Molecular Biology and Immune Regulation of Chronic *Toxoplasma gondii* Infection

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Abstract

The parasite *Toxoplasma gondii* demonstrates superior survival skills because it can survive inside cells until the host dies. Scientists have documented at least 350 different host species of *T. gondii* until now while statistical models predict that 30% of people across the world carry chronic *T. gondii* infections. Human health received its first important warning about *T. gondii* in 1940s with documenting cases of congenital toxoplasmosis infections. Medical experts identified the significance of strong immune defenses during the AIDS epidemic because AIDS patients showed signs of reactivated chronic toxoplasmosis. This presented evidence of how essential unharmed immunity is for controlling *T. gondii* infection. Extensive research during the past four decades allowed scientists to enhance their knowledge of the *T. gondii* infection biology through studies of rodents and human cells as well as analysis of clinical data. Several important aspects remain unknown about the biology of *T. gondii* despite substantial gains made during the last 40 years. Research on *T. gondii* biology requires knowledge about parasite developmental genes and brain and muscle cell-intrinsic defense mechanisms against the parasite together with studies of host metabolic stability after infection. The understanding of chronic infection biology needs immediate improvement because emerging *T. gondii* haplotypes are causing increased ocular diseases yet we lack methods to sterile chronic infection. The Review explores the cellular components together with the host-derived and parasite-derived signaling elements responsible for *T. gondii* survival during persistent infection. This chapter analyze how chronic infection impacts tissue pathology and discuss prevalent questions in this field of Toxoplasma-host relationship research.

Keywords: *Toxoplasma gondii*, Immune Regulation, Chronic Infection, Cyst, Molecular Diagnosis

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Introduction

A single-cell obligate intracellular protozoan parasite called *Toxoplasma gondii* enters the body when humans eat foods containing its parasites. As its definitive host Feline species help the parasite achieve sexual recombination and discharge many infectious environmentally stable oocysts into the environment (Dubey et al., 1970). *T. gondii* maintains its unique transmission qualities through a wide range of intermediate host species that include humans and livestock aside from birds and rodents and additional numerous others (Black & Boothroyd, 2000). The parasite exists in two distinct tissue cyst forms including tachyzoites and bradyzoites because intermediate hosts serve as their supportive environment. The process of filter water for oocysts represents a transmission vector that leads to human exposure (Jones et al., 2009). The intestinal tissue of human and animal hosts becomes infected by *T. gondii* bradyzoite tissue cysts or oocysts that enter their bodies. The parasite can supposedly detect linoleic acid in feline intestines as an essential trigger to differentiate its sexual developmental stages according to research from Laura Knoll's group. The genetic diversity and expanded range of the parasite strongly benefits from cat transmission while the parasite evolutionary pressure seems to prioritize transmission success to cats. Because rodents have a crucial role in predatory relationships with cats they demonstrate special importance to the parasite lifecycle. The infection cycle depends on several factors supported by scientific evidence that includes *T. gondii* effectors targeting mouse immune pathways (Yarovinsky, 2014; Coombes & Hunter, 2015) and rodent behavioral changes toward feline scents and severe tissue loss which may enable rodent predation transmission. During acute infection most parasites get cleared by immune-competent people who experience flu-like symptoms while they fight off the infection. Bradyzoite tissue cysts survive as slowly reproducing cells persisting most commonly in protection-free areas such as brain, eye, cardiac muscle, and skeletal muscle tissue (Dubey et al., 1998). The *T. gondii* infection threatening the life of an unborn fetus in pregnant women also occurs due to their underdeveloped immune system (Assi et al., 2007). Various tissues that historically lacked immune privilege status show parasite presence based on medical observations of organism transmission through organs obtained from infected donors which receive transplant

surgeries into immune-competent patients (Sturge & Yarovinsky, 2014).

The scarcity of parasites in these tissues leads to minimal research about chronic tissue infections with *T. gondii*. Throughout chronic *T. gondii* infection the immune system remains active because *T. gondii*-specific IgG and IFN-γ in the sera persist at elevated levels while performing their parasite restricting functions (Sturge & Yarovinsky, 2014). The immune system suppression experienced during chemotherapy alongside organ transplant or AIDS allows *T. gondii* to switch from latent to active infection. The condition known as recrudescence which occurs when parasitemia remains uncontrolled by drugs poses a fatal threat to patients. When treating *T. gondii* infections doctors use most commonly either pyrimethamine with sulfadiazine or clindamycin or switch to trimethoprim and sulfamethoxazole (Dunay et al., 2018). The antiparasitic drugs for treatment show poor tolerance rates due to high sensitivity toward sulfa-based medicine. Medical researchers have yet to discover any medication that completely eradicates tissue cysts possibly due to bradyzoite slow development speed and brain cell shielding along with drug penetration barriers. This matter represents an urgent requirement because *T. gondii* develops fresh haplotypes which contribute to serious eye illnesses within immune-competent patients. This chapter discusses the cell types, molecular mediators, both host and parasite, that facilitate persistent *T. gondii* infection. This also highlights the consequences of chronic infection for tissue-specific pathology and identify open questions in this area of host-Toxoplasma interactions.

Population Genetics and Diversity of *Toxoplasma gondii*

The *T. gondii* strains detected in the North American and European environments mainly include three main classes known as type I, type II and type III. The different virulence levels of these types result in major mortality differences among various inbred mouse strains including C57BL/6, CBA/J, BALB/c. The aggression of tachyzoite strains differs in vivo as type I shows an LD50 of 1–10 while type II shows 100–1000 and type III demonstrate LD50 of ~100,000 to 1 million (Su et al., 2002). Type II *T. gondii* infections control the human population in North America and Europe yet scientists discovered haplogroup 12 as a new type isolated from American individuals and untamed animals (Khan et al., 2011). Scientists discovered separate clonal lineages which exclusively exist in Asia and Africa (Galal et al., 2019). Multiple South American *T. gondii* strains that do not follow clonal lineage expansion have been identified with haplogroup designations from 4 to 15 (Shwab et al., 2014). Whole genome sequencing demonstrates that genetic diversity of *T. gondii* results from limited ancestral strains exchanging genetic material through admixture. Large gene haploblock analysis allowed researchers to determine the inheritance pattern. The aforementioned haploblocks contain genes that encode parasite effector proteins associated with virulence which implies that each unique combination of effectors could affect pathogenesis and/or transmission dynamics (Lorenzi et al., 2016). Multiple lines of evidence demonstrate that virulent haplotype clusters evolved alongside mouse IFN-inducible immunity-related GTPase (IRG) genes which are essential for parasitic defense within mouse cells (Müller & Howard, 2016; Hassan et al., 2019).

Immune Factors Influencing Dissemination

The activation of a strong immune reaction remains vital for both the survival of the parasite and its host organism. Parasite transmission fails to occur when a host dies prior to developing chronic infection because tachyzoite cysts cannot resist peptic protease breakdown but Bradyzoite cysts remain protected. According to this pattern the parasite developed specific effectors which activate host immune cells while avoiding sterilizing immunity. The parasite activates host immune cell signaling as it develops strategies that prevent sterilizing immunity with both mechanisms. *T. gondii* survives through its growth and persistence phase inside the parasitophorous vacuole membrane (PVM) during acute and chronic infection. The PVM originates from host cell plasma membranes because the parasite uses its effectors to make discontinuous movements inside the cells. The parasite maintains its capacity to infect numerous nucleated cells by utilizing this path because endo/lysosomal environments would otherwise be fatal to it (Mordue et al., 1999). During actual organism infection the parasite can only infect specific cell types. After a mouse ingests a parasite cyst *T. gondii* will invade the distal area of the jejunum located in the small intestine (Molloy et al., 2013). Research does not show which specific cells (M cells, epithelial cells) serve as invasion conduits; nonetheless *T. gondii* sporozoites and tachyzoites have been identified in intestinal epithelial cells (Coombes et al., 2013). Parasites infect immune cells after they penetrate the tissue. Research shows that the CCL2/CCR2 chemokine axis functions identically in human and mouse bodies to recruit monocytes (Safronova et al., 2019). When infecting human and murine dendritic cells Tg14-3-3 and TgWIP cause cells to move excessively. Dendritic cell hypermotility occurs in living tissue which makes the parasites difficult to detect by circulating immune cells according to research (Ólafsson et al., 2019).

Cell-Intrinsic Defense Mechanisms against *Toxoplasma gondii*

The lengthy co-evolutionary interaction between *T. gondii* and its mammalian host species appears in studies of pathways which human cells use to detect and eliminate the parasitic invader. Three primary *T. gondii* recognition pathways exist during infection which include the Toll like receptors (TLRs) and IFN-inducible GTPases together with inflammasomes. Activation of IL-12 secretion requires TLR and IL-1R as in figure 1 signals that pass through MyD88 for protection of the Th1 immune responses against *T. gondii* infection (Scanga et al., 2002). The experimental mice develop infection when this parasite enters their body through the abdominal area.

The parasite protein profilin from *T. gondii* triggers TLR11 activation by direct binding thus promoting IL-12 synthesis together with parasite control (Yarovinsky et al., 2005). The activation pathway for TLR11 signals through endosomal compartments indicates that the majority of activation occurs with phagocytosed dead or dysfunctional parasites because profilin remains sequestered inside parasites as an actin modifying protein. After oral infection TLR11-deficient mice displayed only minor Th1 response impairment compared to MyD88-deficient mice or mice lacking all TLR2, TLR4, TLR9 activity but antibiotic treatment of TLR11- deficient mice demonstrated similar MyD88-deficiency phenotypes. The research findings show gut commensal microbes activate protective *T. gondii* immune responses which occur without parasite detection through TLR11 (Ewald et al., 2014; Gov et al., 2017). Lavages of mice without NLRP3 or both caspase-1 and caspase-11 along with NLRP3 show elevated parasite levels in vitro (Coutermarsh-Ott et al., 2016). The mouse and human cells do not display pyroptosis when stimulated with inflammasome triggers despite extensive research on the NLRP1 protease anthrax lethal toxin and bacterial pathogens that

activate NLRP3. The activation of human monocyte NLRP3 inflammasome operates independently of TLR signaling through Syk and CARD9 pathways which drives IL-1β secretion without gasdermin D pores (Pandori et al., 2019). Scientists have multiple queries about the molecular activation of the inflammasome by *T. gondii* concerning parasite signaling pathways and the mechanisms preventing proptosis and possible parasite regulatory control. The latest scientific findings show that the inflammasome system communicates with IFN-inducible GTPases which monitor cellular membranes to clear foreign objects after IFN-γ production. The PVM attracts the dynamin-superfamily guanylate-binding protein 1 (GBP1) in human cells which results in an activation process. The infected host cell releases parasite DNA into its cytosol so it reaches the inflammasome detector protein AIM2 (Fisch et al., 2019). Researchers have not determined the reasons that prevent a pyroptic inflammasome response from occurring because it triggers an alternative apoptotic host cell death pathway. The p47 IRG family members of mice serve to identify the parasite vacuole post-IFN-γ stimulation while human cells lack this expansion. Mouse IRGM1 along with IRGM3 controls the presence of the IRGa6, IRGb6, and phospholipid complexes at the PVM (Lee et al., 2020). A wider set of mouse GBPs serves to eliminate *T. gondii* parasites although researchers have yet to understand how the parasite-killing process occurs. Scientists do not know how parasites get killed and host cells die in mouse cells (Yamamoto et al., 2012). The IRG system leads to parasite clearance through infected cell responses by which Type I parasites secrete ROP5 and ROP17 and ROP18 effectors which inactivate the GTPase activity of IRGa6 and IRGb6 proteins (Fleckenstein et al., 2012). The virulence of *T. gondii* parasites depends on specific alleles of Rop5 or Rop18 in type II and type III forms which fail to deactivate IRGs efficiently. Research has significantly established which classes of immune signals are cell-autonomously detected by *T. gondii* but an integrated understanding across mouse and human pathways remains difficult to achieve particularly when studying cell types beyond fibroblast, monocyte and macrophage.

Innate Regulation of Adaptive Immunity

The activation of innate immune sensors by *T. gondii* produces a Th1-polarized immune reaction maintained by CD8+ T cells which leads to host survival. Several outstanding articles explain the mechanisms behind the immunobiology of *T. gondii* infection. This chapter provides brief information about essential features of the acute immune response which supports chronic infection development. The parasite overgrowth during acute infection causes death of infected pathways in both mice and humans (Schlüter et al., 2003). The rarity of human IFN-γ and IL-12 deficiency relates to minimal observed links between this pathology and increased toxoplasmosis susceptibility but studies have shown defective *T. gondii* restriction for IFNGR1-deficient patient monocyte-derived macrophages during IFN-γ stimulation when compared to healthy-donor macrophages (Bustamante et al., 2014). The IL-6 pathway deficiency in mice causes insufficient B cell protection which results in death during early chronic infection phases as shown in figure 1 (JEBBARI et al., 1998). Host survival depends equally on IL-10 in combination with regulatory T cells whose function is to prevent excessive inflammatory response and tissue damage (Oldenhove et al., 2009). *T. gondii* effectors which control immune signaling mechanisms are now being identified in increasing numbers while being secreted into host cells. Many of the effectors which originate from rhoptries (ROP) and dense granules (GRA) move between strains and support virulence through secretory pathways. The GRA15 effector promotes NF-κB activation while GRA24 activates p38 MAPK to ensure production of IL-12 and IL-18 which act as regulators for IFN-γ and T cell activation.

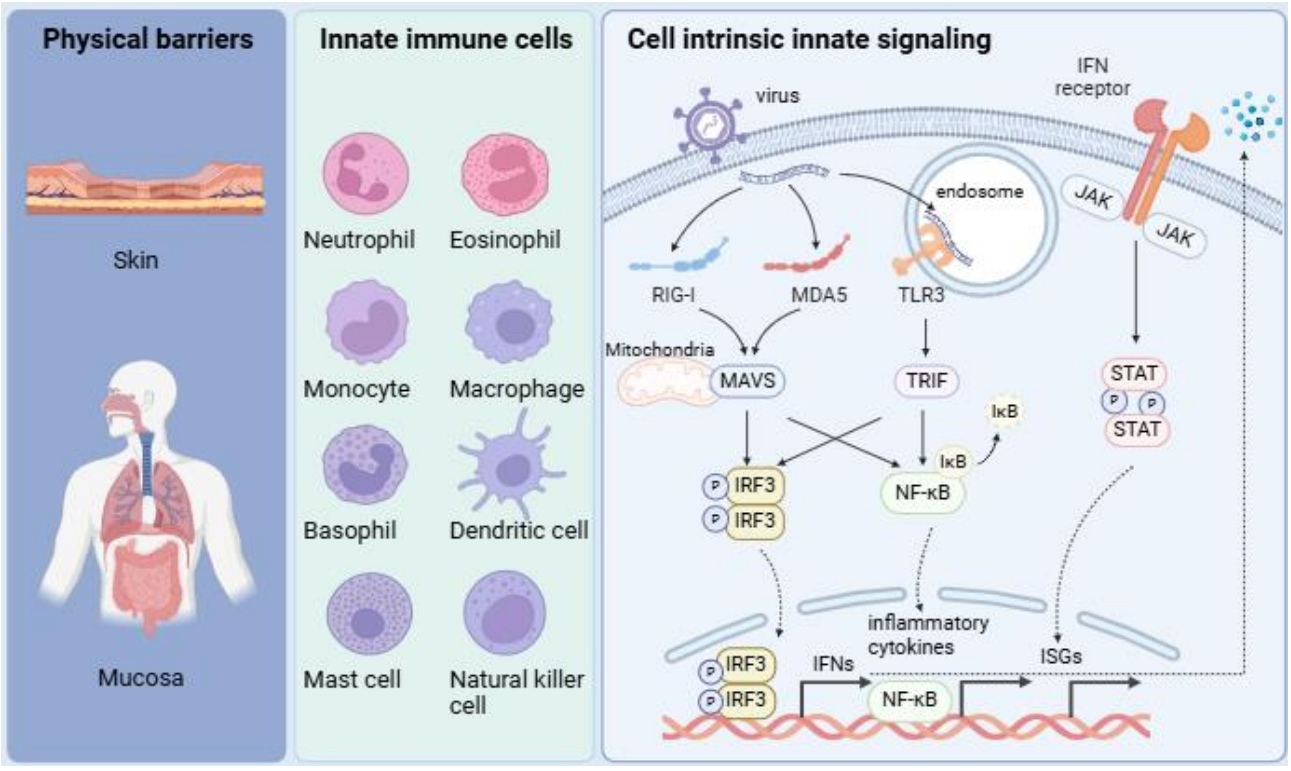

Fig. 1: Innate Immune Signaling

Parasite Invasion into the Brain

The central nervous system during chronic infection has the greatest number of parasites detected in each gram of tissue. A research interest has risen regarding *T. gondii* brain infection biology because of its potential effects on host behavior and homeostasis. The analysis of system infection depends mostly on the use of mouse infection models. The first unanswered question regarding parasite biology involves the BBB penetration process of the parasite. Observational microscopy techniques allowed researchers to study *T. gondii* replication inside brain endothelial cells leading to brain infiltration (Konradt et al., 2016). The brain tissue of mice exhibited higher parasite numbers when infected by *T. gondii* RH strain compared to CPS strain while CPS failed to replicate inside living organisms. During chronic *T. gondii* infection the increased BBB permeability is associated with reduced blood flow and narrowed capillaries that facilitate both immune cell and dye extravasation into the brain (Estato et al., 2018).

Monocytes accumulate at the BBB where they experience rolling followed by cradling behaviors (Schneider et al., 2019). Research evidence suggests immunocytes serve as transportation vehicles to enter the CNS after *T. gondii* infects them and changes their locomotion patterns. Research lacks available direct evidence about the Trojan horse hypothesis but using antibody technology scientists showed that eliminating CD11b+ leukocytes decreased brain parasite numbers.

Chronic Infection in the Central Nervous System

Studies of mouse brain sections together with extremely scarce human brain samples show that most cysts inside cells do not have corresponding immune responses. Different inflammatory regions found inside the same brain section show evidence of parasites or their remnants as well as microglial cells, macrophages and T cells in active states (Mendez & Koshy, 2017). When laboratory animals have their IFN-γ levels decreased and their CD4+ and CD8+ T cells removed parasites resurface in their bodies. The data from various studies implies intracellular cysts remain unnoticed by the immune system while immune cells swiftly contain cysts that either spontaneously rupture or experience recrudescence. Research which combines Cre recombinase expressing parasites with Cre reporter mice indicates neurons act as the primary brain cell that interacts with parasites yet T cells and monocytes or macrophages and microglia and astrocytes reveal early brain infection (Melzer et al., 2010). The obtained data implies that *T. gondii* shows no preference for neurons since it gets cleared from various other non-neuronal brain cell types. Research on mouse astrocytes with STAT1 transcription factor knockout produced more cysts in the tissue alongside increased parasite spread within astrocytes when IFN-γ signaling was inhibited. The protection mechanism of mouse astrocytes when exposed to IFN-γ depends on IRGM3 (IGTP) instead of iNOS; both proteins disrupt the PVM and trigger parasite egress which was observed in one study among others (Melzer et al., 2008).

Human astrocytes demonstrated *T. gondii* killing by producing iNOS in response to TNF- together with IFN-γ stimulation but also adopted tryptophan depletion through IDO induction when exposed to these cytokines. Research shows that the parasite effector TgGRA15 minimizes IDO-mediated parasite restriction in glioblastoma and neuroblastoma cell lines grown in culture (Bando et al., 2019). Multiple studies demonstrate that parasite killing functions of human and murine microglia become activated when exposed to IFN-γ along with TNF-α or LPS through iNOS-dependent pathways as well as pathways that do not rely on iNOS activity. Through producing IFN-γ and TNF-α microglia play an important role in limiting *T. gondii* brain infection (Freund et al., 2001). IFN-γ especially enhances the expression of adhesion molecules on vascular endothelial cells while stimulating brain CXCL9, CXCL10 and CCL5 production which attracts peripheral immune cells (Ochiai et al., 2015). The available data primarily emerge from laboratory dish tests but researchers need advanced systems to analyze this type of data in the brain environment.

Experimental data showing that MHC class I–deficient neurons can process *T. gondii* antigen for CD8+ T cell activation were obtained with OVA-expressing parasites, but how neurons display natural parasite peptides remains unknown. Studies demonstrate that CD8+ T cells which enter the brain control cyst burden primarily via their ability to produce IFN-γ. Research indicates that perforin enables parasite egress within cell culture but other immune cells seem responsible for actual parasite destruction through cell-based immunity (Persson et al., 2007). Also supporting this model is the fact that *T. gondii* clearance through perforin-mediated mechanisms should remain at a minimum since brain neurons possess a very low ability to regenerate themselves.

Parasitic Factors Influencing Cyst Formation and Chronic Infection

Medicine does not possess effective therapeutic tools for targeting bradyzoite cysts to sterilize chronic Toxoplasma infection. We understand the tachyzoites more than we do bradyzoites at the biological level. Scientific research has faced ongoing obstacles when attempting to modify bradyzoite-specific genes for necessary and sufficient experiments. Since CRISPR/Cas9 tools experienced recent exploration there has been advancement in this research domain. Stage conversion between tachyzoite and bradyzoite shows evidence of evolving from the former understanding of "switching" into a continuous process regulated by epigenetic factors and transcriptional mechanisms. The process of bradyzoite development requires cell stressors from alkaline medium or heat shock conditions or exposure to oxidative stress. The expression of bradyzoite genes occurs during IFN-γ treatment specifically within infected macrophages but not fibroblasts because differentiation signals differ by cell type. The infection of neuronal or skeletal muscle cells with *T. gondii* produces better bradyzoite marker expression together with increased cyst formation frequencies when compared to infected fibroblasts (Swierzy et al., 2017). Neurons and muscle cells are notoriously difficult to culture thus suggesting possible relevance of cell stress signals toward bradyzoite development in these systems. Research indicates that terminally differentiated myotubes support more bradyzoite development compared to dividing myoblast progenitor cells suggesting cell cycle provides cues needed for parasite development (Swierzy & Lüder, 2015).

The PVM of a bradyzoite *T. gondii* cyst wall becomes surrounded by heavily glycosylated proteins which leads to cyst definitions. The cyst wall enables parasite transmission by defending *T. gondii* from gastric proteases and protecting the parasite at the low stomach pH. When comparing the oral infectivity and pepsin resistance of *T. gondii* mutants with WT parasites the deficient population showed both higher susceptibility to enzyme degradation along with reduced transmission efficiency. Genes altered to prevent cyst glycoprotein expression

including the disruption of TgNST1 and TgCST1 result in abnormal cyst numbers together with unstable cysts and reduced oral infection success rates (Caffaro et al., 2013). Bradyzoites located inside the cyst wall stay protected from enzymatic attacks which occur during chronic infection. Alternative activated M2 macrophages produced by the Wilson laboratory succeeded in detecting and degrading chitin-like molecules found in cyst wall material. Scientific evidence reveals genetic variants within the human CHIA intergenic area that show connections to *T. gondii* infections (Wang et al., 2019).

Behavioral and Metabolic Alterations in Chronic *Toxoplasma gondii* Infection

Rodents infected with *T. gondii* develop an established loss of native avoidance responses towards cats because parasites might benefit from such transmission opportunity through predators. The primary cause between neural activity modifications and overall inflammatory patterns in producing behavioral changes remains a matter of investigation. Together with its two aromatic amino acid hydrolase enzymes AAH1 and AAH2, *T. gondii* produces l-DOPA which provides the basis to dopaminergic neuron control. The deletion of the AAH2 gene did not modify brain dopamine content or neuroinflammation in addition to behavioral abnormalities observed during *T. gondii* hypertension of mice although these genes prove essential for cat oocyst formation (Wang et al., 2017).

The disrupted behavior persists without persistent infection although chronic infection is not established. Behavioral changes that appear sustained in *T. gondii* infections are likely triggered by acute inflammation but the molecular causes behind these behavioral impacts remain unclear. Scientific research has identified trace amine-associated receptor 4 (TAAR4) as an olfactory GPCR which detects 2-phenylethylamine a compound found at high concentrations in predator urine including felines. Among humans there is no trace of the TAAR4 gene yet mice without TAAR4 fail to avoid spaces scented with bobcat and mountain lion urine (Ferrero et al., 2011). It remains essential to conduct laboratory studies to investigate whether *T. gondii* infection damages or changes these brain areas.

The hallmark of *T. gondii* infection involves long-term immune system contact which is shown by high *T. gondii*-specific IgG and sera cytokine levels in human beings and mice during chronic stages of infection. A growing number of studies connects *T. gondii* infection with mouse cachexia which represents a continuous immune-metabolic muscle wasting disorder. The severity of cachexia grows directly proportional to both parasite quantity and inflammatory conditions yet dietary supplementation fails to reverse the metabolic hyperactivity that causes weight loss. A dysbiotic community fails to cause cachexia although its presence cannot exclude the possibility of intestinal barrier inflammation resolution in oral infection. The research suggests that commensal dysbiosis alone is inadequate to induce cachexic outcomes even though infected mice develop comparable intestinal bacterial populations compared to nondiseased cage mates. Conclusion reveals that volcanic mice who experienced chronic infection sustain permanent structural changes in their lymph nodes and spleen which escalates their vulnerability to secondary viral infection. The biology of *T. gondii* seems to influence rodent behavior and body wasting which provides the parasite with better chances for transmission to appropriate feline hosts. No medical studies report the presence of cachexia in immune-healthy individuals who have chronic *T. gondii* infections. Current experimental tools lack effectiveness to investigate sustained disease while cachexia serves as a mortality predictor in every type of chronic human illness. The study of *T. gondii* and mice interaction remains an effective model to understand disease mechanisms. The cachexia pathophysiological processes provide knowledge that can help explain other medical conditions.

Conclusions and Future Directions

The establishment and maintenance of persistent chronic infections by *T. gondii* forms an essential requirement for parasite transmission processes. Scientists understand only partly this infection stage in animals and humans. The advanced sequencing techniques exposed *T. gondii* contains wider gene diversity than previously understood and this discovery enabled scientists to examine how parasite genetic factors affect chronic infection pathologies. CRISPR/Cas9 tools give researchers enhanced capabilities to experiment with *T. gondii* genome sequences in order to study bradyzoite gene expression patterns and their effects on parasite differentiation and cyst stability as well as oral transmission. The biology of bradyzoites directly relates to how the immune system responds in chronic *T. gondii* infection. The study needs to explore cell-autonomous protective mechanisms against chronic *T. gondii* brain infections along with determining the health impacts brought by ongoing inflammatory responses. To create effective therapeutic strategies that target bradyzoite cysts researchers need better knowledge of their biological characteristics. Studies aiming to understand the immune relationship between mammals and *T. gondii* remain significant because these species coevolved together over a long history. The study has potential to find crucial insights about immune control during the persistent inflammatory state.

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