



Strategies Developed by *Toxoplasma gondii* to Survive in the Host

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One of the most successful intracellular parasites, *Toxoplasma gondii* has developed several strategies to avoid destruction by the host. These include approaches such as rapid and efficient cell invasion to avoid phagocytic engulfment, negative regulation of the canonical CD40-CD40L-mediated autophagy pathway, impairment of the noncanonical IFN- γ -dependent autophagy pathway, and modulation of host cell survival and death to obtain lifelong parasite survival. Different virulent strains have even evolved different ways to cope with and evade destruction by the host. This review aims to illustrate every aspect of the game between the host and *Toxoplasma* during the process of infection. A better understanding of all aspects of the battle between *Toxoplasma* and its hosts will be useful for the development of better strategies and drugs to control the parasite.

Keywords: *Toxoplasma*, intracellular parasites, cell invasion, immune evasion, autophagy

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Specialty section:

This article was submitted to
Infectious Diseases,
a section of the journal
Frontiers in Microbiology

Received: 04 January 2019

Accepted: 09 April 2019

Published: 26 April 2019

Citation:

Zhu W, Li J, Pappoe F, Shen J and
Yu L (2019) Strategies Developed
by *Toxoplasma gondii* to Survive
in the Host.
Front. Microbiol. 10:899.
doi: 10.3389/fmicb.2019.00899

TOXOPLASMA AND HOST IMMUNITY

Toxoplasma gondii is an obligate intracellular protozoan parasite with a unique apical complex composed of specialized cytoskeletal and secretory organelles, including micronemes, rhoptries, and dense granules. *T. gondii* is the single species in the genus *Toxoplasma*, although recent studies revealed that it has many genetic types distributed across the continents. In North America and Europe, populations of *T. gondii* are dominated by three archetypal types (I, II, or III) (Darde et al., 1992; Howe and Sibley, 1995; Howe et al., 1997; Ajzenberg et al., 2002), which vary substantially in virulence. Type I strains are highly virulent to mice with an LD100 as low as a single parasite, whereas strains of types II and III are less virulent (LD100 > 1,000) (Sibley and Boothroyd, 1992; Sibley et al., 2009). Unlike in North America and Europe, strains of *T. gondii* in South America are much more genetically diverse. Chinese 1, however, has been reported to be the most common type in East Asia, especially in China (Zhou et al., 2010, 2011; Chen et al., 2011; Wang et al., 2013; Li et al., 2014).

T. gondii is one of the most successful parasites, capable of invading and replicating within almost all nucleated cells of warm-blooded animals including humans (Dubey, 2010). The distinctive characteristic of this parasite is its ability to induce long-term chronic infections through its interactions with the host, leading to conversion of the prolific tachyzoite stage to the quiescent bradyzoite parasite stage (Aliberti, 2005). Bradyzoite forms of the parasite are not usually harmful in immunocompetent individuals, although in immunodeficient individuals, such as tumor and AIDS patients, they reconvert into cytolytic tachyzoites, resulting in severe toxoplasmosis and distant dissemination (Ayoade et al., 2017). Despite the parasite being the subject of over 100 years of studies and efficient therapies against acute toxoplasmosis have

been developed, no effective approach for chronic infection of bradyzoites has been found because of its survival strategies in the host.

Among different hosts of *T. gondii*, there are natural differences in susceptibility to the parasite, and host innate immunity is known to play a critical role in susceptibility to the infection. Most laboratory mouse strains are susceptible to infection, and therefore they have been widely used for studying immune responses against *T. gondii*. In mice, parasite profilin interacts with Toll-like receptor (TLR)11 and TLR12 on dendritic cells (DCs) to generate a potent interleukin-12 (IL-12) response in a myeloid differentiation factor 88 (MyD88)-dependent manner (Yarovinsky et al., 2005; Koblansky et al., 2013). Distinct from these stimuli, binding of the *T. gondii* protein cyclophilin-18 (C-18) to the chemokine receptor CCR5 can also activate murine DCs to produce IL-12 (Aliberti et al., 2003). As a pro-inflammatory cytokine, IL-12 stimulates NK cells, CD4⁺ T cells, and CD8⁺ T cells to express interferon- γ (IFN- γ), which plays a crucial role in parasite survival during infection. IFN- γ is also produced by neutrophils in response to IL-1 β and TNE. IFN- γ propagates a signal to activate the **signal transducer and activator of transcription 1 (STAT1)** (see Glossary) through the surface receptor, IFN- γ R. STAT1 is critical for the host immune response against *T. gondii* infection. STAT1 upregulates the production of effector molecules such as nitric oxide (NO) and reactive oxygen species (ROS), both of which are responsible for controlling parasite invasion in mice. IFN- γ also triggers the induction of **immunity-related GTPase (IRG)** proteins and guanylate-binding proteins (GBPs) to damage the **parasitophorous vacuole membrane (PVM)** in mice. Additionally, an IFN- γ -independent mechanism in mouse naive macrophages was found recently, in which NADPH oxidase (Nox)-generated ROS and GBP5 restrict the replication of avirulent type III parasites (Matta et al., 2018).

Unlike mice, humans are quite resistant to *T. gondii* infection. Owing to lack of functional genes encoding the key innate sensors TLR11 and TLR12 (Roach et al., 2005), human cells have different innate immune sensing mechanisms for the parasite. A recent research revealed that the human recognition system for this parasite is based on detection of the damage-associated molecule S100A11 released from infected cells and RAGE-dependent induction of CCL2 (Safronova et al., 2019). Human cells also rely on IFN- γ and STAT1 signaling to control the replication of *T. gondii* *in vitro* (Ceravolo et al., 1999), although different mechanisms are explored to control intracellular parasites. Firstly, indoleamine oxidase (IDO), but not inducible nitric oxide synthase (iNOS), has been found to be an important effector to control the parasite replication in several human cell lines after IFN- γ stimulation (Pfefferkorn et al., 1986; Nagineni et al., 1996); secondly, human cells are absent in IFN-inducible full-length IRG genes and proteins (Bekpen et al., 2005; Howard et al., 2011). Although human cells express a wide repertoire of GBPs, the involvement of GBPs in the human anti-*T. gondii* response in different cell lines is controversial (Ohshima et al., 2014; Johnston et al., 2016). Therefore, it appears that two of the main mechanisms of innate resistance mediated by IRGs and GBPs in IFN- γ stimulated mouse cells are not highly active in human cells (Hakimi et al., 2017).

Rats, like humans, are quite resistant to *Toxoplasma* infection but vary in their susceptibilities depending on the rat strain (Dubey et al., 2016). The Lewis (LEW) strain exhibits a complete resistance to *Toxoplasma* infection, and its resistance is partially abrogated by neutralization of endogenous IFN- γ , which showed that IFN- γ plays some role in the resistance of rats (Sergent et al., 2005). The *Toxo1* locus containing *Nlrp1* (nucleotide-binding oligomerization domain, leucine-rich repeat protein 1) was identified to mediate resistance to *T. gondii* infection (Cavaillès et al., 2006). *T. gondii* can activate the NLRP1 inflammasome in macrophages, leading to caspase-1-induced pyroptosis and release of the pro-inflammatory cytokines IL-1 β and IL-18 (Cavaillès et al., 2014; Cirelli et al., 2014). GRA35, GRA42, and GRA43 have been recently found to be required for induction of macrophage pyroptosis in Lewis rats (Wang et al., 2019).

EFFICIENT INVASION IS REQUIRED FOR PARASITE SURVIVAL

Because *T. gondii* is an obligate intracellular parasite, a successful and efficient cell invasion is crucial for its survival. To establish a successful invasion, *T. gondii* needs a coordinated sequential secretion of microneme and rhoptry neck proteins (RON) first to mediate the invasion. A secretion set of *T. gondii*, including ROPs and GRAs, is also involved in host modulation and long-term establishment of the parasite into the host cell. The unique invasion mechanism of *T. gondii* consists of a secretion-regulated **moving junction (MJ)**, which facilitates firm attachment between the parasite and the host plasma membranes (Alexander et al., 2005; Lebrun et al., 2005; Lamarque et al., 2011), and the glideosome, which is a specific motor system of the parasite. Formation of the MJ relies on apical membrane antigen 1 (AMA1), secreted from micronemes and translocated to the parasite's plasma membrane, and a rhoptry neck complex (composed of RON2, RON4, RON5, and RON8 proteins), secreted from rhoptry necks and exported into the host cell (Besteiro et al., 2009; Lamarque et al., 2011; Tyler and Boothroyd, 2011; Guerin et al., 2017). RON2 exposes a short segment at the surface of the host cell that serves as a ligand for AMA1, thus forming an intimate contact to generate an irreversible interaction between the host cell and the parasite (Lamarque et al., 2011; Tonkin et al., 2011; Tyler and Boothroyd, 2011). In addition to AMA1 and RON2, *T. gondii* has three additional AMA paralogs and two additional RON2 paralogs, which form three complexes: AMA2-RON2, AMA3-RON2L2, and AMA4-RON2L1 (Poukchanski et al., 2013; Lamarque et al., 2014; Parker et al., 2016). The exceptional molecular diversity at the parasite-host cell interface may explain why the parasite has such a wide host range. Microneme proteins like MIC4-1-6, MIC2-M2AP, and MIC3-8 complex also play a key role in adhesion that supports gliding motility and host cell invasion (Rabenau et al., 2001; Soldati et al., 2001; Meissner et al., 2002a; Wang and Yin, 2015; Gras et al., 2017). The glideosome is an actin-myosin motor complex in *T. gondii*, and it is composed of a short single-headed myosin heavy chain A (MyoA), a myosin light

chain (TgMLC1), and three gliding-associated proteins, TgGAP45, TgGAP50, and TgGAP40 (Herm-Gotz et al., 2002; Meissner et al., 2002b; Frenal et al., 2010). The connection between the glideosome and the MJ complex was previously thought to be mediated by aldolase (Jewett and Sibley, 2003; Boucher and Bosch, 2015); however, it was recently identified to be mediated by glideosome-associated connector (GAC), which forms a bridge between cell surface adhesins and the actin cytoskeleton in the parasite (Jacot et al., 2016). Finally, the power produced by the motor complex enables the parasite to move to potential host cells and to enter them by pushing forward the host membrane.

After active invasion of the host cell, *Toxoplasma* dissociates from the host membrane and resides within a non-fusogenic parasitophorous vacuole (PV), which provides a physical niche for the parasite (Tahara et al., 2016). PV formation is a result of invagination of the host cell membrane and involves host cytoskeleton rearrangement, ROPs, and GRAs (Clough and Frickel, 2017). For parasite growth and proliferation, PVM is selectively permeable to small molecules and nutrients from the host through GRA17 and GRA23 (Gold et al., 2015). More importantly, as a physical barrier, the PV protects parasites from fusion with host lysosomes and endosomes, thereby enabling survival of the parasite (Mordue and Sibley, 1997; Pavlou et al., 2018).

CELL AUTOPHAGY IN HOST IMMUNITY AND *TOXOPLASMA* EVASION

Classical autophagy, a highly evolutionarily conserved catabolic process, is a multistep lysosomal process in which intracellular

damaged or superfluous proteins and organelles are engulfed by a double-membraned autophagosome and degraded after fusion with a lysosome (Deter et al., 1967; Mizushima et al., 2011; Ohsumi, 2014). Autophagy is also actively involved in the capture of intracellular parasites and routing them for destruction. This selective autophagy process is called xenophagy, a key defense mechanism against a broad range of infections (Deretic et al., 2013; Besteiro, 2018). In addition to classic autophagy, some noncanonical forms of autophagy are also involved in host defense against intracellular pathogens: LC3-associated phagocytosis (LAP) and IFN γ -inducible GTPase-mediated host defense. These processes rely on some but not all components of the autophagy machinery (Zhao et al., 2008; Lai and Devenish, 2012; Haldar et al., 2014).

In *T. gondii*-infected human/murine macrophages and nonhematopoietic cells, CD40 interacts with CD40L (CD154) expressed on the surface of T cells to trigger the killing of the parasite through an autophagy-dependent pathway (Andrade et al., 2006; Portillo et al., 2010; Van Grol et al., 2013). CD40-CD40L interactions activate upstream regulators of the autophagic response such as ULK1/2 and Beclin1-PI3KC3, two important complexes required for the initiation of phagophore (an isolation membrane, precursor of the autophagosomal compartment), and then drive the recruitment of the protein LC3 to the phagophore and promote autophagosome formation (Liu et al., 2016). In contrast, IFN γ -dependent noncanonical autophagy directly binds LC3 and other Atgs to the PVM, leading to recruitment of two subclasses of IFN γ -inducible GTPases for parasite exposure (Selleck et al., 2015). Atgs in both canonical and noncanonical autophagy processes mediate the targeting of parasites and

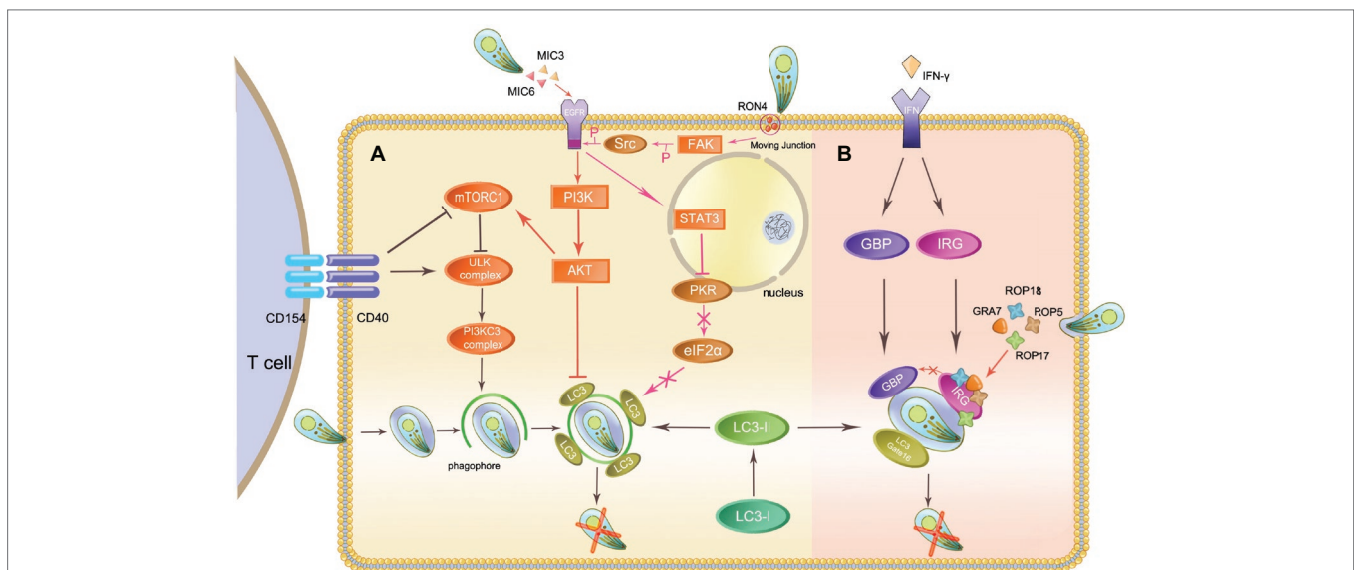


FIGURE 1 | Autophagy initiates host immunity and *Toxoplasma* immune evasion. The host eliminates intracellular *Toxoplasma* through autophagy proteins in two ways: the canonical CD40-CD40L-mediated and the noncanonical IFN- γ -dependent autophagy pathways. *Toxoplasma* can evade elimination through host autophagy by following means. **(A)** In the canonical autophagy pathway, MIC3, and MIC6 secreted from *Toxoplasma* phosphorylate EGFR and activate the PI3K/AKT signaling pathway, which has an impact on LC3 function. The activation of FAK-Src through *Toxoplasma* invasion prevents this parasite from being targeted. **(B)** ROP5, ROP18, and GRA7 form a complex with ROP17 and load onto the PVM, inactivating IRGs through phosphorylation.

expose *Toxoplasma* to host immune surveillance, leading to killing of the parasite. To avoid being targeted, *Toxoplasma* developed a survival strategy against autophagy that involves immune evasion (**Figure 1A**).

The *Toxoplasma* micronemal proteins MIC3, and MIC6 act as ligands for EGFR, inducing phosphorylation of this protein in host cells and activating the PI3K/Akt signaling pathway. This event prevents the expression of the autophagy protein LC3 and vacuole-lysosomal fusion. Subsequently, the parasite is prevented from being targeted by the host autophagy machinery (Muniz-Feliciano et al., 2013; Wang et al., 2016). In mammalian cells, Akt phosphorylation also results in the activation of mTORC1, which negatively regulates autophagosome formation, thus inhibiting autophagy (Kim et al., 2011). During host invasion and MJ formation, *T. gondii* activates a signaling cascade downstream of FAK-Src. It inhibits the activation of the key stimulators of autophagy PKR and eIF2 α , which prevent the parasite from being targeted (Portillo et al., 2017).

ESCAPE FROM GTPases-DEPENDENT ANTIMICROBIAL PROGRAMS

As mentioned above, the IFN γ -inducible GTPase-mediated host defense plays a crucial role in the destruction of the PVM in a murine model. In IFN γ -stimulated cells, a complex containing LC3 and a subset of Atgs attaches to the PVM and recruits IFN γ -inducible GTPases, leading to vesiculation and destruction of the PVM (Lai and Devenish, 2012). Consequently, the parasites are released into the host cell cytoplasm and subsequently become exposed to the host immune system. Recent reports indicate that Gate-16 is also required for this GTPases-dependent antimicrobial program even in the absence of LC3 (Sasai et al., 2017).

Virulent type I strains of *T. gondii* can evade this autonomous host immunity mechanism but type II and III strains cannot. Rhoptry protein kinase ROP18 and pseudokinase ROP5 are known to be polymorphic and determine the virulence of different strains and thwart the IRG system (Niedelman et al., 2012). After being secreted during invasion, ROP18 phosphorylates Thr residues in the switch region 1 (SW1) on host Irga6 and Irgb6 with the cooperation of ROP5. ROP5 regulates the activity of ROP18, and additionally binds directly to monomeric IRGs to prevent oligomerization and support ROP18 phosphorylation. ROP5 is also able to associate with another PVM-associated kinase, ROP17, in phosphorylating and inactivating IRGs (Irgb6) (Etheridge et al., 2014). GRA7 binds to and increases turnover of Irga6, which makes substrates available for ROP18, thereby preventing loading of IRGs (**Figure 1B**; Alaganaan et al., 2014; Hermanns et al., 2016). ROP5 and ROP18 are also able to inhibit GBP1 loading onto the PVM. Pseudokinase ROP54 can move to the cytoplasmic face of the PVM and restrict immune loading of GBP2 to evade the GBP2-mediated immune response (Yang et al., 2017a). In addition, ROP18 in virulent strains can phosphorylate activating transcription factor 6 β (ATF6 β), an important factor for DCs antigen presenting

(Yamamoto et al., 2011; Yamamoto and Takeda, 2012). Phosphorylated ATF6 β may be degraded and affect the antigen-presenting ability of DCs, having an impact on the interferon-inducible GTPase-mediated host defense.

RESISTANCE TO OXIDATIVE STRESS

Escape from GTPase-dependent antimicrobial programs is vital to *T. gondii*, and innate immune cells cytotoxicity is essential for restriction of parasite infection (**Figure 2**). Resistance to cytotoxicity makes sense for *T. gondii*. **Inducible nitric oxide synthase (iNOS)** expressed by mouse macrophages synthesizes NO through oxidation of L-arginine. Large amounts of NO result in parasite death but can be easily inhibited by *T. gondii* for sustained replication. The process is mediated by TGF β 1 induction through Smad2 and Smad3, leading to destruction of iNOS and actin filament (F-actin) depolymerization. After infection, high levels of arginase compete with iNOS for the same substrate, leading to a reduction of NO (Padrao Jda et al., 2014). *T. gondii* HSP70 (TgHSP70), a tachyzoite-specific protein, also contributes to downregulation of NO (Moroda et al., 2017). In human cells, the effect of iNOS is different. It acts as a pro-*Toxoplasma* host factor through the GRA15-dependent virulence mechanism in the THP-1/Huh7 coculture mode (Bando et al., 2018). Upregulation of ROS and IDO generated by many cell types leads to inhibition of parasite replication. An oxidative stress microenvironment is generated by producing hydrogen peroxide, superoxide, and hydroxyl radicals to damage the parasites or reduce tryptophan levels, preventing the parasites from rapid replication. However, *T. gondii* can subvert these mechanisms through an antioxidant network. The cytosolic peroxiredoxins TgPRX1 and TgPRX2 and mitochondrial peroxiredoxin TgPRX3 act downstream of superoxide dismutases (SODs) to detoxify hydrogen peroxide (Kwok et al., 2003). TgSOD2 and TgSOD3, similar to mitochondrial SODs, are able to eliminate the ROS produced by oxidative phosphorylation. *T. gondii* antioxidant glutathione-S-transferase (TgGST), glutaredoxin (TgGrx), and catalase also make a major contribution to decomposing superoxide anion radicals and resisting oxidative damage (Pino et al., 2007; Wang et al., 2015). *T. gondii* thioredoxin reductase (TgTR) maintains a thioredoxin-reduced state during NADPH consumption that protects parasite against oxidative-burst injury (Kim et al., 2017; Xue et al., 2017). However, this survival ability may only occur in virulent strains, whereas avirulent type III parasites are preferentially cleared by NADPH oxidase and induction of GBP5 in human cells (Matta et al., 2018).

REGULATION OF HOST GENE EXPRESSION BY *T. GONDII*

Interferon-inducible cell autonomous immunity or cytotoxicity, necessary for the host to control the parasite, is based on gene expression. These signal transduction pathways enhance

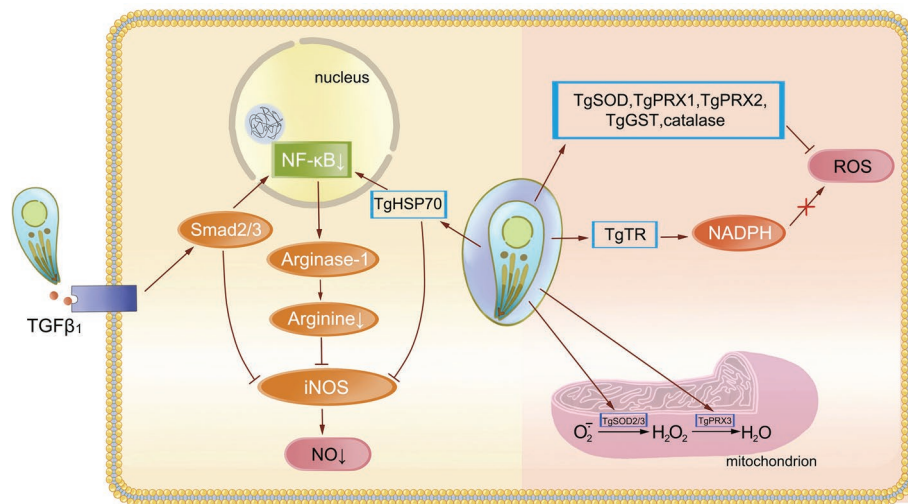


FIGURE 2 | Resistance of *Toxoplasma gondii* to oxidative stress. Oxidative stress is an important way for the host to restrict *Toxoplasma* replication and prevent subsequent infection. Activation of TGF β 1 induced by *Toxoplasma* through Smad2 and Smad3 leads to destruction of iNOS. The NF- κ B pathway is responsible for this decline in NO levels, whereas TgHSP70 also regulates this pathway. Cytosolic peroxiredoxins (TgPRXs) and superoxide dismutases (TgSODs) from *Toxoplasma* are able to eliminate ROS and protect the parasite against oxidative-burst injury.

or regulate the overall immune response in such a way as to become subverted by *T. gondii*, constituting a major part of the *T. gondii* immune evasion mechanism (Figure 3).

STAT pathways modulate the transcription of both pro- and anti-inflammatory molecules for parasite control. The STAT1 transcription factor, the main signal transducer of IFN- γ , mediates interferon-inducible immunity but may be blocked by the *Toxoplasma* inhibitor of STAT1-dependent transcription (TgIST), resulting in blockage of interferon regulatory factor 1 (Irf1), p65 GBPs, iNOS, indoleamine 2, 3-dioxygenase 1, and major histocompatibility complex (MHC). Secreted by *T. gondii* after invasion, TgIST translocates to the nucleus and recruits the Mi-2 nucleosome remodeling and deacetylase (NuRD) complex to STAT1-dependent promoters, leading to chromatin alteration and signal blockage (Gay et al., 2016; Olias et al., 2016). In addition, this mechanism is not virulence-dependent, and thus all *T. gondii* clonal lineages equally inhibit STAT1 transcriptional activity and repress the IFN- γ response (Rosowski and Saeij, 2012). Another mechanism of IFN- γ blockage through STAT1 is dephosphorylation by suppressor of cytokine signaling phosphatase (SOCS1), an anti-inflammatory pathway that is upregulated during parasite infection.

Transcription factors STAT3 and STAT6 are associated with IL-4 and IL-6 production. After being injected into host cells, ROP16 localizes to the host nucleus through nuclear localization signals. ROP16 can disturb the host IFN- γ signal transduction and phosphorylates STAT3 and STAT6, leading to a decrease in IL-12 levels that mainly limits the protective Th1 cytokine responses and the inflammasome. Phosphorylation of STAT6 also induces the expression of arginase-1, SOCS2, and interferon regulatory factor 4 (IRF4). High levels of production of arginase-1 lead to NO degradation, resulting in resistance to host immune

attacks, thereby allowing proliferation of the parasite. Although all three strain types initially induce STAT3 and STAT6 activity, only ROP16 I/III strains suppress IL-12 production in macrophages, because a single amino acid substitution in the kinase domain was identified in ROP16 II that determines the strain difference in terms of Stat3 activation (Yamamoto et al., 2009). ROP16 also induces the phosphorylation and nuclear translocation of STAT5 to generate protective immunity (Chang et al., 2015).

In addition to IRFs, CD40 and TNF, as downstream factors of NF- κ B signaling pathway, are also required for parasite control. The NF- κ B family of transcription factors plays a key role in host immunity against *T. gondii* because it is believed to be an evolutionarily conserved mechanism that regulates host innate and adaptive immune functions for parasite survival. ROP18 in *T. gondii* type I strains is responsible for p65 degradation and thus suppresses NF- κ B activation (Du et al., 2014). NF- κ B can also be inhibited by *T. gondii* excretory/secretory antigens (TgESAs), which limit the functional activity of macrophages and suppress pro-inflammatory cytokine secretion for parasite survival (Wang et al., 2017). In addition, release of GRA15 by type II strains activates the NF- κ B pathway and initiates IL-12 synthesis through enhancing the expression of CD40 in infected cells (Morgado et al., 2014). Thus, type II GRA15 has the ability to effectively control acute *T. gondii* infection and promote the conversion of parasite into bradyzoites at the chronic infection stage. This mechanism is considered another *T. gondii* immune evasion strategy.

Other *T. gondii* GRA and ROP effectors contribute to host gene targeting and signaling interference. GRA6 selectively activates nuclear factor of activated T cells 4 (NFAT4), a host transcription factor, which modulates host immune responses and parasite dissemination in a strain-specific manner

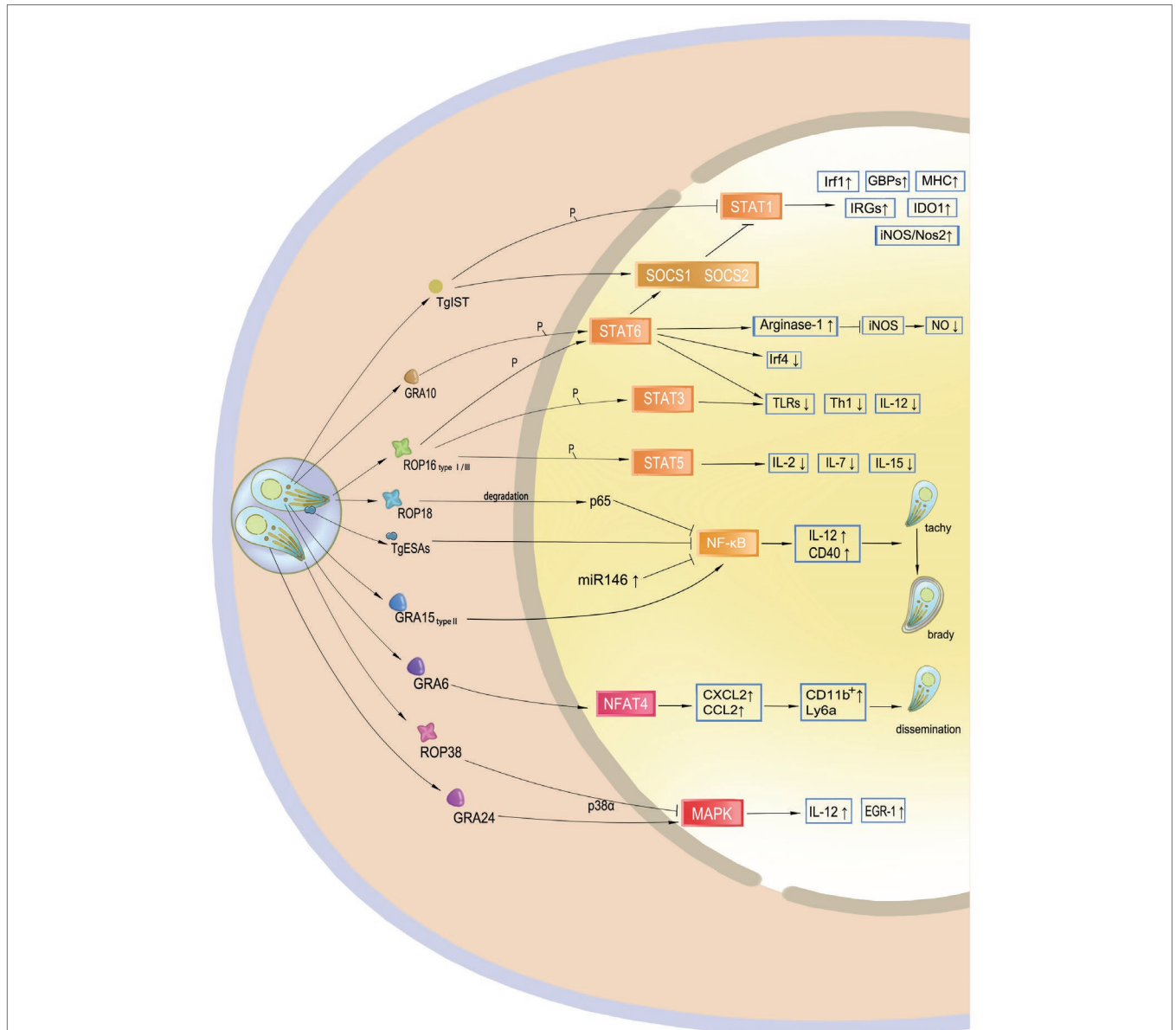


FIGURE 3 | Targeting of host gene expression by *Toxoplasma gondii*. Effectors secreted by *T. gondii* manipulate host gene expression. TgIST translocates to the nucleus after *T. gondii* invasion and inhibits STAT1 by phosphorylation. GRA10 and ROP16 phosphorylate STAT3 and STAT6, mainly leading to a decrease in IL-12 and Th1 response. Additionally, phosphorylation of STAT6 results in resistance to NO. ROP18 and TgESAs block the NF-κB signaling pathway and impair CD40- and TNF-regulated parasite control of the host. However, GRA15 of type II activates this signaling pathway, which may promote cyst formation of the avirulent strain to avoid host immunity. GRA6 activates the host transcription factor NFAT4, and then attracts inflammatory cells and facilitates *T. gondii* dissemination. ROP38 and GRA24 have a diverse role in the modulation of the MAPK pathway.

(Ma et al., 2014). The p38 MAP kinase pathway controls gene expression and the early immune response, such as IL-12 production, to restrain *T. gondii*. GRA24 modulates host immune responses by triggering prolonged autophosphorylation and nuclear translocation of the host cell p38 MAPK (Braun et al., 2013). Interestingly, ROP38 has an adverse influence in downregulating MAPK signaling and some other transcriptional controls without affecting parasite replication and virulence (Peixoto et al., 2010). ROP38 functions in accordance with the demands of parasite survival, including bradyzoite differentiation,

or maintaining the viability of the infected host cells. GRA16 is secreted and eventually exported to the host nucleus to interact with the herpesvirus-associated ubiquitin-specific protease (HAUSP) and modulate host gene expression, such as the p53 tumor suppressor pathway, which promotes host cell survival under stress conditions. The export of the GRA16 and GRA24 effectors into host cells and their accumulation in the nucleus are mediated by the aspartyl protease TgASP5 (Curt-Varesano et al., 2016). According to a recent study, ROP17 downregulates the activation of many immune signaling pathways and

transcription factors to inhibit immune responses during *T. gondii* infection in human cells (Li et al., 2019).

MODULATION OF HOST CELL SURVIVAL AND DEATH FOR PARASITE PROLIFERATION

Intracellular *T. gondii* depends on the sustained life of host cells for its growth, metabolism, and proliferation. Host cell death seriously threatens parasite survival, whereas apoptosis induction in some cells may suppress the immune responses against the parasite (Luder et al., 2001). Modulation of host cell survival and death is one of the strategies for *T. gondii* survival (Figure 4).

Inhibition of host cell apoptosis may preserve intracellular replication and long-term survival of the parasite. *T. gondii* infection inhibits mitochondrial apoptosis by preventing the release of cytochrome-c and phosphorylation of the pro-apoptotic Bad protein and inducing overproduction of the anti-apoptotic Bcl-2 (Hippe et al., 2008; Hwang et al., 2010; Quan et al., 2013). In infected macrophages, *T. gondii* also induces serpin B3/B4 expression through STAT6 activation and activates the STAT3-miR-17-92-Bim pathway to inhibit apoptosis (Song et al., 2012; Cai et al., 2014). In addition to blockage of cytochrome-c release, *T. gondii* targets the holo-apoptosome assembly to inhibit caspase-dependent intrinsic cell death (Graumann et al., 2015). ROP18, an important virulence determinant of the parasite, has been found to play a role in regulating apoptosis of infected cells. It inhibits host cell apoptosis by blocking the release of cytochrome-c, upregulating the ratio

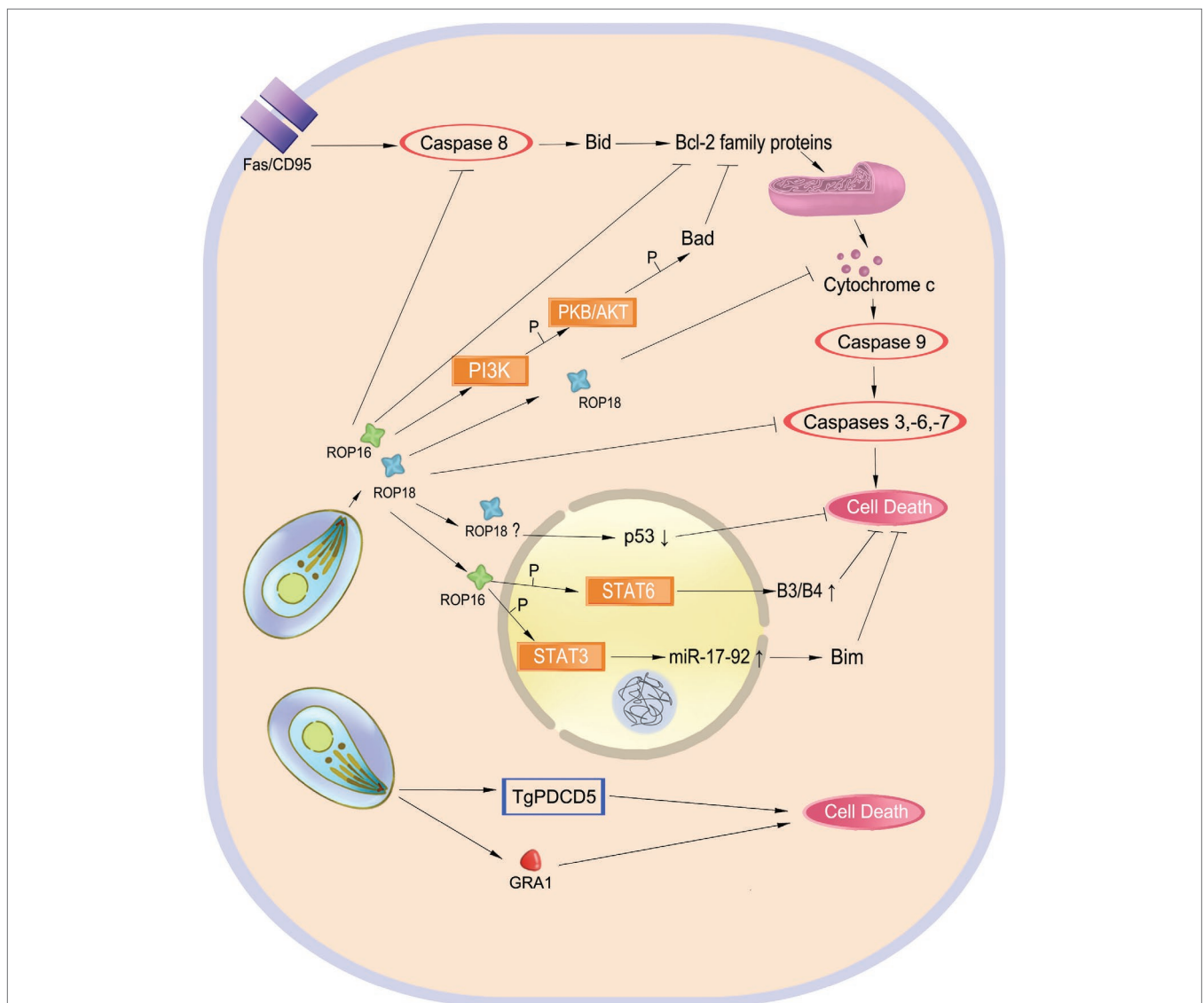


FIGURE 4 | Balancing host cell survival and death. Inhibition of cell apoptosis preserves the intracellular parasite *Toxoplasma gondii*. Effectors such as ROP18 play a role in Fas/CD95-mediated apoptosis to inhibit this process. ROP16 also phosphorylates STAT3 and STAT6 to inhibit cell death. However, TgPDCD5 and GRA1 induce cell death, which may help the parasite survive by killing host's immune cells.

of Bcl-2/Bax, and inducing p53 degradation (Wu et al., 2016; Yang et al., 2017b; Xia et al., 2018).

On the other hand, induction or enhancement of apoptosis in the course of *T. gondii* infection might be beneficial for the parasite (Figure 4). Programmed cell death 5 (TgPDCD5), a protein released from *T. gondii*, enhances apoptosis of uninfected host macrophages, which appears to be a negative regulator of the immune response against the parasite (Bannai et al., 2008, 2009). Similarly, GRA1 secreted by *T. gondii* induces apoptosis of monocytes that is mediated by the TGF- β pathway (Ngo et al., 2017). Apoptosis and cell death in bystander host cells may be caused by nitric oxide and other soluble factors produced by infected cells (Nishikawa et al., 2007).

SURVIVAL STRATEGIES IN THE CHRONIC INFECTION STAGE

After exponential replication as tachyzoites, the increasing host immune response and accompanying stress conditions lead *T. gondii* to differentiate into the latent bradyzoite stage that resides in tissue cysts. This stage allows the parasites to cause chronic disease owing to their ability to evade the immune system and resist common therapies. In addition, when the host immunity becomes impaired, *T. gondii* being an opportunistic pathogen may transform into rapidly replicating tachyzoites. Infectious bradyzoite cysts forming in muscle, heart, and central nervous system (CNS) tissues allow *T. gondii* to spread to a new host following predation of its former host, a part of the parasite's life cycle.

Because of the "Trojan horse" strategy in which tachyzoites move to immune-privileged organs such as the CNS and form cysts under the regulation of multiple genes, bradyzoites within tissue cysts persist for the life of their host (Hong et al., 2017; Huang et al., 2017). Rhopty proteins such as ROP17, ROP35, and ROP38 also promote tachyzoite conversion to encysted bradyzoite. The persistent cyst is cloaked with a glycosylated structure called the cyst wall, which provides a sturdy barrier for bradyzoite survival and infectivity for oral transmission. Cyst wall glycoprotein CST1 glycosylated by Tg.ppGalNAc-Ts confers structural rigidity in brain cysts in a mucin-like domain-dependent manner (Tomita et al., 2013, 2017). A toxoplasma nucleotide-sugar transporter (TgNST1) is also required for cyst wall glycosylation (Caffaro et al., 2013). Bradyzoite-secreted pseudokinase 1 (BPK1) is a component of the cyst wall and necessary for the growth, maintenance, and stability of tissue cysts (Buchholz et al., 2013). Several GRA proteins contribute to cyst wall formation and maintenance. A recent report demonstrated that the *T. gondii* lysosomal vacuolar compartment (TgVAC) is capable of proteolysis and maintains the viability and persistence of *T. gondii* cysts (Di Cristina et al., 2017).

CONCLUDING REMARKS

T. gondii is an intracellular parasite with an efficient invasion system that avoids phagocytosis. After a successful invasion, it secretes many different effectors to disturb the canonical

CD40-CD40L-mediated and the noncanonical IFN- γ -dependent autophagy, regulate host gene expression, modulate host cell survival and death, and counter host defense mechanisms. *T. gondii* needs a balance between establishing a successful infection in the host for ensuring propagation, and avoiding a too rapid multiplication that would kill the host. Additionally, as a successful intracellular parasite, obtaining nutrients from the host is also a critical survival strategy (for a more detailed discussion of nutrients, see Blume and Seeber (2018) and references therein). *T. gondii* employs different approaches in a strain-specific or host-specific manner to fight against different hosts. Striking differences in the strategies adopted by the parasite have been observed between murine and human hosts. Though anti-*Toxoplasma* responses have been extensively investigated in a mouse model, the mechanisms used by human cells to control the parasite and by the parasite to antagonize these responses remain elusive. For instance, what is the major IFN- γ -induced effector in human cells, as there are no IFN γ -inducible IRGs and a reduced GBP repertoire? What are the *Toxoplasma* virulence factors in humans, and how do they defend the PV from host destruction in human cells? As is known that ROP18 and ROP5 are the major virulence factors in strains from North America, Europe, and South America in mice, what are the virulent determinants in the atypical lineages (i.e., types 13/Chinese 1 from China, 14 from Africa, and 11 from North America), and how do these determinants fight the immune system in mice and in humans to help the parasite survive? Addressing these questions will allow a better description of the battle between *T. gondii* and its hosts, and such knowledge will be useful in the development of drugs to control the parasite.

AUTHOR CONTRIBUTIONS

LY and JS designed the work. JL and WZ drafted the article. LY and FP did critical revision of the article. All authors read and approved the final version of the manuscript.

FUNDING

This work was supported by grants from the National Key R&D Program of China (to LY, grant no. 2017YFD0500400) and Natural Science Foundation of China (to LY, grant no. 81572022, 81871671, and JS, grant no. 81471983), Key projects for supporting outstanding young talents in Universities in Anhui (to LY, grant no. gxyqZD2016044).

ACKNOWLEDGMENTS

The authors would like to thank members of our laboratories for many thoughtful discussions, and many thanks to Xinyuan Li (Reproductive Center of the First Affiliated Hospital of Anhui Medical University) for the art works. The authors also apologize to the many investigators whose contributions have not been mentioned owing to space limitations.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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GLOSSARY

<i>Atgs</i>	Autophagy-related proteins. Eukaryotic factors participating in various stages of the autophagic process and required for autophagosome formation.
<i>CDPKs</i>	Ca ²⁺ -dependent protein kinases. A family of enzymes that control multiple process of parasite in motility, adhesion, and egress.
<i>GBPs</i>	IFN- γ -inducible guanylate-binding proteins.
<i>GRAs</i>	Dense granule protein. Proteins secreted from the parasite dense-granule organelles and take part in most steps during parasite invasion and evasion.
<i>IDO</i>	Indoleamine oxidase. Induced by IFN- γ and degrades tryptophan, an essential nutritional amino acid for the intracellular growth of <i>T. gondii</i> in human cells.
<i>iNOS</i>	Inducible nitric oxide synthase. An IFN- γ -inducible protein that mediates parasite clearance and growth inhibition through nitric oxide production.
<i>IRGs</i>	A family of rodent IFN- γ -induced GTPases.
<i>LC3</i>	Microtubule-associated protein1 lightchain3. A mammalian autophagosomal ortholog of yeast Atg8 and contributes to major steps of autophagy. There are two isoforms of LC3, LC3-I (soluble) and LC3-II (membrane-bound).
<i>MICs</i>	Microneme proteins. Proteins secreted from the apically located parasite microneme organelles and contribute to <i>T.gondii</i> invasion and virulence.
<i>MJ</i>	Moving junction. A tight apposition between the host cell and parasite plasma membranes. Anchors the invading parasite to the host cell and facilitates parasite internalization within a parasitophorous vacuole.
<i>MMPs</i>	Matrix metalloproteases. A family of enzymes containing Ca ²⁺ and Zn ²⁺ in structure that participate in metabolism in extracellular matrix.
<i>NLRP1</i>	An inflammasome sensor and a member of the NLR (Nod-like receptor/nucleotide binding domain/leucine rich repeat containing) protein family.
<i>PV (and PVM)</i>	Parasitophorous vacuole. An intracellular compartment that the parasite resides in and is bounded by membrane called PVM.
<i>RONs</i>	Rhoptry neck proteins. Proteins secreted from the neck of the rhoptry organelles. A component of the moving junction that plays a central role during invasion.
<i>ROPs</i>	Rhoptry body proteins. Proteins secreted from the bulb or body of the apically located rhoptry organelles of the parasite and take part in most steps during parasite invasion and evasion.
<i>STAT</i>	Signal transducer and activator of transcription. A group of transcription factors that transmit signals from the extracellular milieu of cells to the nucleus.
