antigen presentation to T lymphocytes [29]. A recent study by Dupont et al. [30] has revealed that *T. gondii* infects disproportionally dendritic cells and macrophages. Infected dendritic cells are required for optimal CD4+ and CD8+ responses whereas phagocytosis of heat-killed or invasion-blocked parasites was not sufficient. The active penetration of DCs leads to many morphological, phenotypic and functional changes such as:

a) rapid rearrangement of the cytoskeleton,
b) taking a spherical form,
c) loss of podosomes (actin-rich structures on the surface of animal cells, responsible for the adhesion on the host cells) and the appearance of numerous filopodia (thin membrane protrusions) as well as veil membranes,

d) transformation of adhesive into hypermigratory phenotype.

T. gondii strains of genotypes II and III induce the transformation more strongly than the strains of genotype I [31,32].

The hypermigratory cells are able to cross polarized epithelial monolayers and membrane filters. Besides, infected DCs start to secrete neurotransmitter GABA (γ-aminobutyric acid), and, as they possess functional $GABA_A$ receptors, they could be defined as GABA-ergic cells. Inhibition of the GABA-ergic signalling system significantly reduces the velocity of infected DCs *in vitro* and thereby the magnitude of the chemotactic response *in vitro* but it does not contribute to the cell morphology changes. The late phase (12-24 h postinfection) is characterised by changes of chemokine receptors, namely CCR7 are up-regulated, whereas CCR5 are down-regulated [33].

Muscle cells as a site of *T. gondii* persistence

The distribution of tissue cysts in chronically infected individuals is dependent on the host species. For instance, in small rodents, intensively exploited in *T. gondii* experimental research, tissue cysts are mainly found in the brain [34], whereas in pigs, sheep and goats – in the skeletal and cardiac muscles [6]. Skeletal muscle cells, besides neurons, are thought to be a preferred cell type for *T. gondii* persistence during chronic toxoplasmosis and this opinion has been confirmed in recent study by Swierzy et al. [35] conducted on pigs and chickens experimentally infected by *T. gondii* DX oocysts. The muscle location plays an important biological role in the transmission of the parasite to carnivorous and omnivorous hosts including humans. For instance, multicenter studies in Europe revealed that the consumption of undercooked or cured meat products is a major risk factor of acute disease in pregnant women [36].

Differentiated skeletal muscle cells (myotubes), similarly to neurons, are permanently arrested in the G1 phase by cell cycle inhibitors $p21^{Waf1/Cip1}$ and retinoblastoma susceptibility protein, Rb [37]. Polynucleated mature myotubes, in contrast to proliferating myoblasts, create the best molecular and cellular conditions for *T. gondii* long-term persistence. They restrict parasite replication and trigger the transformation of tachyzoites to bradyzoites starting the tissue cyst formation and chronic infection. Tachyzoite-bradyzoite inter-conversion correlates with phosphorylation of eIF2a (eukaryotic translation initiation factor 2a) indicating that translational control plays a role in maintaining parasite dormancy [38]. Human division autoantigen, CDA-1 was found to cause inhibition of *T. gondii* replication associated with parallel expression of bradyzoite-specific markers [39]. As compared to myoblasts and fibroblasts, the mature myotubes considerably up-regulated the biosynthesis of pro-inflammatory cytokines (IL-1α, IL-1β, IL-23 as well as chemokine CCL-2) [35]. Besides, after treatment with IFN-γ, the major protective cytokine in anti-*T. gondii* immunity, they exhibited potent toxoplasmacidal activity but did not trigger a tachyzoite-bradyzoite conversion. Restriction of parasite growth was associated with up-regulated $NO^{\cdot}$ and immunity-regulated GTPases (IRGs) activities [40]. The results strongly support the thesis that mature skeletal muscle cells are immunocompetent, active effector cells in the local response to *T. gondii* within the muscle.

Final remarks

Described over 100 years ago and found worldwide, the protozoan *Toxoplasma gondii* is still an interesting object for parasitology, medicine and veterinary research. It is worth noting that the opinion on its pathogenicity to intermediate hosts has evolved, from mild (orphan) through opportunistic to serious pathogen [41], capable of killing immunocompetent individuals. The cases of severe toxoplasmosis recently observed in tropical areas express probably weak adaptation of intermediate hosts to so called exotic zoonotic *T. gondii* strains [42,43]. Numerous observations have also changed an earlier concept of subclinical chronic toxoplasmosis. The latest data show that this global and theoretically asymptomatic infection may result in the development of many pathologies such as psychosis, schizophrenia, systemic sclerosis, melanoma etc. [2]. The real biological success of *T. gondii* results from its perfect interactions with the host and use of several cell types for strictly defined purposes beneficial for the parasite. A cogent example are dendritic cells, which are exploited by the parasite to disseminate in the infected host and enter immune-privileged organs, present parasite antigens, produce pro-inflammatory cytokines and subvert signalling pathways to achieve persistent chronic but non-lethal infection [44]. Recent advances explained

how skilfully *Toxoplasma* manipulates the host physiology preventing both continuation of its species and survival of intermediate hosts.

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