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Article

Trained Immunity and Long-Term Immune Modulation in Toxoplasma gondii Infection

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Abstract: Trained immunity represents a paradigm shift in immunology, describing the capacity of innate immune cells to develop long-lasting functional reprogramming after primary stimulation, leading to enhanced or altered responses upon secondary challenge. Toxoplasma gondii, an obligate intracellular protozoan parasite, provides a unique model for studying trained immunity due to its ability to establish lifelong latent infection and induce sustained immune activation. This review explores current evidence on trained immunity and long-term immune modulation during T. gondii infection, with emphasis on innate immune memory, immunometabolic reprogramming, and epigenetic remodeling. During acute infection, T. gondii triggers strong innate responses mediated by monocytes, macrophages, dendritic cells, and natural killer cells, characterized by the production of interferon-γ and pro-inflammatory cytokines. Emerging data suggest that these early signals can imprint durable changes in innate immune cells and their progenitors, resulting in heightened responsiveness or immune tolerance during chronic infection. Metabolic shifts, including enhanced glycolysis and altered mitochondrial function, alongside epigenetic modifications such as histone methylation and acetylation, appear central to this process. While trained immunity may contribute to improved control of secondary infections, it may also promote chronic inflammation, immune exhaustion, or pathological immune responses, particularly in immunocompromised individuals. Understanding how T. gondii shapes long-term innate immune function has important implications for host susceptibility to co-infections, autoimmune conditions, and vaccine responsiveness. This review highlights recent advances, unresolved questions, and future perspectives on targeting trained immunity pathways as potential strategies for immunomodulation and host-directed therapies in toxoplasmosis and related infectious diseases.

Keywords: Toxoplasma gondii; Trained immunity; Innate immune memory; Immunometabolic reprogramming; Epigenetic modulation

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1. Introduction

Every year, over a billion humans are newly infected with Toxoplasma gondii, the parasite responsible for the prevalent zoonotic disease toxoplasmosis [1]. In acute infection and at the northern edge of its distribution (e.g. Scandinavia, Canada), it can cause severe and even fatal disease, especially in immunocompromised patients (e.g. HIV or organ transplant recipients). Accordingly, the parasite is designated a biosafety level 3 agent [2], and its biology has therefore attracted substantial attention. Infection also occurs in many domestic and wild animals, and it modulates their immune responses. Consequently, T. gondii is a suitable model for exploring complex host-pathogen interactions.

T. gondii elicits a multitude of immune responses classified as innate and adaptive. Innate responses occur during the first 7 days of the infection, sustained by interferon-gamma (IFN-γ). Adaptive responses rely on T and B lymphocytes and target intracellular pathogens, exerting a strong selective pressure on the genome of the parasite. In the

mouse model, T. gondii infection produces long-lasting changes in the development and functionality of immune cells and alters the host's responsiveness to other infections. Such alterations occur 2-12 weeks after acute infection, before antibody presence, and yet can still be observed in nanomolar concentrations of the specific metabolite that indicates ongoing chronic infection [3].

Given the historical and scientific importance of T. gondii as a model species and the fundamental role of immune modulation in host-pathogen interactions, the next sections detail the nature, scope, duration, and underpinning mechanisms of the extended immune modulation that follows exposure to T. gondii. In addition, emerging questions and future research avenues are highlighted [4].

Background on Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular parasite of the phylum Apicomplexa which induces an immune response mediated by IFN-γ and perforin in the brain [5]. The parasite accumulates in tissues and forms cysts, especially in ocular tissues; subsequently differentiation in vivo follows a spontaneous multistage pattern, involving the transition from a type II Hayashi-derived strain to a lineage of type III [6]. Genetic resistance to T. gondii differs among mouse strains in chronic-stage infection. Cyst burden, susceptibility to reactivation, and encephalitis define the resistance spectrum, and QTL mapping indicates additional genetic influences on cyst burden and resistance. T. gondii comprises three clonal lineages, with type II and III being the most prevalent in humans. Certain STR genotypes are associated with ocular toxoplasmosis. The acute stage of infection evokes CD8+ T cells that dominate the early response, followed by IFN-γ–producing helper-like innate lymphoid cells (ILC) which exhibit genetic determination influencing the acute phase [7]. A waning type 1 inflammatory response characterizes the chronic phase. Cysts persist during the chronic phase depending on the initial infectious dose. Strain-specific recognition of T. gondii during chronic infection is associated with GRA15, a dense granule protein that activates pivotal immune pathways such as NF-kB. In the brain, the inflammatory cascade with NF-kB accumulates in response to early T. gondii antigen presentation, maintaining T cell-mediated control of the pathogen [8].

2. Materials and Methods

To this end, the methodology of this review was purposefully directed towards evidence synthesis, including a critical appraisal of the current state of evidence with regards to trained immunity and long-term immune modulation as a result of Toxoplasma gondii infection, with a focus on innate immune memory, epigenetic reprogramming, and immunometabolic reprogramming. The method taken is two-fold: literature review search through peer-reviewed articles, reviews used for comprehensive analysis and experimental studies performed on animal and/or human models of toxoplasmosis, respectively. Studies focusing on innate immunity not only during the acute phase of infection, but particularly those targeting monocyte, macrophage, dendritic cells and bone marrow progenitor reprogramming were prioritized. Using in vitro innate immune priming systems, animal models of acute and chronic infection, and systems immunology approaches, experimental data were compared that identify convergent mechanisms and similarities in host response patterns. Mechanistic studies harnessing transcriptomic, epigenomic, metabolomic, and cytokine profiling approaches to characterize changes in immune cells provoked by T. gondii leading to persistent modifications of immune states were then underscored were placed in the context of trained immunity frameworks adapted from other intracellular pathogens with careful separation of parasite-specific vs generalized inflammatory imprinting. Biological complexity denoted by differences across models, stages of infection, strains of parasite, and hosts of different genetic backgrounds were not averaged out but treated as important signals. When there was indirect or incomplete evidence, this was stated clearly instead of being extrapolated. Overall, we applied an integrative approach instead of a strictly descriptive one, attempting to relate the molecular mechanisms with functional immune outcomes

(heterologous infection resistance, immune tolerance, and pathogenic inflammation). This approach facilitates a nuanced evaluation of trained immunity as an evolutionary conserved but potentially maladaptive outcome of chronic T. gondii infection.

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3. Results and Discussion

Concepts of Trained Immunity

Trained immunity refers to a form of long-lasting immune memory in innate immune cells that involves extensive cellular metabolic, epigenetic, and functional reprogramming [9]. Hematopoietic progenitor cells are epigenetically reprogrammed, giving rise to bone-marrow-derived monocytes that acquire enhanced antimicrobial activity. Trained-immunity protocols increase resistance against multiple bacterial infections mediated through monocytes and macrophages, indicating that this response provides cross-protection against multiple pathogens [10], [11].

The full range of immune response modifications and their implications for interactions between innate and adaptive immunity remain unexplored during Toxoplasma gondii infection [12]. In the acute phase, a type 2 cytokine response is observed which favors T. gondii proliferation and dissemination. It is unknown whether T. gondii-induced innate immune modifications persist post-acute infection, whether the acute phase contributes to long-term adaptation, and how early interactions between T. gondii and the host influence training and memory [13], [14].

Evidence for Trained Immunity in T. gondii Infection

Infection with Toxoplasma gondii induces functional and long-lasting changes in the immune system of the host [15]. These changes are typically classified as trained immunity, which is characterized by innate immune priming of monocytes, macrophages, or dendritic cells that ultimately enhances pathogen clearance through increased production of proinflammatory cytokines or antimicrobial mediators upon a secondary challenge. Vaccination with certain pathogens or antigens may trigger an adaptive immune response characterized by an increased antibody response upon subsequent infection with the same or heterologous pathogens without prior exposure to the corresponding antigens [16], [17]. Trained immunity in the context of T. gondii infection is a unique phenomenon. Primary infection with the parasite does not induce substantial protection against subsequent infections. However, mice infected with the parasite exhibit increased resistance to otherwise lethal infections with other intracellular pathogens, such as Listeria monocytogenes and Salmonella enterica serovar Typhimurium. This enhanced resistance does not arise from long-lived antibodies or memory T cells, suggesting that T. gondii actively reprograms the immune system to establish a form of innate immune memory following primary infection [18].

Innate Immune Priming and Epigenetic Reprogramming

Illumination of cell signaling pathways and feedback loops that govern the immune response of the host provides evidence T. gondii infection triggers innate immune training and induces a long-lasting epigenetic reprogramming of monocytes in the first days of acute infection [19].

T. gondii commonly infects humans, remaining asymptomatic for a majority of the population. Permanent control of chronic T. gondii infection requires protective cell-mediated immunity, serving a crucial role in preventing reactivation of the dormant bradyzoite stage within tissue cysts. In murine models, prior infection with T. gondii alters monocyte differentiation states and enhances resistance to subsequent listeriosis [20]. Silencing of the T. gondii transcriptional regulator TgPIF facilitates bradyzoite conversion in respective strains by blocking parasite-type depletion 3 of RNA and UPF or thermal induction of cellular dormancy. Infection triggers transcription of cytokine-encoding genes essential for late-stage differentiation of interleukin-10-producing regulatory T cells [21],[22].

Monocytes, Macrophages, and Dendritic Cells in T. gondii

Toxoplasma gondii infection triggers long-lasting, T. gondii-specific immune alterations indicative of trained immunity. Infecting mice with the cyst-forming type II

strain ME49 leads to increased parasitemia upon subsequent challenge with the type I strain RH, demonstrating how macrophage and dendritic cell (DC) priming established by the initial infection enhances the parasite-specific response. This immune training occurs independently of adaptive immunity and persists for months. Infection prime monocytes to exhibit epigenetic reprogramming of transcription regulators, pro-inflammatory cytokines, and metabolic and immune-relevant genes, marking the first demonstration of T. gondii-induced innate immune training training that reaches mesenchymal stem cells involved in muscle cystogenesis and persists long after the decline of amyloid-β (Aβ) and T. gondii materials from the periphery. These findings reinforce T. gondii's role as a model pathogen for dissecting the cellular and molecular basis of trained immunity, homing of trained phenotype cells to the brain, and long-lived parasitic protection mediated through innate immune training [23],[24]. Ilang ko

Long-Term Immune Modulation Post-Infection

Long-term immune modulation after Toxoplasma gondii infection incorporates a dual influence of the parasite- and host-derived factors. The persistent form of T. gondii survived in the host, creates an environment for the generation of a retrained immune phenotype, these aspects lead to a balance between parasite propagation and control of concurrent infectious agents. Accumulation of bradyzoite cysts in the central nervous system (CNS) results in continuous antigen production over years. T. gondii antigens that are presented by the aminopeptidase N (CD13) and the intracellular parasite-derived histone H4 during the acute phase of infection shape the retrained monocyte program and the IFN-λ and IL-1β cytokine output at the acute and chronic stages of infection remain present in monocytic cells from previously infected donors. T. gondii, therefore, modulates the long-term properties of human monocytes in a manner that still influences the immune response to unrelated pathogens [25], [26].

Cytokine Profiles and Functional Reprogramming

The Kilham rat virus (KRV), an enterically transmitted murine virus of the Picornaviridae family, was used as an inexpensive immunostimulatory agent to induce long-term functional reprogramming of the innate immune response characterized by increased production of proinflammatory cytokines. The immune base: 10 days after the first KRV exposure, a marked increase in TNF-α expression was observed in bone marrow-derived macrophages elicited by different classes of PRRs stimulation (Vesicular Stomatitis Virus, Poly(I:C), LPS), and these results were maintained at similar levels at least for 24 weeks. At the same time, both type-I and 2 IFNs domain expression, even in basal conditions after LPS stimulation, significantly reduced correlating well with the shortening of IFN-α upon second exposure. The production of IL-1β and IL-6, hallmarks of KRV and Toxoplasma-trained immunity were unaffected at 48h, but markedly reduced 24 weeks upon second infection. Importantly, when stimulation was carried out upon re-infection with the equivalent KRV, under the previous gone conditions the basal TNF-α levels returned back again to pre-trained state after 8 weeks [27]. The KRV therefore as an original and potentially low-cost agent could serve well as an alternative to study a variety of immune training and epigenetic reprogramming phenomena either in chronic infection through intrinsic immune response functions or under distinct pathologies. Repeated sub-lethal dose of the KRV even held the potential to study Toxoplasma independent of the sporozoite and oocyst stages. Toxoplasma Induced-Training on the Innate Myeloid Cells: Macrophages are essential for innate immunity against most pathogens and serve as a link between innate and adaptive immunity through antigen presentation [28], [29].

Peritoneal macrophages from mice infected with Toxoplasma are pre-conditioned with an increased capacity to produce TNF-α and nitric oxide, essential for the control of intracellular pathogens. Pro-primer Macrophages Pyruvate Kinase M2: Similarly, pyruvate kinase M2 (PKM2) plays distinct roles in various stages of innate and adaptive immunity. PKM2 expression peaked in the acute phase of Toxoplasma infection and was down-regulated in the chronic stage, which restored several other metabolic and immune functions across multiple immune cells after a second Toxoplasma challenge [30], [31]. The long-term effects on major night-time cytokines such as IL-12p70, TNF-α, IL-6, and IL-1β remained significantly elevated up to 36 weeks during the chronic phase, able to modulate

excessive tissue-resolving macrophage polarization, and preserve the capacity for inflammatory cytokine production, establishing a permissive environment for reinfection resistance at both systemic and local levels [32].

Adaptive Immune Interactions and Memory

In mice, the Th1 immune response induced by Toxoplasma gondii during chronic infection not only retains functional characteristics long after the resolution of acute infection but also enhances the development of a pathogen-specific Th1 memory response to Listeria monocytogenes. This facilitation of heterologous adaptive immunity does not seem linked to innate lymphoid cells or T helper 9 cells but rather hinges on sustained high-level expression of major histocompatibility complex-II molecules on antigen-presenting cells. Furthermore, memory-like CD8+ T lymphocytes reactive to Listeria monocytogenes acquire the ability to produce interferon-γ and tumor necrosis factor-α following exogenous interleukin-12 stimulation, reflecting a directly facilitated and alternative memory response to other pathogens in mice previously infected with T. gondii [33], [34].

Long-term immune modulation can also influence adaptive immune interactions during mixed infections. Because chronic infection with Toxoplasma gondii in mice affects not only CD4+ Th1 immunity but also the ability of pre-existing CD8+ T cell memory to control a secondary, heterologous Listeria monocytogenes infection, it alters CD8+ antigen exposure during a primary viral infection. Further analysis of the specific memory response mounted against Listeria monocytogenes after vaccination in these chronic Toxoplasma gondii carriers revealed maintenance of the capacity to mount a memory response despite the noted Toxoplasma modulations [35].

Mechanistic Pathways Underpinning Trained Immunity in T. gondii

Innate immunity, a critical line of defense against infectious pathogens, commonly proceeds to a state of memory upon pathogen recognition, enabling rapid and effective responses to subsequent encounters. Memory serves to strengthen the response to multiple infections by the same pathogen, arresting their dissemination and preventing disease. For example, systemic infection with Toxoplasma gondii elicits long-term modulation of innate immunity, termed trained immunity, characterized by established epigenetic reprogramming of monocytes, macrophages, and dendritic cells [36]. This adaptation formally constitutes a form of innate immune memory that extends the temporal breadth of the immune response beyond traditional parameters for this system of immunity. Disease progression is not concealed; ongoing antibody production persists, and modulation of the adaptive response is critically linked to altered control of chronic infection thereafter. Rather than directing control of T. gondii, innate reprogramming substantiates cytokine production and broadens Th1 bias, significantly accelerating temporal dynamics of Th1 polarization and priming adaptive mechanisms. Many of the principles established in T. gondii apply broadly across concerns for trained immunity, transient physiological and pathological remodelling during the proinflammatory phase narrowly circumscribing the generality of their application [37]. Consideration of auxiliary aspects may also be relevant to other forms of long-term immune modulation. Trained immunity exposes evolutionarily conserved pathways that are either engaged or circumvented in adaptation to a wide range of environmental and biological challenges. Innate lymphoid FG2 cells coalesce extensive input from the microbe and the environment to additionally regulate memory formation, adaptive response dynamics, and the initiation of effector functions, establishing strategic overlap with S. aureus cultivated under different conditions and extending the generality of T. gondii insights [38].

Trained immunity and long-term immune modulation following Toxoplasma gondii infection are underpinned by three mechanistic pathways: epigenetic modifications, metabolic reprogramming, and the engagement of pattern recognition receptor (PRR) and downstream signaling networks. Recognition of pathogen-associated and danger-associated molecular patterns via PRR elicits signal transduction cascades that govern cellular, metabolic, and transcriptional programmes at the local level and inform conditioning of bone-marrow (BM)-derived precursors and precursors within the central nervous system at extended ranges. In mice infected with T. gondii, these processes are

accompanied by an extensive cascade of enhanced downstream transcription sustained after systemic clearance of the parasite, initiation of metabolic chain reactions, and further input from sensing of reactive metabolites [39].

Epigenetic Modifications

Modification of histones and non-histone proteins can induce long-term changes in transcriptional activity and chromatin architecture in response to various signals, and these alterations collectively constitute an epigenetic signature that enables the reprogramming and retention of specific genes [40]. Covalent histone modifications involve the addition of acyl or methyl groups by various enzymes and influence the recruitment of proteins that promote the initiation or repression of transcription. Histone methylation modifications occur mainly on lysine and arginine residues and can be either transcriptionally activating or repressing [41]. Histone acetylation and ubiquitination changes are important for the expression of IL-12 and IL-6 cytokines in macrophages and dendritic cells exposed to T. gondii, and modulation of histone acetylation at the IL-6 promoter is necessary for sustained Il-6 expression in monocytes and macrophages after LPS stimulation. The polyubiquitination of histone H2A catalyzed by Ring1B E3 ligase restricts IL-1β production in T. gondii-infected macrophages by suppressing the transcription of the Il1b gene in a post-transcriptional manner. The modulation of histone H2A levels represents another important mechanism controlling IL-1β production by T. gondii in macrophages. The inhibition of ATP-binding cassette subfamily A member 1 (ABCA1) expression controlled by Ring1B-mediated H2A-ubiquitination represents a host-oriented strategy to maintain adequate intracellular cholesterol levels that are essential for the replication of T. gondii in macrophages [42].

Metabolic Reprogramming

In addition to epigenetic modifications, a metabolic remodeling emerges as an important mechanism underlying long-term trained immunity in innate immune cells during T. gondii chronic infection. It has been well established that many pathogens reprogram metabolism upon first exposure to support their immune evasion and replication abilities. Infection by diverse pathogens impedes oxidative phosphorylation by promoting glycolytic metabolism in the infected macrophages. Whereas primary macrophages exhibit a decreased glycolytic capacity and enhanced oxidative phosphorylation following infection with T. gondii, re-exposure to pathogens such as S. aureus and E. coli shifts glucose metabolism toward glycolysis. Consistent with a previously reported attenuated glycolysis upon T. gondii infection, metabolic profiling at sub-chronic, chronic and acute stages of T. gondii infection reveals a reduction in glycolytic and tricarboxylic acid cycle activity and an increase in cholesterol biosynthesis in organ-specific mouse spleen, suggesting a distinct stage-specific host metabolic modulation and an organ-specific immune modulation [43].

Pattern Recognition Receptors and Signaling Networks

The infection with Toxoplasma gondii affects Toll-like receptor expression on monocytes, induces epigenetic modifications in bone marrow-derived macrophages that are retained after parasite clearance, and protects against systemic infection with other pathogens [44], [45].

Microbial antagonism and immune recognition involve the cyclic and persistent interplay between fundaments of infection: avirulence versus virulence and innate versus adaptive. The human pathogen Toxoplasma gondii takes advantage of the parasite's ability to confer protection against future infections in the heterogeneous, polyclonal population of innate and adaptive immune responses. The converse describes the long-term modulation of immune signals within the confines of the primary immune response to guide protection against the ancestral parasite. Pattern-recognition receptors, signalling pathways, cytokines, transcriptomes, epigenetic modifications imposed by early exposure, and digital signal processing mechanisms unfold to construct a theoretical framework for these concepts of trained immunity [46], [47].

Experimental Approaches and Methodological Considerations

The phenomenon of trained immunity has been intensively studied over the last decade. Combination of various experimental approaches may help untangle the complex nature

of T. gondii-mediated trained immunity. These include in vitro models of innate priming, in vivo models of chronic and acute infection and systems-immunology analysis of omics data. Each of these models provides valuable insight into immune-modulatory reprogramming at the level of individual cells and tissue injection after the initial parasite exposure [48].

In Vitro Models of Innate Priming

Toxoplasma gondii is obligate parasite that infects most of warm-blooded vertebrate species. It is an opportunistic pathogen threatening acquired immune deficiency syndrome (AIDS) patients infected with Toxoplasma gondii. Although the brain is a major target organ of infection, the disease immunology is not fully understood [49][50]. Cytokine arrays were performed on brain mononuclear cells, revealing several cytokines involved in T. gondii infection. Characterization of T. gondii-induced infection immunity has been done by investigating cytokine profiles and immune cell/free fatty acid changes using in vitro models. Immune effector molecules involved in T. gondii infection immunity have been validated by comparing splenocyte stimulation assays conducted with free T. gondii tachyzoite and T. gondii antigen extracts [51]. Accumulation of free fatty acids in T. gondii-infected culture supernatants was detected using untargeted lipidomic analysis [52], [53].

In Vivo Models of Chronic and Acute Infection

Trained immunity is established after acute infection with Toxoplasma gondii (T. gondii) and expands with increasing time intervals between re-exposure. Evidence for trained immunity due to T. gondii has been documented in both human and murine experimental models. These models characterize the offspring of Th1-activated macrophages, changes in the metabolic state of macrophages, and alterations or enhancements in the Th1-response of adaptive T-cells 90 or even 120 days post-infection [54],[55]. The temporal kinetics and duration of innate immune training induced by T. gondii distinguish it from several model microbes, such as the vaccine strain of Bacillus Calmette-Guérin (BCG), and make it critical to investigate its host resistance and pathogenesis [56].

Omics and Systems Immunology

Since the 1950s, various concepts and terms have been used to describe phenomena similar to trained immunity. 'Vaccinal immunity' refers to a delayed-type of immunity induced by the production of antibodies following initial exposure to a given pathogen, such that when this pathogen is reintroduced, the immune response through antibody production is significantly enhanced [57], [58]. The terms 'hormonal', 'primed', and 'vested' immunity were proposed to describe an over-commitment of the immune system that prevents it from responding effectively to other pathogens following initial exposure. Criteria for distinguishing between trained immunity and these classical concepts were outlined, although philosophical researchers might question whether those with common interests in specific diseases or broad-scale concepts benefit from setting arbitrary boundaries between observations. Relying on ambiguous terminology weakens the cumulative force and rigour of a particular argument and inhibits potential new insights through comparative work across topics [59], [60].

Implications for Host Resistance and Therapeutic Strategies

Infection with Toxoplasma gondii results in persistent life-long infection in most hosts. However, despite the predominance of chronic infection, the immune status of T. gondii infected hosts exhibits long-lasting and strain-dependent changes that impact resistance against infection with other pathogens [61].

The nature of the immune alterations elicited by T. gondii infection are characterized by a combination of innate immune characteristics and an absence of resistance against secondary parasite challenge. These observations are consistent with an imprinting process for antibacterial broad-spectrum immune responses through epigenetic modifications that induce expression of pro-inflammatory cytokine genes and not the establishment of immunological memory [62], [63].

The regimented immune evolution observed during the T. gondii chronic stage may represent a new pattern of immune ontogeny where infection time stamps the immune

reprogramming identity of the host that could dictate the immune potential against future threats. Notably, T. gondii triggers, in a stage- and strain-specific manner, a regulatory milieu that alters IL-12p70 production by innate immune cells upon subsequent exposure to other microbial agonists. The imprinting process primordially requires NF-kB1 and is regulated at least in part by IL-10 and TNF¿ that differentially modulates the innate immune reprogramming capacity of other pathogens during chronic stage infection [64], [65].

4. Conclusion

Priming of the innate immune system by *Toxoplasma gondii* induces a durable form of trained immunity characterized by long-lasting functional reprogramming of monocytes, macrophages, and dendritic cells, even after parasite clearance. This innate immune memory is retained in bone marrow progenitors and enables enhanced production of pro-inflammatory cytokines and expansion of parasite-specific CD4 T cells. However, unlike other infections, *T. gondii*–induced trained immunity alters cytokine environments in a way that suppresses effector functions of CD4 memory T cells and limits CD8 T-cell expansion, indicating an antagonistic interaction with adaptive immunity. These effects are driven by persistent epigenetic, metabolic, and transcriptional remodeling, including sustained histone modifications at inflammatory gene loci, underscoring the long-term immunological impact of toxoplasmosis and its relevance for future vaccine and therapeutic strategies.

Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study..

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