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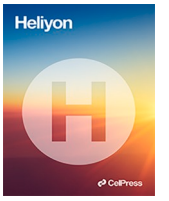

Review article

# Effective factors in the pathogenesis of *Toxoplasma gondii*

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ABSTRACT

*Toxoplasma gondii* (*T. gondii*) is a cosmopolitan protozoan parasite in humans and animals. It infects about 30 % of the human population worldwide and causes potentially fatal diseases in immunocompromised hosts and neonates. For this study, five English-language databases (ScienceDirect, ProQuest, Web of Science, PubMed, and Scopus) and the internet search engine Google Scholar were searched. This review was accomplished to draw a global perspective of what is known about the pathogenesis of *T. gondii* and various factors affecting it. Virulence and immune responses can influence the mechanisms of parasite pathogenesis and these factors are in turn influenced by other factors. In addition to the host's genetic background, the type of *Toxoplasma* strain, the routes of transmission of infection, the number of passages, and different phases of parasite life affect virulence. The identification of virulence factors of the parasite could provide promising insights into the pathogenesis of this parasite. The results of this study can be an incentive to conduct more intensive research to design and develop new anti-*Toxoplasma* agents (drugs and vaccines) to treat or prevent this infection. In addition, further studies are needed to better understand the key agents in the pathogenesis of *T. gondii*.

## 1. Introduction

*Toxoplasma gondii* (*T. gondii*) is an opportunistic intracellular parasitic protozoan that can infect intermediate hosts (including humans, ruminants, rodents, and birds) [1–6]. This parasite has been reported even in cold-blooded animals and they can act as the source of infection for the various hosts that feed on them [7]. Host susceptibility and resistance to infection varies from host to host. For example, Australian marsupials and New World monkeys are highly susceptible to infection, whereas horses, cattle, rats, Old World monkeys, and humans are more resistant. Although the reasons for these differences are still unknown, co-evolution between parasite and host could be one of the reasons [8,9]. The prevalence of this infection varies between 12 % and 90 % [10]. The reasons for the high prevalence of *T. gondii* in the world can be the infectivity of the parasite in both sexual and asexual forms, the ability to cause chronic infection and remain infectious for life [11]. Other factors influencing the prevalence of this infection include geographical region and climate, dietary habits, hygiene, and host susceptibility [12]. *T. gondii* has a complex life cycle containing a sexual phase in definitive hosts, an asexual phase in intermediate hosts, and an exogenous stage [13]. There are three infective forms of parasite: tachyzoites (in tissue sections or smears of body fluid during acute infection), bradyzoites (in cysts of different tissues during the course of chronic infection), and sporozoites (in oocysts identified in feline feces) [14]. The sexual cycle occurs only within the intestinal

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epithelial cells of felids and leads to the release of oocysts into the environment through excretion in the feces. Therefore, it plays an important role in the transmission of *T. gondii* [15]. Intermediate hosts can become infected by consuming food, water, and soil contaminated with oocysts. In addition, *T. gondii* can be transmitted by eating raw/undercooked meat containing the parasite in tissue cysts or by vertical transmission during pregnancy (tachyzoites are transmitted from the infected mother to the fetus via the placenta) [16,17]. Congenital toxoplasmosis can lead to serious complications such as miscarriage, fetal death, congenital anomalies, and damage to the nerves, eyes, or other organs of the fetus [18,19]. Several factors have been associated with the risk of fetal infection, including the timing of maternal infection, the parasite load, the virulence of the strain, and the immunologic competence (both cellular and humoral) of the mother during parasitemia [14]. In addition, infection can cause severe symptoms in immunocompromised patients such as human immunodeficiency virus (HIV)-infected persons, patients receiving chemotherapy, organ transplant recipients, and developing fetuses [11]. However, infection in people with a healthy immune system is usually asymptomatic, but can sometimes lead to ocular toxoplasmosis [20]. Latent toxoplasmosis can also lead to behavioral disorders in mice and humans [21,22]. The results of an analysis of the global burden of mental illness showed that in 2015, neurological disorders were responsible for 250.7 million disability-adjusted life years (DALYs) (i.e. 10.2 % of global DALYs) and 9.4 million deaths (i.e. 16.8 % of global deaths) [23]. In addition, toxoplasmosis is a parasitic zoonosis of veterinary importance and may be a potential factor in reproductive problems in small ruminants worldwide. It causes significant economic losses due to abortions, stillbirths, mummification, and neonatal losses in herds [24,25]. Given these facts and the great success of the parasite in causing the infection, as well as the inability of current treatments to remove the parasite from the body, research into the basic pathogenic mechanisms of toxoplasmosis emphasizes the importance of prevention and provides clues to new therapeutic approaches. Therefore, our research team has attempted to briefly highlight the pathogenesis of the parasite and various factors such as virulence and immune response to better understand the infection caused by this parasite.

## 2. Study design and search strategy

To find related studies, a principled and systematic search of scientific publications was conducted using five English-language databases (ScienceDirect, ProQuest, Web of Science, PubMed, and Scopus) and the internet search engine Google Scholar. The search terms used were: "*Toxoplasma*", "*T. gondii*", "toxoplasmosis", "pathogenesis", "virulence", "invasion", and "immunopathogenesis". Cross-sectional studies, reviews, systematic reviews, and meta-analyzes were selected that evaluated the factors involved in the pathogenesis, immune responses, invasion, and virulence of *T. gondii*, studies demonstrating the role of *Toxoplasma* in causing, exacerbating, or reducing the symptoms of psychiatric disorders, and articles examining the complications caused by toxoplasmosis in pregnancy, ocular toxoplasmosis, patients with acquired immunodeficiency syndrome (AIDS), and transplant recipients. Finally, 476 articles met the eligibility criteria and were analyzed in this review.

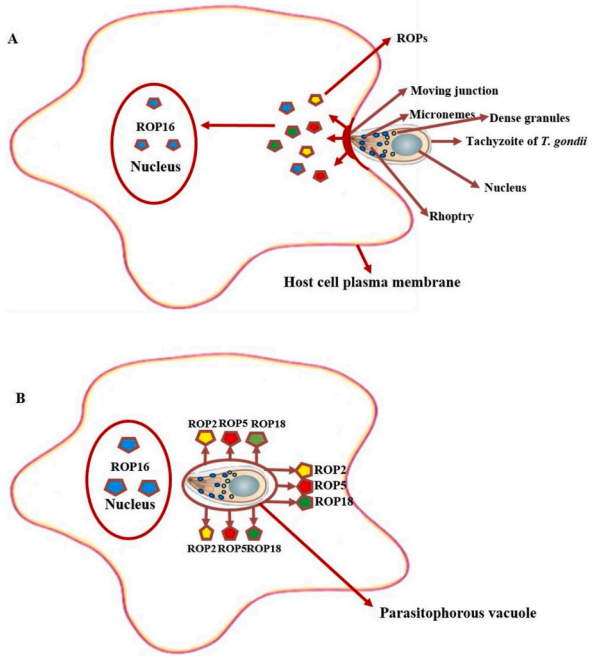


**Fig. 1.** (A) The invasion system of *Toxoplasma gondii*, and **(B)** Role of POPs in invasion.

## 3. Invasion

The complex process of invasion involves different stages of host cell contact, gliding movement, moving junction (MJ), formation of the parasitophorous vacuolar membrane (PVM), and PVM modification. Invasion occurs very rapidly and within 15–40 s [26–28]. Contact with the host cell is initiated by the recognition of surface receptors via glycosylphosphatidylinositol (GPI)-anchored surface antigens (SAGs) [29]. *T. gondii* actively invades non-phagocytic and phagocytic cells [30] by forming the MJ on the surface of the host cell [31]. At this stage, microneme proteins (MICs) accumulate on the apical surface of the parasite, and rhoptry neck proteins (RONs) are secreted and interact with MIC-derived apical membrane antigen 1 (AMA1) to form MJ [32]. Parasite penetration through MJ is directed using its actin motor complex [33]. The parasitophorous vacuole (PV) formed in this way is nonfusogenic with the host's endocytic system, so it escapes from destruction by lysosomes [34]. Asexual reproduction of *T. gondii* is carried out in the PV. Also, dense granule proteins (GRAs) are among the proteins that are secreted during host cell invasion. By increasing the level of calcium, the egress of the parasite from the host cell is modulated; the required power is provided through the actin-myosin motor and is related to the secretion of rhoptry proteins (ROPs), MICs, and RONs (Fig. 1A) [32].

The invasion of host cells is critical for the pathogenicity of *T. gondii* [35]. Consequently, the various stages of invasion and the effective factors in each of these stages, such as surface and secretory antigens of the parasite, are briefly described here. It is thought that the knowledge and understanding of the mechanisms that occur in each of the different stages of invasion may provide a better view of the pathogenesis and the factors affecting this process.

### 3.1. Gliding motility

In the first stage of invasion, *T. gondii* tachyzoites reach the host cell by gliding, and contact is established between the apical tip of the tachyzoite and the host cell membrane [36]. Gliding relies on transposing adhesins from the anterior pole to the posterior pole [37]. A small myosin motor anchored in the inner membrane complex (IMC) provided the force for translocation [38]. The actomyosin motor complex [myosin light chain (TgMLC or PfMTIP), type XIV myosin heavy chain (MyoA), and the glideosome-associated proteins (GAP45 and GAP50)] plays a role in the gliding motility in parasites belonging to the phylum Apicomplexa [39–42]. GAP50 is the principal anchor in the IMC. While, GAP45 covers the space between the cell membrane and the outer membrane of the IMC and ensures the cohesion between the two membranes [43,44]. This motor can reach actin filaments associated with MICs [44]. Polymerization of short actin filaments is necessary for gliding motility in the space between inner and outer membranes [45].

Varieties of surface adhesins are likely to be involved in *T. gondii* motility. MICs play a role in parasite recognition, motility, and adhesion. MIC1, MIC2, MIC4, MIC6, and especially MIC3 can bind to various targets such as glucose, aldolase, lactose, intercellular adhesion molecule-1 (ICAM-1), and heparin [46–48]. Among the different types of MICs, MIC2 plays an essential role in the gliding of *T. gondii* [49]. The release of MICs is strongly coupled to high calcium, and this signal is mediated by calcium-dependent protein kinase 1 (CDPK1) [50]. Following translocation along the surface, the rhomboid proteases play a vital role in releasing adhesins by intramembrane proteolysis [51]. Rhomboid 4 trims surface proteins and maintains the front-to-back adhesion gradient, which is important for gliding [52].

### 3.2. Attachment

After encountering the host cell, the parasite probes the membrane to find a suitable attachment site. Once the binding site is recognized by the apical pole, various factors such as host cell laminin, parasite laminin, parasite surface lectins, and the major parasite surface protein may contribute to the initial attachment of the parasite to the host cell [53,54]. Attachment is essential for host-parasite recognition and invasion events. The primary attachment of tachyzoites to host cells stimulates signaling molecules and increases the secretion of adhesins [55]. GPI-anchored antigens, most of these antigens belong to surface antigen 1 (SAG1) or SAG2 families, and form the surface coating of tachyzoites and bradyzoites of *T. gondii* [56,57]. These molecules participate in invasion, immune modulation, and/or virulence reduction. Also, they may contribute to the protection of parasites to survive in the environment [56]. The SAG1 family encodes GPI-anchored proteins that retain 12 conserved cysteine residues of SAG1 and have an overall identity of approximately 30 % [56]. The importance of GPI for the pathogenesis of toxoplasmosis remains unknown [58]. The SAG1 sequence in *T. gondii* strains has a high degree of homology among the three major clonal lineages [59]. Although cloning of 21 *Toxoplasma* SAG genes has been done, there is still much unknown about their expression patterns [56].

MICs (small apical organelles) are secreted by the tachyzoite tips during the initial contact of the apical end of the parasite with the host's plasma membrane [60]. These proteins are produced in the rough endoplasmic reticulum and are transferred to the MICs by the Golgi apparatus to participate in cell attachment [61]. MICs are also critical for parasite gliding movement because their cytoplasmic domains can bind to aldolase, which is linked to the parasite's actin-myosin motor and forms the basis of active invasion [62]. The MIC complex plays an essential role in the virulence and pathogenicity of the parasite [63]. ROPs are secreted immediately after MICs. They are club-shaped organs with two distinct parts, including the anterior duct (neck) and the posterior bulb [64]. The neck proteins of the rhoptries are called RONs, and the proteins of its posterior part are termed ROPs [65]. They are involved in the active parasite's penetration into the host cell and the biogenesis of the PV as a special intracellular compartment [64]. The parasite is protected from intracellular elimination within the PV and reproduces strongly. ROPs are important in different stages of parasite invasion and for its survival in host cells. Overall, ROPs comprise approximately 1–30 % of the total *Toxoplasma* cell volume [64].

### 3.3. Moving junction

In the second stage of invasion, MJ formation, contact is established between the apical tip of the parasite and the plasma membrane of the host cell. The parasite is surrounded by ring formation, and the protozoan is placed inside the PV [66–68]. This stage is related to MIC exocytosis at the apical ends of the parasite, which is the result of changes in cytoplasmic calcium activating a calmodulin-like domain kinase [69–71]. Different chemicals stimulating calcium stores release, such as ethanol, can enhance it [72]. The cooperation between MICs and RONs in forming the MJ creates a physical link that ensures the internalization of *T. gondii* in the PV [73]. An interaction occurs between the AMA1 (belongs to the MICs family) and RON2; the AMA1 protein forms MJ with RON2, RON4, RON5, and RON8. The AMA1 protein is conserved in all apicomplexan [73–76]. This protein is probably the most interesting MIC protein produced in *T. gondii*. It plays an important role in MJ formation during invasion and promotes intracellular tachyzoite proliferation [77,78], but this point has been recently debated [79]. The formation of a tight junction (TJ) commits the parasite to invasion and requires the secretion of ROPs. RONs are located in the TJ between parasite tachyzoites and target cells [73,80].

### 3.4. Parasitophorous vacuole

Apicomplexan parasites mostly spend their life cycle in the host cells and use different strategies to survive in cells. Many parasites, such as *Toxoplasma* and *Plasmodium*, reside inside a nonfusogenic PV derived from the host plasma membrane [81]. When the MJ begins to glide, it turns from a cap into a ring on the cell surface and the parasite is guided into the developing vacuole. This stage (parasite vacuole formation) is the third stage of invasion [82,83]. By forming MJ, the parasites forcefully enter the host cell membrane via invagination, and finally, a PV is created, and the parasite resides in it [84]. The PVM forms the boundary between the host and the parasite and provides a niche for survival and reproduction [85]. ROP proteins including ROP2, ROP4, ROP5, ROP7, ROP8, and ROP18 are involved in forming PVs (Fig. 1B) [86,87]. During the invasion, as MJ advances around the parasite, proteins such as AMA-1 are released from the parasite's surface; this process is necessary for invasion [88–94]. Several GRA proteins are secreted during or after host cell invasion and target the vacuolar space, PVM, or cytosol of the cell. GRA antigens are stored in secretory vesicular organelles called dense granules that express proteins in different stages of the parasite's life cycle [95]. These proteins are abundantly secreted and form the main component of the vacuole around the tachyzoite and the cyst wall around the bradyzoite [95]. Apicomplexan parasites obtain many of their essential nutrients from host cells. For example, *Toxoplasma* is auxotrophic for amino acids, purines, and sterols [96]. Sterol transporters on the PVM are involved in the scavenging of sterols from the host cell to the PV [97]. Small metabolite transporters have not been placed on the PVM but have been identified on the *Toxoplasma* plasma membrane [98].

### 3.5. Egress

The parasite uses different approaches such as intraparasite egress signaling and exogenous compounds to egress the host cell. $Ca^{2+}$ signaling is necessary in mediating egress but other signals and regulatory genes involved in this process are unclear [99,100]. The signals involved in the egress process are: 1) intraparasitic egress signaling such as MIC proteins: perforin-like protein 1 (TgPLP1) and Toxolysin 4 (TLN4) are both present in MICs and have a calcium-dependent role in parasite egress [101,102]. However, these two proteins do not play a similar role in parasite virulence [103], GRA proteins: some GRAs or GRA-related proteins mediate parasite egress to facilitate *Toxoplasma* growth in the PV [103]. TgLCAT is a GRA-like protein; this protein binds to the PV and parasite plasma membrane. Lacking TgLCAT shows delayed egress [104], and calcium-dependent protein kinases (CDPKs): So far, fourteen CDPKs have been discovered that play their roles during gliding, invasion, and egress [105]. For example, TgCDPK1 is a critical regulator of calcium-dependent MIC content release, including TgPLP1 [50]. *Toxoplasma* produces TgLCAT and releases into the PV lumen. Accumulated TgLCAT is involved in the release of calcium from the host cell cytoplasm into the PV lumen. It exerts this role by using membrane lytic activity and creating holes in the PVM [103]. By increasing calcium levels, TgPLP1 and TLN4 are released from MICs and destroy PVM and host cell membrane invagination (HCM). For parasite egress from the host cell, the damage caused by pore-forming proteins to PVM and HCM is not enough. TgCDPKs phosphorylate TgMyoA, which initiates parasite motility by increasing calcium levels [103], and 2) extra-parasitic egress signaling such as inflammatory factors: *T. gondii* infection induces type I immune responses in the infected host, which is manifested by the proliferation of $CD8^+$ T cells and the production of a variety of inflammatory cytokines such as IL-12 and interferon-gamma (IFN-γ) [103], IFN-γ: this cytokine causes parasite egress, and in some exceptional cases, it severely reduces the replication of *T. gondii* in astrocytes [103], nitric oxide (NO): according to *in vitro* studies, exogenous NO released by sodium nitroferricyanide (III) dihydrate can cause the egress of *T. gondii* tachyzoites from infected peritoneal macrophages and human foreskin fibroblasts [106,107]. Intraparasitic calcium levels and parasite motility affect NO-induced egress [106], death receptor, and perforin: the release of intracellular calcium as a result of caspase activity early in the apoptotic cascade, the death receptor ligation in cells infected with *T. gondii* causes the rapid egress of infectious parasites (tachyzoites) and host cell necrosis [108]. After acting on infected cells, T cells induce the rapid egress of *T. gondii* through death receptor or perforin-dependent pathways [108], and tumor necrosis factor-alpha (TNF-α): high doses of TNF-α induce the egress of parasite from infected HFF cells [109] and this result is related to the conditions where the concentration of TNF-α used was higher than *in vivo* conditions. Nevertheless, the concentration of TNF-α used in this study was higher than *in vivo* situation [103].

Also, different exogenous compounds such as ionophores, ethanol, concentration of $K^+$, TgPLP1, dithiothreitol (DTT), and phytohormone abscisic acid (ABA) are used to investigate the processes of *T. gondii* egress [103]. Different arms of the immune system of the host respond to the presence of *T. gondii*, and some of these pathways are directed toward egress [110–112]. For example, following the response of cytotoxic CD8 T cells, perforin and death receptor (Fas/FasL) damage the host cells [108] and this damage

reduces intracellular potassium ($K^+$), which leads to egress [113]. In the absence of an immune response, the parasite replicates to maturity and uses various mechanisms to egress. This parasite produces ABA during its intracellular reproduction [114]. The intracellular phytohormone ABA is one of the calcium release pathways described in different systems from plant seeds to human granulocytes and is also reported in Apicomplexa [114,115]. The cyclic adenosine diphosphate ribose (ADPR) pathway, mediated by the accumulation of the plant hormone ABA, stimulates the increase of intracellular calcium [114]. Increased levels of intracellular calcium activate the secretion of the TgPLP1, which causes an initial breach and disrupts the vacuole membrane. Consequently, it facilitates egress [101]. Also, egress occurs when pH reduction overcomes the suppression of MIC secretion and motility by $K^+$ ions. parasite proliferation causes PV acidification [116]. Another effective factor in the egress process is nucleotide triphosphate degrading enzymes (NTPases), which are secreted by *T. gondii* into the PV. NTPases cause an increasing evacuation in adenosine triphosphate (ATP) of the host cell, which leads to the drying of the $Na^+/K^+$ -ATPase pumps, a decrease in $K^+$, and finally, egress [44].

Artificially increasing intracellular $Ca^{2+}$ using ionophores triggers MIC production, motility, and egress [103]. In addition, ethanol induces egress through $Ca^{2+}$ ionophores by increasing $Ca^{2+}$ fluxes, and these intracellular reserves involved in MIC secretion and invasion may play a role in egress [103]. DTT, a reducing agent, induces the release of parasite nucleotide triphosphate-degrading enzymes in the PV. The egress of intravascular parasites such as *T. gondii* is increased by adding DTT to the culture medium [117,118].

### 3.6. Dissemination

Tachyzoites of *T. gondii* invade various nucleated host cells through active penetration. In non-activated cells, the parasite multiplies rapidly by endodyogeny in a non-fusogenic vacuole that it has created itself [119]. Finally, the tachyzoite enters the bloodstream and spreads to secondary tissues. By triggering a robust inflammatory response, *T. gondii* plays an important role in controlling the infection and reducing the parasite burden [120]. After the acute stage of infection, the tachyzoite differentiates into bradyzoite and causes chronic infection in various tissues [121]. Tissue cysts containing bradyzoites persist until the end of the host's life. If the host's immune system is weakened, recurrent infection may occur, and the bradyzoite transforms into a rapidly multiplying and destructive tachyzoite [122]. The tachyzoite spends a relatively short time in the extracellular environment compared to the time it spends intracellularly after egress from the host cell. This time is an opportunity for the parasite to spread in new tissues. The parasite makes contact with new host cells through its surface protein coat. SAGs are attached to the surface of the parasite by a GPI. Sulfated proteoglycans are recognized by SAG1 in the host cell [123]. *T. gondii* directly targets neutrophils and is able to survive and replicate in human neutrophils. In infected lymph nodes, a high number of neutrophils contain parasites [124–126]. This amount of neutrophil contamination may be due to an intrinsic or parasite-induced disorder in the ability of neutrophils to destroy the parasite [127]. *T. gondii* can quickly spread from the primary site of infection to secondary lymphoid tissues and then to other tissues [124,128]. Dendritic cells (DCs) as "Trojan horses" disseminate the parasite from infected tissues to the spleen and lymph nodes. *In vitro* studies have reported that parasites preferentially infect and replicate in monocytes and DCs [125]. Also, infection of DCs increases their migration capacity [129–131]. The sequestering mechanism is used by natural killer (NK) and T cells to spread the parasite [108,111,132]. Extracellular tachyzoites (genotype type I) act like a strong transmigratory and can probably facilitate the passage of physiological barriers; this feature is not so prominent in type II and III strains, cystogenic strains. In contrast, type II and III strains induce DC migration more than type I [133]. High growth of type I parasites in mouse cells causes heavy parasite burden and extremely elevated levels of Th1 cytokines [134–136]. Type II parasites produce significant amounts of interleukin (IL)-12, which controls infection [137–139]. To spread the parasite and cause infection, type I parasites rely on virulence traits [133,140]. Type II and III parasites cause minimal damage to the host because they have evolved to migrate ensuring efficient dissemination with low parasite load [141].

## 4. The pathogenesis of *T. gondii*

Virulence and immune responses are the most important factors that can be effective in the pathogenesis of *T. gondii*. Therefore, this article reviewed the possible roles and mechanisms of these factors in the pathogenesis of this parasite (Fig. 2).

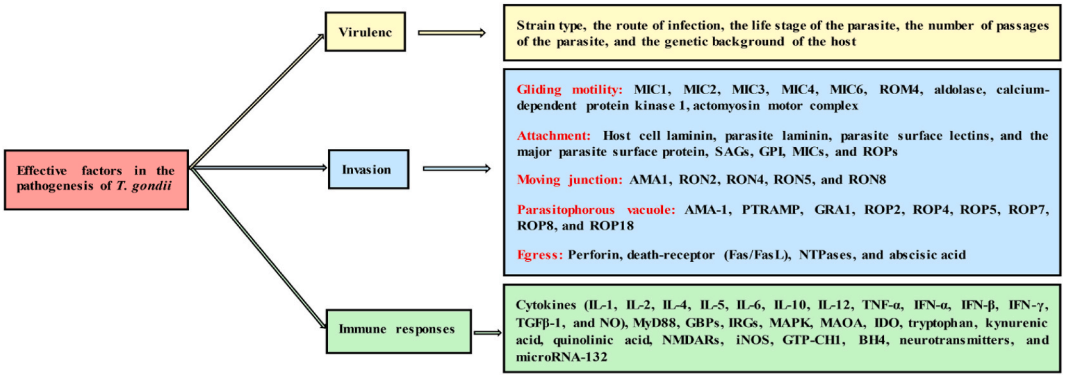


**Fig. 2.** Effective factors in the pathogenesis of *Toxoplasma gondii*.

### 4.1. Virulence

The definition of virulence is different and complex. However, it is usually defined in a murine model after intraperitoneal (IP) injection of a specified number of tachyzoites [142]. Susceptibility to *T. gondii* infection and acute disease is very variable in different hosts; mice can die within a few days, and rats may be completely resistant, which indicates the role of the parasite and host factors in virulence [143]. The virulence of *T. gondii* is determined by both host and parasite factors, including *Toxoplasma* strain type, route of infection, life stage of *T. gondii*, number of passages of the parasite in mice or cell culture, and genetic background of the host.

Despite the opportunity for genetic recombination in felines as definitive hosts, *T. gondii* maintains a highly clonal population structure [144–147]. The genome size of the parasite is approximately 63 Mb and consists of 14 chromosomes [148]. *T. gondii* has many strains classified into these three main types and atypical strains. RH and GTl (type I), Me49 and PRU (type II), and CEP and VEG (type III) are examples of *Toxoplasma* strains [149]. The basis of classification of parasite isolates is their pathogenicity in mice and they are divided into two groups: virulent and avirulent [145,150]. The type I strain is highly virulent in mice and all infected mice die two weeks after infection [144,145] and only one live parasite is fatal for mice. Consequently, mortality is independent of dose. On the contrary, in most strains of *T. gondii* (type II and III), mortality in mice is dose-dependent, and chronic infection is easily caused in mice with low doses [144,145,151–153]. Excessive production of Th1 cytokines is the cause of the virulence of type I strains, which causes tissue damage [136]. Innate growth rate [154], frequency of differentiation, motility and potential to cross biological barriers [133], impaired host cell signaling [155], induction of central nervous system (CNS) pathology during chronic infection [156], and stimulation of gut pathology during acute infection in mice [157] differ among the three main lineages.

In North America, clonal lineages I, II, and III were dominant [158,159]. However, based on a recent single nucleotide polymorphism (SNP) analysis at five loci in ~950 strains, these strains were grouped into 15 haplogroups and a high prevalence of type 12 strains was observed in North America. On the contrary, South America covers most of the divergent strains. Genome-wide SNPs displayed that there is high variety even within these haplogroups (except for haplogroups I, II, III, and 6), and in recent recombination events, most strains may have formed [160,161]. Variability within a *T. gondii* lineage is very low (~0.01 %), and differences between three clonal lineages are estimated to be up to 3 % [161–163]. The lethality of infection caused by type I strains in mice is associated with a gene on chromosome VIIa that is conserved among all type I strains examined [164].

Genetic diversity in parasite strains is greater in Africa, Asia, and South America than in other continents. New genotypes (atypical and exotic types) are more complex due to their diversity and combination of genes. The description of atypical genotypes raises new perspectives in the analysis of virulence [165]. When a cat eats parasite-infected prey, sexual recombination occurs in the cat's gut, causing unusual genotypes [164].

Most cases of recurrent ocular toxoplasmosis in patients suffering from immunodeficiency are caused by type I strains [166]. In Europe and North America, type II strains are the main cause of toxoplasmosis in patients with congenital infection and AIDS [144,158,167,168]. The high prevalence of type II strains in human toxoplasmosis (about 80 % of patient samples) reflects the source of strains that cause infection in humans. Considering that one way of transmission of infection to humans is to eat water and food contaminated with parasites, infection in domestic animals and cats can be a reservoir of infection in humans. Type I strains are rarely reported in North American agricultural and wild animals, but type II strains are the most common [158,168–172]. In *in vitro* conditions, type I strains show more migration than type II and III strains. *In vivo*, the RH strain migrates to the spleen more efficiently than type II or III parasites [149]. The migration phenotype is located on chromosome VIIa, which is associated with acute virulence [173]. The virulence of the parasite is also related to the growth rate. A virulent strain resulting from a cross between type II and III strains has a higher *in vivo* growth rate than that of an avirulent strain from the same cross and spreads more rapidly [174]. The ability of parasite strains to attract cells to the site of infection is different, and this difference can explain the variation in their ability to spread, replicate, and survive [149]. IP injection rapidly attracts inflammatory cells such as neutrophils to the injection site [175,176]. The depletion of neutrophils or a disturbance in their ability to reach the site of infection leads to increased parasite growth [149,175,176]. The attraction of neutrophils by type I strains is more than type II strains; when an equal number of parasites are injected IP into the mice, the number of type I parasites will be more than type II strains in the mouse peritoneum [177].

One of the effective factors in the difference in the virulence of parasite strains is the expression of antigens such as GRA15 and ROP kinases i.e. ROP16, ROP18, and ROP5 pseudokinases secreted by the parasite [10,86,139,155,178–180]. ROPs play a main role in parasite penetration into the host cell. They are also effective in PV formation [181]. ROPs are involved in different stages of parasite invasion and are important for parasite survival in host cells [178,181,182]. By emptying their contents on the host cell membrane, they facilitate the process of the parasite entering the cell [183]. GRA proteins are expressed in tachyzoite, bradyzoite, and sporozoite stages of *T. gondii*. These antigens modify PV and PVM to maintain the parasite in the host cell. They also play a role in the virulence and proliferation of *T. gondii* [95].

#### 4.1.1. GRA15

The role of IFN-γ is to promote antimicrobial activities in different cells; however, in macrophages alone, it cannot control *T. gondii*, and a second signal is required to kill the parasite. The second signals are provided by TNF-α or signal through CD40, both use the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [184,185]. GRA15II leads to the activation of NFκB, resulting in the production of high levels of IL-12 and further enhancement of the classical activation pathway in cells infected with type II parasites [138]. GRA15 expressed by type II strains stimulates IL-12 production. However, the inability of this strain to prolong the activation of signal transducer and activator of transcription 3/6 (STAT3/6) causes the initial production of IL-12, which leads to type 1 cytokine response and control of acute infection [10,186]. In addition, type II strains have a high tendency to differentiate into bradyzoites and their prevalence is higher in chronic diseases, which is a sign of compatibility with this strategy

[155].

#### 4.1.2. ROP kinases

*4.1.2.1. Pseudokinase ROP5.* The expression of the ROP5 allele, associated with high virulence, in a hypovirulent strain, causes a $10^{\hat{}}5$-fold increase in virulence [180]. In addition, deleting the ROP5 locus from parasites of high virulence strain, type I, led to a complete loss of virulence in mice. It was shown in a study that ROP5 is the only main virulence factor between type I and type II strains [187].

*4.1.2.2. ROP16.* ROP16 is a secreted protein kinase that activates two key host transcription factors (STAT3 and STAT6) and in turn downregulates the host's innate immune responses [188]. The type I, II, and III strains of *T. gondii* can stimulate STAT3 and STAT6 activity, but only type I or III strains can maintain this response. Prolonged activation of STAT3/6 by ROP16I/III can reduce the induction of IL-12 and, as a result, limit Th1 cytokine responses, which may lead to reduced inflammation and pathology [139,155]. Defects in ROP16 kinase prevent suppression of host immune responses by *T. gondii* type II strains [189]. Infection with type II strain affects and reduces the activity of STAT3 and STAT6. As a result, the host's ability to mount a protective Th1 immune response is enhanced. This immune response controls parasite proliferation through the production of cytokines such as IL-12 [138,190]. Type I and III strains modulate the expression of their host genes to protect themselves against the host's immune system. In contrast, type II strains are adapted to stimulate early responses and cause more immune-mediated pathology in mucosal and CNS models of infection in mice [178].

*4.1.2.3. ROP18.* A highly active ROP18 is present in acute type I strains, which cooperates with ROP5 to phosphorylate immunity-related guanosine triphosphate (GTP)ase (IRG) of the host, preventing IRG accumulation in the PVM (IRG is essential for controlling toxoplasmosis in mice) and it then blocks the parasite clearance in the activated cells with IFN-γ [155,191]. ROP5 acts independently of ROP18; when ROP5 of type I parasites is deleted, the virulence is reduced more than when ROP18 is deleted [180,192]. ROP5 may regulate the function of ROP16 and ROP18. ROP18 and ROP16 are among the active kinases and their function is necessary to affect the virulence of the parasite [139,140]. To restore virulence to type III strains with the virulent allele ROP5, the type I or type II ROP18 allele can be transferred to them [10,140]. Pair-wise crosses of ROP5 and ROP18 interact and account for almost 90 % of the virulence difference among the three strains [155]. In addition, ROP16 and ROP18 had no role in the virulence difference between type I and II strains. However, ROP18 played an essential role in determining virulence between type I and III strains [140]. Because type III strains express less ROP18 compared to type I or II (100-fold less), they do not have an effective mechanism for blocking IRGs and are easily cleared from IFN-γ-activated murine macrophages [155].

*4.1.2.4. ROP38.* ROP38 is a putative functional kinase whose expression is higher (eightfold) in type II and III strains compared to type I [193]. ROP38 plays a role in modulating mitogen-activated protein kinase (MAPK) signaling in host cells and leads to inflammatory defects [193].

#### 4.1.3. Routes of infection and life stages of the parasite

IP injection (direct parasite deposition in the peritoneal cavity), subcutaneous injection (deposit of *T. gondii* in the subdermis), and oral inoculation (deposition of parasites in the stomach of mice) are three common ways to determine the virulence of *T. gondii* in mice [194,195]. Differences in infectivity and pathogenicity in mice have been reported between the IP and oral route of infection. Mice infected orally with ten tissue cysts did not develop the disease, whereas infection was successfully established in 33 % of mice infected by IP injection. In this study, results for subcutaneous inoculation were comparable to IP injection [194]. An oral oocyst of strain M – 7741 can kill all mice (100 %) after two weeks. While $10^3$ tissue cysts containing bradyzoites can produce the same mortality rate, mice are infected orally with $10^4$ tissue cysts. Infection may not occur in mice orally infected with $10^4$ tachyzoites [194].

*T. gondii* has a complex life cycle. Infectious forms of the parasite (tachyzoites, bradyzoites, and sporozoites) may be used to infect mice. Infection with these forms may lead to various outcomes in terms of virulence in different hosts [8]. The pathogenicity of *T. gondii* oocysts varies in other hosts. The oocyst is less infectious and pathogenic for cats while eating an oocyst orally can cause the death of mice [8,196]. Ingesting 100 or more bradyzoites may not infect mice, but cats can shed millions of oocysts by consuming as few as one bradyzoite [197]. Oocysts are infectious and resistant to the environment and many disinfectants, so handling them is dangerous [8,198,199]. Tachyzoites and bradyzoites are easily destroyed in water [8]. Tachyzoites are relatively sensitive to environmental conditions and therefore are not easily transmitted. In adverse environmental conditions and stress, such as immune response, tachyzoite differentiates into bradyzoite [200]. Proteolytic enzymes have a less destructive effect on bradyzoite than tachyzoite. Although these enzymes destroy the cyst wall very quickly, the bradyzoites inside them are released and infect the next host [201]. Tissue cysts may remain in the infected person's body until the end of life due to the cycle of reaction and re-infection and in case of immunodeficiency; they cause disseminated or local infections [200]. Oocysts are highly virulent compared to other infectious forms [200]. Cats shed oocysts after consuming any of the three infective stages of *T. gondii*. The prepatent period and frequency of oocyst shedding are different depending on the stage of parasite consumption. Prepatent periods, after ingesting tissue cysts (3–10 days) and oocysts (18 days or more) are variable [198]. Also, the oocyst shedding varied from 11 to 17 days after consuming transitional stages between tachyzoites and bradyzoites [202,203]. Almost all cats excrete oocysts after eating tissue cysts, but less than 30 % of cats can excrete oocysts after eating tachyzoites or oocysts [196,204].

#### 4.1.4. Passages of the parasite in mice or cell culture

Passage in mice or cell culture can vary based on the biological characteristics of the parasite strains. *T. gondii* strain M − 7741 loses the ability to produce oocysts in cats after 30–35 continuous passages in mice [205]. In addition, after 40 passages in cell culture, type I strain GT1 loses the capacity to produce oocysts in cats [206]. If the RH strain is maintained for a long time through cell culture or passage in mice, it loses the ability to produce oocysts in cats [207]. Formation of larger plaques, increased extracellular survival, faster growth, and reduced differentiation are phenotypic changes observed in RH-derived clonal lineages [153,208]. Also, genetic variation among RH lineages has been observed [209]. There have been reports of increased virulence in mice for *T. gondii* strains after multiple passages in cell culture [208].

#### 4.1.5. Host strains

The pathogenicity of *T. gondii* and consequently the immune responses to the parasite are different according to different species of mice [210]. The susceptibility of other animal models to *Toxoplasma* varies; mice and hamsters are susceptible, while rats are resistant [211,212]. The genetic background of the host is important for the dynamics of infection [195,213]. Mouse line-dependent sensitivity has been reported in C57BL/6, LACA, and BALB/c mice. BALB/c mice were resistant to infection by IP and oral inoculation with cysts [195]. In the oral administration of *T. gondii* cysts, chronic infection occurs in C57BL/6 mice [157]. LACA mice are susceptible to IP inoculation of brain tissue cysts, while C57BL/6 mice are resistant. Conversely, with oral infection, LACA mice are resistant, and C57BL/6 mice are susceptible [195]. BALB/c mice have few or no brain cysts [212,214–216]. However, the parasite load and inflammatory lesions in the eyes of C57BL/6 mice are higher than those of BALB/c mice [217]. Oral administration of oocysts of the ME49 strain of *T. gondii* was pathogenic for transgenic, inbred, and outbred mouse lines in the order of decreasing [218]. In a study after infecting mice intraperitoneally with a dose of $1 \times 10^5$ tachyzoites of the C56 strain of *T. gondii*, DBA/2, and BALB/c mice died within 12 days and B10.D2 mice within 18 days after inoculation. Outbred mice (SW/SIM) had only 67 % mortality at day 30 post-challenge [219]. In a study, McLeod *et al.* reported that survival is controlled by the H-2 complex and a set of at least five genetic loci. The H-2a haplotype was dominantly associated with resistance, and the H-2b haplotype was recessively associated with susceptibility. Mice with the H-2a haplotype regulate the number of tissue cysts during chronic infection [220].

Adult rats inoculated IP with tachyzoites of *T. gondii* RH strain could harbor the parasite for seven months [221]. Also, the parasite may survive in the brain of mice for up to 2 years after IP injection [222]. When rats are chronically infected with the RH strain, parasites are rarely observed in histological sections [223]. Changes in the RH strain over time in mice and the creation of different sublines of the RH strain may account for the variation in results.

Human studies showed that host factors are effective in the resistance or susceptibility of immunocompromised patients to toxoplasmosis [224]. One of the most polymorphic genetic systems in humans, the human leukocyte antigen (HLA) system, plays a role in fighting against *T. gondii* infection and other microorganisms. For example, in *T. gondii*-seropositive AIDS patients, the HLA-B35 antigen was sensitive to chorioretinitis [225]. Also, the HLA-Bw62 antigen level was increased in patients with severe ocular involvement [226]. In a study, the relationship between HLA-DQ3 and -DQ1 genes and brain sensitivity or resistance to *T. gondii* infection has been shown using a transgenic mouse model [226]. Polymorphism in cytokine genes is an important factor that causes ocular toxoplasmosis. In several studies, the relationship between polymorphism in several cytokine genes, including IL-1, IL-6, IL-10, and IFN-γ, and susceptibility to ocular toxoplasmosis has been reported [227–231]. In severe congenital diseases, the type II serotype is more common in patients with susceptibility alleles of COL2A1 (type II collagen) and/or ABCA4 (ATP-binding cassette transporter, subfamily A, member 4) [232]. The presence of genetic factors can explain how type II parasites cause severe disease [233]. The Rhesus (Rh)-positive blood group system has a protective role against the effects of latent toxoplasmosis on motor performance, personality, and overweight during pregnancy [234–236]. Recently, in a systematic review and meta-analysis, it was shown that there is no statistically significant difference between the prevalence of *Toxoplasma* infection in Rh-positive and Rh-negative people, and the prevalence of infection was high in both blood groups [237].

### 4.2. The role of cysts in the pathogenesis of toxoplasma infection

Each of the various parasite stages of the complex life cycle of *T. gondii* (merozoite, tachyzoite, bradyzoite, and sporozoite) has a specific biological function. The proliferation of merozoites is limited to a few generations (2–4) in the enterocytes of the cat intestine. However, tachyzoites can multiply in all nucleated cells of the host body and spread to various body tissues. Tachyzoites (the proliferative stage) can undergo stage conversion to become bradyzoites (latent tissue cyst stage) development, while merozoites lead to the sexual stages [238]. During an acute infection, dissemination of rapidly dividing tachyzoites continues throughout the body until host immune responses and other unknown factors lead to the transformation of the tachyzoite into a slowly proliferating cystic bradyzoite [239]. Considering that bradyzoites and sporozoites play a role in the transmission of infection between different hosts, they must survive the rigors of the external environment and/or the digestive system of the new host. After entering the new cell, they cannot produce bradyzoites or sporozoites and immediately develop tachyzoites [238]. In immunologically healthy individuals, innate and cellular immune responses can control the proliferating tachyzoites [240]. Despite the influential role of immune responses in the elimination of tachyzoites, some escape the immune system and become tissue cysts [241]. IFN-γ-mediated NO, an external stress factor, is involved in the stabilization of the cyst stage, and in the absence of these factors, reactivation of latent infection may occur [242]. However, the parasite is not completely eliminated, and the tachyzoites differentiate into a slowly reproducing form (bradyzoite). Stage conversion is accompanied by the organization of PV into tissue cysts. These cysts may contain hundreds of parasites and can persist for long periods in the tissues of immunologically healthy hosts [240,243]. Among the important events in parasite transmission and pathogenesis is the process of stage conversion between tachyzoite and bradyzoite. The transformation into a tissue

cyst increases persistence in the host and the possibility of transmission through prey. Therefore, bradyzoites make *Toxoplasma* highly flexible in transmission and allow the parasite to bypass its sexual stage for dissemination [244]. Several ROP proteins (such as ROP17, ROP35, and ROP38) promote tachyzoite conversion to bradyzoite [245]. The RH strain, type I, may fail to transform into mature cysts with high frequency due to long-term propagation *in vitro*. However, strains of type II (such as Pru and ME49) and type III (such as VEG) have a lower proliferation rate and readily transform into cysts *in vitro* and *in vivo* [244].

The cyst has an elastic wall whose thickness is less than 0.5 μm. Chitin and glycoproteins secreted by parasites are the components of the cyst wall [246]. Cyst wall sugars can bind lectins concanavalin A, soybean agglutinin, wheat germ agglutinin, and Dolichos biflorus agglutinin. Dolichos biflorus agglutinin usually plays the role of a diagnostic tool for staining the cyst wall [247]. A matrix material in mature cysts fills the space between the bradyzoites within the PV [248]. The cyst wall comprises different proteins such as cyst wall proteins (CST) [246,249,250], matrix proteins (MAG) [251], and GRA proteins [252]. Several GRA proteins are involved in the formation and maintenance of the cyst wall. GRA5 is highly concentrated in the cyst wall, and less intense staining for GRA1, GRA3, and GRA6 has also been reported [252]. Deletion of BPK1, CST1, or GRA6 has also been shown to reduce cysts in the brains of mice. Although some proteins in the cyst wall have been identified, the molecular mechanism of their cystogenesis is still not fully understood [250]. In an *in vitro* study, a set of proteins that were not previously identified in the cyst wall were described such as CST6/GRA53, CST5/GRA52, CST4, CST3/GRA51, and CST2/GRA50. CST2 is involved in parasite virulence [250]. Also, in the interactome model, MAG1, CST1, and MCP4 were found to be central components of each cyst wall pulldown. CST1 is a significant cyst wall protein that contributes to the structural integrity of the cyst wall [246,249]. This protein is extensively glycosylated and stained with Dolichos biflorus lectin (DBA), which has a high affinity for the glycosylated structure [247,249,253]. This glycosylation is used during chronic infection to protect CSTs from immune responses [254]. A *Toxoplasma* nucleotide sugar transporter (TgNST1) is used for cyst wall glycosylation [255]. Bradyzoite-secreted pseudokinase 1 is part of the cyst wall, and its existence is necessary for the growth, maintenance, and stability of tissue cysts [256]. MAG1 is the only 65 kDa cyst wall matrix protein that induces humoral immune responses in chronically infected hosts [251,257,258]. MAG2 protein is often found inside the cyst wall pulldowns and it defines the exclusive location of the cyst matrix, it is not important in cystogenesis or cyst growth [250]. On the contrary, CST1 and MAG1 proteins are involved in cystogenesis and may be important components of the cyst wall interactome [249,250]. Cyst wall staining is visible in infected human and animal samples, but seronegative samples do not show any staining of intracellular tachyzoites and encysted bradyzoites [259].

Tissue cysts of *T. gondii* may form in any host organ. However, they were mostly detected in the nervous and muscular tissue; for example, cysts are more often detected in the brain, eyes, and skeletal and cardiac muscles [260]. Cysts may be detected in various brain cells, including neurons, astrocytes, and microglia [261,262], although recent studies have shown that the parasite interacts primarily with neurons in mice [263,264]. A subtle tropism has also been reported for the medial and basolateral amygdala [265]. The manifestations of inflammatory processes are probably the result of the rupture of *T. gondii* cysts in the brain and it can be observed as various neurological signs such as headaches [266]. Indeed, chronic toxoplasmosis in the human population is correlated with many psychiatric diseases in humans, including schizophrenia [267,268], bipolar disorder [267,269], addiction [267], obsessive-compulsive disorder [270], Alzheimer's disease [271,272], headache [273], autism [274], epilepsy [275,276], and suicide attempts [277,278]. Considering that most clinically apparent diseases are caused by the reactivation of dormant bradyzoites and their conversion into tachyzoites to better understand the pathogenesis of toxoplasmosis, the signaling pathways responsible for tachyzoite to bradyzoite interconversion should be revealed [279]. Various stress factors such as pH shock, heat shock, chemical stress, mitochondrial inhibitors, IFN-γ and other pro-inflammatory cytokines or agents, high temperature, drugs, the depletion of nutrients, and NO are associated with bradyzoite development [280–284]. Also, the induction of heat shock proteins (Hsps) such as Hsp70 leads to bradyzoite transition [285,286], and the deletion of a bradyzoite-specific small Hsp gene, BAG1, is associated with a decrease in the number of bradyzoites in the mouse brain [287]. Hsps are a group of phylogenetically conserved proteins in all species [288,289]. Based on molecular weight, these proteins are grouped into six prominent families: small heat shock proteins (smHsps), Hsp40, Hsp60, Hsp70, Hsp90, and Hsp100 [290]. The role of Hsp60 and Hsp70 proteins in the growth and survival of the parasite has made them potential drug targets for toxoplasmosis [291]. Hsp60 is involved in the induction of a specific stage of the respiratory tract in *T. gondii* [292]. At the same time, Hsp70 can stimulate the formation of bradyzoites by switching the phases of the parasite's life cycle between tachyzoites and bradyzoites [293]. The role of MAPKs is to regulate cellular stress responses and may be involved in the development of bradyzoites in *Toxoplasma* [294]. Also, stress conditions have been reported to induce the synthesis of the phytohormone ABA by the apicoplast [114]. ABA causes the production of cyclic ADPR, whose role is to control the release of intracellular calcium stores in *Toxoplasma* and induce its release. Application of floridone, an inhibitor of ABA biosynthesis, blocks parasite egress and induces bradyzoite differentiation. Therefore, ABA-mediated calcium signaling is the main factor in whether the parasite is latent [114]. Cyclic guanosine monophosphate and cyclic adenosine monophosphate (cAMP) play a role in the induction of bradyzoite formation. These effects can be caused by increasing cyclic nucleotides of the host or the parasite [279].

Infection with *T. gondii* inhibits host cell signaling pathways, for example, by blocking signal transducer and activator of transcription 1 (STAT1) [295] and NF-κB [296–298]. *T. gondii* uses different ways to subvert IFN-γ signaling. Parasite-infected cells are less responsive to IFN-γ-induced upregulation of various genes (iNOS, MHC class II, and P47 GTPases) [295,299]. Parasite growth control requires IFN-γ activation of the STAT1. *T. gondii* inhibits the STAT1 signaling pathway by upregulating levels of suppressors of cytokine signaling (SOCS) proteins [300]. The SOCS family includes eight proteins [SOCS1-7 and cytokine-inducible SH2-containing protein (CIS)] that attenuate IFN-γ-dependent signaling [301]. These proteins affect IFN-γ signaling by either inhibiting the catalytic activity of the JAKs (SOCS1, SOCS3) or by inhibiting the recruitment of STATs. *T. gondii* in infected macrophages upregulate the abundance of SOCS-1, SOCS-3, and CIS mRNA levels. These proteins are involved in *Toxoplasma* immune evasion, and infected macrophages overexpressing SOCS-1, SOCS-3, or CIS cannot produce NO or limit parasite growth in response to IFN-γ [300]. The NF-kB family of

transcription factors plays a vital role in the immune response against *T. gondii* and regulates many aspects of innate and adaptive immune functions. NFκB activation by type II strains associated with higher levels of IL-12 production contributes to early infection control [138,155]. The antimicrobial activities of IFN-γ in macrophages are usually insufficient to control *T. gondii*, and a second signal is required to fully activate killing. The second signals are provided by TNF-α or signal through CD40, both of which use the NF-κB signaling pathway [185,302,303]. *Toxoplasma*-infected T cells, NK cells, and DCs employ potential mechanisms by which they not only evade cellular immunity but also redirect cell-mediated cytotoxicity to their advantage [108,111]. Rapid egress of parasite resulted from ligation of death receptors in *T. gondii*-infected cells. In this process, intracellular calcium release and caspase activation are involved [108].

The cysts are resistant to existing drug treatments and cause chronic infections that cannot currently be eradicated. In immunocompromised individuals, the high frequency of acute toxoplasmosis results from the ability of bradyzoites to transform into tachyzoites [13]. Also, considering that during experimental toxoplasmosis, bradyzoites are first detected after the initiation of the immune response to the parasite, this suggests that the stress exerted by the host's immune response can lead to the transition from the tachyzoite stage to the bradyzoite stage [240]. Indeed, during latent infection, bradyzoites can reconvert to proliferative tachyzoites in severely immunocompromised hosts and ultimately leading to necrotic lesions and life-threatening reactivated toxoplasmosis [13].

So far, a wide range of cyst wall antigens have been identified and used as vaccine antigens. For example, GRA proteins have been experimentally used for vaccine production [95]. In addition, genetic knockout of the CST1 gene reduces the structural integrity of cysts and prevents their formation in the brains of mice [249]. Therefore, CST1 would be an ideal candidate antigen for *T. gondii* vaccines [304]. One study showed that naturally infected animals and humans develop a strong humoral response to cyst wall antigens [305]. During ingestion of tissue cysts, bradyzoite stage-specific SRS antigens play an important role in binding and invading intestinal epithelial cells [306,307]. These antigens are among the first parasite antigens presented to the immune system [306,307]. However, the immune response, especially the humoral one, against bradyzoite-specific SRS antigens is not known [305]. Strong humoral responses against cyst wall antigens in naturally infected animals and humans can be elicited using *T. gondii*-positive sera [305]. However, the immunogenicity of these proteins and the role of these CST1-specific antibodies in protection are poorly understood. Therefore, assessing the immunogenicity of such candidate antigens may help improve current vaccine design strategies [304].

### 4.3. Immune responses

Toxoplasmosis can cause acute or chronic infection. Acute infection is associated with tachyzoites, while tissue cysts cause chronic infections. During the acute process, the tachyzoites invade all body cells except the host's nucleated cells, such as erythrocytes [308,309]. After interacting with antigens, macrophages can stimulate and activate both T and B cells, leading to the production of many cytokines such as IL-1, IL-2, TNF-α, IFN-γ, NO, and the complement components, as well as antibodies [immunoglobulin (Ig)G, IgM, IgA, and IgE] [310,311]. Cytokines have a protective role against infection, for example, IFN-γ and TNF play a role in destroying tachyzoites by macrophages. The combination and synergistic effect of IFN-γ and TNF increases the production of free radicals and NO, both of which can be effective in killing parasites [185,312,313]. Macrophages play a positive role in *T. gondii* infection due to their phagocytic capacity, which is limited to non-viable parasites [314–316]. However, when peripheral blood macrophages are infected by tachyzoites, macrophages become a shelter for the parasite, so they can also play a negative role [317,318]. These infected cells are responsible for persistent parasitism in humans and animals after infection [319–321]. Tachyzoites stimulate the production of IL-12 by macrophages. Macrophages are also effective in regulating cell-mediated immunity by producing immune mediators [322,323]. Cytotoxic CD8 T cells exert activity against *T. gondii* during the acute phase of infection, and CD4 T cell activity appears when the infection becomes chronic [324]. T cell populations are involved in the control of acute infection due to their ability to produce IFN-γ. CD4 T cells are important in controlling the early stages of acute infection and CD8 T cells are important in the late stages of acute infection [213,325]. However, they also play a role in long-term protection and limiting the parasite to the chronic phase [326]. Severe toxoplasmosis has been reported in HIV-infected patients with reduced CD4 T cell counts [327], and reduced cell counts in these patients increase susceptibility to toxoplasmic encephalitis (TE), an important CNS complication in the late-stage HIV (also known as AIDS) [327]. CD8 T cell immunity against chronic toxoplasmosis is impaired by CD4 T cell depletion in advanced AIDS and leads to reactivation of toxoplasmosis in these individuals [328]. Proinflammatory cytokines such as IL-12 must be produced to control *T. gondii*, which stimulates NK, CD4 T, and CD8 T cells to release IFN-γ [329,330]. Activation of the adapter molecule myeloid differentiation factor 88 (MyD88) is involved in the ability of cells to produce IL-12 during infection [331]. These cytokines are important in maintaining chronic infection. MyD88-deficient mice have been shown to be unable to produce IL-12 and therefore unable to control acute *T. gondii* infection [331]. MyD88 is an adaptor protein required for all Toll-like receptors (TLRs) in response to binding of a pathogen-specific molecule to multiple TLRs of the host [332,333]. CD8 T cells lyse infected cells and expose protected parasites to immune mechanisms, including immunoglobulins, macrophages, complement, and NK cells [334]. After stimulation with parasite antigens and in the presence of IL-12, CD8 T cells secrete cytokines such as IFN-γ, TNF-α, and IL-2 and inhibit the spread of parasitic infection [334]. IFN-γ is the main cytokine that can control and limit intracellular pathogens such as *T. gondii* infection and is crucial for the activation of a variety of antimicrobial activities in different cells [120,335]. Mechanisms such as IFN-regulated GTPases [336,337], induction of reactive nitrogen intermediates [338], tryptophan degradation in human cells [339], and autophagy [184,340] are activated by IFN-γ to eliminate the parasite. In response to IFN stimulation, two families of GTPases, guanylate-binding proteins (GBPs) and IRGs are expressed [341,342]. They are expressed in all types of cells and control parasite replication in the PV [343,344]. Two IRG genes have been reported in humans and 23 genes in rodents [345]. This gene disrupts the integrity of the PVM and releases the parasite into the cytoplasm of the host cell, where the parasite is killed [340]. GBPs are expressed in a large number of hosts and help control parasite load, but their mechanism of action is unknown [11]. They localize to the PV in response to IFN-γ induced by *T. gondii*

[346,347]. Following stimulation with IFN-γ, the concentration of NO increases in macrophages, which inhibits parasite proliferation in all cell types [337,348–350]. *T. gondii* stimulates the production of antibodies (IgG, IgM, IgA, and IgE) against the membrane and excretory-secretory antigens and therefore has a small role in the body's defense against toxoplasmosis. These antibodies have various functions, such as reduction of T cell invasion, lysing parasites by phagocytosis and the catalytic activity of NK and cytotoxic T lymphocyte cells, or activating complement pathways [351]. Specific antibodies prevent the attachment of the parasite to the host cell receptors. As a result of the local production of B cells, tissue cysts are formed. During infection, the body first produces IgM antibodies in the blood, which indicate a recent infection [352,353]. Detection of IgM antibody in human serum alone is not sufficient for the establishment of acute toxoplasmosis [354]. IgA antibody indicates acute toxoplasmosis and the kinetics of this isotype is faster than IgM antibody, but it may persist for months [354]. IgG is the major immunoglobulin class in the humoral immune response against *T. gondii* infection [355]. In humans, specific IgG increases very slowly and reaches a maximum in 6–14 months. In the chronic phase of infection, this antibody may remain positive at low levels in the body until the end of the person's life. A considerable increase or a fourfold rise of specific IgG indicates acute infection [353]. It is important to determine the level of antibodies to *T. gondii* in the first trimester of pregnancy in women. Diagnosing acute toxoplasmosis can help prevent the transmission of infection from mother to fetus, and as a result, provides the opportunity for early and effective treatment [356–359]. The *Toxoplasma* IgG avidity test usually shifts from low to high avidity at about 5–6 months after infection. It is a useful tool to diagnose toxoplasmosis in pregnant women who were positive for *Toxoplasma* antibodies in the first months of pregnancy [360]. If the avidity test in women is high in the first trimester of

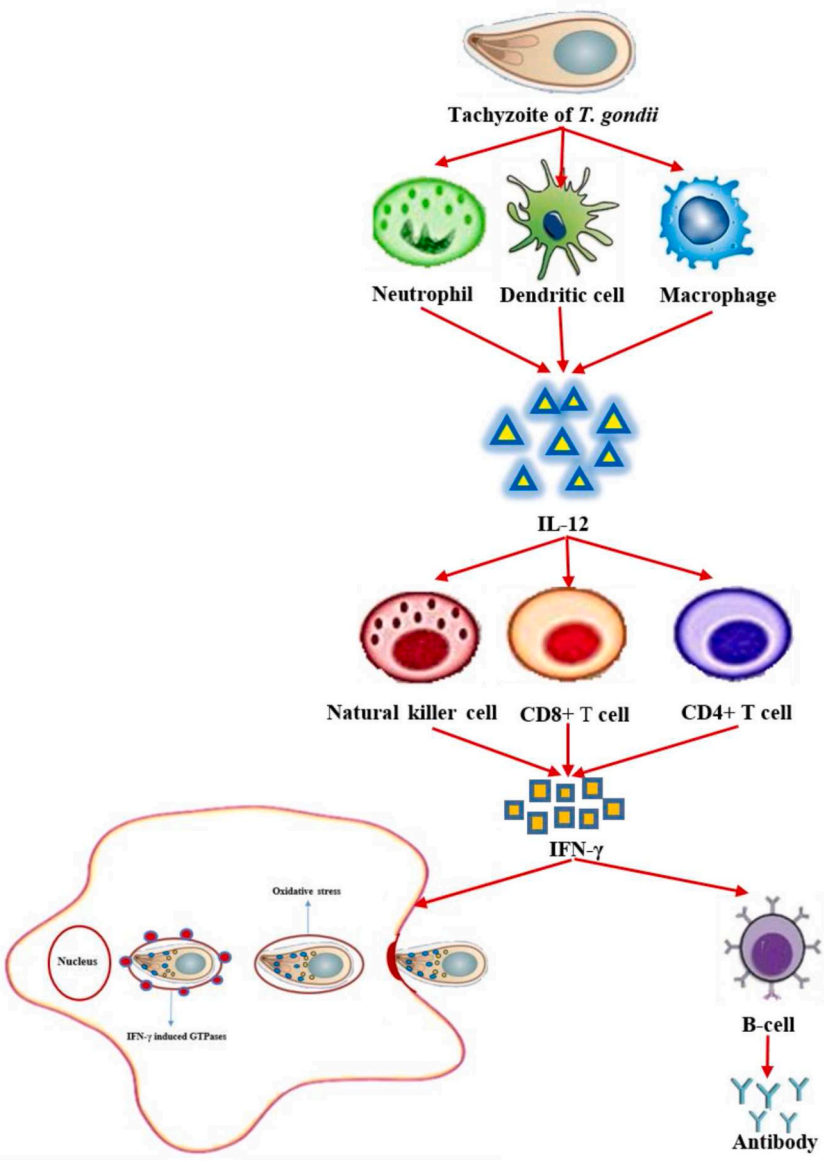


**Fig. 3.** Innate, cellular, and humoral immune responses against *Toxoplasma gondii* infection.

pregnancy, acute infection is not shown in the last trimester. Additionally, elevated IgG avidity levels in pregnant women before the first trimester of gestation can indicate later infections, which shows the usefulness of this test at the beginning of pregnancy. However, this cannot rule out the possibility of fetal involvement during pregnancy [361]. Therefore, possible acquired infections in the first or second trimester of gestation cannot be ruled out by high-avidity titers at the end of gestation [362]. However, according to research, high-avidity titers in pregnant women indicate a possible reduction in the risk of fetal infections. In infections that occur a few weeks before conception, the probability of congenital transmission is very low or even zero [359,363–366]. Chronically infected individuals are usually resistant to re-infection due to circulating immunoglobulins. This phenomenon is called immunosuppression [367] or premonition [368], although concomitant infection of toxoplasmosis may sometimes be reported [369,370] (Fig. 3).

#### 4.3.1. Immune responses in psychiatric disorders

*T. gondii* can actively infect any nucleated cell in the body of intermediate hosts. The parasite spreads throughout the host's body together with infected DCs and monocytes [371]. Some tachyzoites of *T. gondii* differentiate into bradyzoites with slow proliferation and form tissue cysts. The formation of these cysts is more common in muscle and nervous tissues such as the brain, eyes, and skeletal and cardiac muscles; although these cysts can also be formed in visceral organs such as the lungs, liver, and kidneys [372]. Most gray matter areas of the brain showed some degree of infection, suggesting that *T. gondii* does not have a specific propensity for certain regions of the brain [373]. A study in mice also showed that the distribution of cysts was not dependent on a specific region.

Cysts cannot cause behavioral changes directly by disrupting the surrounding tissues [374]. As the cysts grow, the host cells degenerate. Since the parasite is intracellular and the wall of its cyst is highly glycosylated, drugs cannot reach the interior of the tissue cysts; in addition, tissue cysts block immune system responses by unknown mechanisms [241]. When the cysts rupture, they release bradyzoites that can differentiate into tachyzoites. Various factors, such as pregnancy, bacterial and viral infections, different vaccines, drugs, and other substances have been shown to cause reactivation of latent cerebral toxoplasmosis [375].

Tachyzoites activate macrophages to produce IL-12 [322]. IL-12, in turn, stimulates NK cells and T cells to produce IFN-γ. The production of IFN-γ is vital for resistance to the parasite and prevents the proliferation of the parasite through specific mechanisms [376,377]. Many studies have shown that infection with *T. gondii* can disrupt the synthesis of various neurotransmitters [378,379]. Cytokines and inflammatory mediators, such as IFN-γ, IL-1, IL-6, TNF, and NO, affect neurotransmitters through mechanisms such as indoleamine-2,3-dioxygenase enzyme (IDO), MAPK activation, changes in tetrahydropterin (BH4) enzyme activity, excitotoxicity and oxidative stress [380]. The cytokines, such as IFN-γ and IL-2, activate IDO. This enzyme is involved in tryptophan catabolism [381, 382]. IFN-γ uses tryptophan degradation to eliminate intracellular *Toxoplasma* in human cells. Tryptophan is an essential amino acid for the growth and replication of *T. gondii* and precursor of serotonin and melatonin [378]. The IDO degrades intracellular tryptophan and consequently inhibits the intracellular proliferation of *T. gondii* [383,384]. Decreased tryptophan levels increase the production of kynurenic acid (KA) and quinolinic acid (QA [385]. Tryptophan catabolism products in the rise in brain oxidative stress, cell damage, and apoptosis [386]. KA concentration increases in schizophrenia. QA upregulation has been reported in mental disorders such as Alzheimer's disease [387], depression [388], Huntington's disease [389,390], autism [391], and suicide [392].

The QA binds to glutamate N-methyl-D-aspartate receptors (NMDARs) [393,394]. The role of these receptors is essential in the pathophysiology of many mental disorders such as schizophrenia. It may establish a mechanistic link between *T. gondii* infection and the onset of schizophrenia [395–398]. Stimulation of excitotoxicity and oxidative stress occurs in the brain following NMDAR activation [399]. KA is involved in inhibiting alpha seven nicotinic acetylcholine receptors, modulating glutamatergic neurotransmission, and increasing amphetamine-stimulated dopamine release in the striatum [399,400]. Amphetamine, which is a dopamine-releasing agent, aggravates psychotic symptoms in patients, and behavioral defects in response to amphetamine have been reported in mice infected with *T. gondii* [401,402]. In addition, high levels of KA can lead to cognitive impairment. For example, high levels of KA have been reported in the cerebrospinal fluid of people with schizophrenia [403–405].

The production of NO and the destruction of dopamine-producing neurons are among the strategies used by IFN-γ to cause tissue damage [406]. Disorders such as fatigue, sleep as well as gastrointestinal and musculoskeletal disorders are associated with decreased dopamine synthesis [407]. Inflammatory cytokines such as IL-2, IL-6, and NO play a role in the etiology of psychiatric disorders and can increase the level of dopamine in the brain. IFN-γ alters NO levels by different mechanisms [380,408].

The IFN-γ activates transforming growth factor-beta-1, which inhibits NO production and thus limits neurodegeneration in the parasite-infected brain [409,410]. No changes in IFN-γ or TNF-α levels occur in iNOS knockout mice, there is no change in the level of IFN-γ or TNF-α, and although the brain inflammation is less than their parental lines, the burden of brain cysts is high [411,412]. However, in IFN-γ knockout mice, there are lower levels of iNOS in the brain than in wild-type mice, and the level of this enzyme is higher in the lungs [413]. Also, disorders such as depression and anxiety are increased in these mice, but neurogenesis in the hippocampus is reduced [414]. IFN-γ knockout mice are not able to inhibit the growth of parasites [351]. IFN-α, IFN-β, and IFN-γ by activating guanosine triphosphate cyclohydrolase-1 lead to an increase in neoprene production and a decrease in the level of amino acids phenylalanine and tyrosine. These amino acids are precursors for dopamine biosynthesis. In addition, BH4 is involved in the synthesis of dopamine [415]. By reducing the concentration of this substance, cytokines can reduce the availability of dopamine in the brain [416]. During TE, cytokines and inflammatory mediators effect on neurotransmitters through the activation of the MAPK pathway. It can have a dual impact on dopamine. The MAPK signaling results in reduced dopamine recycling and overstimulation of its receptors [417,418]. In addition, this pathway is involved in regulating growth, differentiation, and stress responses. Its activity increases the function of the serotonin transporter and decreases serotonin at the synapse level [417,418]. Also, a mitochondrial membrane enzyme called MAOA is involved in metabolizing neurotransmitters such as dopamine, serotonin, epinephrine, and norepinephrine [419–422]. Since *T. gondii* infection downregulates MAOA gene expression *in vivo* [422], it will probably affect neurotransmitter levels, for example, increasing the activity of this enzyme decreases the levels of dopamine and serotonin [419,420].

Abnormal levels of monoamine oxidase have been reported in schizophrenia [423], depression [424], and alcoholism [425].

IFN-γ reduces tonic gamma-aminobutyric acid (GABA)ergic inhibitory current and thus the severity of seizures. *T. gondii* infection caused by tissue cysts affects the distribution of GABA in the brain and disrupts social activities regulated by IFN-γ in infected mice [426,427]. *T. gondii* infection causes changes in host miRNAs, primarily related to immune and apoptosis processes [428]. The miR-132 is involved in regulating neural and immune functions and the differentiation of dopamine neurons [429,430]. Considering that upregulation of miR-132 modulates a set of main pathways, vital functions of the brain, initiation and regulation of translation, meiosis, mitosis, carcinogenesis and growth, differentiation, survival, and cell proliferation can be affected [422]. Disruption of microRNA-132 expression may be associated with various behavioral and neurological diseases, including schizophrenia, Alzheimer's disease, and Parkinson's disease [430–432].

#### *4.3.2. Immune responses in pregnancy*

Toxoplasmosis in immunologically healthy adults is usually asymptomatic. This parasite should be paid attention to in pregnant women because it can cross the placental barrier and infect the fetus [14,433]. Infection during pregnancy triggers both cell-mediated and humoral immunity. If IgM is produced, it indicates a recent infection and is not a sign of re-infection [434]. This antibody is detectable one week after infection and decreases faster than the IgG antibody. The level of IgM antibody reaches its peak about 1–2 months later, although persistent IgM antibody has sometimes been reported for up to 31 months [354,371,435]. IgM antibodies in the newborn's circulation are a sign of congenital infection, as IgM cannot cross the placenta [436]. IgG appears approximately two weeks after IgM and peaks within 6–8 weeks. The levels of this antibody start to decrease to lower levels after one year slowly, and due to the persistence of latent cysts in immune-privileged organs, low levels of this antibody may be detectable until the end of the infected subject's life [437–439].

The production of IgA occurs in the same way as IgM in the first week, but the peak of this antibody is later than IgM and disappears earlier than IgM. IgA persists for more than 3 or 4 months after the initial infection and may even persist for more than a year [439, 440]. IgA cannot cross the placenta but is present in colostrum [354]. IgA antibody detection is not sufficient to diagnose acute infection in adults [441]. The presence of this antibody at the site of active disease is attributed to the possible presence of transforming growth factor beta (TGF-β), which can play a role in switching to this antibody [442]. It can be detected in newborn infants, and its serological profile at birth depends on the date of infection, being absent if infection of the fetus occurs during the first trimester but present if it occurs during the third trimester. Detection of IgA antibodies in the serum of immune mothers is presumably due to reinfection and not reactivation of chronic disease [443,444]. Specific IgE antibodies are rapidly produced and can be detected less than four months after infection in the serum of adults with acute infection, neonates infected with congenital infection, and children with chorioretinitis [445]. The persistence of IgE can be a sign of active toxoplasmosis [446]. In IgG and IgM-negative pregnant women who have not been previously exposed to *T. gondii*, there is a high risk of transmission of *T. gondii* to the fetus. IgG-positive women are also tested for IgM antibodies, and if they are positive, they must undergo confirmatory tests. In cases of negative IgG and positive IgM, the serology test should be repeated after three weeks [447].

Toxoplasmosis can affect maternal immune responses and affect pregnancy outcomes by altering immune mechanisms at the maternal-fetal interface [448]. Also, immune modulation during pregnancy may help the parasite to evade the immune responses and increase the possibility of transmission of infection from mother to fetus during pregnancy [449]. Studies have shown that trophoblasts are a component of the innate immune system and play a role in producing various anti-inflammatory mediators, including IL-10, TGF-β, and Fas ligand (FasL) [450–452]. In some situations, trophoblasts may initiate signals that cause fetus rejection [453,454].

Progesterone, which is synthesized in the breast, endometrium, brain, ovaries, and fetoplacental unit, plays a role in regulating immune cells and is necessary to maintain pregnancy during pregnancy [455–458]. Among the adverse effects of *T. gondii* on pregnancy are low progesterone levels in infected pregnant women [459], which may adversely affect pregnancy by altering macrophage polarization and T cell responses [460,461]. Progesterone promotes the production of local T helper (Th) 2-related cytokines by mouse placental tissues. It also plays a role in differentiating Th cells into Th1 and Th17 and negatively regulates this process [462,463]. Infection with *T. gondii* initiates a strong Th1 immune response in which IFN-γ, IL-12, and CD8 T cells are predominant. However, pregnancy increases the activities of Th2 and its anti-inflammatory cytokines (IL-4, IL-5, and IL-10). Moreover, damage to the placenta and fetus can be due to the activation of cytotoxic cells (NK or T cells) and inflammatory cytokines (IFN-γ and TNF-a) [464]. IFN-γ and TNF-α are not usually expressed in the placenta. However, these cytokines have been associated with abortion in mouse models [465]. As a result, the occurrence of infection in the first trimester when the level of hormones is low and the bias of Th2 cells is not high, the probability of infection transmission to the fetus is low, and the likelihood of miscarriage increases. On the contrary, the occurrence of infection in the third trimester, when the Th2 bias is high, reduces the risk of miscarriage but increases congenital transmission [380, 466].

#### *4.3.3. Immune responses in ocular toxoplasmosis*

The most crucial reason for infectious posterior uveitis in the world is ocular toxoplasmosis, and it often leads to blindness and vision problems in affected people [467]. Ocular manifestations occur in about 2 % of people with toxoplasmosis. That is, 1 in 400 people worldwide develop posterior uveitis caused by toxoplasmosis [20]. It is unlikely that free tachyzoites in human blood samples can directly infect ocular tissue. Probably, DCs and macrophages act as "Trojan horses" in guiding the parasite to different target organs [468,469]. Invasion of the host cell is an active parasite-driven process based on the interaction between several surface ligands of the parasite and the host [16]. *T. gondii* stimulates the production of IFN-γ and IL-12 and simultaneously suppresses a strong Th1-type immune response. This balanced immune response can control the parasite and at the same time prevent an immunopathology. Th17 cells are an essential regulatory component in this balance of immune pathological response in the eye. IL-23 stimulates IL-17

secretion from DCs and may have protective and pro-inflammatory effects [470–472].

In addition to congenital toxoplasmosis, acquired toxoplasmosis is also a common cause of uveitis [473–475]. CD4 and CD8 T cells contribute to ocular inflammation in a murine model of toxoplasmosis and are associated with the presence of the parasite [312]. Parasite proliferation and CD4 and CD8 T cells are known to play a role in the pathogenesis, and T cells are also involved in protection [476,477]. Fas-FasL-deficient mice develop more severe inflammation following intraocular infection with *Toxoplasma*, indicating that Fas-FasL plays an important role [478]. In studies conducted in mice, the important role of IFN-γ, TNF-α, IL-6, and iNOS in the prevention of parasite dissemination in the eye may be related to the pathogenesis of ocular toxoplasmosis in humans. A less effective immune response against the parasite may cause congenital ocular toxoplasmosis [479]. Interestingly, there is a link between autoinflammatory and immunoregulatory mechanisms in persons with toxoplasmic retinochoroiditis [480]. In children with congenital ocular toxoplasmosis, there is an association with a polymorphism in the nucleotide-binding oligomerization domain-containing protein 2 (NOD2); this gene is an intracellular pattern recognition receptor. NOD2 is involved in the production of IL-17A by CD4 T lymphocytes and may be important in the development of ocular toxoplasmosis [480,481]. In general, all types of gene polymorphisms (TLR2, TLR5, and TLR9), polymorphisms of the cytokines (IFN-γ, TNF-α, IL-10, and IL-6) are associated with ocular toxoplasmosis [228,232,482]. In Brazil, an association between TLR2, TLR5, and TLR9 gene polymorphisms and ocular toxoplasmosis was observed, with a significant association with the C allele of TLR9 rs352140 [482]. This report opens a new way of understanding the interaction between the parasite and TLR9 and how it triggers inflammation in the eye. A polymorphism has also been identified in the gene encoding the purinergic receptor P2X (7) (P2RX7) [483]. This receptor plays an important role in the inflammatory response after microbial infection [484].

#### 4.3.4. Immune responses in AIDS patients

The reactivation of latent *T. gondii* infection in HIV-infected patients causes TE, which threatens the patient's life [13]. This disease was the most common focal infection of the CNS among patients with HIV in the early 1990s [485]. The genetic background of the host and the difference in the virulence of parasite strains play a role in the recrudescence of active infection [58]. Genetics is an essential factor for resistance against the development of TE in mice and humans. The Ld gene in the D region of the H-2 complex is effective in mice resistance. HLA-DQ3 is a genetic marker of susceptibility, and HLA-DQ1 is a resistance marker in AIDS patients [486].

Chronic headaches, cognitive impairment, memory loss, and slowness of verbal responses are among the first clinical symptoms of CNS toxoplasmosis [487]. In addition, complications such as myocarditis occur in HIV-infected individuals with latent toxoplasmosis [488], and pulmonary toxoplasmosis mainly occurs in patients with advanced AIDS [310]. Toxoplasmosis retinochoroiditis is uncommon in AIDS patients. However, when it occurs in immunocompromised patients, it is often rapidly destructive [489]. In these patients, discrete or multifocal lesions, diffuse retinal necrosis, slight inflammation, and many parasites may appear [489]. In immunocompetent individuals who are asymptomatic or have mild symptoms, there are usually no side effects from infection with *T. gondii*. Therefore, the immune response is critical to prevent TE [490]. Many factors, such as the decrease in the number of CD4 T cells, the lack of production of IL-12, IL-2, and IFN-γ and the reduction in the activity of T lymphocytes are influential in the pathogenesis of toxoplasmosis in immunocompromised persons [310]. In patients with AIDS, the level of IFN-γ decreases and can reactivate chronic toxoplasmosis [310]. A decrease in the number of CD4 T cells below 50 cells per microliter leads to the rupture of cysts of the CNS and the reactivation of chronic infection [491]. Reduction of CD4 T cells in HIV patients increases susceptibility to TE, and most cases of toxoplasmosis occur in patients with advanced AIDS [328]. That is when a deficiency in CD8 T cells is evident due to a decrease in the CD4 population [328]. Approximately 30 % of AIDS patients and *Toxoplasma* seropositive who do not receive antiretroviral therapy or anti-parasitic Prophylaxis develop TE [487]. IgG levels are often low or undetectable in immunocompromised persons, but serologic tests for IgM are often negative. The sensitivity of antigen examination in the blood circulation of AIDS patients is lacking [310]. Observation of tachyzoites in biopsy leads to a final diagnosis [310]. The development of TE in *T. gondii*-seropositive AIDS patients shows the crucial role of IFN-γ and CD4 T cells in protection against TE [486]. The *T. gondii* has a tropism to specific tissues such as the brain and can infect astrocytes, neurons, and microglia cells and create cysts in these cells. Control of infection in the brain is highly dependent on IFN-γ production by CD4 and CD8 T cells and, to a lesser extent, on B cells [492]. IFN-γ plays a role in the induction of appropriate protective cytokines such as TNF-α and induces effective protective mechanisms in infected cells [492]. Astrocytes activated with IFN-γ control *T. gondii* infection [492]. IFN-γ and TNF-α are important in preventing the development of TE in murine models. In addition, IL-6 is involved in the immunopathogenesis of TE [493]. The results of the available articles are contradictory; one study showed that treating mice with a monoclonal antibody against IL-6 reduced the inflammatory response and the number of *T. gondii* tachyzoites and cysts in the brains of mice with TE [493]. On the other hand, another study reported that mice with greatly increased intracerebral mRNA for IFN-γ, TNF-a, and IL-6 resulted in better protection against *T. gondii* [494]. IL-6 may play a role in the mechanisms that determine genetic resistance in mice against the development of TE [215,495,496].

#### 4.3.5. Immune responses in transplant recipients

The occurrence of toxoplasmosis in organ transplant recipients can be due to transmission of the parasite with a transplanted organ from a seropositive donor (D+) to a seronegative recipient (R-) or from reactivation of pretransplant latent infection in a seropositive recipient (R+) [497]. It is also possible to transmit the infection through an organ transplant from a seropositive donor to a seropositive recipient [497]. The risk of toxoplasmosis is higher in seronegative recipients who receive organs from seropositive donors, and this disease is more likely to occur in the first three months after transplantation [498]. Late-onset disease can occur in seropositive recipients due to reactivation or reinfection of *Toxoplasma* in the context of increased immunosuppression [498]. Transplant patients such as hematopoietic stem cell transplant (HSCT) and solid organ transplant patients are at risk for toxoplasmosis due to receiving potent immunosuppressive therapy for a long time [499]. In the chronic phase of toxoplasmosis, cysts may form in tissues such as the

brain, eyes, heart muscles, skeletal muscles, liver, lungs, and kidneys [240,500]. Sometimes tissue cysts rupture in immunocompetent hosts, and the immune system destroys the released bradyzoites [501]. Some organs from a donor previously infected with a parasite may contain cysts. In seronegative recipients who do not have specific immunity to *T. gondii* and in cases where immunosuppressive treatment is used for transplant engraftment and tolerance, it is possible that the cysts in the transplanted organ are not controlled; then rupture and lead to active infection [497]. The risk of infection transmission due to the high tendency of *T. gondii* encystation in the myocardium is predominant in heart and heart-lung transplants [497]. It is significantly less in the case of renal, liver, pancreas, and intestine transplants because *T. gondii* does not form persistent cysts in these organs [498,502]. Grafts, such as the cornea, bone, and arteries are not at risk for toxoplasmosis [499]. In addition, it has been estimated that there is no risk of cyst transmission with hematopoietic stem cells [497]. The maximum risk of transmission of infection from a seropositive donor who was infected in the past to a seronegative recipient, in the absence of prevention, is in heart transplant (50–75 %), followed by liver (20 %) and kidney (<1 %) transplantation [503].

Immunosuppressive therapies used to treat the underlying disease and/or to prevent organ rejection in transplant recipients can reactivate latent bradyzoites in the graft or recipient tissues. Then, bradyzoites are transformed into tachyzoites, which can disseminate, lyse infected cells, and lead to life-threatening diseases [504–506]. This risk is due to the reactivation of latent pre-transplantation infection in the HSCT seropositive recipient (R+) and the transfer of cysts in the graft from a seropositive donor (D+) to a seronegative recipient (R-) in solid organ transplant (SOT) [497]. Toxoplasmosis is an infectious complication that has been reported in SOT usually in the first three months after transplantation. Graft transmission is a more common mechanism of reactivation in SOT compared to HSCT [507]. However, the disease may develop more than 3–6 months after SOT due to reactivation or de novo disease following immunosuppressive therapies [508]. Because of longer immunosuppression, toxoplasmosis is more likely in HSCT than in SOT. This risk is exceptionally high in the period 2–4 months after transplantation. Less than 10 % of disease cases occur before one month and 15–20 % after 100 days [509]. The prevalence of toxoplasmosis in seropositive transplant recipients from different parts of the world is 0.2–5.7 % [508]. The incidence of T. gondii reactivation in transplant patients varies in different countries due to the close relationship with the prevalence of *T. gondii* among the general population [497].

PCR screening is mainly used in post-transplant to diagnose *T. gondii* infection in specialized centers [499]. A positive PCR result from blood without organ involvement can only be considered a possible diagnosis of toxoplasmosis [497]. Nonetheless, a negative PCR result cannot rule out toxoplasmosis because cases of toxoplasmosis with negative PCR results from blood have also been observed [510,511]. Organ transmitted infection can be suspected, in case of serological mismatch between donor and transplant recipient (D+/R–). Seroconversion early after transplantation, with the production of IgM and IgG antibodies, and finally IgA and IgE [512], is a sign of acquired infection. In cases of severe immunosuppression, humoral immunity may be absent or atypical, and the diagnosis is made only by observing the parasite or parasite DNA in blood, body fluids, or biopsy samples, guided by clinical symptoms [513]. Seroconversion with the production of IgG and IgM antibodies rarely occurs in HSCT recipients. On the contrary, the transient increase of IgG antibody at a low titer is standard, possibly related to the transmission of passive antibodies via graft or blood transfusion [514]. Reactivation should be suspected if an increase in IgG antibody titer is observed without IgM or IgA antibodies [515]. This antibody produced during reactivation represents an immune recall rather than a primary immune response [516]. Sometimes, in HSCT recipients, an IgM antibody is created, which shows the immediate immune response of grafted cells from seronegative donors. Nevertheless, there is no apparent connection between serological reactivation in the seropositive receptor and clinical disease [497].

## 5. Treatment and prophylaxis of toxoplasmosis

Pyrimethamine and sulfadiazine are the recommended drugs for the treatment or prophylaxis of toxoplasmosis [517]. These drugs cause serious side effects such as neutropenia, leukopenia, significant reductions in platelet counts, thrombocytopenia, increases in serum creatinine and serum liver enzymes, fatal bone marrow suppression, hematologic toxicity, and severe allergic reactions [517–520]. Furthermore, these drugs cause some unusual reactions, including agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hepatic necrosis, which can be fatal in patients with toxoplasmosis [521]. Additionally, other drugs, including spiramycin, azithromycin, atovaquone, clarithromycin, dapsone, and cotrimoxazole (trimethoprim-sulfamethoxazole) are used to treat toxoplasmosis. However, these medications are poorly tolerated and do not affect the bradyzoites [522,523]. Disease management is based on targeting actively growing tachyzoites [524,525]. This drug combination targets folate metabolism due to the synergistic action of pyrimethamine plus sulfadiazine on dihydrofolate reductase and dihydropterate synthase [526]. Tissue cysts and their bradyzoites are resistant to these antifolate drugs, which may be due to a low level of DNA synthesis in the cyst [527]. Recent experimental studies in clinical cases clearly show drug resistance to *Toxoplasma*. Due to treatment failure and increased clinical burden in immunocompromised patients, *T. gondii* strains resistant to existing drugs have emerged, which is worrying. Hence, comprehending the mechanisms of drug resistance is vital for disease control and helps predict which drug combinations will synergize and identify the critical targets of the parasite [517]. In a study, the activities of 80 existing clinical drugs and several new compounds used to treat toxoplasmosis were investigated. Most available drugs are effective only on tachyzoites and very few affect bradyzoites [522]. Currently, toxoplasmosis is incurable because the cysts persist in the host's tissues [528]. An ideal drug should be effective against both tachyzoites and tissue cysts because the most prevalent form of the disease is its chronic type [529]. Then, to achieve a radical cure for *Toxoplasma*, bradyzoites must be eliminated. However, due to the presence of the cyst wall and quiescent metabolism in addition to being intracellular, this is pharmacologically challenging to do [528]. Therefore, in recent years, the development of tolerable and safe immunoprophylaxis has been an important goal for the global control of toxoplasmosis [530]. Immunotherapy strategies to improve toxoplasmosis control may include vaccination that induces strong protective immunity against infection, or passive immunity in cases of disease recrudescence [522]. In recent decades, considerable progress has been made in vaccine research on nucleic acid vaccines,

protein vaccines, live attenuated vaccines, and heterologous vaccines [531,532]. In the vaccination approach, the goal is to prevent congenital defects and abortions in women and various species of livestock such as sheep and goats, to prevent/reduce the number of *T. gondii* tissue cysts in food-producing animals, and to prevent/reduce oocyst shedding in cats [533]. Several vaccine candidates including SAGs, MICs, GRAs, and ROPs have been tested mainly in inbred mice using different strategies [59,60,65,95]. Another point to note is that different parts of an antigen do not stimulate the immune system similarly. The most immunogenic epitopes for epitope-based vaccines were selected by the *in silico* method and used for vaccine production [534–536]. Comparisons are difficult because the genetic background of mice affects the outcome of vaccine trials, and there is no standard challenge protocol [537]. To date, only one live-attenuated vaccine (Toxovax) has been marketed to prevent abortion in sheep, and there is no suitable vaccine for the prevention of toxoplasmosis in humans [538].

## 6. Conclusion and future perspectives

A review of many studies shows that the pathogenesis of toxoplasmosis is a very complex phenomenon involving many aspects. However, this study tried to summarize the important aspects of the pathogenesis of the disease, but there is a lot of ambiguity and many open questions, so the study provides answers to these ambiguities may be an exciting field for future research and facilitate a better understanding of the pathogenesis of the disease.

Addressing the following issues will allow a better description of the pathogenesis of parasite in its hosts: 1) identifying the protein composition of different stages of *T. gondii*, including oocyst and cyst walls, by RNA single-cell sequencing will help to better understand the biology of the parasite, its pathogenesis, and identify possible new vaccines, 2) future studies should focus on targeting bradyzoite formation and/or removal of tissue cysts and further investigate cytokines associated with cyst formation and stability. They should also study the specific molecular triggers to stage conversion from bradyzoite to tachyzoite as they are valuable in identifying new therapeutic options, 3) the use of gene knockout systems is necessary to further investigate the differences between different *Toxoplasma* strains, 4) much research is needed to fully understand the molecular mechanisms that cause latency and the effect of chronic infection on host behavior, 5) it is better to use recent advances in genetic manipulation of parasites to identify new factors effective in the *in vivo* virulence of the parasite, 6) differences in the strategies adopted by the parasite between mouse and human hosts should be further investigated, 7) research in the field of identifying new and effective drug targets is needed, 8) it is necessary to investigate the role and importance of GPI in the pathogenesis of toxoplasmosis for a more precise understanding, 9) further research in the field of polymorphisms related to ocular toxoplasmosis can explain how inflammation in the eye is triggered, and 10) further intensive studies to determine the effect of parasite on altered levels of neurotransmitters and inflammatory markers, the role of neurotransmitters and potential immune mechanisms are required in the etiology of psychiatric disorders.

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## Data availability statement

The data will be made available in the article.

## CRediT authorship contribution statement

**Tooran Nayeri:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Shahabeddin Sarvi:** Writing – review & editing, Methodology. **Ahmad Daryani:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

## Declaration of competing interest

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## References

[1] T.M. Mikaeili Galeh, S. Sarvi, M. Montazeri, M. Moosazadeh, M. Nakhaei, S.A. Shariatzadeh, A. Daryani, Global status of *Toxoplasma gondii* seroprevalence in rodents: a systematic review and meta-analysis, Front. Vet. Sci. 7 (2020) 461.

[2] B. Hajimohammadi, S. Ahmadian, Z. Firoozi, M. Askari, M. Mohammadi, G. Eslami, V. Askari, E. Loni, R. Barzegar-Bafrouei, M.J. Boozhmehrani, A meta-analysis of the prevalence of toxoplasmosis in livestock and poultry worldwide, EcoHealth 19 (1) (2022) 55–74.

[3] V. Rahmanian, K. Rahmanian, A.S. Jahromi, S. Bokaie, Seroprevalence of *Toxoplasma gondii* infection: an umbrella review of updated systematic reviews and meta-analyses, Fam. Med. Prim. Care Rev. 9 (8) (2020) 3848.

[4] S.A. Shariatzadeh, S. Sarvi, S.A. Hosseini, M. Sharif, S. Gholami, A.S. Pagheh, F. Montazeri, T. Nayeri, M. Nakhaei, T. Mikaeili Galeh, A. Daryani, The global seroprevalence of *Toxoplasma gondii* infection in bovines: a systematic review and meta-analysis, Parasitology 148 (12) (2021) 1417–1433.

[5] N. Maspi, T. Nayeri, M. Moosazadeh, S. Sarvi, M. Sharif, A. Daryani, Global seroprevalence of *Toxoplasma gondii* in Camelidae: a systematic review and meta-analysis, Acta Parasitol. 66 (2021) 733–744.

[6] M. Ahaduzzaman, T. Hasan, Seroprevalence of *Toxoplasma gondii* infection in sheep and goats from different geographical regions of the world: systematic review and meta-analysis, Transbound. Emerg. Dis. 69 (6) (2022) 3790–3822.

[7] T. Nayeri, S. Sarvi, A. Daryani, *Toxoplasma gondii* in mollusks and cold-blooded animals: a systematic review, Parasitology 148 (8) (2021) 895–903.

[8] P. Saraf, E.K. Shwab, J.P. Dubey, C. Su, On the determination of *Toxoplasma gondii* virulence in mice, Exp. Parasitol. 174 (2017) 25–30.

[9] A. Cunningham, D. Buxton, K. Thomson, An epidemic of toxoplasmosis in a captive colony of squirrel monkeys (*Saimiri sciureus*), J. Comp. Pathol. 107 (2) (1992) 207–219.

[10] J.P. Saeij, J.P. Boyle, S. Coller, S. Taylor, L.D. Sibley, E.T. Brooke-Powell, J.W. Ajioka, J. Boothroyd, Polymorphic secreted kinases are key virulence factors in toxoplasmosis, Science 314 (5806) (2006) 1780–1783.

[11] K.J. Pittman, L.J. Knoll, Long-term relationships: the complicated interplay between the host and the developmental stages of *Toxoplasma gondii* during acute and chronic infections, Microbiol. Mol. Biol. Rev. 79 (4) (2015) 387–401.

[12] C. Dard, H. Fricker-Hidalgo, M.P. Brenier-Pinchart, H. Pelloux, Relevance of and new developments in serology for toxoplasmosis, Trends Parasitol. 32 (6) (2016) 492–506.

[13] J.G. Montoya, O. Liesenfeld, Toxoplasmosis, Lancet 363 (9425) (2004) 1965–1976.

[14] A.M. Tenter, A.R. Heckeroth, L.M. Weiss, *Toxoplasma gondii*: from animals to humans, Int. J. Parasitol. 30 (12–13) (2000) 1217–1258.

[15] J.P. Dubey, C.P. Bealty, Toxoplasmosis of Animals and Humans, CRC Press, Boca Raton, Florida, 2010.

[16] I.J. Blader, J.P. Saeij, Communication between *Toxoplasma gondii* and its host: impact on parasite growth, development, immune evasion, and virulence, APMIS 117 (5-6) (2009) 458–476.

[17] J. Dubey, Toxoplasmosis–a waterborne zoonosis, Vet. Parasitol. 126 (1–2) (2004) 57–476.

[18] L.X. Piao, J.H. Cheng, F. Aosai, X.D. Zhao, K. Norose, X.J. Jin, Cellular immunopathogenesis in primary *Toxoplasma gondii* infection during pregnancy, Parasite, Immunol. 40 (9) (2018) e12570.

[19] S. Sarvi, T. Nayeri, M. Sharif, M. Montazeri, S.A. Hosseini, A. Amouei, Z. Hosseininejad, D. Anvari, R. Saberi, S. Gohardehi, A. Daryani, Congenital toxoplasmosis among Iranian neonates: a systematic review and meta-analysis, Epidemiol Health 41 (2019).

[20] G.N. Holland, Ocular toxoplasmosis: a global reassessment:. Part I: epidemiology and course of disease, Am. J. Ophthalmol. 136 (6) (2003) 973–988.

[21] B. Kocazeybek, Y.A. Oner, R. Turksoy, C. Babur, H. Cakan, N. Sahip, A. Unal, A. Ozaslan, S. Kılıc, S. Saribas, M. Aslan, Higher prevalence of toxoplasmosis in victims of traffic accidents suggest increased risk of traffic accident in *Toxoplasma*-infected inhabitants of Istanbul and its suburbs, Forensic, Sci. Int. 187 (1–3) (2009) 103–108.

[22] F. Yagmur, S. Yazar, H.O. Temel, M. Cavusoglu, May *Toxoplasma gondii* increase suicide attempt-preliminary results in Turkish subjects? Forensic, Sci. Int. 199 (1–3) (2010) 15–17.

[23] V.L. Feigin, A.A. Abajobir, K.H. Abate, F. Abd-Allah, A.M. Abdulle, S.F. Abera, G.Y. Abyu, M.B. Ahmed, A.N. Aichour, I. Aichour, M.T. Aichour, Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the global burden of disease study 2015, Lancet Neurol. 16 (11) (2017) 877–897.

[24] T. Nayeri, S. Sarvi, M. Moosazadeh, A. Daryani, Global prevalence of *Toxoplasma gondii* infection in the aborted fetuses and ruminants that had an abortion: a systematic review and meta-analysis, Vet. Parasitol. 1290 (2021) 109370.

[25] S. Stelzer, W. Basso, J.B. Silván, L.M. Ortega-Mora, P. Maksimov, J. Gethmann, F.J. Conraths, G. Schares, *Toxoplasma gondii* infection and toxoplasmosis in farm animals: risk factors and economic impact, Food Waterborne Parasitol. 15 (2019) e00037.

[26] J. Dubremetz, N. Garcia-Réguet, V. Conseil, M.N. Fourmaux, Invited review Apical organelles and host-cell invasion by Apicomplexa, Int. J. Parasitol. 28 (7) (1998) 1007–1013.

[27] E. Ortega-Barria, J.C. Boothroyd, A *Toxoplasma* lectin-like activity specific for sulfated polysaccharides is involved in host cell infection, J. Biol. Chem. 274 (3) (1999) 1267–1276.

[28] T. Ni, S.I. Williams, S. Rezelj, G. Anderluh, K. Harlos, P.J. Stansfeld, R.J. Gilbert, Structures of monomeric and oligomeric forms of the *Toxoplasma gondii* perforin-like protein 1, Sci. Adv. 4 (3) (2018) eaaq0762.

[29] A.B. Hehl, W.U. Basso, C. Lippuner, C. Ramakrishnan, M. Okoniewski, R.A. Walker, M.E. Grigg, N.C. Smith, P. Deplazes, Asexual expansion of *Toxoplasma gondii* merozoites is distinct from tachyzoites and entails expression of non-overlapping gene families to attach, invade, and replicate within feline enterocytes, BMC Genom. 16 (1) (2015) 1–16.

[30] H.-J. Peng, X.-G. Chen, D.S. Lindsay, A review: competence, compromise, and concomitance—reaction of the host cell to *Toxoplasma gondii* infection and development, J. Parasitol. Res. 97 (4) (2011) 620–628.

[31] D.G. Mordue, N. Desai, M. Dustin, L.D. Sibley, Invasion by *Toxoplasma gondii* establishes a moving junction that selectively excludes host cell plasma membrane proteins on the basis of their membrane anchoring, J. Exp. Med. 190 (12) (1999) 1783–1792.

[32] L. David Sibley, Invasion and intracellular survival by protozoan parasites, Immunol. Rev. 240 (1) (2011) 72–91.

[33] J.M. Dobrowolski, L.D. Sibley, *Toxoplasma* invasion of mammalian cells is powered by the actin cytoskeleton of the parasite, Cell 84 (6) (1996) 933–939.

[34] K. Joiner, S. Fuhrman, H. Miettinen, L. Kasper, I. Mellman, *Toxoplasma gondii*: fusion competence of parasitophorous vacuoles in Fc receptor-transfected fibroblasts, Science 249 (4969) (1990) 641–646.

[35] A. Bonhomme, A. Bouchot, N. Pezzella, J. Gomez, H. Le Moal, J. Pinon, Signaling during the invasion of host cells by *Toxoplasma gondii*, FEMS Microbiol. Rev. 23 (5) (1999) 551–561.

[36] C. Opitz, D. Soldati, 'The glideosome': a dynamic complex powering gliding motion and host cell invasion by *Toxoplasma gondii*, Mol. Microbiol. 45 (3) (2002) 597–604.

[37] L. Sibley, Intracellular parasite invasion strategies, Science 304 (5668) (2004) 248–253.

[38] M. Meissner, D. Schluter, D. Soldati, Role of *Toxoplasma gondii* myosin A in powering parasite gliding and host cell invasion, Science 298 (5594) (2002) 837–840.

[39] J. Baum, A.T. Papenfuss, B. Baum, T.P. Speed, A.F. Cowman, Regulation of apicomplexan actin-based motility, Nat. Rev. Microbiol. 4 (8) (2006) 621–628.

[40] L.W. Bergman, K. Kaiser, H. Fujioka, I. Coppens, T.M. Daly, S. Fox, K. Matuschewski, V. Nussenzweig, S.H. Kappe, Myosin A tail domain interacting protein (MTIP) localizes to the inner membrane complex of *Plasmodium* sporozoites, J. Cell Sci. 116 (1) (2003) 39–49.

[41] M.L. Jones, E.L. Kitson, J.C. Rayner, *Plasmodium falciparum* erythrocyte invasion: a conserved myosin associated complex, Mol. Biochem. Parasitol. 147 (1) (2006) 74–84.

[42] A. Keeley, D. Soldati, The glideosome: a molecular machine powering motility and host-cell invasion by Apicomplexa, Trends Cell Biol. 14 (10) (2004) 528–532.

[43] K. Frénal, V. Polonais, J.B. Marq, R. Stratmann, J. Limenitakis, D. Soldati-Favre, Functional dissection of the apicomplexan glideosome molecular architecture, Cell Host Microbe 8 (4) (2010) 343–357.

[44] I. Blader, B. Coleman, C.T. Chen, M.J. Gubbels, The lytic cycle of *Toxoplasma gondii*: 15 years later, Annu. Rev. Microbiol. 69 (2015) 463.

[45] N. Sahoo, W. Beatty, J. Heuser, D. Sept, L.D. Sibley, Unusual kinetic and structural properties control rapid assembly and turnover of actin in the parasite *Toxoplasma gondii*, Mol. Biol. Cell 17 (2) (2006) 895–90660.

[46] N. Azzouz, F. Kamena, P. Laurino, R. Kikkeri, C. Mercier, M.F. Cesbron-Delauw, J.F. Dubremetz, L. De Cola, P.H. Seeberger, *Toxoplasma gondii* secretory proteins bind to sulfated heparin structures, Glycobiology 23 (1) (2013) 106–120.

[47] M. Meissner, M. Reiss, N. Viebig, V.B. Carruthers, C. Toursel, S. Tomavo, J.W. Ajioka, D. Soldati, A family of transmembrane microneme proteins of *Toxoplasma gondii* contain EGF-like domains and function as escorters, J. Cell Sci. 115 (3) (2002) 563–574.
[48] E.V. Lourenço, S.R. Pereira, V.M. Faça, A.A. Coelho-Castelo, J.R. Mineo, M.C. Roque-Barreira, L.J. Greene, A. Panunto-Castelo, *Toxoplasma gondii* micronemal protein MIC1 is a lactose-binding lectin, Glycobiology 11 (7) (2001) 541–547.
[49] Y. Zhang, B.S. Lai, M. Juhas, Y. Zhang, *Toxoplasma gondii* secretory proteins and their role in invasion and pathogenesis, Microbiol. Res. 227 (2019) 126293.
[50] S. Lourido, J. Shuman, C. Zhang, K.M. Shokat, R. Hui, L.D. Sibley, Calcium-dependent protein kinase 1 is an essential regulator of exocytosis in *Toxoplasma*, Nature 465 (7296) (2010) 359–362.
[51] T.J. Dowse, J.C. Pascall, K.D. Brown, D. Soldati, Apicomplexan rhomboids have a potential role in microneme protein cleavage during host cell invasion, Int. J. Parasitol. 35 (7) (2005) 747–756.
[52] J.S. Buguliskis, F. Brossier, J. Shuman, L.D. Sibley, Rhomboid 4 (ROM4) affects the processing of surface adhesins and facilitates host cell invasion by *Toxoplasma gondii*, PLoS Pathog. 6 (4) (2010) e1000858.
[53] I.D. Manger, A.B. Hehl, J.C. Boothroyd, The surface of *Toxoplasma* tachyzoites is dominated by a family of glycosylphosphatidylinositol-anchored antigens related to SAG1, Infect. Immun. 66 (5) (1998) 2237–2244.
[54] L. Kasper, J. Mineo, Attachment and invasion of host cells by *Toxoplasma gondii*, Parasitol. Today 10 (5) (1994) 184–188.
[55] D. Soldati, J.F. Dubremetz, M. Lebrun, Microneme proteins: structural and functional requirements to promote adhesion and invasion by the apicomplexan parasite *Toxoplasma gondii*, Int. J. Parasitol. 31 (12) (2001) 1293–1302.
[56] C. Lekutis, D.J. Ferguson, M.E. Grigg, M. Camps, J.C. Boothroyd, Surface antigens of *Toxoplasma gondii*: variations on a theme, Int. J. Parasitol. 31 (12) (2001) 1285–1292.
[57] C. Lekutis, D.J. Ferguson, J.C. Boothroyd, *Toxoplasma gondii*: identification of a developmentally regulated family of genes related to SAG2, Exp. Parasitol. 96 (2) (2000) 89–96.
[58] G. Bhopale, Pathogenesis of toxoplasmosis, Comp. Immunol. Microbiol. Infect. Dis. 26 (4) (2003) 213–222.
[59] A.S. Pagheh, S. Sarvi, M. Sharif, F. Rezaei, E. Ahmadpour, S. Dodangeh, Z. Omidian, H. Hassannia, S. Mehrzadi, A. Daryani, *Toxoplasma gondii* surface antigen 1 (SAG1) as a potential candidate to develop vaccine against toxoplasmosis: a systematic review, Eur. J. Clin. Microbiol. Infect. Dis. 69 (2020) 101414.
[60] S. Dodangeh, A. Daryani, M. Sharif, S.A. Aghayan, A.S. Pagheh, S. Sarvi, F. Rezaei, A systematic review on efficiency of microneme proteins to induce protective immunity against *Toxoplasma gondii*, Eur. J. Clin. Microbiol. Infect. Dis. 38 (2019) 617–629.
[61] M. Foroutan, L. Zaki, F. Ghaffarifar, Recent progress in microneme-based vaccines development against *Toxoplasma gondii*, Clin. Exp. Vaccine Res. 7 (2) (2018) 93–103.
[62] Q. Liu, F.-C. Li, C.-X. Zhou, X.-Q. Zhu, Research advances in interactions related to *Toxoplasma gondii* microneme proteins, Exp. Parasitol. 176 (2017) 89–98.
[63] O. Cérède, J.F. Dubremetz, M. Soête, D. Deslée, H. Vial, D. Bout, M. Lebrun, Synergistic role of micronemal proteins in *Toxoplasma gondii* virulence, J. Exp. Med. 201 (3) (2005) 453–463.
[64] M. Foroutan, F. Ghaffarifar, Z. Sharifi, A. Dalimi, O. Jorjani, Rhoptry antigens as *Toxoplasma gondii* vaccine target, Clin. Exp. Vaccine Res. 8 (1) (2019) 4–26.
[65] R. Faridnia, A. Daryani, S. Sarvi, M. Sharif, H. Kalani, Vaccination against *Toxoplasma gondii* using rhoptry antigens: a systematic review, Comp. Immunol. Microbiol. Infect. Dis. 59 (2018) 32–40.
[66] R. Michel, K. Schupp, W. Raether, F. Bierther, Formation of a close junction during invasion of erythrocytes by *Toxoplasma gondii in vitro*, Int. J. Parasitol. 10 (4) (1980) 309–313.
[67] E. Porchet-Hennere, G. Torpier, Relations entre *Toxoplasma* et sa cellule-hote, PROTISTOLOGICA 19 (3) (1983) 357–370.
[68] M. Lebrun, A. Michelin, H. El Hajj, J. Poncet, P.J. Bradley, H. Vial, J.F. Dubremetz, The rhoptry neck protein RON4 relocalizes at the moving junction during *Toxoplasma gondii* invasion, Cell Microbiol. 7 (12) (2005) 1823–1833.
[69] V.B. Carruthers, L.D. Sibley, Mobilization of intracellular calcium stimulates microneme discharge in *Toxoplasma gondii*, Mol. Microbiol. 31 (2) (1999) 421–428.
[70] J.L. Lovett, N. Marchesini, S.N. Moreno, L.D. Sibley, *Toxoplasma gondii* microneme secretion involves intracellular $Ca^{2+}$ release from inositol 1, 4, 5-triphosphate (IP3)/ryanodine-sensitive stores, J. Biol. Chem. 277 (29) (2002) 25870–25876.
[71] H. Kieschnick, T. Wakefield, C.A. Narducci, C. Beckers, *Toxoplasma gondii* attachment to host cells is regulated by a calmodulin-like domain protein kinase, J. Biol. Chem. 276 (15) (2001) 12369–12377.
[72] V.B. Carruthers, S.N. Moreno, D.L. Sibley, Ethanol and acetaldehyde elevate intracellular [$Ca^{2+}$] and stimulate microneme discharge in *Toxoplasma gondii*, Biochem. J. 342 (2) (1999) 379–386.
[73] S. Besteiro, J.F. Dubremetz, M. Lebrun, The moving junction of apicomplexan parasites: a key structure for invasion, Cell Microbiol. 13 (6) (2011) 797–805.
[74] K.W. Straub, E.D. Peng, B.E. Hajagos, J.S. Tyler, P.J. Bradley, The moving junction protein RON8 facilitates firm attachment and host cell invasion in *Toxoplasma gondii*, PLoS Pathog. 7 (3) (2011) e1002007.
[75] M. Lamarque, S. Besteiro, J. Papoin, M. Roques, B. Vulliez-Le Normand, J. Morlon-Guyot, J.F. Dubremetz, S. Fauquenoy, S. Tomavo, B.W. Faber, C.H. Kocken, The RON2-AMA1 interaction is a critical step in moving junction-dependent invasion by apicomplexan parasites, PLoS Pathog. 7 (2) (2011) e1001276.
[76] T.E. Zhang, L.T. Yin, R.H. Li, H.L. Wang, X.L. Meng, G.R. Yin, Protective immunity induced by peptides of AMA1, RON2 and RON4 containing T-and B-cell epitopes via an intranasal route against toxoplasmosis in mice, Parasites Vectors 8 (1) (2015) 1–9.
[77] D.L. Alexander, J. Mital, G.E. Ward, P. Bradley, J.C. Boothroyd, Identification of the moving junction complex of *Toxoplasma gondii*: a collaboration between distinct secretory organelles, PLoS Pathog. 1 (2) (2005) e17.
[78] J.M. Santos, D.J. Ferguson, M.J. Blackman, D. Soldati-Favre, Intramembrane cleavage of AMA1 triggers *Toxoplasma* to switch from an invasive to a replicative mode, Science 331 (6016) (2011) 473–477.
[79] F. Parussini, Q. Tang, S.M. Moin, J. Mital, S. Urban, G.E. Ward, Intramembrane proteolysis of *Toxoplasma* apical membrane antigen 1 facilitates host-cell invasion but is dispensable for replication, Proc. Natl. Acad. Sci. U.S.A. 109 (19) (2012) 7463–7468.
[80] M. Aikawa, L.H. Miller, J. Johnson, J. Rabbege, Erythrocyte entry by malarial parasites. A moving junction between erythrocyte and parasite, J. Cell Biol. 77 (1) (1978) 72–82.
[81] D.A. Gold, A.D. Kaplan, A. Lis, G.C. Bett, E.E. Rosowski, K.M. Cirelli, A. Bougdour, S.M. Sidik, J.R. Beck, S. Lourido, P.F. Egea, The *Toxoplasma* dense granule proteins GRA17 and GRA23 mediate the movement of small molecules between the host and the parasitophorous vacuole, Cell Host Microbe 17 (5) (2015) 642–652.
[82] L.D. Saffer, O. Mercereau-Puijalon, J.F. Dubremetz, J.D. Schwartzman, Localization of a *Toxoplasma gondii* rhoptry protein by immunoelectron microscopy during and after host cell penetration, J. Protozool. 39 (4) (1992) 526–530.
[83] V.B. Carruthers, L.D. Sibley, Sequential protein secretion from three distinct organelles of *Toxoplasma gondii* accompanies invasion of human fibroblasts, Eur. J. Cell Biol. 73 (2) (1997) 114–123.
[84] D.M. Walker, S. Oghumu, G. Gupta, B.S. McGwire, M.E. Drew, A.R. Satoskar, Mechanisms of cellular invasion by intracellular parasites, Cell. Mol. Life Sci. 71 (7) (2014) 1245–1263.
[85] B. Clough, E.-M. Frickel, The *Toxoplasma* parasitophorous vacuole: an evolving host–parasite frontier, Trends Parasitol. 33 (6) (2017) 473–488.
[86] J.C. Boothroyd, J.F. Dubremetz, Kiss and spit: the dual roles of *Toxoplasma* rhoptries, Nat. Rev. Microbiol. 6 (1) (2008) 79–88.
[87] H. El Hajj, E. Demey, J. Poncet, M. Lebrun, B. Wu, N. Galéotti, M.N. Fourmaux, O. Mercereau-Puijalon, H. Vial, G. Labesse, J.F. Dubremetz, The ROP2 family of *Toxoplasma gondii* rhoptry proteins: proteomic and genomic characterization and molecular modeling, Proteomics 6 (21) (2006) 5773–5784.
[88] M.J. Blackman, H.G. Heidrich, S. Donachie, J. McBride, A. Holder, A single fragment of a malaria merozoite surface protein remains on the parasite during red cell invasion and is the target of invasion-inhibiting antibodies, J. Exp. Med. 172 (1) (1990) 379–382.
[89] M.J. Blackman, Proteases involved in erythrocyte invasion by the malaria parasite function and potential as chemotherapeutic targets, Curr. Drug Targets 1 (1) (2000) 59–83.

[90] S.A. Howell, F. Hackett, A.M. Jongco, C. Withers-Martinez, K. Kim, V.B. Carruthers, M.J. Blackman, Distinct mechanisms govern proteolytic shedding of a key invasion protein in apicomplexan pathogens, Mol. Microbiol. 57 (5) (2005) 1342–1356.
[91] S.A. Howell, C. Withers-Martinez, C.H. Kocken, A.W. Thomas, M.J. Blackman, Proteolytic processing and primary structure of *Plasmodium falciparum* apical membrane antigen-1, J. Biol. Chem. 276 (33) (2001) 31311–31320.
[92] J.L. Green, L. Hinds, M. Grainger, E. Knuepfer, A.A. Holder, *Plasmodium* thrombospondin related apical merozoite protein (PTRAMP) is shed from the surface of merozoites by PfSUB2 upon invasion of erythrocytes, Mol. Biochem. Parasitol. 150 (1) (2006) 114–117.
[93] S.L. Fleck, B. Birdsall, J. Babon, A.R. Dluzewski, S.R. Martin, W.D. Morgan, E. Angov, C.A. Kettleborough, J. Feeney, M.J. Blackman, A.A. Holder, Suramin and suramin analogues inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite *Plasmodium falciparum*, J. Biol. Chem. 278 (48) (2003) 47670–47677.
[94] S. Dutta, J.D. Haynes, A. Barbosa, L.A. Ware, J.D. Snavely, J.K. Moch, A.W. Thomas, D.E. Lanar, Mode of action of invasion-inhibitory antibodies directed against apical membrane antigen 1 of *Plasmodium falciparum*, Infect. Immun. 73 (4) (2005) 2116–2122.
[95] F. Rezaei, M. Sharif, S. Sarvi, S.H. Hejazi, S. Aghayan, A.S. Pagheh, S. Dodangeh, A. Daryani, A systematic review on the role of GRA proteins of *Toxoplasma gondii* in host immunization, J. Microbiol. Methods 165 (2019) 105696.
[96] I. Coppens, Exploitation of auxotrophies and metabolic defects in *Toxoplasma* as therapeutic approaches, Int. J. Parasitol. 44 (2) (2014) 109–120.
[97] K. Ehrenman, A. Sehgal, B. Lige, T.T. Stedman, K.A. Joiner, I. Coppens, Novel roles for ATP-binding cassette G transporters in lipid redistribution in *Toxoplasma*, Mol. Microbiol. 76 (5) (2010) 1232–1249.
[98] S.M. Landfear, Nutrient transport and pathogenesis in selected parasitic protozoa, Eukaryot. Cell 10 (4) (2011) 483–493.
[99] M. Lavine, G. Arrizabalaga, Invasion and egress by the obligate intracellular parasite *Toxoplasma gondii*: potential targets for the development of new antiparasitic drugs, Curr. Pharmaceut. Des. 13 (6) (2007) 641–651.
[100] H. Bisio, D. Soldati-Favre, Signaling cascades governing entry into and exit from host cells by *Toxoplasma gondii*, Annu. Rev. Microbiol. 73 (2019) 579–599.
[101] BrF. Kafsack, J.D. Pena, I. Coppens, S. Ravindran, J.C. Boothroyd, V.B. Carruthers, Rapid membrane disruption by a perforin-like protein facilitates parasite exit from host cells, Science 323 (5913) (2009) 530–533.
[102] M.-H. Huynh, M.S. Roiko, A.O. Gomes, E.N. Schinke, A.J. Schultz, S. Agrawal, C.A. Oellig, T.R. Sexton, J.M. Beauchamp, J. Laliberté, K.K. Sivaraman, *Toxoplasma gondii* Toxolysin 4 contributes to efficient parasite egress from host cells, mSphere 6 (3) (2021) 10–128.
[103] Y. Diao, Y. Yao, S. El-Ashram, M. Bian, Egress regulatory factors: how *Toxoplasma* exits from infected cells? Pathogens 12 (5) (2023) 679.
[104] V. Pszenny, K. Ehrenman, J.D. Romano, A. Kennard, A. Schultz, D.S. Roos, M.E. Grigg, V.B. Carruthers, I. Coppens, A lipolytic lecithin: cholesterol acyltransferase secreted by *Toxoplasma* facilitates parasite replication and egress, J. Biol. Chem. 291 (8) (2016) 3725–3746.
[105] M. Foroutan, F. Ghaffarifar, Calcium-dependent protein kinases are potential targets for *Toxoplasma gondii* vaccine, Clin. Exp. Vaccine Res. 7 (1) (2018) 24–36.
[106] X. Yan, Y. Ji, X. Liu, X. Suo, Nitric oxide stimulates early egress of *Toxoplasma gondii* tachyzoites from Human foreskin fibroblast cells, Parasites Vectors 8 (1) (2015) 1–6.
[107] Y.-s. Ji, X.-m. Sun, X.-Y. Liu, X. Suo, *Toxoplasma gondii*: effects of exogenous nitric oxide on egress of tachyzoites from infected macrophages, Exp. Parasitol. 133 (1) (2013) 70–74.
[108] E.K. Persson, A.M. Agnarson, H. Lambert, N. Hitziger, H. Yagita, B.J. Chambers, A. Barragan, A. Grandien, Death receptor ligation or exposure to perforin trigger rapid egress of the intracellular parasite *Toxoplasma gondii*, J. Immunol. 179 (12) (2007) 8357–8365.
[109] Y. Yao, M. Liu, C. Ren, J. Shen, Y. Ji, Exogenous tumor necrosis factor-alpha could induce egress of *Toxoplasma gondii* from human foreskin fibroblast cells, Parasite 24 (2017) 45.
[110] T. Melzer, A. Duffy, L. Weiss, S. Halonen, The gamma interferon (IFN-γ)-inducible GTP-binding protein IGTP is necessary for *Toxoplasma* vacuolar disruption and induces parasite egression in IFN-γ-stimulated astrocytes, Infect. Immun. 76 (11) (2008) 4883–4894.
[111] C.M. Persson, H. Lambert, P.P. Vutova, I. Dellacasa-Lindberg, J. Nederby, H. Yagita, H.G. Ljunggren, A. Grandien, A. Barragan, B.J. Chambers, Transmission of *Toxoplasma gondii* from infected dendritic cells to natural killer cells, Infect. Immun. 77 (3) (2009) 970–976.
[112] T. Tomita, T. Yamada, L.M. Weiss, A. Orlofsky, Externally triggered egress is the major fate of *Toxoplasma gondii* during acute infection, J. Immunol. 183 (10) (2009) 6667–6680.
[113] R. Moudy, T.J. Manning, C.J. Beckers, The loss of cytoplasmic potassium upon host cell breakdown triggers egress of *Toxoplasma gondii*, J. Biol. Chem. 276 (44) (2001) 41492–41501.
[114] K. Nagamune, L.M. Hicks, B. Fux, F. Brossier, E.N. Chini, L.D. Sibley, Abscisic acid controls calcium-dependent egress and development in *Toxoplasma gondii*, Nature 451 (7175) (2008) 207–210.
[115] S. Bruzzone, I. Moreschi, C. Usai, L. Guida, G. Damonte, A. Salis, S. Scarfi, E. Millo, A. De Flora, E. Zocchi, Abscisic acid is an endogenous cytokine in human granulocytes with cyclic ADP-ribose as second messenger, Proc. Natl. Acad. Sci. USA 104 (14) (2007) 5759–5764.
[116] M.S. Roiko, N. Svezhova, V.B. Carruthers, Acidification activates *Toxoplasma gondii* motility and egress by enhancing protein secretion and cytolytic activity, PLoS Pathog. 10 (11) (2014) e1004488.
[117] E.W. Stommel, K.H. Ely, J.D. Schwartzman, L.H. Kasper, *Toxoplasma gondii*: dithiol-induced $Ca^{2+}$ flux causes egress of parasites from the parasitophorous vacuole, Exp. Parasitol. 87 (2) (1997) 88–97.
[118] J.A. Silverman, H. Qi, A. Riehl, C. Beckers, V. Nakaar, K.A. Joiner, Induced activation of the *Toxoplasma gondii* nucleoside triphosphate hydrolase leads to depletion of host cell ATP levels and rapid exit of intracellular parasites from infected cells, J. Biol. Chem. 273 (20) (1998) 12352–12359.
[119] K. Harker, N. Ueno, M. Lodoen, *Toxoplasma gondii* dissemination: a parasite's journey through the infected host, Parasite Immunol. 37 (3) (2015) 141–149.
[120] Y. Suzuki, M.A. Orellana, R.D. Schreiber, J.S. Remington, Interferon-γ: the major mediator of resistance against *Toxoplasma gondii*, Science 240 (4851) (1988) 516–518.
[121] J. Dubey, Tissue cyst tropism in *Toxoplasma gondii*: a comparison of tissue cyst formation in organs of cats, and rodents fed oocysts, Parasitology 115 (1) (1997) 15–20.
[122] R.E. Lyons, R. McLeod, C.W. Roberts, *Toxoplasma gondii* tachyzoite–bradyzoite interconversion, Trends Parasitol. 18 (5) (2002) 198–201.
[123] X.l. He, M.E. Grigg, J.C. Boothroyd, K.C. Garcia, Structure of the immunodominant surface antigen from the *Toxoplasma gondii* SRS superfamily, Nat. Struct. Biol. 9 (8) (2002) 606–611.
[124] T. Chtanova, M. Schaeffer, S.J. Han, G.G. van Dooren, M. Nollmann, P. Herzmark, S.W. Chan, H. Satija, K. Camfield, H. Aaron, B. Striepen, Dynamics of neutrophil migration in lymph nodes during infection, Immunity 29 (3) (2008) 487–496.
[125] J.Y. Channon, R.M. Seguin, L.H. Kasper, Differential infectivity and division of *Toxoplasma gondii* in human peripheral blood leukocytes, Infect. Immun. 68 (8) (2000) 4822–4826.
[126] M. Nakao, E. Konishi, Proliferation of *Toxoplasma gondii* in human neutrophils *in vitro*, Parasitology 103 (1) (1991) 23–27.
[127] J.L. Coombes, B.A. Charsar, S.-J. Han, J. Halkias, S.W. Chan, A.A. Koshy, B. Striepen, E.A. Robey, Motile invaded neutrophils in the small intestine of *Toxoplasma gondii*-infected mice reveal a potential mechanism for parasite spread, Proc. Natl. Acad. Sci. USA 110 (21) (2013) E1913–E1922.
[128] M.H. Sumyuen, Y.J.F. Garin, F. Derouin, Early kinetics of *Toxoplasma gondii* infection in mice infected orally with cysts of an avirulent strain, J. Parasitol. (1995) 327–329.
[129] J. Diana, C. Vincent, F. Peyron, S. Picot, D. Schmitt, F. Persat, *Toxoplasma gondii* regulates recruitment and migration of human dendritic cells via different soluble secreted factors, Clin. Exp. Immunol. 141 (3) (2005) 475–484.
[130] J. Diana, F. Persat, M.J. Staquet, O. Assossou, J. Ferrandiz, M.J. Gariazzo, F. Peyron, S. Picot, D. Schmitt, C. Vincent, Migration and maturation of human dendritic cells infected with *Toxoplasma gondii* depend on parasite strain type, FEMS Immunol. Med. Microbiol. 42 (3) (2004) 321–331.
[131] H. Lambert, N. Hitziger, I. Dellacasa, M. Svensson, A. Barragan, Induction of dendritic cell migration upon *Toxoplasma gondii* infection potentiates parasite dissemination, Cell Microbiol. 8 (10) (2006) 1611–1623.
[132] H. Lambert, A. Barragan, Modelling parasite dissemination: host cell subversion and immune evasion by *Toxoplasma gondii*, Cell Microbiol. 12 (3) (2010) 292–300.

[133] A. Barragan, L.D. Sibley, Transepithelial migration of *Toxoplasma gondii* is linked to parasite motility and virulence, J. Exp. Med. 195 (12) (2002) 1625–1633.
[134] L.C. Gavrilescu, E.Y. Denkers, IFN-γ overproduction and high level apoptosis are associated with high but not low virulence *Toxoplasma gondii* infection, J. Immunol. 167 (2) (2001) 902–909.
[135] N. Hitziger, I. Dellacasa, B. Albiger, A. Barragan, Dissemination of *Toxoplasma gondii* to immunoprivileged organs and role of Toll/interleukin-1 receptor signalling for host resistance assessed by *in vivo* bioluminescence imaging, Cell Microbiol. 7 (6) (2005) 837–848.
[136] D.G. Mordue, F. Monroy, M. La Regina, C.A. Dinarello, L.D. Sibley, Acute toxoplasmosis leads to lethal overproduction of Th1 cytokines, J. Immunol. 167 (8) (2001) 4574–4584.
[137] L. Kim, B.A. Butcher, C.W. Lee, S. Uematsu, S. Akira, E.Y. Denkers, *Toxoplasma gondii* genotype determines MyD88-dependent signaling in infected macrophages, J. Immunol. 177 (4) (2006) 2584–2591.
[138] P.M. Robben, D.G. Mordue, S.M. Truscott, K. Takeda, S. Akira, L.D. Sibley, Production of IL-12 by macrophages infected with *Toxoplasma gondii* depends on the parasite genotype, J. Immunol. 172 (6) (2004) 3686–3694.
[139] J. Saeij, S. Coller, J. Boyle, M. Jerome, M. White, J. Boothroyd, *Toxoplasma* co-opts host gene expression by injection of a polymorphic kinase homologue, Nature 445 (7125) (2007) 324–327.
[140] S. Taylor, A. Barragan, C. Su, B. Fux, S. Fentress, K. Tang, W.L. Beatty, H.E. Hajj, M. Jerome, M.S. Behnke, M. White, A secreted serine-threonine kinase determines virulence in the eukaryotic pathogen *Toxoplasma gondii*, Science 314 (5806) (2006) 1776–1780.
[141] H. Lambert, P.P. Vutova, W.C. Adams, K. Loré, A. Barragan, The *Toxoplasma gondii*-shuttling function of dendritic cells is linked to the parasite genotype, Infect. Immun. 77 (4) (2009) 1679–1688.
[142] M. Dardé, *Toxoplasma gondii*,"new" genotypes and virulence, Parasite 15 (3) (2008) 366–371.
[143] J.F. Dubremetz, M. Lebrun, Virulence factors of *Toxoplasma gondii*, Microb. Infect. 14 (15) (2012) 1403–1410.
[144] M. Dardé, B. Bouteille, M. Pestre-Alexandre, Isoenzyme analysis of 35 *Toxoplasma gondii* isolates and the biological and epidemiological implications, J. Parasitol. (1992) 786–794.
[145] L.D. Sibley, J.C. Boothroyd, Virulent strains of *Toxoplasma gondii* comprise a single clonal lineage, Nature 359 (6390) (1992) 82–85.
[146] J. Dubey, J. Frenkel, Cyst-induced toxoplasmosis in cats, J. Protozool. 19 (1) (1972) 155–177.
[147] E. Pfefferkorn, L.H. Kasper, *Toxoplasma gondii*: genetic crosses reveal phenotypic suppression of hydroxyurea resistance by fluorodeoxyuridine resistance, Exp. Parasitol. 55 (2) (1983) 207–218.
[148] B. Gajria, A. Bahl, J. Brestelli, J. Dommer, S. Fischer, X. Gao, M. Heiges, J. Iodice, J.C. Kissinger, A.J. Mackey, D.F. Pinney, ToxoDB: an integrated *Toxoplasma gondii* database resource, Nucleic Acids Res. 36 (suppl_1) (2007) D553–D556.
[149] J.P. Saeij, J.P. Boyle, J.C. Boothroyd, Differences among the three major strains of *Toxoplasma gondii* and their specific interactions with the infected host, Trends Parasitol. 21 (10) (2005) 476–481.
[150] H.E. Kaufman, M.L. Melton, J.S. Remington, L. Jacobs, Strain differences of *Toxoplasma gondii*, J. Parasitol. 45 (2) (1959) 189–190.
[151] D.K. Howe, B.C. Summers, L.D. Sibley, Acute virulence in mice is associated with markers on chromosome VIII in *Toxoplasma gondii*, Infect. Immun. 64 (12) (1996) 5193–5198.
[152] A. Khan, M.S. Behnke, I.R. Dunay, M.W. White, L.D. Sibley, Phenotypic and gene expression changes among clonal type I strains of *Toxoplasma gondii*, Eukaryot. Cell 8 (12) (2009) 1828–1836.
[153] A. Khan, S. Taylor, J.W. Ajioka, B.M. Rosenthal, L.D. Sibley, Selection at a single locus leads to widespread expansion of *Toxoplasma gondii* lineages that are virulent in mice, PLoS Genet. 5 (3) (2009) e1000404.
[154] J.R. Radke, B. Striepen, M.N. Guerini, M.E. Jerome, D.S. Roos, M.W. White, Defining the cell cycle for the tachyzoite stage of *Toxoplasma gondii*, Mol. Biochem. Parasitol. 115 (2) (2001) 165–175.
[155] C.A. Hunter, L.D. Sibley, Modulation of innate immunity by *Toxoplasma gondii* virulence effectors, Nat. Rev. Microbiol. 10 (11) (2012) 766–778.
[156] Y. Suzuki, K. Joh, Effect of the strain of *Toxoplasma gondii* on the development of toxoplasmic encephalitis in mice treated with antibody to interferon-gamma, Parasitol. Res. 80 (2) (1994) 125–130.
[157] O. Liesenfeld, Oral infection of C57BL/6 mice with *Toxoplasma gondii*: a new model of inflammatory bowel disease? J. Infect. Dis. 185 (Supplement_1) (2002) S96–S101.
[158] D.K. Howe, L.D. Sibley, *Toxoplasma gondii* comprises three clonal lineages: correlation of parasite genotype with human disease, J. Infect. Dis. 172 (6) (1995) 1561–1566.
[159] A. Khan, J. Dubey, C. Su, J.W. Ajioka, B.M. Rosenthal, L.D. Sibley, Genetic analyses of atypical *Toxoplasma gondii* strains reveal a fourth clonal lineage in North America, Int. J. Parasitol. 41 (6) (2011) 645–655.
[160] C. Su, A. Khan, P. Zhou, D. Majumdar, D. Ajzenberg, M.L. Dardé, X.Q. Zhu, J.W. Ajioka, B.M. Rosenthal, J.P. Dubey, L.D. Sibley, Globally diverse *Toxoplasma gondii* isolates comprise six major clades originating from a small number of distinct ancestral lineages, Proc. Natl. Acad. Sci. U.S.A. 109 (15) (2012) 5844–5849.
[161] S. Minot, M.B. Melo, F. Li, D. Lu, W. Niedelman, S.S. Levine, J.P. Saeij, Admixture and recombination among *Toxoplasma gondii* lineages explain global genome diversity, Proc. Natl. Acad. Sci. U.S.A. 109 (33) (2012) 13458–13463.
[162] J.P. Boyle, B. Rajasekar, J.P. Saeij, J.W. Ajioka, M. Berriman, I. Paulsen, D.S. Roos, L.D. Sibley, M.W. White, J.C. Boothroyd, Just one cross appears capable of dramatically altering the population biology of a eukaryotic pathogen like *Toxoplasma gondii*, Proc. Natl. Acad. Sci. U.S.A. 103 (27) (2006) 10514–10519.
[163] J.W. Ajioka, *Toxoplasma gondii*: ESTs and gene discovery, Int. J. Parasitol. 28 (7) (1998) 1025–1031.
[164] C. Su, D.K. Howe, J. Dubey, J.W. Ajioka, L.D. Sibley, Identification of quantitative trait loci controlling acute virulence in *Toxoplasma gondii*, Proc. Natl. Acad. Sci. USA 99 (16) (2002) 10753–10758.
[165] D. Ajzenberg, A. Banuls, C. Su, A. Dumetre, M. Demar, B. Carme, M.L. Dardé, Genetic diversity, clonality and sexuality in *Toxoplasma gondii*, Int. J. Parasitol. 34 (10) (2004) 1185–1196.
[166] M.E. Grigg, J.C. Boothroyd, Rapid identification of virulent type I strains of the protozoan pathogen *Toxoplasma gondii* by PCR-restriction fragment length polymorphism analysis at the B1 gene, J. Clin. Microbiol. 39 (1) (2001) 398–400.
[167] D. Ajzenberg, N. Cogné, L. Paris, M.H. Bessières, P. Thulliez, D. Filisetti, H. Pelloux, P. Marty, M.L. Dardé, Genotype of 86 *Toxoplasma gondii* isolates associated with human congenital toxoplasmosis, and correlation with clinical findings, J. Infect. Dis. 186 (5) (2002) 684–689.
[168] D.K. Howe, S. Honoré, F. Derouin, L.D. Sibley, Determination of genotypes of *Toxoplasma gondii* strains isolated from patients with toxoplasmosis, J. Clin. Microbiol. 35 (6) (1997) 1411–1414.
[169] S. Honore, A. Couvelard, Y. Garin, C. Bedel, D. Henin, M. Darde, F. Derouin, Genotyping of *Toxoplasma gondii* strains from immunocompromised patients, Pathol. Biol. 48 (6) (2000) 541–547.
[170] J.P. Dubey, D. Graham, E. Dahl, C. Sreekumar, T. Lehmann, M. Davis, T.Y. Morishita, *Toxoplasma gondii* isolates from free-ranging chickens from the United States, J. Parasitol. 89 (5) (2003) 1060–1062.
[171] P.S. Mead, L. Slutsker, V. Dietz, L.F. McCaig, J.S. Bresee, C. Shapiro, P.M. Griffin, R.V. Tauxe, Food-related illness and death in the United States, Emerg. Infect. Dis. 5 (5) (1999) 607.
[172] R. Mondragon, D.K. Howe, J. Dubey, L.D. Sibley, Genotypic analysis of *Toxoplasma gondii* isolates from pigs, J. Parasitol. (1998) 639–641.
[173] A. Barragan, L.D. Sibley, Migration of *Toxoplasma gondii* across biological barriers, Trends Microbiol. 11 (9) (2003) 426–430.
[174] J.P. Saeij, J.P. Boyle, M.E. Grigg, G. Arrizabalaga, J.C. Boothroyd, Bioluminescence imaging of *Toxoplasma gondii* infection in living mice reveals dramatic differences between strains, Infect. Immun. 73 (2) (2005) 695–702.
[175] S.K. Bliss, L.C. Gavrilescu, A. Alcaraz, E.Y. Denkers, Neutrophil depletion during *Toxoplasma gondii* infection leads to impaired immunity and lethal systemic pathology, Infect. Immun. 69 (8) (2001) 4898–4905.
[176] L. Del Rio, S. Bennouna, J. Salinas, E.Y. Denkers, CXCR2 deficiency confers impaired neutrophil recruitment and increased susceptibility during *Toxoplasma gondii* infection, J. Immunol. 167 (11) (2001) 6503–6509.

[177] D.G. Mordue, L.D. Sibley, A novel population of Gr-1+-activated macrophages induced during acute toxoplasmosis, J. Leukoc. Biol. 74 (6) (2003) 1015–1025.
[178] P.J. Bradley, L.D. Sibley, Rhoptries: an arsenal of secreted virulence factors, Curr. Opin. Microbiol. 10 (6) (2007) 582–587.
[179] T. Steinfeldt, S. Könen-Waisman, L. Tong, N. Pawlowski, T. Lamkemeyer, L.D. Sibley, J.P. Hunn, J.C. Howard, Phosphorylation of mouse immunity-related GTPase (IRG) resistance proteins is an evasion strategy for virulent *Toxoplasma gondii*, PLoS Biol. 8 (12) (2010) e1000576.
[180] M.L. Reese, G.M. Zeiner, J.P. Saeij, J.C. Boothroyd, J.P. Boyle, Polymorphic family of injected pseudokinases is paramount in *Toxoplasma* virulence, Proc. Natl. Acad. Sci. U.S.A. 108 (23) (2011) 9625–9630.
[181] H. Dlugonska, *Toxoplasma* rhoptries: unique secretory organelles and source of promising vaccine proteins for immunoprevention of toxoplasmosis, BioMed Res. Int. 2008 (2008).
[182] A. Camejo, D.A. Gold, D. Lu, K. McFetridge, L. Julien, N. Yang, K.D. Jensen, J.P. Saeij, Identification of three novel *Toxoplasma gondii* rhoptry proteins, Int. J. Parasitol. 44 (2) (2014) 147–160.
[183] E.D. Phelps, K.R. Sweeney, I.J. Blader, *Toxoplasma gondii* rhoptry discharge correlates with activation of the early growth response 2 host cell transcription factor, Infect. Immun. 76 (10) (2008) 4703–4712.
[184] R.M. Andrade, M. Wessendarp, M.J. Gubbels, B. Striepen, C.S. Subauste, CD40 induces macrophage anti–*Toxoplasma gondii* activity by triggering autophagy-dependent fusion of pathogen-containing vacuoles and lysosomes, J. Clin. Invest. 116 (9) (2006) 2366–2377.
[185] L. Sibley, L. Adams, Y. Fukutomi, J. Krahenbuhl, Tumor necrosis factor-alpha triggers antitoxoplasmal activity of IFN-gamma primed macrophages, J. Immunol. 147 (7) (1991) 2340–2345.
[186] S. Goerdt, O. Politz, K. Schledzewski, R. Birk, A. Gratchev, P. Guillot, N. Hakiy, C.D. Klemke, E. Dippel, V. Kodelja, C.E. Orfanos, Alternative versus classical activation of macrophages, Pathobiology 67 (5–6) (1999) 222–226.
[187] M.S. Behnke, A. Khan, J.C. Wootton, J.P. Dubey, K. Tang, L.D. Sibley, Virulence differences in *Toxoplasma* mediated by amplification of a family of polymorphic pseudokinases, Proc. Natl. Acad. Sci. U.S.A. 108 (23) (2011) 9631–9636.
[188] Y.C. Ong, M.L. Reese, J.C. Boothroyd, *Toxoplasma* rhoptry protein 16 (ROP16) subverts host function by direct tyrosine phosphorylation of STAT6, J. Biol. Chem. 285 (37) (2010) 28731–28740.
[189] M. Yamamoto, D.M. Standley, S. Takashima, H. Saiga, M. Okuyama, H. Kayama, E. Kubo, H. Ito, M. Takaura, T. Matsuda, D. Soldati-Favre, A single polymorphic amino acid on *Toxoplasma gondii* kinase ROP16 determines the direct and strain-specific activation of Stat3, J. Exp. Med. 206 (12) (2009) 2747–2760.
[190] B.A. Butcher, L. Kim, A.D. Panopoulos, S.S. Watowich, P.J. Murray, E.Y. Denkers, Cutting edge: IL-10-independent STAT3 activation by *Toxoplasma gondii* mediates suppression of IL-12 and TNF-α in host macrophages, J. Immunol. 174 (6) (2005) 3148–3152.
[191] J.C. Howard, J.P. Hunn, T. Steinfeldt, The IRG protein-based resistance mechanism in mice and its relation to virulence in *Toxoplasma gondii*, Curr. Opin. Microbiol. 14 (4) (2011) 414–421 (Reese).
[192] D.R. Weilhammer, A. Rasley, Genetic approaches for understanding virulence in *Toxoplasma gondii*, Brief. Funct. Genom. 10 (6) (2011) 365–373.
[193] L. Peixoto, F. Chen, O.S. Harb, P.H. Davis, D.P. Beiting, C.S. Brownback, D. Ouloguem, D.S. Roos, Integrative genomic approaches highlight a family of parasite-specific kinases that regulate host responses, Cell Host Microbe 8 (2) (2010) 208–218.
[194] J. Dubey, J. Frenkel, Experimental *Toxoplasma* infection in mice with strains producing oocysts, J. Parasitol. (1973) 505–512.
[195] A.M. Johnson, Strain-dependent, route of challenge-dependent, murine susceptibility to toxoplasmosis, Z, Parasite 70 (3) (1984) 303–309.
[196] J. Dubey, Infectivity and pathogenicity of *Toxoplasma gondii* oocysts for cats, J. Parasitol. (1996) 957–961.
[197] J. Dubey, Oocyst shedding by cats fed isolated bradyzoites and comparison of infectivity of bradyzoites of the VEG strain *Toxoplasma gondii* to cats and mice, J. Parasitol. 87 (1) (2001) 215–219.
[198] J. Dubey, Comparative infectivity of oocysts and bradyzoites of *Toxoplasma gondii* for intermediate (mice) and definitive (cats) hosts, Vet. Parasitol. 140 (1–2) (2006) 69–75.
[199] A. Dumètre, M.-L. Dardé, How to detect *Toxoplasma gondii* oocysts in environmental samples? FEMS Microbiol. Rev. 27 (5) (2003) 651–661.
[200] K. Kim, L.M. Weiss, *Toxoplasma*: the next 100 years, Microb. Infect. 10 (9) (2008) 978–984.
[201] L. Jacobs, J.S. Remington, M.L. Melton, The resistance of the encysted form of *Toxoplasma gondii*, J. Parasitol. 46 (1) (1960) 11–21.
[202] J. Dubey, Unexpected oocyst shedding by cats fed *Toxoplasma gondii* tachyzoites: *in vivo* stage conversion and strain variation, Vet. Parasitol. 133 (4) (2005) 289–298.
[203] J. Dubey, Tachyzoite-induced life cycle of *Toxoplasma gondii* in cats, J. Parasitol. 88 (4) (2002) 713–717.
[204] J. Dubey, J. Frenkel, Feline toxoplasmosis from acutely infected mice and the development of *Toxoplasma* cysts, J. Protozool. 23 (4) (1976) 537–546.
[205] J. Frenkel, J. Dubey, R. Hoff, Loss of stages after continuous passage of *Toxoplasma gondii* and *Besnoitia jellisoni*, J. Protozool. 23 (3) (1976) 421–424.
[206] D.S. Lindsay, J. Dubey, B.L. Blagburn, M. Toivio-Kinnucan, Examination of tissue cyst formation by *Toxoplasma gondii* in cell cultures using bradyzoites, tachyzoites, and sporozoites, J. Parasitol. (1991) 126–132.
[207] J. Dubey, S. Shen, O. Kwok, J. Frenkel, Infection and immunity with the RH strain of *Toxoplasma gondii* in rats and mice, J. Parasitol. (1999) 657–662.
[208] J. Frenkel, P. Ambroise-Thomas, Genomic drift of *Toxoplasma gondii*, Parasitol. Res. 83 (1) (1996) 1–5.
[209] D.K. Howe, L.D. Sibley, *Toxoplasma gondii*: analysis of different laboratory stocks of the RH strain reveals genetic heterogeneity, Exp. Parasitol. 78 (2) (1994) 242–245.
[210] M.S. Behnke, J. Dubey, L.D. Sibley, Genetic mapping of pathogenesis determinants in *Toxoplasma gondii*, Annu. Rev. Microbiol. 70 (2016) 63–81.
[211] J. Dubey, J. Frenkel, Toxoplasmosis of rats: a review, with considerations of their value as an animal model and their possible role in epidemiology, Vet. Parasitol. 77 (1) (1998) 1–32.
[212] Y. Lee, L. Kasper, Immune responses of different mouse strains after challenge with equivalent lethal doses of *Toxoplasma gondii*, Parasite 11 (1) (2004) 89–97.
[213] O. Liesenfeld, J. Kosek, J.S. Remington, Y. Suzuki, Association of CD4+ T cell-dependent, interferon-gamma-mediated necrosis of the small intestine with genetic susceptibility of mice to peroral infection with *Toxoplasma gondii*, J. Exp. Med. 184 (2) (1996) 597–607.
[214] C. Brown, C. Hunter, R. Estes, E. Beckmann, J. Forman, C. David, J.S. Remington, R. McLeod, Definitive identification of a gene that confers resistance against *Toxoplasma* cyst burden and encephalitis, Immunology 85 (3) (1995) 419.
[215] W. Luo, F. Aosai, M. Ueda, K. Yamashita, K. Shimizu, S. Sekiya, A. Yano, Kinetics in parasite abundance in susceptible and resistant mice infected with an avirulent strain of *Toxoplasma gondii* by using quantitative competitive PCR, J. Parasitol. (1997) 1070–1074.
[216] Y. Suzuki, X. Wang, B.S. Jortner, L. Payne, Y. Ni, S.A. Michie, B. Xu, T. Kudo, S. Perkins, Removal of *Toxoplasma gondii* cysts from the brain by perforin-mediated activity of CD8+ T cells, Am. J. Pathol. 176 (4) (2010) 1607–1613.
[217] F. Lu, S. Huang, M.S. Hu, L.H. Kasper, Experimental ocular toxoplasmosis in genetically susceptible and resistant mice, Infect. Immun. 73 (8) (2005) 5160–5165.
[218] J. Dubey, L. Ferreira, J. Martins, R. McLeod, Oral oocyst-induced mouse model of toxoplasmosis: effect of infection with *Toxoplasma gondii* strains of different genotypes, dose, and mouse strains (transgenic, out-bred, in-bred) on pathogenesis and mortality, Parasitology 139 (1) (2012) 1–13.
[219] F.G. Araujo, D.M. Williams, F.C. Grumet, J.S. Remington, Strain-dependent differences in murine susceptibility to *Toxoplasma*, Infect. Immun. 13 (5) (1976) 1528–1530.
[220] R. McLeod, E. Skamene, C. Brown, P. Eisenhauer, D. Mack, Genetic regulation of early survival and cyst number after peroral *Toxoplasma gondii* infection of A x B/B x A recombinant inbred and B10 congenic mice, J. Immunol. 143 (9) (1989) 3031–3034.
[221] L. Jacobs, F.E. Jones, The parasitemia in experimental toxoplasmosis, J. Infect. Dis. 87 (1) (1950) 78–89.
[222] I. Ruchman, J.C. Fowler, Localization and persistence of *Toxoplasma* in tissues of experimentally infected white rats, Proc. Soc. Exp. Biol. Med. 76 (4) (1951) 793–796.
[223] T. Hellbrügge, W. Spiegler, W. Grewing, Klinische, morphologische und serologische befunde bei der generalisierten toxoplasmose der ratte, Zentralbl. Bakteriol. Orig. 165 (1956) 495–506.

[224] D. Ajzenberg, H. Yera, P. Marty, L. Paris, F. Dalle, J. Menotti, D. Aubert, J. Franck, M.H. Bessières, D. Quinio, H. Pelloux, Genotype of 88 *Toxoplasma gondii* isolates associated with toxoplasmosis in immunocompromised patients and correlation with clinical findings, J. Infect. Dis. 199 (8) (2009) 1155–1167.

[225] M.V. Rodrigues, A.L.G. Demarco, E.A. Donadi, L. Demarco, N. Deghaide, E. Romão, J.F. Figueiredo, HLA class I profile in patients with AIDS and *Toxoplasma gondii* chorioretinitis, Investig. Ophthalmol. Vis. Sci. 45 (13) (2004) 1672.

[226] C. Meenken, A. Rothova, L. De Waal, A. Van der Horst, B.J. Mesman, A. Kijlstra, HLA typing in congenital toxoplasmosis, Br. J. Ophthalmol. 79 (5) (1995) 494–497.

[227] M.C.d. Albuquerque, A.L.Q.d.C. Aleixo, E.I. Benchimol, A.C.C.S. Leandro, L.B.d. Neves, R.T. Vicente, M.D. Bonecini-Almeida, M.R. Amendoeira, The IFN-$^{3}$+ 874T/A gene polymorphism is associated with retinochoroiditis toxoplasmosis susceptibility, Mem. Inst. Oswaldo Cruz 104 (2009) 451–455.

[228] R.G. Peixe, M.S.B. Boechat, A.L.P. Rangel, R.F.G. Rosa, M.L. Petzl-Erler, L.M. Bahia-Oliveira, Single nucleotide polymorphisms in the interferon gamma gene are associated with distinct types of retinochoroidal scar lesions presumably caused by *Toxoplasma gondii* infection, Mem. Inst. Oswaldo Cruz 109 (2014) 99–107.

[229] C.A. Cordeiro, P.R. Moreira, M.S. Andrade, W.O. Dutra, W.R. Campos, F. Oréfice, A.L. Teixeira, Interleukin-10 gene polymorphism (− 1082G/A) is associated with toxoplasmic retinochoroiditis, Invest. Ophthalmol. Vis. Sci. 49 (5) (2008) 1979–1982.

[230] C.A. Cordeiro, P.R. Moreira, G.C. Costa, W.O. Dutra, W.R. Campos, F. Oréfice, A.L. Teixeira, Interleukin-1 gene polymorphisms and toxoplasmic retinochoroiditis, Mol. Vis. 14 (2008) 1845.

[231] C.A. Cordeiro, P.R. Moreira, T.F. Bessa, G.C. Costa, W.O. Dutra, W.R. Campos, F. Oréfice, L.H. Young, A.L. Teixeira, Interleukin-6 gene polymorphism (−174 G/C) is associated with toxoplasmic retinochoroiditis, Acta Ophthalmol. 91 (4) (2013) e311–e314.

[232] R. McLeod, K.M. Boyer, D. Lee, E. Mui, K. Wroblewski, T. Karrison, A.G. Noble, S. Withers, C.N. Swisher, P.T. Heydemann, M. Sautter, Prematurity and severity are associated with *Toxoplasma gondii* alleles (NCCCTS, 1981–2009), Clin. Infect. Dis. 54 (11) (2012) 1595–1605.

[233] J. Xiao, R.H. Yolken, Strain hypothesis of *Toxoplasma gondii* infection on the outcome of human diseases, Acta, Physiol. 213 (4) (2015) 828–845.

[234] J. Flegr, M. Novotná, J. Lindová, J. Havlicek, Neurophysiological effect of the Rh factor. Protective role of the RhD molecule against *Toxoplasma*-induced impairment of reaction times in women, Neuroendocrinol. Lett. 29 (4) (2008) 475.

[235] M. Novotná, J. Havlíček, A.P. Smith, P. Kolbeková, A. Skallová, J. Klose, Z. Gašová, M. Písačka, M. Sechovská, J. Flegr, *Toxoplasma* and reaction time: role of toxoplasmosis in the origin, preservation and geographical distribution of Rh blood group polymorphism, Parasitology 135 (11) (2008) 1253–1261.

[236] Š. Kaňková, J. Šulc, J. Flegr, Increased pregnancy weight gain in women with latent toxoplasmosis and RhD-positivity protection against this effect, Parasitology 137 (12) (2010) 1773–1779.

[237] T. Nayeri, M. Moosazadeh, A. Dalimi Asl, F. Ghaffarifar, S. Sarvi, A. Daryani, *Toxoplasma infection* and Rhesus blood group system: a systematic review and meta-analysis, PLoS One 18 (7) (2023) e0287992.

[238] J. Dubey, Bradyzoite-induced murine toxoplasmosis: stage conversion, pathogenesis, and tissue cyst formation in mice fed bradvzoites of-different strains of *Toxoplasma gondii*, J. Eukaryot. Microbiol. 44 (6) (1997) 592–602.

[239] J. Dubey, D. Lindsay, C. Speer, Structures of *Toxoplasma gondii* tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts, Clin. Microbiol. Rev. 11 (2) (1998) 267–299.

[240] U. Gross, W. Bohne, M. Soete, J. Dubremetz, Developmental differentiation between tachyzoites and bradyzoites of *Toxoplasma gondii*, Parasitol. Today 12 (1) (1996) 30–33.

[241] E.A. Wohlfert, I.J. Blader, E.H. Wilson, Brains and brawn: *Toxoplasma* infections of the central nervous system and skeletal muscle, Trends Parasitol. 33 (7) (2017) 519–531.

[242] U. Gross, M.C. Kempf, F. Seeber, C.G. Luder, R. Lugert, W. Bohne, Reactivation of chronic toxoplasmosis: is there a link to strain-specific differences in the parasite? Behring Inst. Mitt. (99) (1997) 97–106.

[243] M.D. da Silva, H.S. Barbosa, U. Groß, C.G. Lüder, Stress-related and spontaneous stage differentiation of *Toxoplasma gondii*, Mol. Biosyst. 4 (8) (2008) 824–834.

[244] W.J. Sullivan Jr., V. Jeffers, Mechanisms of *Toxoplasma gondii* persistence and latency, FEMS Microbiol. Rev. 36 (3) (2012) 717–733.

[245] W. Zhu, J. Li, F. Pappoe, J. Shen, L. Yu, Strategies developed by *Toxoplasma gondii* to survive in the host, Front. Microbiol. 10 (2019) 899.

[246] Y.W. Zhang, S.K. Halonen, Y.F. Ma, M. Wittner, L.M. Weiss, Initial characterization of CST1, a *Toxoplasma gondii* cyst wall glycoprotein, Infect. Immun. 69 (1) (2001) 501–507.

[247] K. Sethi, A. Rahman, B. Pelster, H. Brandis, Search for the presence of lectin-binding sites on *Toxoplasma gondii*, J. Parasitol. Res. (1977) 1076–1080.

[248] D. Ferguson, W. Hutchison, An ultrastructural study of the early development and tissue cyst formation of *Toxoplasma gondii* in the brains of mice, Parasitol. Res. 73 (1987) 483–491.

[249] T. Tomita, D.J. Bzik, Y.F. Ma, B.A. Fox, L.M. Markillie, R.C. Taylor, K. Kim, L.M. Weiss, The *Toxoplasma gondii* cyst wall protein CST1 is critical for cyst wall integrity and promotes bradyzoite persistence, PLoS Pathog. 9 (12) (2013) e1003823.

[250] T. Tomita, T. Sugi, R. Yakubu, V. Tu, Y. Ma, L.M. Weiss, Making home sweet and sturdy: *Toxoplasma gondii* ppGalNAc-Ts glycosylate in hierarchical order and confer cyst wall rigidity, mBio 8 (1) (2017) 10–128.

[251] S.F. Parmley, S. Yang, G. Harth, L.D. Sibley, A. Sucharczuk, J.S. Remington, Molecular characterization of a 65-kilodalton *Toxoplasma gondii* antigen expressed abundantly in the matrix of tissue cysts, Mol. Biochem. Parasitol. 66 (2) (1994) 283–296.

[252] D. Ferguson, Use of molecular and ultrastructural markers to evaluate stage conversion of *Toxoplasma gondii* in both the intermediate and definitive host, Int. J. Parasitol. 34 (3) (2004) 347–360.

[253] J.C. Boothroyd, M. Black, S. Bonnefoy, A. Hehl, L.J. Knoll, I.D. Manger, E. Ortega–Barria, S. Tomavo, Genetic and biochemical analysis of development in *Toxoplasma gondii*, Phil. Trans. Roy. Soc. Lond. B 352 (1359) (1997) 1347–1354.

[254] L.M. Weiss, K. Kim, The development and biology of bradyzoites of *Toxoplasma gondii*, Front. Biosci. 5 (2000) D391.

[255] C.E. Caffaro, A.A. Koshy, L. Liu, G.M. Zeiner, C.B. Hirschberg, J.C. Boothroyd, A nucleotide sugar transporter involved in glycosylation of the *Toxoplasma* tissue cyst wall is required for efficient persistence of bradyzoites, PLoS Pathog. 9 (5) (2013) e1003331.

[256] K.R. Buchholz, P.W. Bowyer, J.C. Boothroyd, Bradyzoite pseudokinase 1 is crucial for efficient oral infectivity of the *Toxoplasma gondii* tissue cyst, Eukaryot. Cell 12 (3) (2013) 399–410.

[257] M. Di Cristina, P. Del Porto, W. Buffolano, E. Beghetto, A. Spadoni, S. Guglietta, E. Piccolella, F. Felici, N. Gargano, The *Toxoplasma gondii* bradyzoite antigens BAG1 and MAG1 induce early humoral and cell-mediated immune responses upon human infection, Microb. Infect. 6 (2) (2004) 164–171.

[258] L. Holec, E. Hiszczynska-Sawicka, A. Gasior, A. Brillowska-Dabrowska, J. Kur, Use of MAG1 recombinant antigen for diagnosis of *Toxoplasma gondii* infection in humans, Clin. Vaccine Immunol. 14 (3) (2007) 220–225.

[259] A.S. Deshmukh, B.K. Hebbar, P. Mitra, S. Shinde, S. Chaudhari, S.B. Barbuddhe, Seroprevalence and risk factors of *Toxoplasma gondii* infection among veterinary personnel and abattoir workers in Central India, Parasitol. Int. 84 (2021) 102402.

[260] J. Dubey, Advances in the life cycle of *Toxoplasma gondii*, Int. J. Parasitol. 28 (7) (1998) 1019–1024.

[261] D. Ferguson, W. Hutchison, E. Pettersen, Tissue cyst rupture in mice chronically infected with *Toxoplasma gondii*: an immunocytochemical and ultrastructural study, Parasitol. Res. 75 (1989) 599–603.

[262] V. Jeffers, Z. Tampaki, K. Kim, W.J. Sullivan, A latent ability to persist: differentiation in *Toxoplasma gondii*, Cell. Mol. Life Sci. 75 (2018) 2355–2373.

[263] C.M. Cabral, S. Tuladhar, H.K. Dietrich, E. Nguyen, W.R. MacDonald, T. Trivedi, A. Devineni, A.A. Koshy, Neurons are the primary target cell for the brain-tropic intracellular parasite *Toxoplasma gondii*, PLoS Pathog. 12 (2) (2016) e1005447.

[264] A.A. Koshy, H.K. Dietrich, D.A. Christian, J.H. Melehani, A.J. Shastri, C.A. Hunter, J.C. Boothroyd, *Toxoplasma* co-opts host cells it does not invade, PLoS Pathog. 8 (7) (2012) e1002825.

[265] A. Vyas, S.-K. Kim, N. Giacomini, J.C. Boothroyd, R.M. Sapolsky, Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors, Proc. Natl. Acad. Sci. USA 104 (15) (2007) 6442–6447.

[266] J. Prandota, The importance of *Toxoplasma gondii* infection in diseases presenting with headaches. Headaches and aseptic meningitis may be manifestations of the Jarisch-Herxheimer reaction, Int. J. Neurosci. 119 (12) (2009) 2144–2182.

[267] A.L. Sutterland, G. Fond, A. Kuin, M.W. Koeter, R. Lutter, T. van Gool, R. Yolken, A. Szoke, M. Leboyer, L. De Haan, Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis, Acta Psychiatr. Scand. 132 (3) (2015) 161–179.

[268] E.F. Torrey, J.J. Bartko, Z.R. Lun, R.H. Yolken, Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis, Schizophr. Bull. 33 (3) (2007) 729–736.

[269] J. de Barros, I.G. Barbosa, H. Salem, N.P. Rocha, A. Kummer, O.O. Okusaga, J.C. Soares, A.L. Teixeira, Is there any association between *Toxoplasma gondii* infection and bipolar disorder? a systematic review and meta-analysis, J. Affect. Disord. 209 (2017) 59–65.

[270] T. Nayeri, S. Sarvi, A. Amouei, M. Moosazadeh, Z. Hosseininejad, S.A. Aghayan, A. Daryani, Relationship between toxoplasmosis and obsessive compulsive disorder: a systematic review and meta-analysis, PLoS Negl. Trop. Dis. 13 (4) (2019) e0007306.

[271] T. Nayeri, S. Sarvi, M. Moosazadeh, M. Sharif, S.A. Aghayan, A. Amouei, Z. Hosseininejad, A. Daryani, Is *Toxoplasma gondii* a potential risk factor for Alzheimer's disease? a systematic review and meta-analysis, Microb. Pathog. 137 (2019) 103751.

[272] M. Bayani, S.M. Riahi, N. Bazrafshan, H. Ray Gamble, A. Rostami, *Toxoplasma gondii* infection and risk of Parkinson and Alzheimer diseases: a systematic review and meta-analysis on observational studies, Acta Trop. 196 (2019) 165–171.

[273] T. Nayeri, S. Sarvi, M. Moosazadeh, Z. Hosseininejad, A. Amouei, A. Daryani, Association between *Toxoplasma gondii* infection and headache: a systematic review and meta-analysis, Infect. Disord.: Drug Targets 21 (4) (2021) 643–650.

[274] T. Nayeri, S. Sarvi, M. Moosazadeh, Z. Hosseininejad, M. Sharif, A. Amouei, A. Daryani, Relationship between toxoplasmosis and autism: a systematic review and meta-analysis, Microb. Pathog. 147 (2020) 104434.

[275] M. Sadeghi, S.M. Riahi, M. Mohammadi, V. Saber, S. Aghamolaie, S.A. Moghaddam, S. Aghaei, M. Javanian, H.R. Gamble, A. Rostami, An updated meta-analysis of the association between *Toxoplasma gondii* infection and risk of epilepsy, Trans. R. Soc. Trop. Med. Hyg. 113 (8) (2019) 453–462.

[276] E.B. Ngoungou, D. Bhalla, A. Nzoghe, M.L. Darde, P.M. Preux, Toxoplasmosis and epilepsy–systematic review and meta analysis, PLoS Negl. Trop. Dis. 9 (2) (2015) e0003525.

[277] A.L. Sutterland, A. Kuin, B. Kuiper, T. van Gool, M. Leboyer, G. Fond, L. de Haan, Driving us mad: the association of *Toxoplasma gondii* with suicide attempts and traffic accidents - a systematic review and meta-analysis, Psychol. Med. 49 (10) (2019) 1608–1623.

[278] A. Amouei, M. Moosazadeh, T. Nayeri, S. Sarvi, A. Mizani, M. Pourasghar, S. Hosseini Teshnizi, Z. Hosseininejad, S. Dodangeh, A. Pagheh, A.H. Pourmand, Evolutionary puzzle of *Toxoplasma gondii* with suicidal ideation and suicide attempts: an updated systematic review and meta-analysis, Transbound. Emerg. Dis. 67 (5) (2020) 1847–1860.

[279] L.A. Kirkman, L.M. Weiss, K. Kim, Cyclic nucleotide signaling in *Toxoplasma gondii* bradyzoite differentiation, Infect. Immun. 69 (1) (2001) 148–153.

[280] W. Bohne, J. Heesemann, U. Gross, Induction of bradyzoite-specific *Toxoplasma gondii* antigens in gamma interferon-treated mouse macrophages, Infect. Immun. 61 (3) (1993) 1141–1145.

[281] W. Bohne, J. Heesemann, U. Gross, Reduced replication of *Toxoplasma gondii* is necessary for induction of bradyzoite-specific antigens: a possible role for nitric oxide in triggering stage conversion, Infect. Immun. 62 (5) (1994) 1761–1767.

[282] M. Soete, D. Camus, J. Dubrametz, Experimental induction of bradyzoite-specific antigen expression and cyst formation by the RH strain of *Toxoplasma gondii in vitro*, Exp. Parasitol. 78 (4) (1994) 361–370.

[283] L.M. Weiss, D. Laplace, P.M. Takorian, H.B. Tanowitz, A. Cali, M. Wittner, A cell culture system for study of the development of *Toxoplasma gondii* bradyzoites, J. Eukaryot. Microbiol. 42 (2) (1995) 150–157.

[284] W. Bohne, M. Holpert, U. Gross, Stage differentiation of the protozoan parasite *Toxoplasma gondii*, Immunobiology 201 (2) (1999) 248–254.

[285] N.M. Silva, R.T. Gazzinelli, D.A. Silva, E.A. Ferro, L.H. Kasper, J.R. Mineo, Expression of *Toxoplasma gondii*-specific heat shock protein 70 during *in vivo* conversion of bradyzoites to tachyzoites, Infect. Immun. 66 (8) (1998) 3959–3963.

[286] L.M. Weiss, Y.F. Ma, P.M. Takvorian, H.B. Tanowitz, M. Wittner, Bradyzoite development in *Toxoplasma gondii* and the hsp70 stress response, Infect. Immun. 66 (7) (1998) 3295–3302.

[287] Y.W. Zhang, K. Kim, Y.F. Ma, M. Wittner, H.B. Tanowitz, L.M. Weiss, Disruption of the *Toxoplasma gondii* bradyzoite-specific gene BAG1 decreases *in vivo* cyst formation, Mol. Microbiol. 31 (2) (1999) 691–701.

[288] G. Kaul, H. Thippeswamy, Role of heat shock proteins in diseases and their therapeutic potential, Indian J. Microbiol. 51 (2011) 124–131.

[289] P. Mitra, A.S. Deshmukh, C. Choudhury, Molecular chaperone function of stress inducible Hsp70 is critical for intracellular multiplication of *Toxoplasma gondii*, Biochim. Biophys. Acta - Mol. Cell Res. 1868 (2) (2021) 118898.

[290] C. Jolly, R.I. Morimoto, Role of the heat shock response and molecular chaperones in oncogenesis and cell death, J. Natl. Cancer Inst. 92(19) 92000)1564-1572.

[291] K. Ashwinder, M.T. Kho, P.M. Chee, W.Z. Lim, I.K. Yap, S.B. Choi, W.K. Yam, Targeting heat shock proteins 60 and 70 of *Toxoplasma gondii* as a potential drug target: *In silico* approach, Interdiscip. sci. comput. life sci. 8 (2016) 374–387.

[292] C. Toursel, F. Dzierszinski, A. Bernigaud, M. Mortuaire, S. Tomavo, Molecular cloning, organellar targeting and developmental expression of mitochondrial chaperone HSP60 in *Toxoplasma gondii*, Mol. Biochem. Parasitol. 111 (2) (2000) 319–332.

[293] N. Yokoyama, M. Hirata, K. Ohtsuka, Y. Nishiyama, K. Fujii, M. Fujita, K. Kuzushima, T. Kiyono, T. Tsurumi, Co-expression of human chaperone Hsp70 and Hsdj or Hsp40 co-factor increases solubility of overexpressed target proteins in insect cells, Biochim. Biophys. Acta - Mol. Cell Res. 1493 (1–2) (2000) 119–124.

[294] M.R. Lacey, M.J. Brumlik, R.E. Yenni, M.E. Burow, T.J. Curiel, *Toxoplasma gondii* expresses two mitogen-activated protein kinase genes that represent distinct protozoan subfamilies, J. Mol. Evol. 64 (2007) 4–14.

[295] C.G. Lüder, W. Walter, B. Beuerle, M.J. Maeurer, U. Gross, *Toxoplasma gondii* down-regulates MHC class II gene expression and antigen presentation by murine macrophages via interference with nuclear translocation of STAT1α, Eur. J. Immunol. 31 (5) (2001) 1475–1484.

[296] B.A. Butcher, L. Kim, P.F. Johnson, E.Y. Denkers, *Toxoplasma gondii* tachyzoites inhibit proinflammatory cytokine induction in infected macrophages by preventing nuclear translocation of the transcription factor NF-κB, J. Immunol. 167 (4) (2001) 2193–2201.

[297] S. Shapira, O.S. Harb, J. Margarit, M. Matrajt, J. Han, A. Hoffmann, B. Freedman, M.J. May, D.S. Roos, C.A. Hunter, Initiation and termination of NF-κB signaling by the intracellular protozoan parasite *Toxoplasma gondii*, J. Cell Sci. 118 (15) (2005) 3501–3508.

[298] S. Shapira, K. Speirs, A. Gerstein, J. Caamano, C. Hunter, Suppression of NF-κB activation by infection with *Toxoplasma gondii*, J. Infect. Dis. 185 (Supplement_1) (2002) S66–S72.

[299] S.-K. Kim, A.E. Fouts, J.C. Boothroyd, *Toxoplasma gondii* dysregulates IFN-γ-inducible gene expression in human fibroblasts: insights from a genome-wide transcriptional profiling, J. Immunol. 178 (8) (2007) 5154–5165.

[300] S. Zimmermann, P.J. Murray, K. Heeg, A.H. Dalpke, Induction of suppressor of cytokine signaling-1 by *Toxoplasma gondii* contributes to immune evasion in macrophages by blocking IFN-γ signaling, J. Immunol. 176 (3) (2006) 1840–1847.

[301] P.J. Murray, The JAK-STAT signaling pathway: input and output integration, J. Immunol. 178 (5) (2007) 2623–2629.

[302] G. Reichmann, W. Walker, E.N. Villegas, L. Craig, G. Cai, J. Alexander, C.A. Hunter, The CD40/CD40 ligand interaction is required for resistance to toxoplasmic encephalitis, J. Immunol. 68 (3) (2000) 1312–1318.

[303] E.Y. Denkers, B.A. Butcher, L. Del Rio, L. Kim, Manipulation of mitogen-activated protein kinase/nuclear factor-κB-signaling cascades during intracellular *Toxoplasma gondii* infection, Immunol. Rev. 201 (1) (2004) 191–205.

[304] G.-D. Eom, K.-B. Chu, H.-J. Kang, M.-J. Kim, K.-W. Yoon, J. Mao, S.H. Lee, M.A. Ahmed, E.K. Moon, F.S. Quan, Protective mucosal and systemic immunity induced by virus-like particles expressing *Toxoplasma gondii* cyst wall protein, PLoS One 18 (4) (2023) e0283928.

[305] A.S. Deshmukh, R. Gurupwar, P. Mitra, K. Aswale, S. Shinde, S. Chaudhari, *Toxoplasma gondii* induces robust humoral immune response against cyst wall antigens in chronically infected animals and humans, Microb. Pathog. 152 (2021) 104643.

[306] S.-K. Kim, J.C. Boothroyd, Stage-specific expression of surface antigens by *Toxoplasma gondii* as a mechanism to facilitate parasite persistence, J. Immunol. 174 (12) (2005) 8038–8048.

[307] S.-K. Kim, A. Karasov, J.C. Boothroyd, Bradyzoite-specific surface antigen SRS9 plays a role in maintaining *Toxoplasma gondii* persistence in the brain and in host control of parasite replication in the intestine, Infect. Immun. 75 (4) (2007) 1626–1634.

[308] P. Waree, Toxoplasmosis: pathogenesis and immune response, Thammasat. Med. J. 8 (2008) 487–496.
[309] I. Yuliawati, N. Nasronudin, Pathogenesis, diagnostic and management of toxoplasmosis, IJTID 5 (4) (2015) 100–105.
[310] F.A. Jakobiec, J. Lefkowitch, D.M. Knowles II, B-and T-lymphocytes in ocular disease, Ophthalmology 91 (6) (1984) 635–654.
[311] F. Roberts, C.W. Roberts, D.J. Ferguson, R. McLeod, Inhibition of nitric oxide production exacerbates chronic ocular toxoplasmosis, Parasite, Immunol. 22 (1) (2000) 1–5.
[312] A. Sher, I. Oswald, S. Hieny, R. Gazzinelli, *Toxoplasma gondii* induces a T-independent IFN-gamma response in natural killer cells that requires both adherent accessory cells and tumor necrosis factor-alpha, J. Immunol. 150 (9) (1993) 3982–3989.
[313] J. Langermans, M. Van der Hulst, P. Nibbering, P. Hiemstra, L. Fransen, R. Van Furth, IFN-gamma-induced L-arginine-dependent toxoplasmastatic activity in murine peritoneal macrophages is mediated by endogenous tumor necrosis factor-alpha, J. Immunol. 148 (2) (1992) 568–574.
[314] N.E. Reiner, Altered cell signaling and mononuclear phagocyte deactivation during intracellular infection, Immunol. Today 15 (8) (1994) 374–381.
[315] R.G. Douglas, J.E. Bennett, G.L. Mandell, Principles and Practice of Infectious Diseases, John Wiley and Sons, New York, 1985.
[316] T.C. Jones, S. Yeh, J.G. Hirsch, The interaction between *Toxoplasma gondii* and mammalian cells: I. Mechanism of entry and intracellular fate of the parasite, J. Exp. Med. 136 (5) (1972) 1157–1172.
[317] C.B. Wilson, J.S. Remington, Activity of human blood leukocytes against *Toxoplasma gondii*, J. Infect. Dis. 140 (6) (1979) 890–895.
[318] C.B. Wilson, V. Tsai, J.S. Remington, Failure to trigger the oxidative metabolic burst by normal macrophages: possible mechanism for survival of intracellular pathogens, J. Exp. Med. 151 (2) (1980) 328–346.
[319] M.J. Miller, A. Wj, R. Js, Late parasitemia in asymptomatic acquired toxoplasmosis, Ann. Intern. Med. 71 (1) (1969) 139–145.
[320] J.S. Remington, M.L. Melton, L. Jacobs, Induced and spontaneous recurrent parasitemia in chronic infections with avirulent strains of *Toxoplasma gondii*, J. Immunol. 87 (5) (1961) 578–581.
[321] G. Huldt, Experimental toxoplasmosis. Parasitemia in Guinea-pigs, acta pathol, Microbiol. Scand. 58 (4) (1963) 457–470.
[322] R.T. Gazzinelli, S. Hieny, T.A. Wynn, S. Wolf, A. Sher, Interleukin 12 is required for the T-lymphocyte-independent induction of interferon gamma by an intracellular parasite and induces resistance in T-cell-deficient hosts, Proc. Natl. Acad. Sci. U.S.A. 90 (13) (1993) 6115–6119.
[323] A. Sher, Ignition of the type 1 response to intracellular infection by dendritic cell-derived interleukin-12, Eur. Cytokine Netw. 9 (3 Suppl) (1998) 65–68.
[324] P. Herion, R. Saavedra, Human T-cell clones as tools for the characterization of the cell-mediated immune response to *Toxoplasma gondii*, Res. Immunol. 144 (1) (1993) 48–51.
[325] I. Khan, K. Ely, L. Kasper, Antigen-specific CD8+ T cell clone protects against acute *Toxoplasma gondii* infection in mice, J. Immunol. 152 (4) (1994) 1856–1860.
[326] S. Hwang, I.A. Khan, CD8+ T cell immunity in an encephalitis model of *Toxoplasma gondii* infection. Seminars in immunopathology, Springer, 2015.
[327] G. Shearer, D. Bernstein, K. Tung, C. Via, R. Redfield, S. Salahuddin, R.C. Gallo, A model for the selective loss of major histocompatibility complex self-restricted T cell immune responses during the development of acquired immune deficiency syndrome (AIDS), J. Immunol. 137 (8) (1986) 2514–2521.
[328] I.A. Khan, C. Ouellette, K. Chen, M. Moretto, *Toxoplasma*: immunity and pathogenesis, Curr. Clin. Microbiol. Rep. 6 (2019) 44–50.
[329] I.A. Khan, T. Matsuura, L.H. Kasper, Interleukin-12 enhances murine survival against acute toxoplasmosis, Infect. Immun. 62 (5) (1994) 1639–1642.
[330] L.L. Johnson, SCID mouse models of acute and relapsing chronic *Toxoplasma gondii* infections, Infect. Immun. 60 (9) (1992) 3719–3724.
[331] C.A. Scanga, J. Aliberti, D. Jankovic, F. Tilloy, S. Bennouna, E.Y. Denkers, R. Medzhitov, A. Sher, Cutting edge: MyD88 is required for resistance to *Toxoplasma gondii* infection and regulates parasite-induced IL-12 production by dendritic cells, J. Immunol. 168 (12) (2002) 5997–6001.
[332] F. Yarovinsky, D. Zhang, J.F. Andersen, G.L. Bannenberg, C.N. Serhan, M.S. Hayden, S. Hieny, F.S. Sutterwala, R.A. Flavell, S. Ghosh, A. Sher, TLR11 activation of dendritic cells by a protozoan profilin-like protein, Science 308 (5728) (2005) 1626–1629.
[333] F. Debierre-Grockiego, M.A. Campos, N. Azzouz, J. Schmidt, U. Bieker, M.G. Resende, D.S. Mansur, R. Weingart, R.R. Schmidt, D.T. Golenbock, R.T. Gazzinelli, Activation of TLR2 and TLR4 by glycosylphosphatidylinositols derived from *Toxoplasma gondii*, J. Immunol. 179 (2) (2007) 1129–1137.
[334] O. Liesenfeld, J.C. Kosek, Y. Suzuki, Gamma interferon induces Fas-dependent apoptosis of Peyer's patch T cells in mice following peroral infection with *Toxoplasma gondii*, Infect. Immun. 65 (11) (1997) 4682–4689.
[335] G.S. Yap, A. Sher, Effector cells of both nonhemopoietic and hemopoietic origin are required for interferon (IFN)-γ–and tumor necrosis factor (TNF)-α–dependent host resistance to the intracellular pathogen, *Toxoplasma gondii*, J. Exp. Med. 189 (7) (1999) 1083–1092.
[336] Y.O. Zhao, A. Khaminets, J.P. Hunn, J.C. Howard, Disruption of the *Toxoplasma gondii* parasitophorous vacuole by IFNγ-inducible immunity-related GTPases (IRG proteins) triggers necrotic cell death, PLoS Pathog. 5 (2) (2009) e1000288.
[337] Y. Zhao, D.J. Ferguson, D.C. Wilson, J.C. Howard, L.D. Sibley, G.S. Yap, Virulent *Toxoplasma gondii* evade immunity-related GTPase-mediated parasite vacuole disruption within primed macrophages, J. Immunol. 182 (6) (2009) 3775–3781.
[338] T.M. Scharton-Kersten, G. Yap, J. Magram, A. Sher, Inducible nitric oxide is essential for host control of persistent but not acute infection with the intracellular pathogen *Toxoplasma gondii*, J. Exp. Med. 185 (7) (1997) 1261–1274.
[339] E. Pfefferkorn, Interferon gamma blocks the growth of *Toxoplasma gondii* in human fibroblasts by inducing the host cells to degrade tryptophan, Proc. Natl. Acad. Sci. U.S.A. 81 (3) (1984) 908–912.
[340] Y.M. Ling, M.H. Shaw, C. Ayala, I. Coppens, G.A. Taylor, D.J. Ferguson, G.S. Yap, Vacuolar and plasma membrane stripping and autophagic elimination of *Toxoplasma gondii* in primed effector macrophages, J. Exp. Med. 203 (9) (2006) 2063–2071.
[341] Y. Cheng, R.J. Colonno, F.H. Yin, Interferon induction of fibroblast proteins with guanylate binding activity, J. Biol. Chem. 258 (12) (1983) 7746–7750.
[342] U. Boehm, L. Guethlein, T. Klamp, K. Ozbek, A. Schaub, A. Fütterer, K. Pfeffer, J.C. Howard, Two families of GTPases dominate the complex cellular response to IFN-γ, J. Immunol. 161 (12) (1998) 6715–6723.
[343] D. Degrandi, E. Kravets, C. Konermann, C. Beuter-Gunia, V. Klümpers, S. Lahme, E. Rasch, A.K. Mausberg, S. Beer-Hammer, K. Pfeffer, Murine guanylate binding protein 2 (mGBP2) controls *Toxoplasma gondii* replication, Proc. Natl. Acad. Sci. U.S.A. 110 (1) (2013) 294–299.
[344] M. Yamamoto, M. Okuyama, J.S. Ma, T. Kimura, N. Kamiyama, H. Saiga, J. Ohshima, M. Sasai, H. Kayama, T. Okamoto, D.C. Huang, A cluster of interferon-γ-inducible p65 GTPases plays a critical role in host defense against *Toxoplasma gondii*, Immunity 37 (2) (2012) 302–313.
[345] C. Bekpen, J.P. Hunn, C. Rohde, I. Parvanova, L. Guethlein, D.M. Dunn, E. Glowalla, M. Leptin, J.C. Howard, The interferon-inducible p47 (IRG) GTPases in vertebrates: loss of the cell autonomous resistance mechanism in the human lineage, Genome Biol. 6 (11) (2005) 1–18.
[346] S. Virreira Winter, W. Niedelman, K.D. Jensen, E.E. Rosowski, L. Julien, E. Spooner, K. Caradonna, B.A. Burleigh, J.P. Saeij, H.L. Ploegh, E.M. Frickel, Determinants of GBP recruitment to *Toxoplasma gondii* vacuoles and the parasitic factors that control it, PLoS One 6 (9) (2011) e24434.
[347] A. Kresse, C. Konermann, D. Degrandi, C. Beuter-Gunia, J. Wuerthner, K. Pfeffer, S. Beer, Analyses of murine GBP homology clusters based on *in silico, in vitro* and *in vivo* studies, BMC Genom. 9 (1) (2008) 1–12 (Lacey).
[348] M. Koide, Y. Kawahara, T. Tsuda, M. Yokoyama, Cytokine-induced expression of an inducible type of nitric oxide synthase gene in cultured vascular smooth muscle cells, FEBS Lett. 318 (3) (1993) 213–217.
[349] C.C. Chao, W.R. Anderson, S. Hu, G. Gekker, A. Martella, P.K. Peterson, Activated microgila inhibit multiplication of *Toxoplasma gondii* via a nitric oxide mechanism, Clin. Immunol. Immunopathol. 67 (2) (1993) 178–183.
[350] C. Jun, S. Kim, C. Soh, S. Kang, H. Chung, Nitric oxide mediates the toxoplasmastatic activity of murine microglial cells *in vitro*, Immunol. Invest. 22 (8) (1993) 487–501.
[351] E. Petersen, B. Edvinsson, B. Lundgren, T. Benfield, B. Evengard, Diagnosis of pulmonary infection with *Toxoplasma gondii* in immunocompromised HIV-positive patients by real-time PCR, Eur. J. Clin. Microbiol. 25 (6) (2006) 401–404.
[[3][52] L. Gras, R. Gilbert, M. Wallon, F. Peyron, M. Cortina-Borja, Duration of the IgM response in women acquiring *Toxoplasma gondii* during pregnancy: implications for clinical practice and cross-sectional incidence studies, Epidemiol. Infect. 132 (3) (2004) 541–548.
[353] S. Hegab, S. Al-Mutawa, Immunopathogenesis of toxoplasmosis, Clin. Exp. Med. 3 (2) (2003) 84–105.
[354] G. Saadatnia, M. Golkar, A review on human toxoplasmosis, Scand. J. Infect. Dis. 44 (11) (2012) 805–814.

[355] M.J. Ronday, J.V. Ongkosuwito, A. Rothova, A. Kijlstra, Intraocular anti–*Toxoplasma gondii* IgA antibody production in patients with ocular toxoplasmosis, Am. J. Ophthalmol. 127 (3) (1999) 294–300.
[356] S. Singh, Mother-to-child transmission and diagnosis of *Toxoplasma gondii* infection during pregnancy, Indian J. Med. Microbiol. 21 (2) (2003) 69–76.
[357] B.S. Akoijam, S. Singh, S. Kapoor, Seroprevalence of *Toxoplasma* infection among primigravid women attending antenatal clinic at a secondary level hospital in North India, J. Indian Med. Assoc. 100 (10) (2002) 591–592, 4.
[358] S. Emna, A. Karim, K.C. Mohamed, B. Aïda, Difficulty in dating primary infections by *Toxoplasma gondii* in pregnant women in Tunisia, Tunis, Méd. 84 (2) (2006) 85–87.
[359] M.M. Reis, M.M. Tessaro, P.A. D'azevedo, *Toxoplasma*-IgM and IgG-avidity in single samples from areas with a high infection rate can determine the risk of mother-to-child transmission, Rev. Inst. Med. Trop. 48 (2006) 93–98.
[360] J.S. Remington, P. Thulliez, J.G. Montoya, Recent developments for diagnosis of toxoplasmosis, J. Clin. Microbiol. 42 (3) (2004) 941–945.
[361] M.M. Avelino, W.N. Amaral, I.M. Rodrigues, A.R. Rassi, M.B. Gomes, T.L. Costa, A.M. Castro, Congenital toxoplasmosis and prenatal care state programs, BMC Infect. Dis. 14 (1) (2014) 1–13.
[362] O. Liesenfeld, J.G. Montoya, S. Kinney, C. Press, J.S. Remington, Effect of testing for IgG avidity in the diagnosis of *Toxoplasma gondii* infection in pregnant women: experience in a US reference laboratory, J. Infect. Dis. 183 (8) (2001) 1248–1253.
[363] H. Yamada, A. Nishikawa, T. Yamamoto, Y. Mizue, T. Yamada, M. Morizane, S. Tairaku, J. Nishihira, Prospective study of congenital toxoplasmosis screening with use of IgG avidity and multiplex nested PCR methods, J. Clin. Microbiol. 49 (7) (2011) 2552–2556.
[364] W. Buffolano, M. Lappalainen, L. Hedman, F. Ciccimarra, M. Del Pezzo, R. Rescaldani, N. Gargano, K. Hedman, Delayed maturation of IgG avidity in congenital toxoplasmosis, Eur. J. Clin. Microbiol. Infect. Dis. 23 (2004) 825–830.
[365] J.S. Remington, J.O. Klein. Infectious diseases of the fetus and newborn infant, WB Saunders, London, 2001 (2001.
[366] K. Hedman, M. Lappalainen, I. Seppäiä, O. Mäkelä, Recent primary *Toxoplasma* infection indicated by a low avidity of specific IgG, J. Infect. Dis. 159 (4) (1989) 736–740.
[367] I. Roitt, Typ V–stimulatory hypersensitivity, in: I. Roitt (Ed.), Roitt's Essential Immunology, Blackwell Science, 1997, pp. 348–349.
[368] A. Hafizi, F. Modabber, Effect of cyclophosphamide on *Toxoplasma gondii* infection: reversal of the effect by passive immunization, Clin. Exp. Immunol. 33 (3) (1978) 389.
[369] S.G. Coutinho, M.A. Leite, M.R. Amendoeira, M.C. Marzochi, Concomitant cases of acquired toxoplasmosis in children of a single family: evidence of reinfection, J. Infect. Dis. 146 (1) (1982) 30–33.
[370] R. Norrby, T. Eilard, Recurrent toxoplasmosis, Scand. J. Infect. Dis. 8 (4) (1976) 275–276.
[371] R.C. da Silva, H. Langoni, *Toxoplasma gondii*: host-parasite interaction and behavior manipulation, Parasitol. Res. 105 (4) (2009) 893–898.
[372] S. Skariah, M.K. McIntyre, D.G. Mordue, *Toxoplasma gondii*: determinants of tachyzoite to bradyzoite conversion, Parasitol. Res. 107 (2010) 253–260.
[373] G.A. McConkey, H.L. Martin, G.C. Bristow, J.P. Webster, *Toxoplasma gondii* infection and behaviour - location, location, location? J. Exp. Biol. 216 (Pt1) (2013) 113–119.
[374] J. Gatkowska, M. Wieczorek, B. Dziadek, K. Dzitko, H. Dlugonska, Behavioral changes in mice caused by *Toxoplasma gondii* invasion of brain, Parasitol. Res. 111 (1) (2012) 53–58.
[375] J. Prandota, Autism spectrum disorders may be due to cerebral toxoplasmosis associated with chronic neuroinflammation causing persistent hypercytokinemia that resulted in an increased lipid peroxidation, oxidative stress, and depressed metabolism of endogenous and exogenous substances, Res. Autism Spectr. Disord 4 (2) (2010) 119–155.
[376] R.T. Gazzinelli, M. Wysocka, S. Hayashi, E.Y. Denkers, S. Hieny, P. Caspar, G. Trinchieri, A. Sher, Parasite-induced IL-12 stimulates early IFN-gamma synthesis and resistance during acute infection with *Toxoplasma gondii*, J. Immunol. 153 (6) (1994) 2533–2543.
[377] W. Däubener, C. Remscheid, S. Nockemann, K. Pilz, S. Seghrouchni, C. Mackenzie, U. Hadding, Anti-parasitic effector mechanisms in human brain tumor cells: role of interferon-γ and tumor necrosis factor-α, Eur. J. Immunol. 26 (2) (1996) 487–492.
[378] S. Fabiani, B. Pinto, U. Bonuccelli, F. Bruschi, Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases, J. Neurol. Sci. 351 (1–2) (2015) 3–8.
[379] T. Nayeri, S. Sarvi, A. Daryani, Toxoplasmosis: targeting neurotransmitter systems in psychiatric disorders, Metab. Brain Dis. (2021) 1–24.
[380] E. Haroon, C.L. Raison, A.H. Miller, Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior, Neuropsychopharmacology 37 (1) (2012) 137–162.
[381] N. Müller, M. Schwarz, Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission, Neurotox. Res. 10 (2) (2006) 131–148.
[382] L. Tan, J.T. Yu, L. Tan, The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations, J. Neurol. Sci. 323 (1–2) (2012) 1–8.
[383] W. Daubener, B. Spors, C. Hucke, R.d. Adam, M. Stins, K.S. Kim, H. Schroten, Restriction of *Toxoplasma gondii* growth in human brain microvascular endothelial cells by activation of indoleamine 2, 3-dioxygenase, Infect. Immun. 69 (10) (2001) 6527–6531.
[384] A.H. Miller, V. Maletic, C.L. Raison, Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression, Biol. Psychiatry. 65 (9) (2009) 732–741.
[385] A. Parlog, D. Schluter, I.R. Dunay, *Toxoplasma gondii*-induced neuronal alterations, Parasite, Immunol. 37 (3) (2015) 159–170.
[386] R. Schwarcz, J.P. Bruno, P.J. Muchowski, H.Q. Wu, Kynurenines in the mammalian brain: when physiology meets pathology, Nat. Rev. Neurosci. 13 (7) (2012) 465–477.
[387] E. Gulaj, K. Pawlak, B. Bien, D. Pawlak, Kynurenine and its metabolites in Alzheimer's disease patients, Adv. Med. Sci. 55 (2) (2010) 204–211.
[388] J. Steiner, M. Walter, T. Gos, G.J. Guillemin, H.G. Bernstein, Z. Sarnyai, C. Mawrin, R. Brisch, H. Bielau, L.M. zu Schwabedissen, B. Bogerts, Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J. Neuroinflammation 8 (1) (2011) 1–9.
[389] M.T.S. AL-Hadad, R.A. Kadhim, A.F. Al-Rubaye, Effect of chronic toxoplasmosis on levels of some neurotransmitters (Dopamine, Adrenaline, and Noradrenaline) in human serum, Int. J. Pharm. Sci. Res. 11 (2) (2019) 402–405.
[390] P. Guidetti, G.P. Bates, R.K. Graham, M.R. Hayden, B.R. Leavitt, M.E. MacDonald, E.J. Slow, V.C. Wheeler, B. Woodman, R. Schwarcz, Elevated brain 3-hydroxykynurenine and quinolinate levels in Huntington disease mice, Neurobiol. Dis. 23 (1) (2006) 190–197.
[391] A.W. Zimmerman, H. Jyonouchi, A.M. Comi, S.L. Connors, S. Milstien, A. Varsou, M.P. Heyes, Cerebrospinal fluid and serum markers of inflammation in autism, Pediatr. Neurol. 33 (3) (2005) 195–201.
[392] S. Erhardt, C.K. Lim, K.R. Linderholm, S. Janelidze, D. Lindqvist, M. Samuelsson, K. Lundberg, T.T. Postolache, L. Träskman-Bendz, G.J. Guillemin, L. Brundin, Connecting inflammation with glutamate agonism in suicidality, Neuropsychopharmacology 38 (5) (2013) 743–752.
[393] G.J. Guillemin, G. Smythe, O. Takikawa, B.J. Brew, Expression of indoleamine 2, 3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons, Glia 49 (1) (2005) 15–23.
[394] R. Schwarcz, R. Pellicciari, Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities, J. Pharmacol. Exp. Ther. 303 (1) (2002) 1–10.
[395] D.C. Javitt, Current and emergent treatments for symptoms and neurocognitive impairment in schizophrenia, Curr. Treat. 1 (2) (2014) 107–120.
[396] T. Papouin, J.M. Dunphy, M. Tolman, K.T. Dineley, P.G. Haydon, Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness, Neuron 94 (4) (2017) 840–854. e7.
[397] G. Lucchese, From toxoplasmosis to schizophrenia via NMDA dysfunction: peptide overlap between *Toxoplasma gondii* and N-methyl-d-aspartate receptors as a potential mechanistic link, Front. Psychiatry. 8 (2017) 37.
[398] T. Wang, Z.h. Tang, J.f. Li, X.n. Li, X. Wang, Z.j. Zhao, A potential association between *Toxoplasma gondii* infection and schizophrenia in mouse models, Exp. Parasitol. 135 (3) (2013) 497–502.

[399] H.M. Elsheikha, X.Q. Zhu, *Toxoplasma gondii* infection and schizophrenia: an inter-kingdom communication perspective, Curr. Opin. Infect. Dis. 29 (3) (2016) 311–318.
[400] S. Beggiato, T. Antonelli, M.C. Tomasini, S. Tanganelli, K. Fuxe, R. Schwarcz, L. Ferraro, Kynurenic acid, by targeting α7 nicotinic acetylcholine receptors, modulates extracellular GABA levels in the rat striatum *in vivo*, Eur. J. Neurosci. 37 (9) (2013) 1470–1477.
[401] M. Laruelle, A. Abi-Dargham, C.H. Van Dyck, R. Gil, C.D. D'Souza, J. Erdos, E. McCance, W. Rosenblatt, C. Fingado, S.S. Zoghbi, R.M. Baldwin, Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects, Proc. Natl. Acad. Sci. U.S.A. 93 (17) (1996) 9235–9240.
[402] J. Xiao, Y. Li, E. Prandovszky, G. Kannan, R.P. Viscidi, M.V. Pletnikov, R.H. Yolken, Behavioral abnormalities in a mouse model of chronic toxoplasmosis are associated with MAG1 antibody levels and cyst burden, PLOS Negl. Trop. Dis. 10 (4) (2016) e0004674.
[403] I. Wonodi, R. Schwarcz, Cortical kynurenine pathway metabolism: a novel target for cognitive enhancement in schizophrenia, Schizophr. Bull. 36 (2) (2010) 211–218.
[404] L. Nilsson, K. Linderholm, G. Engberg, L. Paulson, K. Blennow, L. Lindström, C. Nordin, A. Karanti, P. Persson, S. Erhardt, Elevated levels of kynurenic acid in the cerebrospinal fluid of male patients with schizophrenia, Schizophr. Res. 80 (2–3) (2005) 315–322.
[405] R. Schwarcz, C.A. Hunter, *Toxoplasma gondii* and schizophrenia: linkage through astrocyte-derived kynurenic acid? Schizophr. Bull. 33 (3) (2007) 652–653.
[406] O.Y. Kusbeci, O. Miman, M. Yaman, O.C. Aktepe, S. Yazar, Could *Toxoplasma gondii* have any role in Alzheimer disease? Alzheimer Dis. Assoc. Disord. 25 (1) (2011) 1–3.
[407] P.C. Hsu, M. Groer, T. Beckie, New findings: depression, suicide, and *Toxoplasma gondii* infection, J. Am. Assoc. Nurse Pract. 26 (11) (2014) 629–637.
[408] F. Yarovinsky, Innate immunity to *Toxoplasma gondii* infection, Nat. Rev. Immunol. 14 (2) (2014) 109–121.
[409] C. Rozenfeld, R. Martinez, S. Seabra, C. Sant'Anna, J.G.R. Gonçalves, M. Bozza, V. Moura-Neto, W. De Souza, *Toxoplasma gondii* prevents neuron degeneration by interferon-γ-activated microglia in a mechanism involving inhibition of inducible nitric oxide synthase and transforming growth factor-β1 production by infected microglia, Am. J. Pathol. 167 (4) (2005) 1021–1031.
[410] L. Möhle, N. Israel, K. Paarmann, M. Krohn, S. Pietkiewicz, A. Müller, In Lavrik, J.S. Buguliskis, B.H. Schott, D. Schlüter, E.D. Gundelfinger, Chronic *Toxoplasma gondii* infection enhances β-amyloid phagocytosis and clearance by recruited monocytes, Acta Neuropathol. Commun 4 (1) (2016) 1–19.
[411] Q. Sa, A. Tiwari, E. Ochiai, J. Mullins, Y. Suzuki, Inducible nitric oxide synthase in innate immune cells is important for restricting cyst formation of *Toxoplasma gondii* in the brain but not required for the protective immune process to remove the cysts, Microb. Infect. 20 (4) (2018) 261–266.
[412] I.A. Khan, J.D. Schwartzman, T. Matsuura, L.H. Kasper, A dichotomous role for nitric oxide during acute *Toxoplasma gondii* infection in mice, Proc. Natl. Acad. Sci. U.S.A. 94 (25) (1997) 13955–13960.
[413] S. Fujigaki, K. Saito, M. Takemura, N. Maekawa, Y. Yamada, H. Wada, M. Seishima, L-tryptophan-L-kynurenine pathway metabolism accelerated by *Toxoplasma gondii* infection is abolished in gamma interferon-gene-deficient mice: cross-regulation between inducible nitric oxide synthase and indoleamine-2, 3-dioxygenase, Infect. Immun. 70 (2) (2002) 779–786.
[414] A.C. Campos, G.N. Vaz, V.M. Saito, A.L. Teixeira, Further evidence for the role of interferon-gamma on anxiety-and depressive-like behaviors: involvement of hippocampal neurogenesis and NGF production, Neurosci. Lett. 578 (2014) 100–105.
[415] G. Neurauter, K. Schrocksnadel, S. Scholl-Burgi, B. Sperner-Unterweger, C. Schubert, M. Ledochowski, D. Fuchs, Chronic immune stimulation correlates with reduced phenylalanine turnover, Curr. Drug Metabol. 9 (7) (2008) 622–627.
[416] T. Kitagami, K. Yamada, H. Miura, R. Hashimoto, T. Nabeshima, T. Ohta, Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: role of nitric oxide as a signal crossing the blood–brain barrier, Brain Res. 978 (1–2) (2003) 104–114.
[417] C.B. Zhu, A.M. Carneiro, W.R. Dostmann, W.A. Hewlett, R.D. Blakely, p38 MAPK activation elevates serotonin transport activity via a trafficking-independent, protein phosphatase 2A-dependent process, J. Biol. Chem. 280 (16) (2005) 15649–15658.
[418] C.B. Zhu, K.M. Lindler, A.W. Owens, L.C. Daws, R.D. Blakely, W.A. Hewlett, Interleukin-1 receptor activation by systemic lipopolysaccharide induces behavioral despair linked to MAPK regulation of CNS serotonin transporters, Neuropsychopharmacology 35 (13) (2010) 2510–2520.
[419] R. Cáceda, Suicidal behavior: risk and protective factors, Rev. Bras. de Neurol. e Psiquiatr. 77 (1) (2014) 3–18.
[420] P. Courtet, F. Jollant, C. Buresi, D. Castelnau, D. Mouthon, A. Malafosse, The monoamine oxidase A gene may influence the means used in suicide attempts, Psychiatr. Genet. 15 (3) (2005) 189–193.
[421] J. Grimsby, K. Chen, L.J. Wang, N.C. Lan, J.C. Shih, Human monoamine oxidase A and B genes exhibit identical exon-intron organization, Proc. Natl. Acad. Sci. U.S.A. 88 (9) (1991) 3637–3641.
[422] J. Xiao, Y. Li, E. Prandovszky, S.S. Karuppagounder, C.C. Talbot Jr., V.L. Dawson, T.M. Dawson, R.H. Yolken, MicroRNA-132 dysregulation in *Toxoplasma gondii* infection has implications for dopamine signaling pathway, Neuroscience 268 (2014) 128–138.
[423] R.J. Wyatt, D.L. Murphy, Low platelet monoamine oxidase activity and schizophrenia, Schizophr. Bull. 2 (1) (1976) 77.
[424] K. White, J. Shih, T. Fong, H. Young, R. Gelfand, J. Boyd, G. Simpson, R.B. Sloane, Elevated platelet monoamine oxidase activity in patients with nonendogenous depression, Am. J. Psychiatr. 137 (10) (1980) 1258–1259.
[425] J.L. Sullivan, J. Cavenar, A. Maltbie, P. Lister, W. Zung, Familial biochemical and clinical correlates of alcoholics with low platelet monoamine oxidase activity, Biol. Psychiatry. 14 (2) (1979) 385–394.
[426] J.M. Brooks, G.L. Carrillo, J. Su, D.S. Lindsay, M.A. Fox, I.J. Blader, *Toxoplasma gondii* infections alter GABAergic synapses and signaling in the central nervous system, mBio 6 (6) (2015) e01428, 15.
[427] S. Tyebji, S. Seizova, A.J. Hannan, C.J. Tonkin, Toxoplasmosis: a pathway to neuropsychiatric disorders, Neurosci. Biobehav. Rev. 96 (2019) 72–92.
[428] M.J. Xu, D.H. Zhou, A.J. Nisbet, S.Y. Huang, Y.F. Fan, X.Q. Zhu, Characterization of mouse brain microRNAs after infection with cyst-forming *Toxoplasma gondii*, Parasites Vectors 6 (1) (2013) 1–7.
[429] D. Yang, T. Li, Y. Wang, Y. Tang, H. Cui, Y. Tang, X. Zhang, D. Chen, N. Shen, W. Le, miR-132 regulates the differentiation of dopamine neurons by directly targeting Nurr1 expression, J. Cell Sci. 125 (7) (2012) 1673–1682.
[430] A. Wanet, A. Tacheny, T. Arnould, P. Renard, miR-212/132 expression and functions: within and beyond the neuronal compartment, Nucleic Acids Res. 40 (11) (2012) 4742–4753.
[431] D. Hinze-Selch, *Toxoplasma gondii* infection and neuropsychiatric disease: current insight, Rep. Parasitol. 4 (2015) 43–51.
[432] B.H. Miller, Z. Zeier, L. Xi, T.A. Lanz, S. Deng, J. Strathmann, D. Willoughby, P.J. Kenny, J.D. Elsworth, M.S. Lawrence, R.H. Roth, MicroRNA-132 dysregulation in schizophrenia has implications for both neurodevelopment and adult brain function, Proc. Natl. Acad. Sci. U.S.A. 109 (8) (2012) 3125–3130.
[433] Y. Sukthana, Toxoplasmosis: beyond animals to humans, Trends Parasitol. 22 (3) (2006) 137–142.
[434] O. Villard, B. Cimon, C. L'ollivier, H. Fricker-Hidalgo, N. Godineau, S. Houze, L. Paris, H. Pelloux, I. Villena, E. Candolfi, Serological diagnosis of *Toxoplasma gondii* infection: recommendations from the French national reference center for toxoplasmosis, Diagn. Microbiol. Infect. Dis. 84 (1) (2016) 22–33.
[435] Y. Naot, D.R. Guptill, J.S. Remington, Duration of IgM antibodies to *Toxoplasma gondii* after acute acquired toxoplasmosis, J. Infect. Dis. (1982) 770.
[436] K. Janitschke, U. Senk, H. Hoffmann, S. Dempe, Detection of *toxoplasma*-IgG-antibodies and IgM-antibodies by enzyme-linked immunosorbent-assay, Z. Geburtshilfe Perinatol. 193 (5) (1989) 203–207.
[437] E. Rorman, C.S. Zamir, I. Rilkis, H. Ben-David, Congenital toxoplasmosis—prenatal aspects of *Toxoplasma gondii* infection, Reprod. Toxicol. 21 (4) (2006) 458–472.
[438] F. Robert-Gangneux, M.L. Dardé, Epidemiology of and diagnostic strategies for toxoplasmosis, Clin. Microbiol. Rev. 25 (2) (2012) 264–296.
[439] M. Bessieres, C. Roques, A. Berrebi, V. Barre, M. Cazaux, J. Seguela, IgA antibody response during acquired and congenital toxoplasmosis, J. Clin. Pathol. 45 (7) (1992) 605–608.
[440] J. Murat, A. Souvignet, H. Fricker-Hidalgo, M. Brenier-Pinchart, C. Bost-Bru, H. Pelloux, Assessment of the IgA immunosorbent agglutination assay for the diagnosis of congenital toxoplasmosis on a series of 145 toxoplasmic seroconversions, Clin. Vaccine Immunol. 22 (4) (2015) 456–458.
[441] P. Stepick-Biek, P. Thulliez, F.G. Araujo, J.S. Remington, 19A Antibodies for diagnosis of acute congenital and acquired toxoplasmosis, J. Infect. Dis. 162 (1) (1990) 270–273.

[442] J. Stavnezer, Regulation of antibody production and class switching by TGF-beta, J. Immunol. 155 (4) (1995) 1647–1651.
[443] C. Hennequin, P. Dureau, L. N'guyen, P. Thulliez, B. Gagelin, J.L. Dufier, Congenital toxoplasmosis acquired from an immune woman, J. Pediatr. Infect. Dis. 16 (1) (1997) 75–77.
[444] B. Fortier, E. Aissi, F. Ajana, P. Dieusart, P. Denis, E. Martin de Lassalle, Spontaneous abortion and reinfection by *Toxoplasma gondii*, Lancet 338 (8764) (1991).
[445] J. Pinon, D. Toubas, C. Marx, G. Mougeot, A. Bonnin, A. Bonhomme, M. Villaume, F. Foudrinier, H. Lepan, Detection of specific immunoglobulin E in patients with toxoplasmosis, J. Clin. Microbiol. 28 (8) (1990) 1739–1743.
[446] F. Foudrinier, I. Villena, R. Jaussaud, D. Aubert, C. Chemla, F. Martinot, J.M. Pinon, Clinical value of specific immunoglobulin E detection by enzyme-linked immunosorbent assay in cases of acquired and congenital toxoplasmosis, J. Clin. Microbiol. 41 (4) (2003) 1681–1686.
[447] P.R. Torgerson, P. Mastroiacovo, The global burden of congenital toxoplasmosis: a systematic review, Bull. World Health Organ. 91 (2013) 501–508.
[448] W. Wujcicka, J. Wilczyński, D. Nowakowska, Do the placental barrier, parasite genotype and Toll-like receptor polymorphisms contribute to the course of primary infection with various *Toxoplasma gondii* genotypes in pregnant women? Eur. J. Clin. Microbiol. 33 (5) (2014) 703–709.
[449] K. Rezende-Oliveira, N. Silva, J. Mineo, V.R. Junior, Cytokines and chemokines production by mononuclear cells from parturient women after stimulation with live *Toxoplasma gondii*, Placenta 33 (9) (2012) 682–687.
[450] M.R. Du, S.C. Wang, D.J. Li, The integrative roles of chemokines at the maternal–fetal interface in early pregnancy, Cell. Mol. Immunol. 11 (5) (2014) 438–448.
[451] V. Abrahams, G. Mor, Toll-like receptors and their role in the trophoblast, Placenta 26 (7) (2005) 540–547.
[452] V.M. Abrahams, S.L. Straszewski-Chavez, S. Guller, G. Mor, First trimester trophoblast cells secrete Fas ligand which induces immune cell apoptosis, Mol. Hum. Reprod. 10 (1) (2004) 55–63.
[453] K. Koga, I. Cardenas, P. Aldo, V.M. Abrahams, B. Peng, S. Fill, R. Romero, G. Mor, Activation of TLR3 in the trophoblast is associated with preterm delivery, Am. J. Reprod. Immunol. 61 (3) (2009) 196–212.
[454] L. Krishnan, T. Nguyen, S. McComb, From mice to women: the conundrum of immunity to infection during pregnancy, J. Reprod. Immunol. 97 (1) (2013) 62–73.
[455] A. Schumacher, S.D. Costa, A.C. Zenclussen, Endocrine factors modulating immune responses in pregnancy, Front. Immunol. 5 (2014) 196.
[456] M. Halasz, J. Szekeres-Bartho, The role of progesterone in implantation and trophoblast invasion, J. Reprod. Immunol. 97 (1) (2013) 43–50.
[457] M.L. Wolfson, J.A. Schander, M.V. Bariani, F. Correa, A.M. Franchi, Progesterone modulates the LPS-induced nitric oxide production by a progesterone-receptor independent mechanism, Eur. J. Pharmacol. 769 (2015) 110–116.
[458] D. Lissauer, S.A. Eldershaw, C.F. Inman, A. Coomarasamy, P.A. Moss, M.D. Kilby, Progesterone promotes maternal–fetal tolerance by reducing human maternal T-cell polyfunctionality and inducing a specific cytokine profile, Eur. J. Immunol. 45 (10) (2015) 2858–2872.
[459] M.d.l.L. Galvan-Ramirez, A.F. Gutiérrez-Maldonado, F. Verduzco-Grijalva, J.M.D. Jiménez, The role of hormones on *Toxoplasma gondii* infection: a systematic review, Front. Microbiol. 5 (2014) 503.
[460] J. Szekeres-Bartho, The role of progesterone in feto-maternal immunological cross talk, Med. Princ. Pract. 27 (4) (2018) 301–307.
[461] M. Borges, T. Magalhães Silva, C. Brito, N. Teixeira, C.W. Roberts, How does toxoplasmosis affect the maternal-foetal immune interface and pregnancy? Parasite, Immunol. 41 (3) (2019) e12606.
[462] F.M. Menzies, F.L. Henriquez, J. Alexander, C.W. Roberts, Selective inhibition and augmentation of alternative macrophage activation by progesterone, Immunology 134 (3) (2011) 281–291.
[463] Y. Maeda, H. Ohtsuka, M. Tomioka, M. Oikawa, Effect of progesterone on Th1/Th2/Th17 and regulatory T cell-related genes in peripheral blood mononuclear cells during pregnancy in cows, Vet. Res. Commun. 37 (1) (2013) 43–49.
[464] A. Abdoli, M. Pirestani, Are pregnant women with chronic helminth infections more susceptible to congenital infections? Front. Immunol. 5 (2014) 53.
[465] G. Entrican, Immune regulation during pregnancy and host-pathogen interactions in infectious abortion, J. Comp. Pathol. 126 (2–3) (2002) 79–94.
[466] C.W. Roberts, W. Walker, J. Alexander, Sex-associated hormones and immunity to protozoan parasites, Clin. Microbiol. Rev. 14 (3) (2001) 476–488.
[467] L.E. Bosch-Driessen, T.T. Berendschot, J.V. Ongkosuwito, A. Rothova, Ocular toxoplasmosis: clinical features and prognosis of 154 patients, Ophthalmology 109 (5) (2002) 869–878.
[468] S.M. Lachenmaier, M.A. Deli, M. Meissner, O. Liesenfeld, Intracellular transport of *Toxoplasma gondii* through the blood–brain barrier, J. Neuroimmunol. 232 (1–2) (2011) 119–130.
[469] N. Courret, S. Darche, P. Sonigo, G. Milon, D. Buzoni-Gâtel, I. Tardieux, CD11c-and CD11b-expressing mouse leukocytes transport single *Toxoplasma gondii* tachyzoites to the brain, Blood 107 (1) (2006) 309–316.
[470] A. Sauer, E. Rochet, I. Lahmar, J. Brunet, M. Sabou, T. Bourcier, E. Candolfi, A.W. Pfaff, The local immune response to intraocular *Toxoplasma* re-challenge: less pathology and better parasite control through Treg/Th1/Th2 induction, Int. J. Parasitol. 43 (9) (2013) 721–728.
[471] R. Guiton, V. Vasseur, S. Charron, M. Torres Arias, N. Van Langendonck, D. Buzoni-Gatel, B. Ryffel, I. Dimier-Poisson, Interleukin 17 receptor signaling is deleterious during *Toxoplasma gondii* infection in susceptible BL6 mice, J. Infect. Dis. 202 (2010) 427–435.
[472] W. O'Connor Jr., M. Kamanaka, C.J. Booth, T. Town, S. Nakae, Y. Iwakura, J.K. Kolls, R.A. Flavell, A protective function for interleukin 17A in T cell–mediated intestinal inflammation, Nat. Immunol. 10 (6) (2009) 603–609.
[473] P.D. Glasner, C. Silveira, D. Kruszon-Moran, M.C. Martins, M. Burnier Jr., S. Silveira, M.E. Camargo, R.B. Nussenblatt, R.A. Kaslow, R. Belfort Jr., An unusually high prevalence of ocular toxoplasmosis in southern Brazil, Am. J. Ophthalmol. 114 (2) (1992) 136–144.
[474] C. Silveira, R. Belfort Jr., C. Muccioli, M.T. Abreu, M.C. Martins, C. Victora, B. Robert, A follow-up study of *Toxoplasma gondii* infection in southern Brazil, Am. J. Ophthalmol. 131 (3) (2001) 351–354.
[475] L.H. Bosch-Driessen, S. Karimi, J.S. Stilma, A. Rothova, Retinal detachment in ocular toxoplasmosis, Ophthalmology 107 (1) (2000) 36–40.
[476] M.S. Hu, J.D. Schwartzman, A.C. Lepage, I.A. Khan, L.H. Kasper, Experimental ocular toxoplasmosis induced in naive and preinfected mice by intracameral inoculation, Ocul. Immunol. Inflamm. 7 (1) (1999) 17–26.
[477] F. Lu, S. Huang, L.H. Kasper, Interleukin-10 and pathogenesis of murine ocular toxoplasmosis, Infect. Immun. 71 (12) (2003) 7159–7163.
[478] F. Roberts, R. McLeod, Pathogenesis of toxoplasmic retinochoroiditis, Parasitol. Today 15 (2) (1999) 51–57.
[479] E. Su, A. Honda, P.A. Latkany, Ocular disease due to *Toxoplasma gondii*, Toxoplasma gondii (2014) 161–192.
[480] U. Pleyer, D. Schlüter, M. Mänz, Ocular toxoplasmosis: recent aspects of pathophysiology and clinical implications, Ophthalmic Res. 52 (3) (2014) 116–123.
[481] M.H. Shaw, T. Reimer, C. Sánchez-Valdepeñas, N. Warner, Y.G. Kim, M. Fresno, G. Nuñez, T cell–intrinsic role of Nod2 in promoting type 1 immunity to *Toxoplasma gondii*, Nat. Immunol. 10 (12) (2009) 1267–1274.
[482] A.L. Peixoto-Rangel, E.N. Miller, L. Castellucci, S.E. Jamieson, R.G. Peixe, L.d.S. Elias, R. Correa-Oliveira, L.M. Bahia-Oliveira, J.M. Blackwell, Candidate gene analysis of ocular toxoplasmosis in Brazil: evidence for a role for toll-like receptor 9 (TLR9), Mem. Inst. Oswaldo Cruz 104 (2009) 1187–1190.
[483] S.E. Jamieson, A.L. Peixoto-Rangel, A.C. Hargrave, L.-A. de Roubaix, E.J. Mui, N.R. Boulter, E.N. Miller, S.J. Fuller, J.S. Wiley, L. Castellucci, K. Boyer, Evidence for associations between the purinergic receptor P2X7 (P2RX7) and toxoplasmosis, Gene Immun. 11 (5) (2010) 374–383.
[484] C.M. Miller, N.R. Boulter, S.J. Fuller, A.M. Zakrzewski, M.P. Lees, B.M. Saunders, J.S. Wiley, N.C. Smith, The role of the P2X7 receptor in infectious diseases, PLoS Pathog. 7 (11) (2011) e1002212.
[485] F. Belanger, F. Derouin, L. Grangeot-Keros, L. Meyer, Incidence and risk factors of toxoplasmosis in a cohort of human immunodeficiency virus-infected patients, 1988–1995, Clin. Infect. Dis. 28 (3) (1999) 575–581.
[486] Y. Suzuki, Host resistance in the brain against *Toxoplasma gondii*, J. Infect. Dis. 185 (Supplement_1) (2002) S58–S65.
[487] B.J. Luft, J.S. Remington, Toxoplasmic encephalitis in AIDS, Clin. Infect. Dis. 15 (2) (1992) 211–222.
[488] G. Cuervo, A.F. Simonetti, O. Alegre, J.C. Sanchez-Salado, D. Podzamczer, *Toxoplasma* myocarditis: a rare but serious complication in an HIV-infected late presenter, AIDS 30 (14) (2016) 2253–2254.
[489] G.N. Holland, R.E. Engstrom Jr., B.J. Glasgow, B.B. Berger, S.A. Daniels, Y. Sidikaro, J.A. Harmon, D.H. Fischer, D.S. Boyer, N.A. Rao, R.C. Eagle Jr., Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome, Am. J. Ophthalmol. 106 (6) (1988) 653–667.

[490] Y. Suzuki, S. Rani, O. Liesenfeld, T. Kojima, S. Lim, T.A. Nguyen, S.A. Dalrymple, R. Murray, J.S. Remington, Impaired resistance to the development of toxoplasmic encephalitis in interleukin-6-deficient mice, Infect. Immun. 65 (6) (1997) 2339–2345.
[491] B. Wong, Parasitic diseases in immunocompromised hosts, Am. J. Med. 76 (3) (1984) 479–486.
[492] J.S. Stumhofer, A. Laurence, E.H. Wilson, E. Huang, C.M. Tato, L.M. Johnson, A.V. Villarino, Q. Huang, A. Yoshimura, D. Sehy, C.J. Saris, Interleukin 27 negatively regulates the development of interleukin 17–producing T helper cells during chronic inflammation of the central nervous system, Nat. Immunol. 7 (9) (2006) 937–945.
[493] Y. Suzuki, Q. Yang, F.K. Conley, J.S. Abrams, J.S. Remington, Antibody against interleukin-6 reduces inflammation and numbers of cysts in brains of mice with toxoplasmic encephalitis, Infect. Immun. 62 (7) (1994) 2773–2778.
[494] M. Deckert-Schlüter, S. Albrecht, H. Hof, O. Wiestler, D. Schlüter, Dynamics of the intracerebral and splenic cytokine mRNA production in *Toxoplasma gondii*-resistant and-susceptible congenic strains of mice, Immunology 85 (3) (1995) 408.
[495] Y. Suzuki, K. Joh, M. Orellana, F. Conley, J. Remington, A gene (s) within the H-2D region determines the development of toxoplasmic encephalitis in mice, Immunology 74 (4) (1991) 732.
[496] Y. Suzuki, K. Joh, O.C. Kwon, Q. Yang, F.K. Conley, J.S. Remington, MHC class I gene (s) in the D/L region but not the TNF-alpha gene determines development of toxoplasmic encephalitis in mice, J. Immunol. 153 (10) (1994) 4649–4654.
[497] F. Derouin, H. Pelloux, ESCMID study group on clinical parasitology, prevention of toxoplasmosis in transplant patients, Clin. Microbiol. Infect. 14 (12) (2008) 1089–1101.
[498] A.L. Campbell, C.L. Goldberg, M.S. Magid, G. Gondolesi, C. Rumbo, B.C. Herold, First case of toxoplasmosis following small bowel transplantation and systematic review of tissue-invasive toxoplasmosis following noncardiac solid organ transplantation, Transplantation 81 (3) (2006) 408–417.
[499] C. Dard, P. Marty, M.-P. Brenier-Pinchart, C. Garnaud, H. Fricker-Hidalgo, H. Pelloux, C. Pomares, Management of toxoplasmosis in transplant recipients: an update, Expert Rev. Anti Infect. Ther. 16 (6) (2018) 447–460.
[500] J.S. Remington, E.N. Cavanaugh, Isolation of the encysted form of *Toxoplasma gondii* from human skeletal muscle and brain, N. Engl. J. Med. 273 (24) (1965) 1308–1310.
[501] J. Frenhel, B.M. Nelson, J. Arias-Stella, Immunosuppression and toxoplasmic encephalitis: clinical and experimental aspects, Hum. Pathol. 6 (1) (1975) 97–111.
[502] M. Hommann, U. Schotte, R. Voigt, H. Glutig, T. Grube, B. Küpper, A. Kornberg, K. Richter, J. Scheele, Cerebral toxoplasmosis after combined liver-pancreas-kidney and liver-pancreas transplantation, Transplant, SAVE Proc. 34 (6) (2002) 2294–2295.
[503] A. Schaffner, Pretransplant evaluation for infections in donors and recipients of solid organs, Clin. Infect. Dis. 33 (Supplement_1) (2001) S9–S14.
[504] C. Hartono, T. Muthukumar, M. Suthanthiran, Immunosuppressive drug therapy, Cold Spring Harb. Perspect. Med. 3 (9) (2013).
[505] F. Dzierszinski, M. Nishi, L. Ouko, D.S. Roos, Dynamics of *Toxoplasma gondii* differentiation, Eukaryot. Cell 3 (4) (2004) 992–1003.
[506] V. Tu, R. Yakubu, L.M. Weiss, Observations on bradyzoite biology, Microb. Infect. 20 (9–10) (2018) 466–476.
[507] L.O.B. Coster, Parasitic infections in solid organ transplant recipients, Infect. Dis. Clin. 27 (2) (2013) 395–427.
[508] S. Khurana, N. Batra, Toxoplasmosis in organ transplant recipients: evaluation, implication, and prevention, Tropenmed. Parasitol. 6 (2) (2016) 123.
[509] R. Martino, Toxoplasmosis after hematopoietic stem cell transplantation, Transplant Infections: Fourth Edition (2016) 773–780.
[510] T. Held, D. Krüger, A. Switala, J. Beyer, D. Kingreen, C. Busemann, K. Janitschke, W. Siegert, Diagnosis of toxoplasmosis in bone marrow transplant recipients: comparison of PCR-based results and immunohistochemistry, Bone Marrow Transplant. 25 (12) (2000) 1257–1262.
[511] S. Bretagne, Molecular diagnostics in clinical parasitology and mycology: limits of the current polymerase chain reaction (PCR) assays and interest of the real-time PCR assays, Clin. Microbiol. Infect. 9 (6) (2003) 505–511.
[512] D. Aubert, F. Foudrinier, I. Villena, J. Pinon, M. Biava, E. Renoult, PCR for diagnosis and follow-up of two cases of disseminated toxoplasmosis after kidney grafting, J. Clin. Microbiol. 34 (5) (1996) 1347.
[513] F. Botterel, P. Ichai, C. Feray, P. Bouree, F. Saliba, R. Tur Raspa, D. Samuel, S. Romand, Disseminated toxoplasmosis, resulting from infection of allograft, after orthotopic liver transplantation: usefulness of quantitative PCR, J. Clin. Microbiol. 40 (5) (2002) 1648–1650.
[514] F. Derouin, E. Gluckman, B. Beauvais, A. Devergie, R. Melo, M. Monny, M. Lariviere, *Toxoplasma* infection after human allogeneic bone marrow transplantation: clinical and serological study of 80 patients, Bone Marrow Transplant. 1 (1) (1986) 67–73.
[515] A. Sulahian, C. Nugues, Y. Garin, H. Pelloux, P. Longuet, B. Slizewicz, F. Derouin, Serodiagnosis of toxoplasmosis in patients with acquired or reactivating toxoplasmosis and analysis of the specific IgA antibody response by ELISA, agglutination and immunoblotting, Immunol. Infect. Dis. 3 (1993) 63–69.
[516] Bnd Mechain, Y.J.Fo Garin, F. Robert-Gangneux, J. Dupouy-Camet, F. Derouin, Lack of utility of specific immunoglobulin G antibody avidity for serodiagnosis of reactivated toxoplasmosis in immunocompromised patients, Clin. Diagn. Lab. Immunol. 7 (4) (2000) 703–705.
[517] M. Montazeri, S. Mehrzadi, M. Sharif, S. Sarvi, A. Tanzifi, S. Aghayan A, A. Daryani, Drug resistance in *Toxoplasma gondii*, Front. Microbiol. 9 (2018) 2587.
[518] L.H. Bosch-Driessen, F.D. Verbraak, M.S. Suttorp-Schulten, R.L. van Ruyven, A.M. Klok, C.B. Hoyng, A. Rothova, A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis, Am. J. Ophthalmol. 134 (1) (2002) 34–40.
[519] D.R. Schmidt, B. Hogh, O. Andersen, S.H. Hansen, K. Dalhoff, E. Petersen, Treatment of infants with congenital toxoplasmosis: tolerability and plasma concentrations of sulfadiazine and pyrimethamine, Eur. J. Pediatr. 165 (2006) 19–25.
[520] C. Silveira, R. Belfort Jr., C. Muccioli, G.N. Holland, C.G. Victora, B.L. Horta, F. Yu, R.B. Nussenblatt, The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis, Am. J. Ophthalmol. 134 (1) (2002) 41–46.
[521] R. McLeod, K. Boyer, T. Karrison, K. Kasza, C. Swisher, N. Roizen, J. Jalbrzikowski, J. Remington, P. Heydemann, A.G. Noble, M. Mets, Outcome of treatment for congenital toxoplasmosis, 1981–2004: the national collaborative Chicago-based, congenital toxoplasmosis study, Clin. Infect. Dis. 42 (10) (2006) 1383–1394.
[522] M. Montazeri, M. Sharif, S. Sarvi, S. Mehrzadi, E. Ahmadpour, A. Daryani, A systematic review of *in vitro* and *in vivo* activities of anti-*Toxoplasma* drugs and compounds (2006–2016), Front. Microbiol. 8 (2017) 25.
[523] M. Montazeri, S. Mehrzadi, M. Sharif, S. Sarvi, S. Shahdin, A. Daryani, Activities of anti-*Toxoplasma* drugs and compounds against tissue cysts in the last three decades (1987 to 2017), a systematic review, Parasitol. Res. 117 (2018) 3045–3057.
[524] A. Kaye, Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants, J. Pediatr. Health Care 25 (6) (2011) 355–364.
[525] S. Rajapakse, M. Chrishan Shivanthan, N. Samaranayake, C. Rodrigo, S. Deepika Fernando, Antibiotics for human toxoplasmosis: a systematic review of randomized trials, Pathog. Glob. Health 107 (4) (2013) 162–169.
[526] J.E. Hyde, Targeting purine and pyrimidine metabolism in human apicomplexan parasites, Curr. Drug Targets 8 (1) (2007) 31–47.
[527] A.P. Sinai, E.A. Watts, A. Dhara, R.D. Murphy, M.S. Gentry, A. Patwardhan, Reexamining chronic *Toxoplasma gondii* infection: surprising activity for a "dormant" parasite, Curr. Clin. Microbiol. Rep. 3 (2016) 175–185.
[528] B. Samuel, B. Hearn, D. Mack, P. Wender, J. Rothbard, M. Kirisits, E. Mui, S. Wernimont, C.W. Roberts, S.P. Muench, D.W. Rice, Delivery of antimicrobials into parasites, Proc. Natl. Acad. Sci. USA 100 (24) (2003) 14281–14286.
[529] I. Benmerzouga, L.A. Checkley, M.T. Ferdig, G. Arrizabalaga, R.C. Wek, W.J. Sullivan Jr., Guanabenz repurposed as an antiparasitic with activity against acute and latent toxoplasmosis, Antimicrob. Agents Chemother. 59 (11) (2015) 6939–6945.
[530] S.S.-Y. Lim, R.Y. Othman, Recent advances in *Toxoplasma gondii* immunotherapeutics, Kor. J. Parasitol. 52 (6) (2014) 581.
[531] N.-Z. Zhang, J. Chen, M. Wang, E. Petersen, X.-Q. Zhu, Vaccines against *Toxoplasma gondii*: new developments and perspectives, Expert Rev. Vaccines 12 (11) (2013) 1287–1299.
[532] N.-Z. Zhang, M. Wang, Y. Xu, E. Petersen, X.-Q. Zhu, Recent advances in developing vaccines against *Toxoplasma gondii*: an update, Expert Rev. Vaccines 14 (12) (2015) 1609–1621.
[533] E.A. Innes, C. Hamilton, J.L. Garcia, A. Chryssafidis, D. Smith, A one health approach to vaccines against *Toxoplasma gondii*, Food Waterborne Parasitol. 15 (2019) e00053.

[534] T. Nayeri, S. Sarvi, M. Fasihi-Ramandi, R. Valadan, H. Asgarian-Omran, A. Ajami, Z. Hosseininejad, S. Dodangeh, J. Javidnia, A. Daryani, Enhancement of immune responses by vaccine potential of three antigens, including ROP18, MIC4, and SAG1 against acute toxoplasmosis in mice, Exp. Parasitol. 244 (2023) 108427.
[535] S. Dodangeh, M. Fasihi-Ramandi, A. Daryani, R. Valadan, H. Asgarian-Omran, Z. Hosseininejad, T. Nayeri, A.S. Pagheh, J. Javidnia, S. Sarvi, Protective efficacy by a novel multi-epitope vaccine, including MIC3, ROP8, and SAG1, against acute *Toxoplasma gondii* infection in BALB/c mice, Microb. Pathog. 153 (2021) 104764.
[536] M. Foroutan, M. Barati, F. Ghaffarifar, Enhancing immune responses by a novel multi-epitope ROP8 DNA vaccine plus interleukin-12 plasmid as a genetic adjuvant against acute *Toxoplasma gondii* infection in BALB/c mice, Microb. Pathog. 147 (2020) 104435.
[537] M.-N. Mévélec, Z. Lakhrif, I. Dimier-Poisson, Key limitations and new insights into the *Toxoplasma gondii* parasite stage switching for future vaccine development in human, livestock, and cats, Front. Cell. Infect. Microbiol. 10 (2020) 607198.
[538] Q. Liu, L.D. Singla, H. Zhou, Vaccines against *Toxoplasma gondii*: status, challenges and future directions, Hum. Vaccines Immunother. 8 (9) (2012) 1305–1308.