Chapter

Introductory Chapter: The Significance of *Toxoplasma gondii* in Humans, and in Domestic and Wild Animals

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1. Introduction

1.1 *Toxoplasma gondii* and life cycle

Since 1908, when *Toxoplasma gondii* was isolated in a rodent (*Ctenodactylus gundi*), from which the parasite gained its name [1], more than a century has passed. Because of the crescent-shaped form of the parasite, the genus name was taken from the Greek word toxin, which means bow. It was not until 1970 that the entire life cycle of the parasite was revealed, considering cat (*Felis catus*) the only definitive host (DH) in which the parasite could complete its entire sexual life cycle [2]. *T. gondii* belongs to the *phylum Ampicomplexa*, which contains intercellular parasites with a polarized cell structure and an apical complex [3]. *T. gondii* life cycle is considered sexual and asexual with a characteristic complexity; it reproduces sexually in the DH and asexually in the intermediate hosts (IH) [4] with three distinct stages of reproduction: tachyzoites (replicating fast), bradyzoites (replicating slowly), and sporozoites (in sporulated oocysts). As described briefly, after consuming any of the three stages, wild and domestic cats are infected [5]; prepatent period typically lasts between 3 and 10 days until 19 days or more [6]. Digestive enzymes break down the cyst wall, releasing the bradyzoites [7] and allowing the infection of intestinal epithelial cells through asexual reproduction (schizonts). Merozoites are discharged and reinvade the intestinal epithelium when the schizont reaches maturity. After this stage, sexual differentiation is observed [5, 8], rising to flagellated microgametes and macrogametes and beginning fertilization [6], resulting in the production of a zygote (diploid) and growing into an unsporulated oocyst, which is discharged into the intestinal lumen and expelled from the DH. Sporulation of the oocysts takes from 1 to 5 days, depending on environmental variables such as temperature and humidity [9, 10]. Oocysts

have impermeable walls and are resistant to physical and chemical stimuli, living in damp soil and staying infectious for months [11]. The asexual cycle of *T. gondii* begins when an IH consumes contaminated water or food. In the gut, the sporozoites are released and infect the intestinal epithelial cells [5]. The IH may also gain *Toxoplasma* infection by consuming raw or undercooked meat, harboring bradyzoite-bearing tissue cysts. The freshly released bradyzoites convert into tachyzoites after entering the intestinal epithelium after the rupture of the cyst wall [12]. After successful cell invasion, intracellular proliferation takes place until the host cell can no longer sustain its development [13]. Eventually, the tachyzoites egress from the host cell and disperse through the circulatory system to organs such as the liver, lungs, brain, eye, placenta, and heart, completing the asexual life cycle [14]. Once the host's immunological response is elicited, the multiplying tachyzoites develop into bradyzoites, form tissue cysts, and stay dormant in the host [15, 16]. In healthy individuals, tissue cysts may survive throughout life without eliciting an immune response from the host. However, when the immune system is compromised or weakened, bradyzoites may revert quickly to replicating and invasive tachyzoites, leading to infection [13].

1.2 *Toxoplasma* genotypes

T. gondii genome is composed of a 65 Mb nuclear genome with 14 chromosomes [17]. The genome of *T. gondii* is bigger than that of other *apicomplexans* [18], which might be attributed to the large number of IHs of *T. gondii* [19]. Online database (ToxoDB (http://toxodb.org/toxo/)) contains complete information on the genome of *T. gondii* [20], including the three main types of *T. gondii*: GT-1 (type I), Me49 (type II), and VEG (type III) [21, 22]. Genotypes vary substantially across different geographic locations; Asia, Europe, and North and South Americas present type I, and all the continents present types II and III [23]. Thus, diversity in pathogenicity and virulence is directly correlated with genetic differences [24]. A median lethal dose (LD_{50}) to mice in laboratory settings is a common way to describe virulence strain. LD_{50}, for as little as one parasite, in type I strain of the parasite may kill mice. Types II and III, in contrast, are less virulent and only result in LD_{50} following infection with several parasites. Multi-locus restriction fragment length polymorphism (RFLP) is used to detect strains with distinct genotypes compared to types I, II, and III, which were first found in isolated populations of exotic animals, but they have lately been reported in chickens, pigs, and sheep [25]. Human primary infections of ocular illness are associated with atypical toxoplasmosis strains [26]. These atypical strains are characterized primarily by unique alleles and allele-shuffled combinations from the three major types [27]. Microsatellite genotyping of immunocompromised patients with toxoplasmosis revealed three novel genotypes, Africa I, Africa II, and Caribbean I, and subsequently determined a different Africa III genotype [28, 29]. The impact of secreted *Toxoplasma* virulence effectors and genetic diversity of *T. gondii* vary in encystment rates and acute pathogenicity in mice [30]. *T. gondii* strains grouped lineages (types I, II, and III) are based on variations in acute virulence in mice and genetic markers, RFLPs, and single-nucleotide polymorphisms (SNPs) [31, 32]. Highly pathogenic type I strain presents a LD_{100} of 1 [31], in contrast to strain type II with a LD_{50} of 10^3–10^4, and type III strain with a LD_{50} of 10^4–10^5 [33]. Advances in sequencing capabilities resulted in a broader diversity of *T. gondii* strains, giving rise to a new classification scheme, which separates strains into 15 genetic haplotypes, with types I, II, and III being referred to as haplotype 1, 2, and 3 and clade A, D, and C, respectively [33]. Strain-specific alleles of two proteins, ROP5 and ROP18, were

found to explain the differential in virulence [34, 35]. The virulent alleles of these proteins operate together to inhibit families of interferon-inducible gene families [35, 36].

1.3 Cats' susceptibility to *Toxoplasma* infection: determinants

Even though DH presents more than 180 parasite species [37], *T. gondii* appears more often than others in literature because of its effects on the health of humans, livestock, and wildlife [38]. Interactions between the three essential "ecological components," (a) DH, (b) environment (Env), and (c) IH influence the sustainability of these parasites, resulting in the fecal-oral route as the most common mode of transmission. A rise in parasite shedding and environmental contamination should be positively associated with the number of DHs. The likelihood of oocysts contributing to parasite transmission may also be influenced by specific host behaviors, and by physically separating the DH and IH niches, it may be possible to reduce parasite transmission. Env conditions may impact *Toxoplasma* oocyst survival, while the behavior of IH (such as grazing) may affect transmission [39]. Oocysts have the potential to survive in the environment at 4°C or room temperature for 6 months, resulting in oocysts sporulating and living for an extended period of time [40]. Oocysts are resistant to freezing [41] but are destroyed by prolonged desiccation [42], high temperatures (60°C), and exposure to UV light [43]. Therefore, any Env parameters, DH, and IH influence the completion of *T. gondii* life cycle. Since cats only shed it once, seropositive cats no longer shed *T. gondii* after their first infection; the presence of IHs encourages the transmission of parasites throughout an environment if the IHs provide a scarce source of food for the DH.

1.4 *T. gondii* in humans and animals

Humans, as IH, present a third or more people who have been exposed to infection with *T. gondii*. The prevalence ranges widely (10–85%) between nations, geographical areas within a country [7], socioeconomic conditions, climate (warm, humid tropical areas, cold-temperate, or desert regions), poor sanitation, a lack of clean water, and poor hygiene [44]. Toxoplasmosis is classified into an acute acquired infection (horizontal transmission) and a congenital infection (CT) [45] with an incubation period from 10 to 23 days after consuming tissue cysts and from 5 to 10 days following the consumption of oocysts [10, 46]. CT to the fetus (transplacental) may occur if the mother gets a primary infection or the chronically infected mother becomes immunocompromised during pregnancy [13]. Also, blood transfusion, solid organ transplant, or bone marrow transplant from a seropositive donor might be considered for infection [47]. Sexual transmission is established in many animal species, and circumstantial evidence implies that it may also occur in humans [48–50]. Because most infections are subclinical or misdiagnosed, it is challenging to establish the human toxoplasmosis and welfare effects [42]. Moderate flu-like symptoms, such as fever, muscle discomfort, and fatigue, may occur in some people [51]. Cases of severe toxoplasmosis and ocular disease are documented [52]. The most common cause is thought to be consuming raw or undercooked meat from an infected animal [53]. Unpasteurized milk; contaminated meat, vegetables, and fruits; and contaminated water might be a source of infection [54]. Infection may be caused by consuming water or food contaminated with feline excrement [55]. Disease transmission can be prevented by adequately boiling or freezing; temperatures over 67°C or below −12°C render tissue cysts nonviable [56, 57], and salted and cured meat often weakens the

viability. However, *Toxoplasma* tissue cysts seem refractory to these approaches [58]. The efficiency of thermal, nonthermal, and chemical/biochemical treatments for inactivating *T. gondii* in foods destined for human consumption has been reviewed [59]. When these individuals have a healthy immune system, the infection may not cause any symptoms. However, if the immune system is suppressed, the parasite can reactivate and cause potentially fatal complications [60]. Clinical signs of the disease include encephalitis, schizophrenia, bipolar disorders, depression, obsessive-compulsive disorders, retinochoroiditis, myocarditis, and fetal abnormalities following transplacental infection in immunocompromised people [61]. Both immunocompetent and immunocompromised pregnant women are at risk of transmitting *T. gondii* to their unborn children if they become infected with the parasite during their pregnancies [62]. The prevalence of CT varies by nation and location. Pregnancy-related fever, eating unwashed vegetables, and diagnosis in the third trimester were all linked to CT [63]. It is believed that the high genetic diversity of *T. gondii* seen in animals from this country correlates with illness severity. Infections after birth are usually undetectable, and toxoplasmosis predominantly affects immunocompromised patients where the clinical course of the illness is frequently considerably more severe [51]. Infected newborns might have nonspecific symptoms [64]. However, most infections are asymptomatic because the organism has developed several strategies to prevent significant inflammatory and immune responses. In the case of infections in wildlife populations, *T. gondii* infects any warm-blooded wildlife by ingesting environmental oocysts or, in omnivores and carnivores, both oocysts and tissue cysts [65, 66]. Production species are also affected by *T. gondii*, such as poultry [67]. Like chickens, *T. gondii* is the IH in livestock [68, 69], sheep [70, 71], and swine [72]. During infection of IH, first contact is made when parasites infiltrate enterocytes or cross the epithelial barrier to infect resident macrophages, dendritic cells (DCs), and lymphocytes [73] and rapidly multiply, infecting any cell with a nucleus; the resulting cell lysis may trigger rapid disease onset. A solid first line of defense is encouraged by the innate immune response. Within a few days of infection, the body develops an adaptive immune response that limits the infection and strengthens resistance to the disease. In response, the parasite undergoes a transition into the bradyzoite, a latent stage that develops inside the parasite cysts within the host. The immune system cannot combat these tissue cysts [16]. The complex relationship between *T. gondii* and innate immune system cells has been the subject of several researches and serves as a model for various microbial illnesses [74].

1.5 Conclusion

Since the first isolation over a century ago, *Toxoplasma gondii* has been extensively studied to understand its biology, transmission, life cycle, and implications for the health of its definitive hosts and intermediate hosts, including the human being. The life cycle of this protozoan of the phylum Apicomplexa presents different stages (sexual and asexual), which, in combination with a capacity for resistance to the environment and multiple hosts, makes this organism highly adaptable and easy to transmit and spread. Sequencing of *T. gondii* genome allowed the development of databases applied to the study, diagnosis, and typification, as well as the analysis of pathogenic factors associated with the capacity. Particularly, *T. gondii* is mainly mentioned in the literature due to its potential effect on various species, including humans. The DH-environment-IH interactions form the essential ecological components for its dissemination, mainly by fecal material/oral cycle. Human infection is

highly impacted worldwide since it is presumed that more than a third of the human population has been infected by this protozoan. Due to the immune system being actively involved in controlling infection, clinical signs range from a simple cold to severe illness in the case of an immunodeficient situation (eye lesions, lymphopathy, embryonic damage, and mental disorders). Its study demonstrated its presence in many foods of animal and vegetable origin, placing this infection as one of the main risks of food-borne diseases. Its presence in wildlife is also an intrinsically related factor in its worldwide distribution. Due to this, *T. gondii* represents a high risk for humans and a great variety of IHs that can be affected by this parasite; therefore, the study is highly relevant for its control and research worldwide.

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