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TOXOPLASMOSIS

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Abstract

Toxoplasma gondii, an Apicomplexan, is a pathogen that can infect the central nervous system. Infection during pregnancy can result in a congenial infection with severe neurological sequela. In immune compromised individuals reactivation of latent neurological foci can result in encephalitis. Immune competent individuals infected with *T. gondii* are typically asymptomatic and maintain this infection for life. However, recent studies suggest that these asymptomatic infections may have effects on behavior and other physiological processes. *T. gondii* infects approximately one-third of the world population, making it one of the most successful parasitic organisms. Cats and other felidae serve as the definite host producing oocysts, an environmentally resistant life cycle stage found in cat feces, which can transmit the infection when ingested orally. A wide variety of warm-blooded animals, including humans, can serve as the intermediate host in which tissue cysts (containing bradyzoites) develop. Transmission also occurs due to ingestion of the tissue cysts. There are 3 predominant clonal lineages, termed types I, II and III and an association with higher pathogenicity with the Type I strains in humans has emerged. This chapter presents a review of the biology of this infection including the life cycle, transmission, epidemiology, parasite strains, and the host immune response. The major clinical outcomes of congenital infection, chorioretinitis, and encephalitis, and the possible association of infection of toxoplasmosis with neuropsychriatric disorders such as schizophrenia, are reviewed.

TOXOPLASMA GONDII: BRIEF HISTORY AND OVERVIEW

Toxoplasma gondii was first described in 1908 by both Nicolle and Manceaux in the North African rodent, *Ctenodactylus gondii* and by Splendore in rabbits in Brazil (Ferguson, Henriquez et al. 2005; Ferguson 2009). The parasite has since been recognized as a common infection in numerous warm-blooded animals, including humans. With approximately 2 billion people infected it is one of the most successful human parasites. The clinical significance of toxoplasmosis was first recognized in the 1920s in congenitally infected children presenting with hydrocephalus, retinochoroiditis and encephalitis. In the 1980s, *T. gondii* emerged as a major opportunistic infection in the setting of AIDS, presenting as a severe and potentially fatal encephalitis due to the reactivation of latent infections in the setting of HIV associated immune suppression (Luft and Remington 1992). Toxoplasmosis is also a clinically important opportunistic infection in other immune suppressed individuals such as patients undergoing cancer treatment or organ transplant. Immune competent individuals infected with *T. gondii* are typically asymptomatic; however, infection has been

associated with neuropsychriatric disorders suggesting that latent infection may have subtle neurological effects.

THE PARASITE AND ITS LIFE CYCLE

Toxoplasma gondii is an obligate intracellular protozoan parasite belonging to the Phylum Apicomplexa. There are three basic infectious life cycle stages of this parasite: sporozoites, tachyzoites and bradyzoites (Dubey, Lindsay et al. 1998). Cats and other felidae serve as the definite host producing oocysts, an environmentally resistant form found in infected cat feces, transmitted by ingestion which cause infection transforming to tachyzoites. Bradyzoites are located primarily in tissue cysts in muscle and brain of the intermediate host and when ingested bradyzoites cause infection transforming to bradyzoites. Tachyzoites are the rapidly replicating form of this organism that disseminate throughout the body. Tachyzoites can transmit infection if they are injected into a host (e.g. laboratory accident or via blood transfusion). *T. gondii* sporozoites, tachyzoites and bradyzoites are all crescent-shaped, approximately 2 to 6μm in width and 4 to 8μm in length, with an anterior end containing secretory organelles, called the apical complex, that are used in invasion. Locomotion occurs via a process, called gliding motility, an actin-based based mechanism, which is essential for parasite migration through tissues, across biological barriers, in host cell invasion and egress (Sibley, Hakansson et al. 1998; Soldati and Meissner 2004; Bullen, Tonkin et al. 2009; Daher, Plattner et al. 2010). This form of ‘gliding motility’ is unique to the Apicomplexa and is an active target for drug development (Sibley 2010).

Cats are the definitive host in which schizogony (asexual reproduction) and gametogony (sexual reproduction) occur in the epithelial cells of the small intestine, leading to the production of unsporulated oocysts. These are shed in feces and maturation to infectious sporulated oocysts occurs in the environment. Infection in the cat can occur due to ingestion of bradyzoites, tachyzoites or oocysts; however, the prepatent period (i.e. the time to shedding of oocysts after infection) varies according to the life cycle stage ingested. The shortest prepatent period follows ingestion of tissue cysts (3-10 days) then tachyzoites (13 days) and the longest follows oocyst ingestion (≥ 18 days)(Dubey 1998).

The tachyzoite is present during acute infection. Tachyzoites replicate every 6 to 8 hours in a process called endodyogeny. They replicate within an intracellular compartment termed the parasitophorous vacuole. This vacuole avoids fusion with the endolysosomal pathway of the host cell and is essential to intracellular growth of the parasite (Mordue, Hakansson et al. 1999). Several excellent papers describe our understanding of this unique intracellular niche (Sinai and Joiner 1997; Sinai, Webster et al. 1997; Martin, Liu et al. 2007; Sinai 2008). The parasite induces profound affects in host gene expression, including molecules involved in signal transduction pathways and immune defenses, such as STAT pathways and apoptosis that facilitate the parasite survival in host cells (Blader, Manger et al. 2001; Kim, Fouts et al. 2007; Saeij, Coller et al. 2007; Laliberte and Carruthers 2008). Tachyzoites are capable of infecting every type of nucleated cell and disseminate throughout the body. Due to the host immune response tachyzoites are eliminated from the host within a few weeks following acute infection.

The bradyzoite, a slower replicating form, differentiates from the tachyzoite stage and is prevalent in chronic infections. Bradyzoite replication does not lead to rupture of the host cell but rather, vacuoles containing bradyzoites mature into cysts that have a thick wall containing a parasite glycoprotein called CST1, which may be important in stability and protection of cysts from the host immune response (Zhang, Halonen et al. 2001). Cysts develop intracellularly reaching diameters of up to 100 μm, and can contain thousands of bradyzoites. Tissue cysts are located primarily in the grey matter and within neurons (Ferguson and Hutchison 1987). Bradyzoites can be found in the brain as early as 3 days following infection (Dubey 1997). Cysts containing viable bradyzoites, persist for years and probably for the life of the host (Ferguson and Hutchison 1987; Frenkel 1988). Brain and muscle are the most common sites of the chronic, latent infection, although cysts have also been found in lung, liver, kidney and other visceral organs (Dubey 1998).

TRANSMISSION

Transmission occurs predominantly via ingestion of the tissue cysts, ingestion of oocysts from contaminated food or water, or congenital transmission (Hill and Dubey 2002). It is not yet clear which of these routes is the most important epidemiologically in transmission although this may vary depending upon culture and eating habits (Tenter, Heckeroth et al. 2000). Infections from tachyzoites in tissue transplants, blood products and unpasteurized milk may also occur (Tenter, Heckeroth et al. 2000).

Tissue cyst transmission

Tissue cysts are present in the muscle and brain of the intermediate hosts. Cats acquire toxoplasmosis by eating infected prey (rodents, birds) wherein the enteroepithelial cycle, sexual reproduction and production of oocysts occurs (Dubey, Miller et al. 1970). WIld carnivorous animals, including bears, fox, raccon and skunks, also can acquire toxoplasmosis via ingestion of tissue cysts. Man can acquire the infection via consumption of undercooked contaminated meat such as pork or lamb (Dubey, Hill et al. 2005; Hill, Haley et al. 2010). When a tissue cyst is ingested the cyst wall is disrupted by proteolytic enzymes in the stomach and the released bradyzoites are resistant to proteolytic digestion allowing them to survive digestion initiating infection in the small intestine.

Oocyst transmission

Infected cats excrete oocysts in large numbers (up to 10 million cysts during a single day) with excretion occurring for up to 2 weeks following infection. Once shed, the oocyst sporulates in 1 to 5 days, becoming infective and may remain infective for more than 1 year in unfrozen, moist soil (Dubey, Lindsay et al. 1998). Humans can become infected from food or water contaminated with oocysts. Eating of unwashed raw vegetables or fruits or ingestion of water contaminated with oocysts, have been identified as important risk factors (Dubey 2010; Pereira, Franco et al. 2010). Circumstantial evidence suggests that oocyst-induced infections in humans are clinically more severe than tissue cyst-acquired infections (Dubey 2010). While water-borne infections were once thought to be rare, the widespread infection of marine mammals in the USA as well as outbreaks linked to contamination of a municipal water reservoir in Canada by wild felids has lead to the recognition that

toxoplasmosis can be a water-borne disease (Dubey 2004). Because of the short duration of oocyst shedding, the passing of non-infective oocysts, and the fastidious nature of cats, direct contact with cats is not thought to be a primary risk for human infection (Elmore, Jones et al. 2010). Oocysts have been found to survive in seawater for up to 6 months, suggesting that in coastal marine environments they could be a source of infection via transport hosts (Lindsay and Dubey 2009). In support of this idea, it has recently been demonstrated that oocysts can survive in filter feeders such as anchovies and sardines, and remain infectious inside their alimentary canal (Massie, Ware et al. 2010)

Congenital transmission

Congenital transmission occurs during acute toxoplasmosis in a seronegative mother when tachyzoites present in the blood may cross the placenta and infect the fetus (Jones, Lopez et al. 2003; Montoya and Remington 2008). The stage of pregnancy in which maternal toxoplasmosis is acquired is an important factor in the frequency of transmission and severity of congenital infection. During the first trimester, transmission is relatively low (< 20%) but increases to near 80% by the end of the pregnancy (Jones, Lopez et al. 2003; Ortiz-Alegria, Caballero-Ortega et al. 2010). Early in gestation cases are severe with infection resulting in spontaneous abortion, hydrocephaly and mental retardation while during the last trimester, transmission rates are highest but the majority of these cases are subclinical resulting in asymptomatic infections or recurrent chorioretinitis throughout early adulthood that can lead to vision problems and potentially blindness (Montoya and Liesenfeld 2004). In most populations the overall incidence of congenital toxoplasmosis is from 1 in 1000 to 1 in 10,000 live births (Tenter, Heckeroth et al. 2000; Dubey and Jones 2008). A recent study measuring vertical transmission rates in humans using a PCR detection of the umbilical cord tissue, obtained at birth, found transmission rates of 19.8% (Hide, Gerwash et al. 2007). In studies in sheep this rate was 65% and in experimental mouse models 75%. Overall, this suggests that the human vertical transmission rates may be underreported when they are based upon serological approaches (Hide, Morley et al. 2009).

EPIDEMIOLOGY

Toxoplasmosis is one of the most common infections in humans and warm-blooded animals, with a worldwide distribution. It has been demonstrated in virtually every species of mammal and many species of birds (Hill, Chirukandoth et al. 2005). In humans, toxoplasmosis has been found in all parts of the world and it is estimated about one-third of the worlds population is infected with latent toxoplasmosis. The incidence of toxoplasmosis differs, however, with underdeveloped countries having a higher incidence than developed countries. Areas of high prevalence exist in Latin America, parts of Eastern/Central Europe, the Middle East, and parts of south-east Asia and Africa (Pappas, Roussos et al. 2009). In the US, seroprevalence is 15 to 22% (CDC), a slight drop from the preceding decade, consistent with the same trend in Europe (Dubey and Jones 2008; Pappas, Roussos et al. 2009). This variation in prevalence can be explained by several factors including the number and presence of the cats, climate, cultural and ethnic practices. Direct contact with cats is not required for transmission due to the longevity of oocysts in the environment (Dabritz and Conrad 2010). Prevalence is higher in warm temperature and wet countries as oocysts lose

their virulence when dried or frozen. The seroprevalence for *T. gondii* in cats is 30 to 40% with regional prevalence varying with climate; prevalence being lowest in the drier southwestern regions (16.1 % in New Mexico, Utah and Arizona) and highest in humid areas (59.2% for Hawaii) (Elmore, Jones et al. 2010). Cooking habits, such as whether meat is eaten well cooked or underdone, is another important factor (Tenter, Heckeroth et al. 2000; Tenter 2009). In the US, eating raw oysters, clams or mussels, has been identified as a new risk factor for *T. gondii* infection (Jones, Dargelas et al. 2009).

The Population Structure of T.gondii

The population structure of *T. gondii* results from the ability of the parasite to propagate via both asexual and sexual reproduction. Asexual propagation due to direct oral infectivity from intermediate host to intermediate host, allows circumvention of sexual transmission and clonal expansion (Su, Evans et al. 2003). Sexual reproduction produces new parasite lines in the definitive host that spread through the population via clonal reproduction (Su, Zhang et al. 2006; Grigg and Sundar 2009). The combination of genetic out-crossing followed by clonal amplification of a single strain through self-mating, may be a key adaptation of the parasite enabling the epidemic expansion and transmission of newly emerged parasite clones (Wendte, Miller et al. 2010). This population structure of *T. gondii* thus may contribute to disease outbreaks and evolution of parasite virulence (Sibley, Khan et al. 2009).

T. gondii has a clonal population structure in North America and Europe with 3 predominant lineages, termed types I, II and III (Grigg et al. 2001; Howe & Sibley 1995; Sibley & Boothroyd 1992). A recent report indicates a similar population structure exists in Africa (Velmurugan, Tewari et al. 2008). In South America, however, strains appear to be more genetically diverse and comprise distinct genotypes from those in North America and Europe (Khan, Jordan et al. 2006; Lehmann, Marcet et al. 2006; Belfort-Neto, Nussenblatt et al. 2007; Dubey, Velmurugan et al. 2008; Pena, Gennari et al. 2008). The initial analysis of North America and European strains identified a small number of highly divergent isolates which were called ‘exotic genotypes’ (Sibley and Boothroyd 1992). A more recent phylogenetic analysis, including *T. gondii* strains from North and South America, identified 11 distinct ‘haplogroups‘(Sibley, Khan et al. 2009). Three of these 11 haplogroups correspond to the previously recognized clonal lineages, I, II and III, while the remaining 8 are newly recognized lineages. Of the new haplotype groups, four of these lineages were almost exclusively found in South America. While most strains in North America are Type II, recent samplings in North America in lambs and wildlife found atypical ‘virulent’ genotypes suggesting that diverse and atypical genotypes of *T. gondii* may also be present some livestock and wildlife in North America (Dubey, Rajendran et al. 2010). Isolates from *T. gondii* in sea otters off the coast of California which exhibit enhanced mortality to *T. gondii* infection, were also found be infected with a unique genotype, called Type X strain (Miller, Grigg et al. 2004; Miller, Miller et al. 2008).

In North American and in Europe, the majority of human infections, in both congenital and in patients with AIDS, are caused by Type II strains (Howe & Sibley, 1995; Howe et 1997; Honore 2000; Ajzenberg 2002). In South America, however Type I strains are responsible

for ocular infections in human patients in Brazil (Vallochi 2005). Additionally Type I strains have been seen in Brazilian patients with AIDS and unusual genotypes in patients in Brazil with ocular toxoplasmosis (Khan, Jordan et al. 2006; Ferreira, Vidal et al. 2008). Thus, there is now a recognized association of increased pathogenicity of Type I strains in humans with an intact immune system (Darde 2008).

Type I, II and III strains have different virulence phenotypes in mouse models; with type I strains being the most virulent, and Type II and Type III being avirulent (Howe, Summers et al. 1996; Mordue, Monroy et al. 2001). Type I strains can cause a lethal infection in mice at a dose of 1 parasite (lethal dose [LD_{100}] = 1), whereas Type II and Type III strains have a medial lethal dose (LD_{50}) of ≥ 10^5 (Sibley and Boothroyd 1992). *In vitro* studies on Types I, II and III, have identified a number of characteristics that may correlate with virulence in a host including phenotypic differences in growth, migration, and transmigration, with Type I strains growing faster and with greater migration abilities than strains II and III (Barragan and Sibley 2003). Virulence correlates with effects on the immune response with Type I parasites inducing a stronger Th1- inflammatory response than Type II or III. Genetic studies have identified secretory proteins discharged from apical organelles, called rhoptries (ROPs), as the determinant of acute virulence (Taylor, Barragan et al. 2006; Saeij, Coller et al. 2007).

IMMUNE RESPONSE

Resistance to *T. gondii* is mediated primarily by a Th-1 type cell-mediated immune response that depends upon the production of interleukin-12 (IL-12) and interferon-γ (IFN-γ) (Gazzinelli, Denkers et al. 1993; Sher, Collazzo et al. 2003). Synthesis of IL-12 is stimulated by dendritic cells (DCs), macrophages and neutrophils, which are infected by the parasite, early in infection and induces IFN-γ synthesis by NK and T lymphocytes. IFN-γ is the main cytokine controlling both the acute and chronic stages of infection (Suzuki, Orellana et al. 1988; Suzuki 2002). IFN-γ activates anti-parasitic effector mechanisms in both hemopoietic cells, such as macrophages, and non-hemopoietic cells such as endothelial cells, fibroblasts, and astrocytes; both cell populations have been found to be necessary for control of the parasite (Yap and Sher 1999). In immunodeficient hosts, such as AIDS patients, when $CD4^+$ T cells fall and correspondingly, IFN-γ levels decline, reactivation of the chronic infection in the brain results. In most healthy (immunocompetant) hosts, the immune response controls replication during the acute infection and due to immune response and/or physiological stress, the tachyzoites differentiate into bradyzoites forming cysts, primarily in the brain and muscle, that then persist throughout the host's life (John, Weninger et al. 2010).

The immune response to *T. gondii* requires both innate and adaptive immune responses, involving a coordinated series of cellular interactions between the parasite, enterocytes, monocytes, DCs, macrophages, NK cells, and neutrophils. DCs play a central role in the stimulation of the innate immune response and the initiation of the adaptive immune response. IFN-γ dependent cell immunity plays a major role in resistance against both acute and chronic *T. gondii* infection, with IFN-γ activated effector cells in both hemopoietic and non-hemopoietic cell compartments controlling *T. gondii* via several antimicrobial mechanisms. CD8+ T cells are crucial for protection against *T. gondii*, The development of

imaging techniques such as bioluminescent imaging, confocal and multiphoton microscopy, in combination with fluorescent and bioluminescence markers have permitted visualization of parasites and immune cells in real-time and are providing new insights into the molecular nature of the host-parasite interactions (Saeij, Boyle et al. 2005; John, Harris et al. 2009; John, Weninger et al. 2010).

Innate Immune Responses

Intermediate hosts become infected with *T. gondii* by ingestion of oocysts or tissue cysts, where the parasite invades the enterocytes in the small intestine and replicates. Parasite replication in the intestine leads to host cell lysis and release of tachyzoites. Parasites can also traverse epithelium, powered by gliding motility, without the disruption of the endothelial layer and infect the lamina propria directly (Barragan and Sibley 2002). Enterocytes infected with parasites secrete chemokines that recruit dendritic cells (DCs) in the lamina propria. Within the lamina propria, the parasite can either invade DCs or macrophages or enter directly into the lymphatic or circulatory systems. Infected DC and macrophages can disseminate the infection to distant sites, including the brain (Courret, Darche et al. 2006; Lambert, Hitziger et al. 2006). Macrophages and DC produce IL-12 after parasite infection, which then triggers IFN-γ synthesis by NK, NKT, and T cells. Intraepithelial cells within the lamina propria also contribute to innate immunity in the lamina propria (Buzoni-Gatel, Schulthess et al. 2006).

Role of Monocytes and Neutrophils—Monocytes play a key role in mucosal immunity to *T. gondii* (Dunay, Fuchs et al. 2010). Inflammatory monocytes are recruited from the bone marrow to the site of infection in the gut. Inflammatory monocytes can restrict the growth of *T. gondii* through the production of nitric oxide (NO) and recent studies indicate monocytes are necessary in control of *T. gondii* proliferation in the lamina propria via a NO-dependent mechanism (Mordue and Sibley 2003; Dunay and Sibley 2010). Neutrophils are also one of the first cell types to arrive at the site of infection with *T. gondii*. They secrete IL-12 and can directly kill the parasite via oxygen-dependent and independent mechanisms and thus have also been touted as having a protective role in mucosal immunity (Denkers, Butcher et al. 2004). More recent studies however have shown neutrophils to be involved in adverse pathological events (Dunay and Sibley 2010).

Role of Dendritic Cells (DCs)—Dendritic cells (DCs) play a central role in orchestrating the innate immune response and bridging innate and adaptive immunity. DCs are the initial antigen-presenting cell at the site of infection and they are either directly infected by the parasite where they multiply and are processed for antigen presentation, or ingest apoptotic enterocytes that are then digested and processed for antigen presentation (Dunay and Sibley 2010). While macrophages and neutrophils are also infected with *T. gondii* and can secrete IL-12, recent evidence indicates DC production of IL-12, but not macrophages or neutrophils, is essential for IFN-γ activation of NK cells and recruitment of inflammatory monocytes (Hou, Benson et al. 2011). Both conventional and plamacytoid DC subsets are activated by *T. gondii* infection, with the plasmacytoid DC subset inducing high levels of IL-12, upregulating MHC I and MHC II, and accessory molecules, such as CD86, indicating their ability to prime $CD4^+$ T and suggesting the plasmacytoid DC subpopulation may be

particularly important in the initial stages of the immune response to *T. gondii* (Pepper, Dzierszinski et al. 2008).

DCs are also involved in priming CD8+ T cells and shaping the early T cell response. Cognate formation between DCs and CD8+ T cells occurs in the draining lymph nodes early in the immune response (John, Harris et al. 2009). The DC/CD8+ interaction only occurs only in the presence of cognate antigen and not infected DCs, suggesting that cross presentation by bystander DCs rather than infected DCs is an important route of antigen presentation during acute toxoplasmosis. An enhanced migratory response is induced in infected DCs, which likely facilitates parasite dissemination and DCs trafficking to the draining lymph nodes (Lambert, Dellacasa-Lindberg et al. 2011). Additionally, the infected DC also contribute to parasite dissemination in a strain-specific manner with Type II avirulent strains more efficiently exploiting DCs for parasite dissemination than the virulent, Type I strains. (Lambert, Vutova et al. 2009). Avirulent strains induce a more robust activation of DCs at the site of infection and the draining lymph node than the virulent strains, further indicating the role of DCs in shaping the immune response to *T. gondii* (Tait, Jordan et al. 2010).

Role of TLR's in Innate Immune Response—Several Toll like receptors (TLRs) function in recognition of *T. gondii* (Yarovinsky 2008; Denkers 2010). TLR11 is required for DC production of IL-12 production and thus is important in induction of innate immunity (Yarovinsky 2008). TLR11 recognizes the parasite protein profilin, which is an actin-binding protein that is used in gliding motility, involved in tissue migration, host cell invasion and egress (Yarovinsky, Zhang et al. 2005). In addition to triggering host immune response, TLR11 may also be involved in the prevention of immunopathology via regulating IFN-γ secretion by NK cells (Yarovinsky, Hieny et al. 2008). TLR2 also contributes to the host response to *T. gondii*, inducing macrophage activation and NO production and secretion of the chemokine, CCL2 (Del Rio, Butcher et al. 2004). The ligands for TLR2 are glycophosphatidylinositol (GPI) anchors of the parasite (Debierre-Grockiego, Campos et al. 2007). TLR4 also recognizes GPIs of the parasite, with some suggestion that TL2 and TLR4 may work cooperatively during *T. gondii* infection. These studies indicate TLRs may be involved in a cooperative regulation of the innate immune response against *T. gondii*.

Adaptive Immune Response

The adaptive immune response is initiated by antigen-presenting cells (APCs), which recognize that the host is infected through pattern recognition receptors such as TLRs, stimulating secretion of IL-12, which induces IFN-γ production by NK cells and $CD4^+$ and $CD8^+$ T cells (Tait and Hunter 2009). Activated CD4+ cells produce IL-2, a T-cell mitogen, which in conjunction with IFN-γ, results in large numbers of parasite-specific $CD4^+$ and $CD8^+$ T cells that produce IFN-γ at the sites of parasite invasion. IFN-γ signaling, in a STAT-1 dependent pathway, leads to the generation of anti-parasitic effector mechanisms such as nitric oxide (NO), reactive oxygen intermediates (ROI) and the immunity-regulated GTPases (IRGs). $CD8^+$ T cells play a crucial role in the protective immunity to *T. gondii* both via the production of IFN-γ, which activates anti-microbial killing mechanisms but also via direct killing of the parasite via a perforin-dependent pathway. The chronic infection in

the brain is controlled by CD8+ T cells and the resident glial cells, microglia and astrocytes, which can act as immune effector cells in the brain.

Role of CD8+ T cells—CD8+ T cells are a key mediator of the adaptive immune response to *T. gondii*. The role of CD8+ T cells in the protective response to *T. gondii* was established in early studies in which transfer of CD8+ T cells from immunized mice provided protection to naïve mice challenged with *T. gondii* and correspondingly protection was ablated by the depletion of CD8+ T cells (Suzuki and Remington 1988; Parker, Roberts et al. 1991; Shirahata, Yamashita et al. 1994). CD8+ T cells are the principle T lymphocyte population involved in the control of the chronic infection and prevention of reactivated infection in the brain (Suzuki and Remington 1988; Gazzinelli, Xu et al. 1992; Wang, Claflin et al. 2005). $CD4^+$ T cells, are not required for induction or maintenance of CD8+ T cells but are necessary to regulate the functional activity of intracerebral $CD8^+$ T cells (Lutjen, Soltek et al. 2006).

CD8+ T cells are activated via presentation of major histocompatibility complex class I (MHC-I)-restricted parasite antigens. Activation of T cells occurs via direct interaction with infected host cells as opposed to cross-presentation as has been found in the initial priming of CD8+ T cells by DC in the lymph nodes (Dzierszinski, Pepper et al. 2007). Professional APCs, such as dendritic cells and macrophages, are involved as in direct antigen presentation, but non-professional APCs, such as endothelial cells, epithelial cells and astrocytes, are equally as efficient in activating CD8+ T cells in this MHC-I restricted response.

The anti-parasitic effector mechanisms mediated by activated CD8+ T cells include production of cytokines, the predominant of which is IFN-γ, which stimulates anti-parasitic IFN-γ effector mechanisms in a variety of cell types including macrophages, microglia, and astrocytes. The importance of IFN-γ-mediated mechanism is illustrated by the loss of protection against both the acute and chronic stages of infection when IFN-γ is deficient or absent. CD8+ T cells are also known to produce the anti-inflammatory cytokines, IL-17 and IL-27, both of which are associated with down regulation of the inflammatory response to *T. gondii* during infection (Johnson 1992; Stumhofer, Laurence et al. 2006).

Activated CD8+ T cells can also mediate cytotoxic activity (CTL) against *Toxoplasma*-infected cells in the context of MHC presenting parasite antigen on their cell surface. The ability of parasite-specific CD8+ T cells to lyse Toxoplasma-infected cells has been demonstrated in *in vitro* studies (Hakim, Gazzinelli et al. 1991; Khan, Ely et al. 1991; Subauste, Koniaris et al. 1991; Denkers, Sher et al. 1993). *In vivo* studies using mice deficient in the cytotoxic molecule, perforin, demonstrated the CTL response did not affect resistance to the acute stage but was necessary for resistance to the chronic infection (Denkers, Sher et al. 1993; Denkers, Yap et al. 1997). CD8+ T cells may also be able to eliminate *Toxoplasma* cysts in the brain (Suzuki, Wang et al. 2010). Surprisingly the CD8+ T cells did not require production of IFN-γ but did require perforin-mediated cytotoxic activity.

IFN-γ Effector mechanisms and IFN-γ Effector Cells—IFN-γ activated macrophages acquire anti-microbicidal activity that is largely dependent upon the production of reactive nitrogen intermediates. The Interferon Response Genes (IRGs), are a family of IFN-γ induced proteins, that have recently been recognized as an important resistance system to target vacuolar pathogens including *T. gondii* (Taylor 2007; Zhao, Rohde et al. 2009). In macrophages the IRG mechanism induces disruption of the *Toxoplasma* vacuole leading to degradation of intracellular parasites via autophagomal delivery to the lysosomes (Butcher, Greene et al. 2005; Ling, Shaw et al. 2006). The IRG mechanism involves a coordinated loading of IRG GTPases on the *Toxoplasma* vacuole (Khaminets, Hunn et al. 2010). Virulent strains of *T. gondii* evade vacuolar disruption by IRG proteins via phosphorylation of several IRG proteins, via the parasite kinase, ROP18, thereby inhibiting the accumulation of IRG proteins on the vacuole (Zhao, Ferguson et al. 2009; Steinfeldt, Konen-Waisman et al. 2010). IFN-γ induced damage to the *T. gondii* vacuole can also occur via an autophagosome-independent process involving the autophagy protein, Atg5 (Zhao, Fux et al. 2008).

IFN-γ also induces anti-*Toxoplasma* activity in non-phagocytic cells such as fibroblasts, epithelial cells, endothelial cells and astrocytes and in these nonphagocytic cells, the mechanism of IFNγ inhibition is via nitric oxide independent mechanisms. The known mechanisms of IFNγ inhibition in non-phagocytic cells includes induction of indoleamine 2,3-dioxygenase (IDO), which degrades intracellular tryptophan, increases in reactive oxygen species, and iron deprivation (Pfefferkorn 1984; Pfefferkorn, Rebhun et al. 1986; Daubener, Remscheid et al. 1996; Nagineni, Pardhasaradhi et al. 1996; Brunton, Wallace et al. 2000). The IRG mediated parasite degradation has also been found in fibroblasts and astrocytes (Martens, Parvanova et al. 2005; Zhao, Rohde et al. 2009).

Intracerebral Immune Response

Infected DCs and macrophages can carry the parasite into the brain. The parasite can infect microglial, astrocytes and neurons during acute Toxoplasmic encephalitis (TE) and then persist in primarily in neurons during chronic TE (Ferguson, Huskinson-Mark et al. 1994). CD8+ and CD4+ T cells are recruited in the brain in acute TE (Schluter, Meyer et al. 2002; Kwok, Lutjen et al. 2003). The recruitment of inflammatory cells into the brain is regulated by cytokines and chemokines. Trafficking of CD8+ T cells into the brain depends upon IFN-γ induction of VCAM1 on endothelial cells that binds to an integrin on CD8 T cells, guiding CD8 T cells into the brain (Wang et al, 2007). Both IFN-γ activated astrocytes and microglia produce chemokines in response to parasite infection that guide the inflammatory cells to the site of infection (Strack, Asensio et al. 2002).

CD4+ and CD8+ T cells increase in the brain during the first weeks following infection, and during the transition from acute to chronic TE gradually decline with CD8+ T cells persisting at low levels in the brain during chronic TE (Schluter, Meyer et al. 2002; Kwok, Lutjen et al. 2003). More recent studies using Ag-specific CD8+ T cells, have found that recruited CD8 T cells persist in the brains of infected mice in the presence of ongoing antigen recognition (Schaeffer, Han et al. 2009). In this study cerebral CD8+ T cells, made transient contact with granuloma-like structures containing parasites and with individual

macrophages (CD11b+ cells) but surprisingly not with intact Ag-bearing cysts, infected neurons containing parasites or the cysts, or individual neurons or astrocytes, indicating macrophages serve as APCs in the brain, while astrocytes and neurons may not. Live cell imaging, using 2-photon microscopy, observing CD8+ T cells in the brain revealed 2 distinct populations of cells, one with a constrained pattern of migration and one with a highly migratory subset, the proportion of which changed over time and varied with antigen availability (Wilson, Harris et al. 2009). Unexpectedly, CD8 T cells moved along infection induced reticular fibers, to guide CD8 T cells to the site of infection. These studies have revealed features of the intracerebral immune response and behavior of CD8+ T cells that were unanticipated and not fully understood, but that likely will be the focus of future studies.

Role of Microglial Cells—Microglia are the resident macrophage population of the central nervous system and are rapidly activated in murine Toxoplasmic Encephalitis (TE). Activated microglia express elevated levels of the cytokines, IL-12, IL-1β1, TNFα, and the cell surface ligands, MHC I and II and ICAM-1, indicating their role in recruitment and activation of T cells in the brain and ability to act as an APC in the brain (Schluter, Meyer et al. 2001; Wang, Michie et al. 2007). CD8+ T cells regulate cytokine production of microglia, while cell surface molecules are less dependent upon T cells (Schluter, Meyer et al. 2001). Macrophages and microglia can also be source of IFN-γ in the brain and produce IFN-γ independently of T cells during acute toxoplasmosis in the brain (Suzuki, Claflin et al. 2005; Wang and Suzuki 2007). Microglial production of IFN-γ independent of T cells, may be important in the early stages of tachyzoite proliferation in the brain, serving to limiting parasite growth, prior to the recruitment of CD8 T cells into the brain. Microglia can also serve as IFN-γ activated immune effector cells in the brain (Deckert-Schluter, Bluethmann et al. 1999; Suzuki 2002; Suzuki, Claflin et al. 2005). The mechanism of IFNγ inhibition of *T. gondii* infection in murine microglia is primarily mediated via inducible nitric oxide synthase (iNOS) and the production of nitric oxide (Suzuki 2002b). Nitric oxide (NO) is believed to be toxoplasmacidal, and in sufficient amounts may produce stasis and/or intracellular killing of parasites (Chao, Gekker et al. 1994; Gross, Bohne et al. 1996). Activated microglial cells can inhibit growth of the parasite via CD40-autophagy pathway in microglia (Portillo 2010). Microglia can also function in the down-regulation of the intracerebral immune response via the secretion of TGF-β which prevents neuron degeneration, indicating microglial play an important neuroprotective function in the brain in chronic TE (Rozenfeld, Martinez et al. 2005).

Role of Astrocytes—Astrocytes are also important immune effector cells in the brain, controlling parasite growth and immunopathological responses to the chronic infection (Wilson and Hunter 2004). IFN-γ activated astrocytes significantly inhibit the growth of *T. gondii* (Halonen, Taylor et al. 2001; Scheidegger, Vonlaufen et al. 2005). IFN-γ inhibition in astrocytes in mice is via the IRG-mediated mechanism while inhibition in human astrocytes is via nitric oxide (Peterson, Gekker et al. 1995; Halonen, Chiu et al. 1998; Halonen and Weiss 2000; Halonen, Taylor et al. 2001; Martens, Parvanova et al. 2005). Astrocytes, are efficient in MHC I presentation, indicating they may be an important antigen presenting cell controlling *T. gondii* in the brain, capable of stimulating $CD8^+$ T cells (Dzierszinski, Pepper

et al. 2007). Soluble factors produced by secreted by infected astrocytes down modulate NO-production by IFN-γ activated microglia and prevent neuronal degeneration (Rozenfeld, Martinez et al. 2003). Finally, astrocytes have been shown to be essential for control of *Toxoplasma* encephalitis, serving to contain sites of parasite replication and the inflammatory lesions in the brain (Drogemuller, Helmuth et al. 2008).

Humoral Immune Response

Although the predominant protective response to *T. gondii* is a Type I-mediated cell mediated immune response, humoral immunity also participates in controlling *T. gondii* (Suzuki 2002). Antibodies are produced in response to *T. gondii* infection and individuals with a chronic infection maintain the *Toxoplasma*-antibodies for life. Evidence from antibody deficient mice (μ^-/μ^-) indicate while antibody did not affect the acute infection, antibodies did play a role in limiting tachyzoite replication in mice, especially in the lung and in the brain (Kang, Remington et al. 2000). Additionally it is known that B cells can modulate CD4 and CD8 responses and likewise, B cells have been found acquire the ability to amplify IFN-γ production by CD4+ and CD8+ T cells during the course of the Th1 inflammatory response to *T. gondii* infection (Menard, Minns et al. 2007).

Immunoregulation during T. gondii infection

IL-10 is a cytokine with anti-inflammatory properties including counteracting the function of Th1 lymphocytes. IL-10 plays a vital role in controlling the inflammatory response during chronic phase of *T. gondii* infection (Wilson, Wille-Reece et al. 2005). IL-10 inhibits the production of IL-12, IFN-γ, TNF-γ and IL-6 from macrophages and microglia in the brain. Macrophages and CD4+ T cells are the major sources of IL-10 in the brain. Depletion of IL-10 in the brain results in an increase in CD4+ T cells and macrophages and a lethal inflammatory response, indicating the critical role of IL-10 to limit inflammation in the brain during TE. The down regulation of the Type 1-immune response in the brain may facilitate the persistence of the parasite in the brain resulting in the chronic infection. Host protective IL-10 derives in an autocrine manner from IFN-γ producing Tbet(+) Foxpβ(neg) Th1 cells, indicating that IL-10 may be an important self-regulatory function of CD4+ T lymphocytes (Jankovic 2010).

TOXOPLASMOSIS: CLINICAL ASPECTS

The major categories of infection with *T. gondii* infection are: (1). Acquired Toxoplasmosis in immune competent individuals; (2). Congenital Toxoplasmosis: (3). Ocular Toxoplasmosis, which can be acquired or congenital; and (4). Cerebral Toxoplasmosis resulting from reactivated infections in immune deficient patients. Additionally, recent data suggests that latent infection may lead to neuropsychiatric disease in some immune competent individuals.

Drug treatment for Toxoplasmosis

Several drugs are available for the treatment of Toxoplasmosis (Nath and Sinai 2003; Montoya and Liesenfeld 2004). The typical choice of drugs includes pyrimethamine in combination with sulfonamide. Folinic acid usually added to prevent bone marrow

suppression from pyrimethamine. Clindamycin is an alternate choice if sulfonamides cannot be tolerated. Atovaquone is an alternative in patients unable to tolerate either sulfonamides or clndamycin. Spiramycin is recommended for treatment in women because it achieves high concentration in the placenta; however it does not have good CNS penetration. Prophylactic treatment with chronic disease is indicated only in high-risk patients, because none of the available drugs kill the cysts effectively in humans. In *T. gondii* seropositive patients with AIDS trimethoprim/sulfamethoxazole has been shown to prevent cerebral toxoplasmosis.

Acquired toxoplasmosis

Acquired acute infections are asymptomatic in at least 80% of immune competent individuals (Luft and Remington 1992). Those with clinical disease most commonly present with lymphadenopathy of the head and neck region; although presentations can also occur involving axillary, inguinal, retroperitoneal and mesenteric lymph nodes. A single site is usually affected with enlarged nodes from 0.5 to 3 cm in diameter. Lymphadenopathy may also be accompanied by fever, malaise, sore throat, rash and hepatosplenomegaly. Acute infection is usually benign and self-limiting. After 2 to 3 weeks of infection, due to an effective host immune response, tachyzoites are cleared from the host tissues and differentiation into the bradyzoites occurs. In the chronic phase bradyzoites are found in tissue cysts located primarily in muscular and neural tissue. These cysts persist for long periods of time. Acute infection, in general, protects the host from symptomatic re-infection. In immune competent hosts chronic infection is typically asymptomatic. In contrast, in chronically infected individuals with immune deficiency, such as patients with AIDS, reactivation of the latent infection in the brain or other sites can occur. In reactivation in the brain bradyzoites convert to the actively replicating tachyzoites resulting in necrotizing encephalitis, which can be life threatening.

Diagnosis of Acquired Toxoplasmosis—Diagnosis of a chronic infection is typically done via the serological detection of antibodies to parasite specific antigens (Montoya 2002; Remington, Thulliez et al. 2004). A combination of IgM and IgG ELISA assays are most commonly used. IgM is indicative of an acute infection, but it is now appreciated that IgM may persist for as long as a year following infection (Montoya and Remington 2008). The IgG avidity test was developed to help discriminate between past and recently acquired infections as IgG affinity results from an antigen-driven B-cell selection process, and thus an increase in affinity will occur over time (Remington, Thulliez et al. 2004). Therefore, low avidity IgG antibodies are consistent with acute infection. To confirm diagnosis, samples can be tested in a reference laboratory that provides specialized testing for this pathogen. For example, The Toxoplasma Serology Reference Laboratory of the Palo Alto Medical Foundation Research Institute (TSL-PAMFRI), conducts a serological panel that consists of ELISA for IgM, IgA and IgE, avidity testing, the Dye test which measures IgG antibodies and the differential agglutination test (Montoya 2002). The combination of these tests can be useful in determining when an infection occurred, which is of critical importance in counseling during pregnancy; as infection before pregnancy does not result in transmission in utero. Other serological tests that can be used include the indirect hemagglutination test, latex agglutination test, indirect fluorescent antibody tests.

Commercially available tests commonly use *T. gondii* native antigens, derived from whole cell lysate of *T. gondii*, and a display wide variation in test accuracy. The use of recombinant antigens has been proposed as an alternative to reduce the problems of antigen standardization and assay reproducibility currently faced by diagnostic laboratories in some parts of the world and in resource-poor settings (Kotresha and Noordin 2010). The parasite recombinant antigens shown to be more sensitive in detecting toxoplasmosis include combinations of rSAG2A, rGRA2, rGRA4, rROP2, rGRA8 and rGRA7 for use in detecting IgG antibodies in human serum and rROP1, rSAG1, rGRA7, rGRA8 and rGRA6 for detecting IgM antibodies in human serum.

Treatment of Acquired Toxoplasmosis—Many of these infections are self limited and resolve without specific treatment or with symptomatic management (i.e. ibuprofen for pain and fever). Treatment with pyrimethamine and sulfadiazine for 4 weeks is effective and is used for moderate to severe cases.

Congenital Toxoplasmosis

Congenital Toxoplasmosis is the result of a primary infection with *T. gondii* during pregnancy in which transplacental passage of the tachyzoite stage occurs (vertical transmission) and infects the fetus(Montoya and Remington 2008). It has been estimated that from 400 to 4000 cases of congenital toxoplasmosis occur in the United States each year (Jones, Lopez et al. 2003). Uterine transmission varies during gestation with transmission low (5-25%) in the first trimester and increasing up to 90% by the end of pregnancy (McLeod, Kieffer et al. 2009; Garcia-Meric, Franck et al. 2010). Recent studies indicate the balance between parasite virulence and host Th1 is important and genes involved in these phenomena, such as TLRs, cytokines, chemokines or their receptors, immunoglobulins or Fc receptors (FcRs) may represent candidate host genes relevant for understanding vertical transmission and pathogenesis of congenital toxoplasmosis (Ortiz-Alegria, Caballero-Ortega et al. 2010).

Fetal involvement is most severe when maternal toxoplasmosis is contracted early in pregnancy leading to spontaneous abortion or severe neurological effects. Conversely, infection (Montoya and Liesenfeld 2004) in the third trimester is often asymptomatic, with development of chorioretinitis commonly occurring later in life. Congenital transmission occurs almost solely in seronegative women who have acute infection during pregnancy (Montoya and Rosso 2005; Montoya and Remington 2008) and is not seen in women who are seropositive before pregnancy. The exception to this rule is the occasional report of congenital transmission in women with immune suppression who have reactivation of latent *T. gondii* during pregnancy (Jones, Lopez et al. 2003).

The classic triad of symptoms of congenital toxoplasmosis is chorioretinitis, hydrocephalus, and intracranial calcifications, although a variety of symptoms can occur (Freij and Sever 1991; Swisher, Boyer et al. 1994; Jones, Lopez et al. 2003). Systemic manifestations include fever, hepatosplenomegaly, jaundice, lymphadenopathy, anemia and abnormal spinal fluid. Other neurologic findings include seizures, bulging fontanelle, with development of serious neurological sequelae such as mental retardation, blindness and epilepsy in infancy or later

in life. Infants infected congenitally often are asymptomatic at birth and subsequently develop retinal disease during childhood (Wallon, Cozon et al. 2001).

Diagnosis of Congenital Toxoplasmosis—Diagnosis of toxoplasmosis in pregnant women depends is serological testing (Montoya 2002). In acute infection, IgG and IgM levels rise during the first 2 weeks of infection. Elevation of Toxoplasma-specific IgG antibodies indicates that infection has occurred, but does not discriminate between recent and past infection. A negative IgM in combination with a positive IgG result usually indicates infection at least six months duration. However IgM antibodies can persist for up to 18 months after infection and can be non-specific generating false-positive reactions. As noted above, avidity testing, IgA, IgE and differential agglutination tests can be useful in determining when an infection occurred and are critical adjuncts in understanding if a positive IgM test in pregnancy will be associated with a risk of congenital transmission of infection. Once a diagnosis of acute *Toxoplasma* infection is made in a pregnant mother the diagnosis of congenital transmission of infection in the fetus *in utero* can be done via polymerase chain reactions (PCR)-assays from amniotic fluid. Treatment of the mother with Spiramycin is often instituted with the diagnosis of acute infection while further diagnostic testing is being done to determine if congenital infection has occurred. PCR assays from amniotic fluid, typically based on the B1 gene, have reported sensitivities of 65% - 91% (Romand, Wallon et al. 2001; Thalib et al. 2005, Gras et al. 2005; Bessieres, Berrebi et al. 2009; Eida, Eida et al. 2009). A recently reported real-time PCR with a sensitivity of 98% further improves detection of *T. gondii* in amniotic fluid (Wallon, Franck et al. 2010; Abdul-Ghani 2011). If congenital transmission is determined then treatment should be instituted to decrease the complications of congenital toxoplasmosis.

Prenatal, Neonatal and Postnatal Treatment of Congenital Toxoplasmosis—In the US, routine pre-natal testing is not routinely done. In contrast in countries with a higher incidence, universal prenatal screening procedures have been adopted. In France, for example, screening of pregnant women, *in utero* diagnosis and treatment are routine with the effect that severe disease has been reduced as indicated by several studies (Bessieres, Berrebi et al. 2001; Bessieres, Berrebi et al. 2009; Garcia-Meric, Franck et al. 2010). Routine prenatal treatment has been advocated given the suggested improved clinical outcome in reducing transplacental transmission and disease (McLeod, Boyer et al. 2006; McLeod, Kieffer et al. 2009). Spiramycin is often used for treatment while waiting for diagnostic testing for prenatal transmission and in some studies is continued for women in whom acute toxoplasmosis is documented even if tests for prenatal transmission are negative. Spiramycin is stopped and treatment with pyrimethamine and sulfadizine is recommended for documented prenatal transmission (McLeod, Boyer et al. 2006; McLeod, Kieffer et al. 2009).

Treatment of the neonatal infant during the first year of life and longer has been demonstrated to significantly improve clinical outcome (Montoya and Remington 2008). Treatment with pyrimethamine and sulfadiazine during at least the first year of life reduces parasite burden and may help prevent adverse sequelae such as retinal damage and loss of vision (Kieffer, Wallon et al. 2008; Phan, Kasza et al. 2008; Phan, Kasza et al. 2008). In

severe cases steroids may be useful to decrease inflammation. Results from long-term studies found individuals with treated congenital toxoplasmosis had no significant reduction in visual function, as compared to uninfected individuals (Peyron, Garweg et al. 2011).

Ocular Toxoplasmosis

Ocular Toxoplasmosis (OT) can be acquired congenitally, can be a postnatal acquired infection, or can be the result of disease reactivation in immune-compromised and pregnant individuals (Jones, Alexander et al. 2006). The disease typically causes chorioretinitis with recurrence episodes of inflammation and subsequent healing, occurring for years after acute infection. These bouts of recurrent chorioretinitis are typically in the posterior pole of the eye, which overtime result in blurred vision, photophobia, loss of central vision and blindness. In developing countries Toxoplasmic retinochoroiditis is the most frequent cause of infectious blindness and visual problems among young children (Vallochi, Nakamura et al. 2002; Garweg and Candolfi 2009). It is also a common retinal infection in the US, although the proportion of individuals with active disease is only about 2% (Jones and Holland 2010). Although it had been thought that infection of the eye was rare in postnatally acquired infections, recent findings indicate that chorioretinitis resulting from acute infection occurs at a higher rate than earlier suspected (Holland 1992; Bowie, King et al. 1997; Arevalo, Belfort et al. 2010).

T. gondii primarily infects the retina, but the choroid, vitreous and anterior chamber of the eye are also involved (Commodaro, Belfort et al. 2009; Delair, Latkany et al. 2011). This infection is characterized by necrotizing retinopathy triggered by activation of dormant cyst stage located within the retina and the optic nerve. Active lesions present as grey-white focuses of retinal necrosis with adjacent choroiditis, vasculitis, haemorrhage and vitreitis with formation of chorioretinal scars. Ocular complications most commonly seen in children include choroidal neovascularization, cataract, glaucoma, optic nerve atropy and retinal detachment (Bosch-Driessen, Karimi et al. 2000; Eckert, Melamed et al. 2007). Retinochoroidal scars are the most common manifestation of congenital or prenatal infection (Mets and Chhabra 2008; Commodaro, Belfort et al. 2009). Active lesions become quiescent with treatment but may recur at any age (Mets, Holfels et al. 1997). Immune compromised individuals present with a more severe form of the disease characterized by extensive multifocal, often bilateral, retinal necrosis and uveitis (Commodaro, Belfort et al. 2009; Delair, Latkany et al. 2011).

A predominance of Type I strains have been found to be associated with ocular infection in the US, Poland and Brazil (Grigg, 2001; Khan 2006; Vallochi 2005; Zaborowski). In Brazil where the incidence and severity of ocular toxoplasmosis is high it was found that most cases were not congenital, but acquired later in life, and that divergent parasite genotypes present in this area appear to be more virulent (Holland 2009). In France, most cases were due to Type II strains indicating that ocular toxoplasmosis are not caused exclusively by Type I strains (Fekkar, Ajzenberg et al. 2011). Local epidemiological factors and host genetic background also plays a role in the development of ocular disease (Holland, Crespi et al. 2008; Vallochi, Goldberg et al. 2008).

Diagnosis and Treatment—In most cases, diagnosis is based upon characteristic finding on the ocular examination and the presence circulating specific antibodies against *T. gondii.* PCR, which can determine the parasite directly, can be utilized to demonstrate this organism in vitreous fluid samples. Analysis of intraocular fluids, such as aquaeous, vitreous and chorioretinal biopsies is usually reserved for difficult cases in which the differential diagnosis is broad, e.g. immune compromised hosts such as those with AIDS, and includes other infections such as cytomegalovirus and Herpes virus where a delay in diagnosis and treatment may have significant adverse outcomes. This is especially true in children, when vision is often lost because of retinochoroiditis or retinal complications. Disease should be monitored and treated through the first 2 years of life (Kieffer, Wallon et al. 2008).

Anti-toxoplasmic therapy is effective with active lesions becoming quiescent in ten to 14 days (Mets, Holfels et al. 1997). Pyrimethamine and sulfadiazine as well as Trimethoprim/ sulfamethoxazole have been effective therapeutic agents. Systemic steroids can be added to avoid further damage of the retina by the inflammation. Treatment needs to be started before necrosis and damage to the retina, caused by recurrent bouts of the retinochroiditis occurs (Montoya and Rosso 2005) (Mets, Holfels et al. 1997; Phan, Kasza et al. 2008; Phan, Kasza et al. 2008). (Pereira-Chioccola, Vidal et al. 2009). Retinochroiditis occurs in clusters over time, with recurrence influenced by age and duration of infection (Holland, Crespi et al. 2008). Treatment does not avoid recurrences and long-tem follow-up is recommended into the second decade of life (Phan, Kasza et al. 2008b).

Cerebral Toxoplasmosis

Cerebral Toxoplasmosis with necrotizing encephalitis usually is due to reactivation of a latent infection in the brain in immune suppressed patients (Luft and Remington 1992). Cerebral Toxoplasmosis is the most common opportunistic disease in AIDS patients in both developed and underdeveloped countries (Pereira-Chioccola, Vidal et al. 2009). The incidence of cerebral toxoplasmosis varies by country influenced by the prevalence of *T. gondii* infection in the general population. Additionally differences in genotypes of *T. gondii* isolates and the mode of transmission have been found to make a difference in some locations, as for example Brazil where divergent strains predominant (Khan, Jordan et al. 2006). The introduction of active anti-retroviral therapy (cART) has dramatically reduced the incidence of cerebral toxoplasmosis. In the pre-cART era, rates in the US and UK varied between 16 to 40%, in Spain it was 60%, in Brazil 50 to 80%, and in France 75 to 90% (Hill and Dubey 2002). Survival of HIV-patients has improved dramatically since the introduction of cART although cerebral toxoplasmosis is still a major cause of morbidity and mortality among HIV-infected patients, especially from developing countries. Persistent neurological deficits are often present in surviving patients, indicating there still a need for improved understanding and treatments for cerebral toxoplasmosis (Hoffmann, Ernst et al. 2007).

Cerebral toxoplasmosis causes unifocal or multifocal lesions (Pereira-Chioccola, Vidal et al. 2009). Clinical manifestations depend upon the location and number of lesions. Clinical symptoms include headache, fever, focal deficits, seizures, mental confusion, ataxia, lethargy and visual alterations (Mamidi, DeSimone et al. 2002; Skiest 2002; Manzardo, Del

Mar Ortega et al. 2005; Vidal, Hernandez et al. 2005; Moulignier 2006). Other symptoms can include cognitive dysfunction, intracranial pressure and involuntary movements (Pereira-Chioccola, Vidal et al. 2009).

Diagnosis—Diagnosis depends on a combination of clinical, serological and radiological information (Mamidi, DeSimone et al. 2002). A presumptive diagnosis is often confirmed with a positive response to anti-*Toxoplasma* therapy. A favorable clinical response is expected within 14 days of specific treatment. Molecular diagnosis using PCR can be a useful tool for diagnosis of *T. gondii* (Pereira-Chioccola, Vidal et al. 2009). Imaging using computed tomography (CT) of MRI is essential for the presumptive diagnosis of cerebral toxoplasmosis. Single or multiple focal lesions are usually observed with CT or MRI, with a typical pattern of a hypodense lesion with ring-enhancing and perilesional edema evident (Pereira-Chioccola, Vidal et al. 2009). The differential diagnosis includes primary lymphoma of the CNS, which constitutes the most common differential diagnosis of cerebral toxoplasmosis in developed countries, while in developing countries focal forms of cerebral TB is also a common alternative diagnosis (Manzardo, Del Mar Ortega et al. 2005; Trujillo, Jaramillo-Rangel et al. 2005). In addition to these neurologic complications, the differential diagnosis of brain lesions in HIV-infected patients also includes infections such as cryptococcosis, aspergillosis, microsporidiosis and *Trypanosoma cruzi* or metastases of disseminated lymphomas and glioblastoma tumors.

Immunological diagnosis using antibodies in serum is complicated by the fact that healthy individuals with chronic *Toxoplasma* infection maintain *T. gondii* IgG antibodies. Thus, serological testing cannot discriminate between reactivated versus latent infection. The presence of a negative serology would make cerebral toxoplasmosis less likely and is an indication for brain biopsy in cases consistent with cerebral toxoplasmosis as the probability of an alternative diagnosis is higher. Nonetheless, it should be appreciated that a negative serological result or low titer, does not exclude a positive diagnosis for cerebral toxoplasmosis especially in the context of compatible clinical and radiological findings (Antinori, Larussa et al. 2004).

Over the last two decades, the development of PCR based molecular diagnostic methodologies has allowed detection of *T. gondii* in a variety of clinical specimens. PCR-based methods using cerebrospinal fluid (CSF) or peripheral blood samples have been demonstrated to have utility in the diagnosis of cerebral toxoplasmosis (Bastien 2002). Molecular methods are particularly appropriate for AIDS patients since these methods are not affected by immunological status and are rapid, sensitive and specific (Colombo, Vidal et al. 2005; Pereira-Chioccola, Vidal et al. 2009). PCR using CSF has been reported to have a high specificity of 96 to 100% (Pereira-Chioccola, Vidal et al. 2009; Correia, Melo et al. 2010). However collection of CSF is invasion and may be inappropriate for patients with extensive cerebral lesions with extensive edema. Reports on the utility of PCR using peripheral blood samples for diagnosing cerebral toxoplasmosis have been variable (Correia, Melo et al. 2010).

The wide range of variation in the sensitivities of PCR methods is a reflection of the variations in PCR protocols and the target gene. Conventional PCR (cnPCR), nested PCR

(nPCR), and quantitative real time PCR (gPCR) methods have all been used to detect *T. gondii*. The most common targets used include the B1 gene and the 529 bp repeat element. A European study found the B1 gene was more sensitive than the 529-bp sequence while conversely a study conducted in Brazil found that the B1 gene was more sensitive than the 529 bp sequence for diagnosis of both cerebral and congenital toxoplasmosis in both cnPCR and qPCR (Pereira-Chioccola, Vidal et al. 2009; Mesquita, Vidal et al. 2010). Thus uncertainty exists surrounding the best target(s) and PCR methods for accurate molecular diagnosis of cerebral toxoplasmosis. Some of this variation may also depend upon the dominant strain of the parasite present in geographic location. Molecular characterization techniques are also used for genetic characterization and identification of parasite strains in epidemiological and genetic studies. The commonly used methods for these purposes are multilocus PCR-RFLP, microsatellite, or multilocus sequence typing (MLST). An integrated approach for the molecular detection and genetic characterization of *T. gondii* has recently been propsed (Su, Shwab et al. 2010). This approach consists of detection of *T. gondii* infection in biological samples by nPCR or qPCR of repetitive DNA sequences using the B1 gene or the 529-bp repeat element, followed by multiplexed multilocus nested-PCR-RFLP technique for the subsequent genetic identification of *T. gondii*.

Treatment of Cerebral Toxoplasmosis—Therapy with pyrimethamine and sulfadiazine is usually effective. In patients with sulfadiazine intolerance either clindamycin or atovaquone can be used in combination with pyrimethamine. Therapy is continued for at least 6 weeks and if immune suppression is present secondary prophylaxis with trimethropim/sulfamethoxazole or pyrimethamine/sulfadiazine is continued indefinitely. Recent data suggests that. trimethoprim/sulfamethoxazole can be used for primary therapy in place of pyrimethamine/sulfadiazine with good outcomes (particularly in resource poor settings)(Aberg and Powderly 2010). Steroids may be useful in cases with significant cerebral edema. Neurological imaging should be done 2 weeks after initiating therapy should be done to assess efficacy of treatment. If patients fail to respond to therapy, a biopsy of the lesion is indicated to look for an alternative diagnosis.

Primary prophylaxis with trimethoprim/sulfamethoxazole is effective in preventing cerebral toxoplasmosis in *T. gondii* seropositive patients with AIDS who have a CD4+ T-cell count below100 cells/mm^3. Primary prophylaxis can be discontinued in patients with a good response to cART, defined as a CD4+ T-cell count above 200 cells/mm^3 after 3 months. Secondary prophylaxis can be discontinued when HIV-infected patients receiving cART have a sustained increase of CD4+ T-cell count above 200 cell/mm^3 after about 6 months of cerebral toxoplasmosis drug therapy (Lejeune, Miro et al. 2011).

Neuropsychiatric disease and chronic T. gondii infection

Over the past decade there has been an increasing interest in the possibility of an association of *T. gondii* infection and psychiatric disorders (Torrey and Yolken 2003; Yolken, Dickerson et al. 2009; Zhu 2009; Fekadu, Shibre et al. 2010). The idea that infection with *T. gondii* was associated with schizophrenia initially arose from clinical observations of patients infected with *T. gondii*, presenting with psychotic symptoms (Pariser, Zunich et al. 1978; Choi, Yoo et al. 1983; Torrey and Yolken 2003). Support for the hypothesis that *T.*

gondii infection may have an etiological role in the development of Schizophrenia has come from numerous studies including: (1) epidemiological studies that have found an higher prevalence of antibodies to *T. gondii* toxoplasmosis in individuals with schizophrenia; (2). studies in rodents showing the parasite affects host behavior and induces elevated levels of dopamine, as is commonly seen in Schizophrenia patients; (3) studies in humans showing *Toxoplasma*-infected individuals have a significant shift in personality traits and a decreased level of novelty seeking, amongst other behavioral changes; and (4). cell culture studies showing anti-psychotic medications inhibit the replication of parasite. These studies have been recently reviewed (da Silva and Langoni 2009; Yolken, Dickerson et al. 2009; Zhu 2009; Fekadu, Shibre et al. 2010; Flegr 2010). Collectively these data suggest that *T. gondii* infection is a risk factor for Schizophrenia and raise the hypothesis that infection may have an etiological role in the development of schizophrenia in some patients.

Several studies have investigated if *T. gondii* infection may also be a risk factor for development of depression and other psychiatric disorders (Hinze-Selch 2002; Henriquez, Brett et al. 2009; Groer, Yolken et al. 2011). A recent investigation which systematically examined almost 900 patients with personality disorders including schizophrenia, major depression, and bipolar disorder, found that the diagnosis of a personality disorder was significantly associated with *T. gondii* infection, supporting the hypothesis that infection with *T. gondii* can modulate human behavior and personality traits (Hinze-Selch, Daubener et al. 2010). The establishment of a definite association between *T. gondii* infection and schizophrenia would be a major breakthrough in the understanding of the etiology and pathophysiological mechanism(s) of schizophrenia and its treatment and prevention. For example, as the effect of *T. gondii* infection is thought to occur early in life at the neurodevelopmental stage, intervention early in childhood among high-risk groups such as those with a family history of severe mental disorders such as schizophrenia may be effective. The establishment of *T. gondii* infection in psychiatric disorders such as depression or bipolar disorder could have similar effects on understanding of pathophysiological mechanisms, treatment and prevention, of these psychiatric disorders.

Parasite strain has been suggested to influence the role of *T. gondii* on the development of schizophrenia (Yolken, Dickerson et al. 2009). Type I strains have been associated with an increased risk of psychosis in offspring, supporting the suggestion that parasite strain may influence the propensity to develop schizophrenia (Xiao, Buka et al. 2009). A recent *in vitro* study found Type I strains had a greater affect on host cell gene expression in neuroepithelial cells as compared to Type II and Type III strains (Xiao, Jones-Brando et al. 2011). Furthermore, Type I strains largely affected genes relating to the central nervous system. The effect of parasite strain would help explain why, despite the fact that approximately one-third of the world population is chronically infected with *T. gondii*, only a small fraction of the population exhibits psychiatric disorders.

The mechanisms involved in an etiological role for the parasite on psychiatric disorders are not fully understood. Several factors have been suggested including a direct impact of the parasite on the brain, immune modulatory mechanisms and effects on neurotransmission, and parasite strain (Novotna, Hanusova et al. 2005; Henriquez, Brett et al. 2009; Zhu 2009; Fekadu, Shibre et al. 2010).

Direct Effect—The parasite exhibits a neurotrophism forming cysts predominantly in the brain during a chronic infection and thus it is well placed anatomically to mediate direct effects on neurological functions in the host. The parasite encysts in neurons, glia cells and astrocytes, potentially affecting all these cell type (Halonen, Lyman et al. 1996; Carruthers and Suzuki 2007). Furthermore, in chronic infection in mice, cysts are found predominantly in neurons, occurring in all parts of the neuron (dendrites, axons and the cell body), indicating the parasite could directly impact neuronal function (Ferguson and Hutchison 1987). While cysts persist in the brain for the lifetime of the host, studies in chronically infected mice found microglial nodules containing parasites are present throughout the chronic infection, indicating cysts might periodically degenerate releasing parasites during the latent phase of infection (Frenkel 1988; Ferguson, Huskinson-Mark et al. 1994). Damage to the brain in congenital and reactivated infections in immunocompromised individuals is characterized by necrosis and microglia nodules in the cortex, basal ganglia and other areas of the brain, indicating the potential direct impact the parasite may have on brain tissue (Fekadu, Shibre et al. 2010).

Neuroimmunological Mechanisms—Cytokines may influence mood and behavior by modulating dopaminergic and glutamatergic neurotransmission (Deutsch, Mastropaolo et al. 1989; Lang, Puls et al. 2007). It has been suggested that proinflammatory cytokines produced by infected astrocytes and microglia, may influence mood and behavior by modulating these monoamine and glutamate pathways in the brain (Carruthers and Suzuki 2007; Fekadu, Shibre et al. 2010). Activated astrocytes are a hallmark of Toxoplasma encephalitis and have also been suggested to affect neurotransmitters via the production of kynurenic acid (KYNA) which may contribute to excessive inhibition of glutamine and nicotine neurotransmitter receptors, a effect that is believed to cause the cognitive impairment observed in schizophrenic patients (Schwarcz and Hunter 2007) Finally, the parasite has two genes encoding tyrosine hydroxylase that produce L-DOPA, one which is induced during the formation of bradyzoites in the brain, and thus it is plausible the parasite can directly affect dopamine and/or serotonin biosynthesis, which are neurotransmitter know to be important in psychotic and mood disorders (Gaskell, Smith et al. 2009; Henriquez, Brett et al. 2009). Dopamine has been found to play a role in behavioral changes in infected rodents and is suggested to play a role in behavioral changes of infected individuals (Novotna, Hanusova et al. 2005; Webster and McConkey 2010).

SUMMARY

T. gondii is a common central nervous system infection, although it is usually latent in immune competent hosts. It can, in the setting of congenital infection or immune compromised hosts cause severe neurological disease. In the approximately 100 years since its discovery, much has been learned about the basic biology, life history, epidemiology, immune responses and pathophysiology and of the major clinical sequel of infection. Recent advances in our understanding of the population structure as well as the virulent and divergent genotypes of *T. gondii*, will likely lead to further understanding of disease outbreaks and evolution of parasite virulence of this ubiquitous parasite. Advances in the imaging of the innate and adaptive immune response are providing new insights into the host-parasite interactions which should result in new treatments and immunotherapeutic

approaches to this infection. Finally, the recent association of latent infection with schizophrenia and possibly other psychiatric disorders may result in advances in our understanding of the effect of infection on psychiatric disease and provide new therapeutic approaches for treatment or prevention of these illnesses. As approximately one-third of the world's population is latently infected with Toxoplasmosis, these advances in our understanding and treatment of this infection will provide important benefits for this common infectious disease.

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