Original Research Article

The Egyptian Journal of Immunology

Immune modulation and evasion by *Toxoplasma gondii*: Roles of IFN-γ, TNF-α, IL-10, and IgM in murine infection

The Egyptian Journal of Immunology,
E-ISSN (2090-2506)
Volume 33 (3), July, 2026
Pages: 09–18.
www.Ejimmunology.org
https://doi.org/10.55133/eji.330302

Rahma E. A. Eldeghedy[1], Mohamed H. Emam[2], Ibrahim R. Shalash[3], Mahmoud E. Elshahat[1], Mohammed S. El Faramawy[2], Noha F. Zahran[1] and Tarek K. Zaalouk[2]

[1]Department of Medical Parasitology, Faculty of Medicine, Al-Azhar University, Damietta, Egypt.
[2]Department of Medical Parasitology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
[3]Department of Medical Parasitology, Theodor Bilharz Research Institute, Giza, Egypt.

Corresponding author: Tarek K. Zaalouk, Department of Medical Parasitology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
Email: tkzaalouk@gmail.com

Abstract

Toxoplasma gondii persists lifelong in the host by manipulating the balance between protective T helper type 1 (Th1) immunity and regulatory pathways that limit immunopathology. Among these regulators, interleukin-10 (IL-10) is proposed to be a pivotal suppressor of anti-parasite immunity, yet its precise functional contribution during chronic toxoplasmosis remains incompletely defined. This study dissected the immunoregulatory role of IL-10 during experimental *T. gondii* infection by integrating analyses of brain cyst kinetics, systemic cytokine dynamics, humoral responses, correlation networks, and tissue pathology. The study included 45 female Swiss albino mice, divided in three equal groups (G), G1 non-infected; G2, *T. gondii*–infected mice; and G3, *T. gondii*–infected mice and treated with anti-IL-10 monoclonal antibody. Mice were infected intraperitoneally with 10 ME49 cysts and G3 were treated with anti-IL-10 mAb starting one-week post-infection. Mice were sacrificed at 14-, 28-, and 42-days post-infection for brain cyst counting, liver and brain histopathology, and measurement of serum IFN-γ, TNF-α, IL-10, and IgM by ELISA. Infection induced robust elevations of IFN-γ and TNF-α, confirming a dominant Th1 response essential for early parasite control. IL-10 level increased concurrently, indicating activation of a compensatory regulatory axis. IL-10 neutralization dramatically reshaped disease outcomes: anti-IL-10–treated mice exhibited significantly reduced cerebral cyst burdens and heightened IgM levels, accompanied by pronounced amplification of IFN-γ and TNF-α response. Network analysis revealed strong positive coupling between IFN-γ and TNF-α, while IL-10 displayed marked negative correlations with both cytokines, identifying IL-10 as a master suppressor of inflammatory immunity. However, IL-10 blockades resulted in severe hepatic and neural tissue damage, demonstrating the cost of unrestrained inflammation. IL-10 mediates a crucial balance in toxoplasmosis by suppressing protective Th1 immunity to allow parasite persistence while preventing lethal immunopathology, highlighting its potential as a therapeutic target in severe or reactivated disease.

Keywords: *Toxoplasma gondii*; IL-10; Th1 immunity; IFN-γ; TNF-α; Immunoregulation; Chronic infection.

Date received: 23 December 2025; **accepted:** 16 April 2026

Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite and a major zoonotic pathogen with significant global distribution.[1] Human infection occurs through ingestion of oocysts from contaminated food or water, consumption of undercooked meat harboring tissue cysts, or trans placental transmission during primary maternal infection.[2,3] Although infection in immunocompetent individuals is often asymptomatic or self-limiting, severe disease can develop in immunocompromised patients and congenitally infected infants, in whom toxoplasmosis may result in spontaneous abortion, hydrocephalus, and ocular sequelae.[4]

Effective host resistance to *T. gondii* is primarily mediated by a robust T helper type 1 (Th1)-polarized immune response. Interferon-gamma (IFN-γ) represents the central cytokine in protective immunity, driving macrophage activation, nitric oxide production, and induction of immunity-related GTPases essential for restricting intracellular tachyzoite replication.[5-7]

Tumor necrosis factor-alpha (TNF-α) acts synergistically with IFN-γ to amplify antimicrobial effector pathways and sustain inflammatory microenvironments required for early parasite control.[8,9]

Despite the potency of these pro-inflammatory mechanisms, *T. gondii* has evolved sophisticated immune-evasion strategies that modulate host responses to ensure long-term persistence. A key component of this modulation is the induction of regulatory cytokines, particularly interleukin-10 (IL-10), which suppresses excessive Th1 activity.[10,11] Elevated IL-10 dampens IFN-γ and TNF-α production, reduces antigen-presenting cell function, and facilitates parasite survival during both acute and chronic stages of infection.[12-14] Experimental IL-10 blockade in murine models enhances parasite clearance but leads to severe immunopathology, underscoring the delicate balance between protective immunity and tissue damage.[15,16]

Humoral immune responses also contribute to host defense against *T. gondii*. Parasite-specific immunoglobulin M (IgM) appears early after primary infection and participates in tachyzoite containment through opsonization and complement activation.[17,18] Although transient, IgM serves as an important marker of recent infection and supports early parasite control prior to the development of class-switched antibody responses.[18]

Understanding the coordinated actions of IFN-γ, TNF-α, IL-10, and IgM, as well as the parasite's ability to manipulate these pathways, is essential for elucidating the immunological mechanisms underlying susceptibility, persistence, and pathogenesis in toxoplasmosis. Such insights may inform the development of improved diagnostic approaches and targeted immunomodulatory strategies.

Materials and Methods

The study adhered to the TBRI Guidelines for the Ethical Use of Animals in Research and complied with the principles of the Declaration of Helsinki.[19] The study was conducted at the Biological Unit of the TBRI, Giza, Egypt, from October 2024 to September 2025.

Parasites

T. gondii ME49 strain was obtained from the Parasitology Department, TBRI. The strain was maintained through serial passage in Swiss albino mice by intraperitoneal inoculation of 0.1 ml of brain homogenate containing approximately 1×10^2 tissue cysts/ml. Chronic infection was established over six weeks following the protocol of Djurković-Djaković et al., 2002.[20]

Mice and Experimental Infection

A total of 45 laboratory-bred female Swiss albino mice, aged six weeks and weighing 20–25 g, were used in this study. Animals were housed in groups of two to three per cage in wire-floored cages under controlled environmental conditions (25 °C; 12 h light/12 h dark cycle) and provided with sterile water and a balanced commercial dry diet containing 14% protein, as previously described by Grujić et al., 2005.[21]

Mice were randomly assigned into three equal groups (n = 15): G1, non-infected control mice; G2, *T. gondii*–infected mice; and G3, *T.*

gondii–infected mice and treated with anti-IL-10 monoclonal antibody.

T. gondii tissue cysts were enumerated using a hemocytometer, and the suspension was adjusted to 10^2 cysts/ml in sterile saline. Mice in G2 and G3 were inoculated intraperitoneally with 0.1 ml of the suspension (10 cysts per mouse), as previously described.[20] Control mice (G1) received an equal volume of sterile saline. Animals were sacrificed at 14-, 28-, and 42-days post-infection (dpi).

Neutralization of IL-10 was performed using a rat anti-mouse IL-10 monoclonal antibody (BioSource International, Camarillo, CA, USA). The antibody was administered intraperitoneally, starting one-week post-infection, at a dose of 62.5 µg per mouse, and subsequently every third day until two days before sacrifice.

Parasitological Assessment

At 14-, 28-, and 42-days post-infection, mice were sacrificed and their brains removed. Brain suspensions were prepared in 1 ml saline using a tissue homogenizer (Wheaton, USA). A 0.1 ml aliquot of each suspension was examined microscopically, and tissue cysts were counted across 10 high-power fields (HPF).[20]

Histopathological Examination

Brain and liver tissues were collected from all mice, fixed in 10% neutral buffered formalin, processed, and embedded in paraffin. Sections (5 µm) were stained with hematoxylin and eosin (H&E) and examined under a light microscope according to the method described by Macsween et al., 1997.[22]

Blood Sample Collection

Blood samples were obtained by caudal vein puncture. Sera were separated by centrifugation at ~1000 ×g for 5 minutes, transferred into sterile Eppendorf tubes, and stored at −20 °C until further cytokine and immunoglobulin analysis.

Cytokine and IgM Determination

Serum concentrations of IFN-γ, TNF-α, IL-10, and *Toxoplasma*-specific IgM antibodies were measured using commercial mouse enzyme-linked immunosorbent assay (ELISA) kits (BioSource International, Camarillo, CA, USA) following the manufacturer's instructions. All assays were performed in duplicate, and absorbance was read using a microplate reader at the appropriate wavelength.

Statistical Analysis

Data were verified, coded, and analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Results were expressed as mean ± standard deviation (SD). Statistical significance between groups was determined using a two-tailed Student's t-test for unpaired samples. A p-value < 0.05 was considered statistically significant.

Results

Serum IFN-γ Responses in T. gondii–Infected Mice

Serum IFN-γ concentrations were quantified at 14, 28, and 42 dpi in all experimental groups (Figure 1A). Normal control mice (G1) maintained consistently low IFN-γ levels throughout the study period (5±0.43, 7±0.65, and 8±0.76 pg/ml, respectively). In contrast, infection with *T. gondii* induced a marked Th1-polarized response in infected control mice (G2), with IFN-γ levels peaking at 14 dpi (210 ± 19.7 pg/ml) and gradually declining at 28 dpi (103 ± 9.8 pg/ml) and 42 dpi (57±4.71 pg/ml) (p<0.01 vs. G1).

Notably, mice receiving anti-IL-10 monoclonal antibody (G3) exhibited a pronounced augmentation of IFN-γ production at all-time points, reaching 415.2±39.7 pg/ml, 295±27.1 pg/ml, and 199±18.3 pg/ml at 14, 28, and 42 dpi, respectively (p<0.05 vs. G2). These findings demonstrated that *T. gondii* infection elicits a robust IFN-γ –driven immune response that is tightly constrained by IL-10–mediated regulation.

Serum TNF-α Responses

TNF-α levels displayed a pattern similar to IFN-γ, reflecting coordinated Th1-associated inflammatory activation (Figure 1B). Infected control mice showed a significant elevation in TNF-α compared with normal controls at all-

time points (p<0.001), with peak levels detected at 14 dpi (2491±239.2 pg/ml), followed by a progressive decline at 28 dpi (1715±169.7 pg/ml) and 42 dpi (474±43.6 pg/ml).

Neutralization of IL-10 markedly intensified TNF-α production. The infected/anti-IL-10 group exhibited significantly higher TNF-α concentration than infected controls, measuring 5019±478 pg/ml, 3341±297 pg/ml, and 1663±157 pg/ml at 14, 28, and 42 dpi, respectively (p<0.05 vs. G2). These results indicated that IL-10 plays a critical role in suppressing excessive TNF-α–mediated inflammation during toxoplasmosis.

Serum IL-10 Levels and Confirmation of Effective Cytokine Neutralization

Baseline IL-10 levels in normal control mice remained low and stable throughout the experimental period (7.9 ± 0.66 pg/ml, 10.23 ± 0.77 pg/ml, and 10.68 ± 0.82 pg/ml at 14, 28, and 42 dpi, respectively; Figure 1C). Infection with *T. gondii* induced a pronounced up-regulation of IL-10, with serum concentrations rising sharply at 14 dpi (863.7±58.7 pg/ml), peaking at 28 dpi (1775.8±176.3 pg/ml), and remaining elevated at 42 dpi (1197.9 ± 99.8 pg/ml) (p< 0.001 vs. G1).

Administration of anti-IL-10 monoclonal antibody resulted in a significant reduction of circulating IL-10 at all-time points (p< 0.003), confirming effective cytokine blockade. IL-10 levels decreased to 218.9 ± 16.2 pg/ml, 451.8±30.3 pg/ml, and 320.1± 29.7 pg/ml at 14, 28, and 42 dpi, respectively. The inverse relationship between IL-10 and Th1 cytokines underscores IL-10's dominant regulatory role in modulating inflammatory immunity during infection.

Correlation Analysis among Serum IFN-γ, *TNF-α, and IL-10 Demonstrates Immune Modulation and Evasion during T. gondii Infection*

To elucidate the immunoregulatory interactions that shape host responses during *T. gondii* infection, the Pearson correlation analysis was performed on $\log_{10}$-transformed serum concentrations of IFN-γ, TNF-α, and IL-10 in infected control mice (G2) at 14, 28, and 42 dpi (Figure 2).

A strong positive correlation was observed between IFN-γ and TNF-α (r = 0.94, p< 0.05), reflecting the tightly coordinated Th1-mediated pro-inflammatory axis essential for early control of tachyzoite replication. Both cytokines reached maximal expression at 14 dpi, followed by a marked decline at later time points, indicating attenuation of the inflammatory response as infection progressed.

Conversely, IFN-γ exhibited a moderate negative correlation with IL-10 (r = –0.85, p< 0.05), and TNF-α similarly correlated negatively with IL-10 (r = –0.78, p< 0.05). IL-10 levels progressively increased, peaking at 28 dpi, coinciding with the downturn in IFN-γ and TNF-α. This inverse relationship underscores IL-10's critical role in moderating Th1-driven inflammation and preventing host-mediated tissue damage.

Importantly, the temporal rise in IL-10 concurrent with declining pro-inflammatory cytokines reflects a parasite-favorable environment. By promoting regulatory pathways and dampening Th1 effector mechanisms, elevated IL-10 facilitates *T. gondii* immune evasion, supporting its transition from acute tachyzoite proliferation to chronic bradyzoite persistence.

Collectively, these findings highlight a dynamic immunological balance in which IL-10-mediated modulation suppresses protective IFN-γ/TNF-α responses, thereby enabling long-term parasite survival while limiting immunopathology.

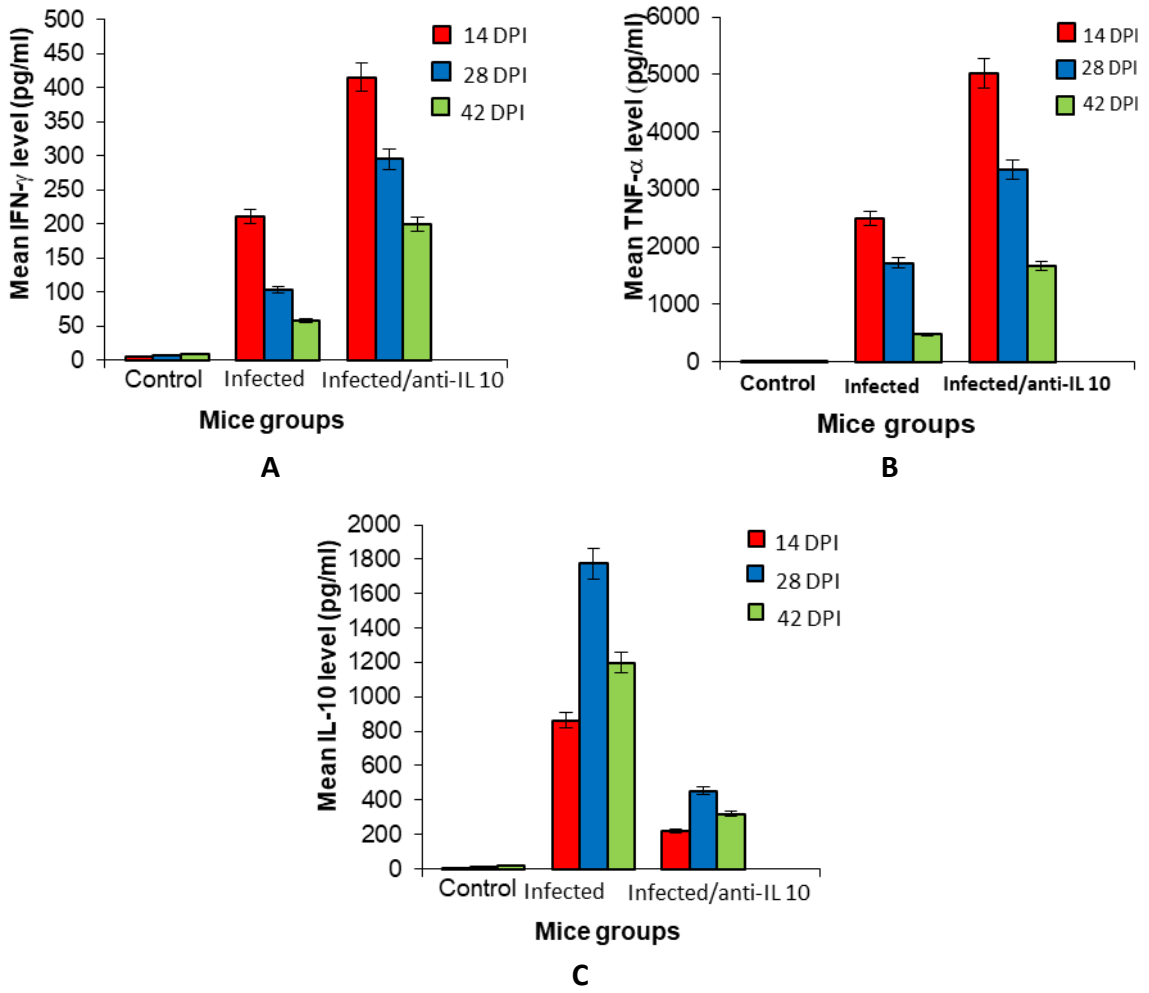

Figure 1. Serum cytokine responses in *Toxoplasma gondii*–infected mice and the effect of IL-10 neutralization. (A) Serum IFN-γ levels measured at 14-, 28-, and 42-days post-infection (dpi) in normal control mice (G1), infected control mice (G2), and infected mice treated with anti-IL-10 monoclonal antibody (G3). Infection induced a significant elevation in IFN-γ compared to normal controls, with the highest levels observed in the anti-IL-10–treated group ($p<0.05$). (B) Serum TNF-α level at corresponding time points. TNF-α was markedly increased in infected mice relative to controls ($p<0.001$), and IL-10 neutralization further amplified TNF-α production ($p<0.05$). (C) Serum IL-10 levels showing minimal concentrations in normal controls and a significant increase following *T. gondii* infection ($p< 0.001$). Administration of anti-IL-10 monoclonal antibody resulted in a substantial reduction of circulating IL-10 ($p<0.003$), confirming effective cytokine neutralization. Values are expressed as mean ± SD. Statistical significance was assessed using one-way analysis of variance (ANOVA) followed by appropriate post-hoc tests.

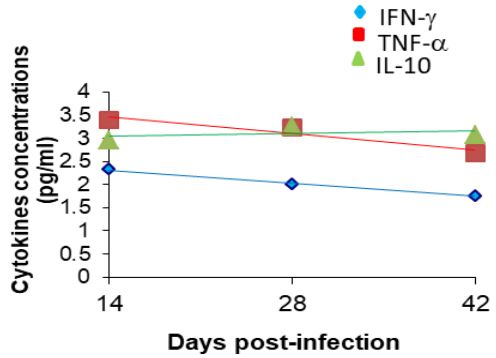

Figure 2. Logarithmic correction of serum cytokine levels during *Toxoplasma gondii* infection. Line graph showing the $\log_{10}$-transformed concentrations of IFN-γ, TNF-α and IL-10 measured at 14-, 28-, and 42-days post-infection (dpi). IFN-γ exhibited a progressive decline across the infection period, reflecting attenuation of the Th1 response during the chronic phase. TNF-α showed a marked decrease by 42 dpi following an early peak at 14 dpi. IL-10 displayed a modest elevation at 28 dpi before declining toward 42 dpi, indicating regulatory immune activation. Data represent mean cytokine levels used for logarithmic conversion.

Serum Levels of Toxoplasma-Specific IgM

Toxoplasma-specific IgM antibodies were measured to assess early humoral immune activation (Figure 3). Infected control mice (G2) exhibited significantly elevated IgM levels at 14 dpi (134.2 ± 15.0 IU/ml), followed by a gradual decline at 28 dpi (73.4 ± 6.9 IU/ml) and 42 dpi (38.0 ± 4.0 IU/ml), consistent with progression toward chronic infection and antibody class switching. Normal control mice maintained baseline IgM concentrations throughout the study.

IL-10 neutralization significantly enhanced IgM responses at all-time points. Anti-IL-10–treated mice displayed IgM levels of 210.0 ± 19.0 IU/ml, 140.0 ± 12.0 IU/ml, and 85.0 ± 7.9 IU/ml at 14, 28, and 42 dpi, respectively ($p < 0.05$ vs. G2), indicating that IL-10 suppresses early humoral immunity during *T. gondii* infection.

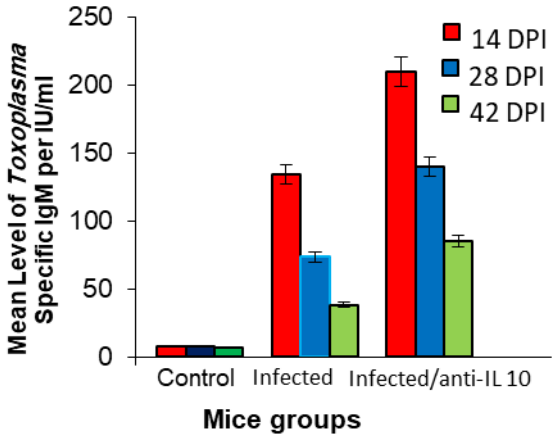

Figure 3. *Toxoplasma*-specific IgM concentrations measured by ELISA in serum of experimental mouse groups. IgM levels were significantly higher in infected/anti-IL-10-treated mice (G3) than in infected controls (G2) and normal controls (G1) at all-time points ($p < 0.05$). Values are shown as mean ± SD.

Mean Number of Toxoplasma gondii Brain Cysts

Brain cyst burden was evaluated as a marker of chronic parasite persistence (Figure 4). No cysts were detected in either infected group at 14 dpi, consistent with the acute tachyzoite phase. By 28 dpi, tissue cysts were evident in both groups; however, infected control mice exhibited significantly higher cyst counts (278.0 ± 29.8) compared with anti-IL-10–treated mice (158.0 ± 20.6) ($p < 0.05$).

At 42 dpi, cyst burden increased markedly in both groups, yet remained significantly higher in infected controls (3086.0 ± 192.5) than in IL-10-neutralized mice (1750.0 ± 160.2) ($p< 0.05$). These findings demonstrate that IL-10 promotes parasite persistence and cyst establishment during chronic toxoplasmosis.

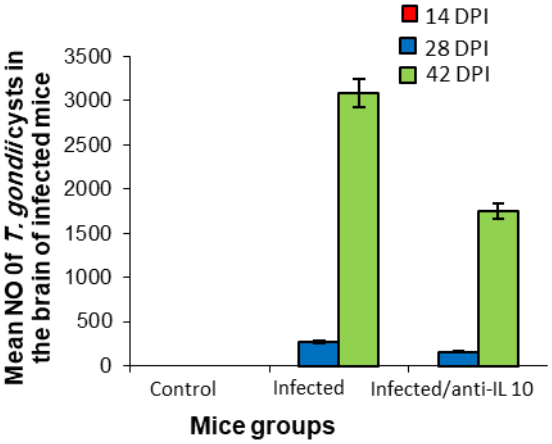

Figure 4. Brain cyst burden of *T. gondii*-infected mice at different time points post-infection. Cyst counts remained undetectable at 14 dpi in both infected groups. At 28 and 42 dpi, the infected control group (G2) showed significantly higher cyst numbers than the anti-IL-10-treated group (G3) ($p < 0.05$). Values represent mean ± SD.

Histopathological Changes in the Liver of Toxoplasma gondii–Infected Mice

Liver samples were formalin-fixed, paraffin-embedded, sectioned at 5 µm, H&E-stained, and evaluated under a light microscope. In infected control mice, liver sections showed multifocal inflammatory infiltrates and mild hepatocellular degeneration at 14 dpi, progressing to more pronounced periportal inflammation and focal necrosis at 28 dpi, with persistent but organized chronic lesions at 42 dpi. In contrast, anti-IL-10–treated mice exhibited markedly exacerbated pathology, including extensive inflammatory infiltrates, widespread hepatocellular necrosis, and severe parenchymal destruction at all-time points, demonstrating loss of inflammatory control (Figure 5).

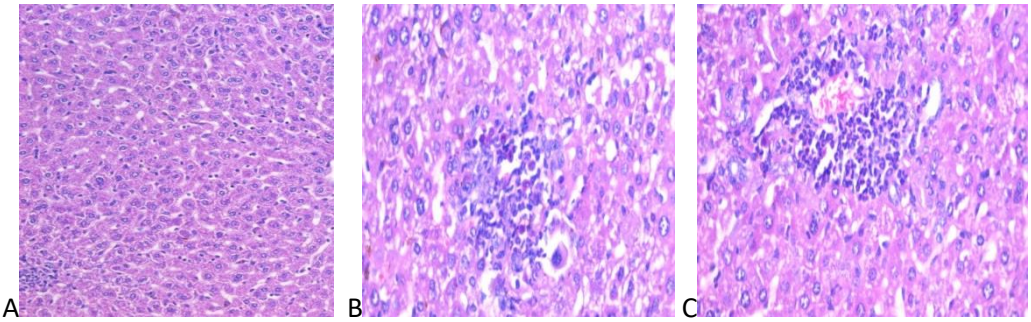

Figure 5. Histopathological alterations in the liver of the experimental groups. (A) Normal control mice showing preserved hepatic architecture. H&E, ×200. (B) Infected control mice at 42 dpi showing *T. gondii* cysts, mild hepatocellular degeneration, and moderate lymphocytic infiltration, consistent with relatively regulated IL-10–mediated inflammation. H&E, ×400. (C) *T. gondii*-infected mice treated with anti-IL-10 at 42 dpi showing vascular congestion, sinusoidal dilatation, vacuolization, granuloma formation, necrosis, and severe inflammatory infiltration, indicating dysregulated inflammation following IL-10 neutralization. H&E, ×400.

Histopathological Alterations in the Brain during T. gondii Infection

Brain tissues from all mice groups were fixed in 10% neutral buffered formalin, paraffin-embedded, sectioned (5 µm), stained with H&E, and examined microscopically. Infected control mice developed typical toxoplasmic encephalitis, characterized by mild perivascular cuffing and gliosis at 14 dpi, moderate inflammatory infiltration and tissue cyst formation at 28 dpi, and localized chronic lesions at 42 dpi. Anti-IL-10–treated mice showed substantially more severe neuropathology, with diffuse gliosis, neuronal degeneration, dense inflammatory infiltrates, necrotic foci, and increased parasite burden, particularly at 28 and 42 dpi (Figure 6).

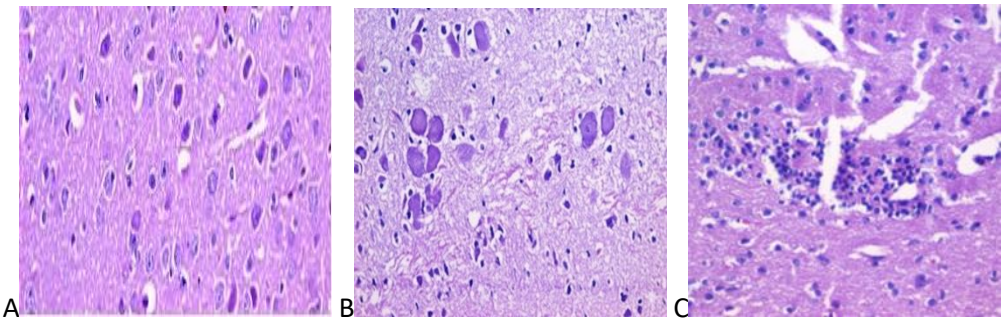

Figure 6. Histopathological alterations in the brain of the experimental groups. (A) Normal control mice showing preserved neural architecture with minimal inflammatory infiltration (H&E, ×200). (B) Infected control mice at 42 dpi showing intact and disrupted *T. gondii* cysts, mild neuronal degeneration, and limited lymphocytic infiltration, consistent with regulated IL-10–mediated inflammation (H&E, ×400). (C) *T. gondii*-infected mice treated with anti-IL-10 at 42 dpi showing marked neuronal degeneration, focal lymphocytic infiltration, and interstitial edema, indicating exacerbated neuroinflammation following IL-10 neutralization (H&E, ×400).

Discussion

This study provided a comprehensive analysis of the dynamic immunoregulatory networks that shape host–parasite interactions during *T. gondii* infection, with particular emphasis on the central role of IL-10 in balancing protective immunity and immunopathology. IL-10 emerges as a pivotal immunological checkpoint that fine-tunes Th1-driven responses, thereby enabling parasite persistence while safeguarding host tissues from excessive inflammatory damage.[1,2]

In the present study, the early and robust induction of IFN-γ and TNF-α reflected effective activation of innate and adaptive Th1 immune responses, which are essential for controlling acute *T. gondii* replication. These findings are consistent with previous studies, reported that IFN-γ and TNF-α are key cytokines in the host immune response to *T. gondii*, acting synergistically to inhibit parasite growth.[3,4] IFN-γ, produced predominantly by natural killer cells and $CD4^+$ and $CD8^+$ T lymphocytes, activates infected macrophages and microglia, promoting intracellular parasite killing through induction of nitric oxide synthase, indoleamine 2,3-dioxygenase, and immunity-related GTPases.[5-7] TNF-α synergizes with IFN-γ to enhance macrophage microbicidal activity, promote granuloma formation, and restrict parasite dissemination.[8,9] Our findings of a strong positive correlation between IFN-γ and TNF-α during early infection underscore the coordinated inflammatory signaling required for efficient parasite control.

Our observations of a progressive decline in IFN-γ and TNF-α levels during the later stages of infection, concomitant with a marked rise in IL-10, indicate a deliberate immunological shift toward regulation and tolerance. IL-10 is produced by multiple immune subsets during toxoplasmosis, including regulatory T cells, type 1 regulatory (Tr1) cells, alternatively activated macrophages, and effector Th1 cells themselves.[10-13] Through inhibition of antigen presentation, down-regulation of major histocompatibility complex (MHC) class II and costimulatory molecules, and suppression of pro-inflammatory cytokine production, IL-10 effectively restrains excessive Th1 activity and limits immune-mediated tissue injury.[14]

Our results demonstrated that the functional significance of this regulatory axis is further supported by IL-10 neutralization, which resulted in sustained elevation of IFN-γ and TNF-α throughout the course of infection. These findings are consistent with previous reports demonstrating that IL-10 acts as a dominant negative feedback regulator of Th1 responses during toxoplasmosis and other intracellular infections.[15,16] While this suppression preserves host tissue integrity, it simultaneously creates a permissive environment for parasite survival and chronic persistence.

Humoral immunity was similarly modulated by IL-10–mediated regulation. In the present study, enhanced IgM responses following IL-10 blockade indicated that IL-10 suppresses early B-cell activation and antibody production, likely through the inhibition of dendritic cell maturation and T-cell–dependent B-cell help. These findings are consistent with previous reports demonstrating that, given the critical role of IgM in opsonization, complement activation, and neutralization of extracellular tachyzoites, IL-10–dependent suppression of humoral immunity may further promote parasite persistence.[17,18,23]

Importantly, IL-10 blockades significantly reduced cerebral cyst burden, providing direct evidence that regulatory suppression contributes to the establishment and maintenance of chronic toxoplasmosis. [24,25] Sustained IFN-γ –dependent activation of microglia and astrocytes likely enhances control of bradyzoite differentiation and survival within the central nervous system.[26,27] However, this improved parasite control came at the cost of severe hepatic and cerebral pathology, characterized by excessive inflammatory infiltrates, necrosis, and neuronal damage. These findings are consistent with earlier studies demonstrated that IL-10 deficiency or blockade leads to fatal immunopathology despite improved parasite clearance.[28,29]

Collectively, these findings highlight the dual and paradoxical role of IL-10 in *T. gondii* infection. While IL-10 undermines optimal parasite elimination and promotes chronic

infection, it is indispensable for preventing excessive inflammation and preserving host survival.[30-32] This delicate immunological balance illustrated how *T. gondii* exploits host regulatory pathways to evade immunity while avoiding lethal immunopathology. Targeted and context-dependent modulation of IL-10 signaling may therefore represent a promising therapeutic strategy for controlling severe or reactivated toxoplasmosis without precipitating excessive tissue damage.[33-35]

Author Contributions

REAE and IRS; planned and participated in the study design, performed the laboratory work, made critical reviews and approved the final version. TKZ; the corresponding author, planned & participated in the study design, analyzed the data, wrote the manuscript, made critical reviews and approved the final version. MHE, MEE, MSE and NFZ; planned and participated in the study design, data interpretation and wrote the manuscript, and made critical reviews and approved the final version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study protocol was reviewed and approved by the Research Ethics committee for animal research (dated 10/2024). All animal procedures were performed in accordance with the ethical standards and policies approved by the Ethics Committee of Theodor Bilharz Research Institute (TBRI).

ORCID iD

Tarek K. Zaalouk iD https://orcid.org/0000-0001-8395-3373..

References

1. Gazzinelli RT, Wysocka M, Hayashi S, et al. (1994). Parasite-induced interleukin-12 stimulates early interferon-gamma synthesis and resistance during acute infection with *Toxoplasma gondii*. *J Immunol.* 153(6):2533–2543.

2. Suzuki Y, Orellana MA, Schreiber RD, et al. (1988). Interferon-gamma: the major mediator of resistance against *Toxoplasma gondii. Science.* 240(4851):516–518.

3. Denkers EY, Gazzinelli RT. (1998). Regulation and function of T-cell-mediated immunity during *Toxoplasma gondii* infection. *Clin Microbiol Rev.* 11(4):569–588.

4. Hunter CA, Sibley LD. (2012). Modulation of innate immunity by *Toxoplasma gondii* virulence effectors. *Nat Rev Microbiol.* 10(11):766–778.

5. Pfefferkorn ER. (1984). Interferon-gamma blocks the growth of *Toxoplasma gondii* in human fibroblasts by inducing the host cells to degrade tryptophan. Proc Natl Acad Sci USA. 81(3):908–912.

6. Taylor GA, Collazo CM, Yap GS, et al. (2000). Pathogen-specific loss of host resistance in mice lacking the IFN-gamma-inducible gene IGTP. *Proc Natl Acad Sci USA*. 97(2):751–755.

7. Yap GS, Sher A. (1999). Cell-mediated immunity to *Toxoplasma gondii*: initiation, regulation and effector function. *Immunobiology.* 201(2):240–247.

8. Jankovic D, Kullberg MC, Feng CG, et al. (2007). Conventional T-bet^{+} Foxp3^{-} Th1 cells are the major source of host-protective regulatory IL-10 during intracellular protozoan infection. *J Exp Med.* 204(2):273–283.

9. Saraiva M, O'Garra A. (2010). The regulation of IL-10 production by immune cells. *Nat Rev Immunol.* 10 (3):170–181.

10. Moore KW, de Waal Malefyt R, Coffman RL, et al. (2001). Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol.* 2001; 19:683–765.

11. Suzuki Y, Sher A, Yap GS, et al. (2000). Interleukin-10 is required to prevent necrosis in the small intestine and mortality during acute *Toxoplasma gondii* infection. *J Immunol.* 164(10):5375–5382.

12. Gazzinelli RT, Oswald IP, James SL, et al. (1992). Interleukin-10 inhibits parasite killing and nitric oxide production by interferon-gamma–activated macrophages. *J Immunol.* 148(6):1792–1796.

13. Kang H, Remington JS, Suzuki Y. (2000). Decreased resistance to *Toxoplasma gondii* infection in B cell-deficient mice. *Infect Immun.* 68(2):823–831.

14. Wilson EH, Wille-Reece U, Dzierszinski F, et al. (2005). A critical role for IL-10 in limiting inflammation during toxoplasmic encephalitis. *J Neuroimmunol.* 165(1–2):63–74.

15. Schluter D, Deckert M, Hof H, et al. (1999). Toxoplasma encephalitis: immunopathological

mechanisms in the central nervous system. *Am J Pathol.* 154(4):1259–1270.

16. Neyer LE, Grunig G, Fort M, et al. (1997). Role of interleukin-10 in regulation of immunity and pathology during *Toxoplasma gondii* infection. *J Immunol.* 158(7):3089–3096.

17. O'Garra A, Vieira PL, Vieira P, et al. (2004). IL-10-producing and naturally occurring $CD4^+$ regulatory T cells: limiting collateral damage. *J Clin Invest.* 114(10):1372–1378.

18. Fillatreau S, Gray D, Anderton SM. (2008). Not always the bad guys: B cells as regulators of autoimmune pathology. *Nat Rev Immunol*. 2008;8(5):391–397.

19. World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013; 310(20):2191–2194.

20. Djurković-Djaković O, Djokić V, Vujanić M, et al. (2002). Murine model of drug-induced reactivation of *Toxoplasma gondii*. *Acta Protozool*. 40:99–106.

21. Grujić J, Djurković-Djaković O, Nikolić A, et al. (2025). Effectiveness of spiramycin in murine models of acute and chronic toxoplasmosis*. Int J Antimicrob Agents*. 2005; 25(3):226–230.

22. MacSween RNM, Whaley K, Burt AD. (1997). Muir's Textbook of Pathology. 14th ed. London: *Arnold Publishers;* 1997.

23. Khan IA, Ouellette C, Chen K, Moretto M. (2019). Toxoplasma: immunity and pathogenesis. *Curr Clin Microbiol Rep.* 6(1):44–50. doi:10.1007/s40588-019-0114-5.

24. Wilson EH, Hunter CA. (2006). Host-pathogen interactions in chronic cerebral toxoplasmosis. *Parasite Immunol.* 28(11):587–596.

25. Matta SK, Rinkenberger N, Dunay IR, et al. (2021). *Toxoplasma gondii* infection and its implications within the central nervous system. *Nat Rev Microbiol.* 19:467–480.

26. Hunter CA, Subauste CS, Van Cleave VH, et al. (1994). Production of gamma interferon by natural killer cells from *Toxoplasma gondii*-infected SCID mice: regulation by interleukin-10, interleukin-12, and tumor necrosis factor alpha. *Infect Immun*. 62(9):3558–3563.

27. Sasai M, Yamamoto M. (2019). Innate, adaptive, and cell-autonomous immunity against *Toxoplasma gondii* infection. *Exp Mol Med.* 51:1–10. doi:10.1038/s12276-019-0353-9.

28. Suzuki Y, Sa Q, Gehman M, et al. (2011). Interferon-γ– and perforin-mediated immune responses for resistance against *Toxoplasma gondii* in the brain. *Expert Rev Mol Med.* 13:e31.

29. Dupont CD, Christian DA, Hunter CA. (2012). Immune response and immunopathology during toxoplasmosis*. Immunopathol*. 2012; 34(6):793–813. doi:10.1007/s00281-012-0339-3.

30. O'Garra A, Vieira PL, Vieira P, et al. (2004). IL-10 and regulatory T cells: balancing protective and pathological immunity. *J Clin Invest.* 114(10):1372–1378.

31. Khan IA, Moretto M. (2022). Immune responses to *Toxoplasma gondii*. *Curr Opin Immunol.* 77:102226.

32. Li J, Gao W, Yan Z, Yan B, Zhang J. (2025). Cellular immune response during *Toxoplasma gondii* infection: deciphering diverse population immune variations. *Trends Parasitol.* 41(11):1030–1045.

33. Hunter CA, Kastelein R. (2012). Interleukin-27: balancing protective and pathological immunity. *Immunity*. 37(6):960–969.

34. Erazo Flores BJ, Knoll LJ. (2025). *Toxoplasma gondii* at the host interface: immune modulation and translational strategies for infection control. *Vaccines.* 13(8):819.

35. Eberhard JN, Shallberg LA, Winn A, et al. (2025). Immune targeting and host-protective effects of the latent stage of *Toxoplasma gondii*. *Nat Microbiol.*; 10:992–1005.