Artículo de opinión

Immunology of *Toxoplasma gondii* infection. A basic approach

Inmunología de la infección por *Toxoplasma gondii*. Una aproximación básica

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ABSTRACT

Introduction: *Toxoplasma gondii* is a widespread intracellular protozoan that affects around one-third of the world's human population. The clinical expression of toxoplasmosis is closely related to the host's immunocompetence. While most immunocompetent persons are asymptomatic after primary acquired infection, immunocompromised patients may develop a range of severe clinical

manifestations. From our perspective, the knowledge about numerous aspects of toxoplasmosis, including immunity to *T. gondii* infection, is insufficient or controversial. A recent work published in the pages of this journal evidenced such deficiencies.

Objective: Establishing a concise and comprehensive overview of the host immune responses to this parasite.

Development: *Toxoplasma gondii* induces vigorous innate and adaptive immune responses characterized by a strong T cell immunity. CD4 and CD8 T cells are protagonists in the control of acute infection and are essential for preventing cyst reactivation during chronic latent infection. This parasite can evade and modulate host innate and adaptive immune responses, and establish long-term niches in immune-privileged areas like the brain and retina. As we underline in this paper, *T. gondii* infection reveals a delicate balance between protective immunity and immunopathology.

Conclusions: From our perception, the peculiarities of this *sui generis* host-parasite interaction must be deeply known by professionals involved in its diagnosis, treatment, and control. In harmony with it, the texts of this work could contribute to a better understanding of numerous aspects of this parasitosis.

Keywords: *Toxoplasma gondii*, Toxoplasmosis; Immune Response; Natural Immunity; Adaptive Immunity; Immune Evasion.

RESUMEN

Introducción: *Toxoplasma gondii* es un protozoo intracelular ampliamente distribuido que afecta aproximadamente un tercio de la población mundial. La expresión clínica de la toxoplasmosis está estrechamente relacionada con la inmunocompetencia del hospedero. Mientras que la mayoría de las personas inmunocompetentes son asintomáticas, los pacientes inmunocomprometidos pueden desarrollar un amplio rango de manifestaciones clínicas. Desde nuestra perspectiva, el conocimiento sobre numerosos aspectos de la toxoplasmosis, incluida la inmunidad a la infección por *T. gondii*, resulta insuficiente o

controversial. Un reciente trabajo publicado en las páginas de esta revista evidenció tales deficiencias.

Objetivo: Establecer una precisa y comprensible visión general de la respuesta inmune del hospedero a este parásito.

Desarrollo: *Toxoplasma gondii* induce vigorosas respuestas inmunes innatas y adaptivas caracterizadas por una fuerte inmunidad de células T. las células T CD4 y CD8 son protagónicas en el control de la fase aguda de la infección y en la prevención de la reactivación durante la infección crónica latente. Este parásito puede evadir y modular las respuestas inmunes y adaptativas, y establecer nichos de larga duración en áreas inmunoprivilegiadas como el cerebro y la retina. En esta publicación se destaca la infección por *T. gondii* que revela un delicado balance entre inmunidad protectora e inmunopatología.

Conclusiones: Desde nuestra perspectiva, las particularidades de esta *sui generis* interacción hospedero-parásito debe ser profundamente conocida por los profesionales involucrados en sus diagnóstico, tratamiento y control. En armonía con ello, los textos de este trabajo podrían contribuir a un mejor entendimiento de numerosos aspectos de esta parasitosis.

Palabras clave: *toxoplasma gondii*, toxoplasmosis; respuesta inmune; inmunidad natural; inmunidad adaptativa; evasión inmune.

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Introduction

The term toxoplasmosis refers to the infection of humans and other animals by the obligate intracellular protozoan *Toxoplasma gondii*.[1,2] This parasitosis, which shows a wide geographical distribution, has been demonstrated in countries with very different climates and socioeconomic development.[1] Using diverse

seroepidemiological tools, it has been shown that this parasitic infection affects between 15 and 85% of the individuals studied[3,4,5] Approximately, 30% of the world´s human population is infected with *T. gondii.*[6]

Two important facts distinguish *T. gondii* infection:

- Its high transmissibility and prolonged presence in the host it parasitizes (due to these features, this protozoan is considered one of the most successful microorganisms on the biological scale)[7,8,9]
- Most infected people, since they do not suffer from symptoms attributable to the parasitosis, do not know that they are infected[1,7,8,9]

T. gondii includes three primary clonal lineages (types I, II, and III).[9,10] Those lineages display distinct profiles of virulence, immune modulation abilities, and disease outcomes in experimental models and natural infections.[10,11] Type I strains are highly virulent, suppres host immunity, and are associated with severe ocular toxoplasmosis.[2,12,13,14] Type II strains are less virulent, more immunogenic, and the most common cause of human infections.[9,15] Type III strains are least virulent, induce comparatively weak immune responses and are often found in domesticated and wild animals and less commonly in humans.[2,9]

The complex life cycle of *T. gondii* takes place in two phases:

- Sexual, which only develops in the intestinal epithelial cells of the definitive hosts, felines, in which unsporulated oocysts are generated and eliminated in the feces (allowing an explanation for this peculiarity, it was recently discovered that the sexual development of *T. gondii* is triggered by high levels of linoleic acid, which are a consequence of the deficiency in felines of the intestinal enzyme delta-6-desaturase, necessary for the conversion of linoleic acid to arachidonic acid)[1,9,16]
- Asexual, which begins with the ingestion of the oocysts by intermediate hosts, animals in which the sexual phase cannot develop, including

humans.(1) The sporozoites, which emerge from the ingested oocysts, invade the epithelial cells of the intestine and become tachyzoites that spread, inside dendritic cells (DCs) and circulating monocytes, as "Trojan horse", to practically all organs, with a special tropism toward the muscles, the retina, and the central nervous system (CNS).[1,2] It has been demonstrated that *T. gondii*-infected DCs synthesize and secrete the neurotransmitter γ-aminobutyric acid (GABA), which activates GABA-A receptors and induces a hypermigratory phenotype in the cells, ultimately promoting parasite transmission.[17] Once in their final destination, they transform into bradyzoites, which are structured into cysts within various types of cells, mainly muscle cells and CNS neurons. Bradizoites are resistant to the host's immune responses and, in an essentially silent course, survive in it until its death.[1]

The clinical presentation of *T. gondii* infection mainly depends on the immune competence of the host. In healthy individuals, primary infection is usually asymptomatic or manifests moderately with general malaise, fever and lymph node inflammation.[18] Generally, lymphadenopathy is of short duration, lasting just a few weeks, is located symmetrically in the cervical region, is neither painful nor confluent, and the swollen lymph nodes do not exceed 3 cm in diameter.[6] In immunocompromised individuals, such as HIV/aids patients or those who have undergone organ transplants, the symptoms of primary infection are more intense or latent toxoplasmosis may reactivate. This reactivation is characterized by the conversion of bradyzoites into tachyzoites and, consequently, by the development of clinically severe forms, such as toxoplasmic encephalitis.[18]

The transmission, and consequences, of *T. gondii* infection during pregnancy deserve special mention. If the primary infection occurs before gestation, the immunity generated makes it unlikely for the parasite to pass to the fetus if a new infectious episode takes place during the current pregnancy (and during subsequent ones) and, consequently, adverse clinical events rarely develop. But if

the primary infection occurs during pregnancy, there will be a higher risk of fetal involvement, since the developing embryo is not immunologically prepared to face the protozoan. In these cases, circulating tachyzoites can cross the placental barrier and cause severe clinical complications, such as neurological impairment, ocular lesions, or stillbirth.[19]

During its evolution, *T. gondii* has developed a complex life cycle and sophisticated strategies that enable it to thrive within host cells and evade immune detection. When the parasite reaches the interior of a host cell, it reprograms host functions to create a protective intracellular niche and evade immune clearance.[20,21,22,23] For an efficient medical practice, it is necessary to have an adequate understanding of how the host's immune system responds to *T. gondii* infection, as it allows predicting the possible outcomes of the infectious process and provides information about potential preventive and therapeutic targets to limit the replication of the parasite and avoid the progression of the infection and its consequences. From our perspective, the knowledge about numerous aspects of toxoplasmosis, including immunity to *T. gondii* infection, is insufficient or controversial. A recent work published in the pages of this journal evidenced such deficiencies in gynecologists-obstetrician of Havana.[24] In response to that problem, this Opinion-type paper aims to provide a concise and comprehensive overview of the host immune responses to this parasite. The texts of this paper delve into the host's innate and adaptive immune mechanisms, including cytokine signaling, humoral and cellular immune responses, and the activation of various regulatory pathways. Finally, we briefly comment the mechanisms and consequences of the immune evasion strategies employed by the parasite.

Development

Innate immunity: Immune cells in the intestinal mucosa, mainly dendritic cells (DC), form the first line of defense against *T. gondii* infection.[25,26,27] These cells detect the presence of the parasite and initiate early immune responses to prevent its spread. Detection is facilitated by pattern recognition receptors, such as Toll-like

receptors (TLRs), which identify pathogen-associated molecular patterns (PAMPs) in the parasite.[26,28,29,30] In humans, *T. gondii* PAMPS detection appears mediated through TLR3, TLR7, TLR8, and TLR9, which trigger a MyD88-dependent signaling cascade and the subsequent production of IL-12 by DC.[26,31] IL-12 then stimulates natural killer cells and T cells to produce IFN-γ, a critical cytokine for controlling the parasite.[32,33] IFN-γ plays a central role in activating antimicrobial pathways, including the induction of immunity-related GTPases (IRGs) and guanylate-binding proteins (GBPs),[34,35] which disrupt the parasitophorous vacuole and compromise parasite survival.[36,37] Interestingly, and in our opinion revealing the delicate balance between protective immunity and immunopathology that we describe later, nitric oxide (NO) produced by activated macrophages aids in parasite killing, but excessive NO production can lead to immunopathology.[26,38,39]

Adaptive immunity: The adaptive immune response to *T. gondii* is initiated and shaped by early proinflammatory cytokines on the innate phase, notably IL-12.[40] The adaptive responses include both humoral and cellular components:

- -Although serum detection of antibodies to *T. gondii* can be used as an approach to the diagnosis of toxoplasmosis, in our opinion the systemic antibody response to the parasite does not play a significant role in adaptive immunity to it.[41] IgM antibodies are produced during the early stage of acute infection, whereas IgG antibodies are secreted later.[4] These antibodies can neutralize remanent extracellular tachyzoites and hinder additional invasion of host cells.[41] In addition, mucosal IgA response can provide some resistance to oral infection with *T. gondii* cysts.[42]
- CD4 and CD8 T cells are highly active in the control of acute infection and are essential for preventing cyst reactivation during chronic latent infection.[2,9,43]As such, patients with defects in T cell–mediated immune responses (e.g., HIV/aids patients or those who have undergone organ transplants) are at risk of suffering a severe acute episode or a reactivation of a latent infection.[41] IL-12, first produced during innate phase, drives

differentiation of Th1 CD4 T cells and terminally differentiated effector CD8 T cells (Killer cell lectin-like receptor G1 positive [KLRG1+]) in the response to *T. gondii* infection.[41] Th1 CD4 T cells play a key role in the secretion of IFN-γ,[44] mainly during early stage of the acute infection.[45] IFN-γ triggers macrophage functions,[46,47] such as antigen presentation,[48] and microbicidal activities (production of reactive oxygen and nitrogen species) to eradicate intracellular parasites.[49,50] CD8 T cells also release IFN-γ[51] and, additionally, contribute to eliminate *T. gondii*-infected cells via perforin and granzymes.[52,53] This cytotoxic activity is critical for eliminating the parasite when it is already located intracellularly. Apparently, CD8 T cells mediated protection during the late stages of the acute infection can be attributed to their ability to produce IFN-γ,[54] which plays a pivotal role in immune-protection against *T. gondii* infection.[47] However, during chronic toxoplasmosis perforin/granzymes dependent cytotoxic ability of CD8 T cell population appears involved in restricting the parasite to chronic state.[55]

Inflammation and immunopathology

T. gondii triggers a strong proinflammatory Th1 immune response to control the infection.[40,56] In immunocompetent individuals, this response usually eliminates most parasites, with any remaining ones confined to the tissue cysts, resulting in an asymptomatic infection.[2,9,43] In immunocompromised persons, failing to mount an effective proinflammatory response leads to uncontrolled parasite replication and severe disease manifestations, such as toxoplasmic encephalitis.[57]

Although inflammation is necessary to restrain parasite replication, an excessively vigorous immune response can cause collateral tissue damage.[58,59] The most frequent sites of immunopathological lesions related to *T. gondii* infection are the brain and the eyes.[9] Examples include the following:

- Chronic *T. gondii* infection is characterized by increased levels of host immune activity and neuroinflammation (in line with this, the immune

response to this pathogen has been considered a potential contributor to neurological and behavioral disorders, such as Alzheimer's and Huntington's diseases)[60]

- immune-driven inflammation can damage retinal tissues, contributing to vision loss that characterizes ocular toxoplasmosis[9]
- experimentally, oral infection of mice with *T. gondii* can result in the overproduction of inflammatory cytokines, leading to severe damage in the small intestine and necrotizing ileitis[61]

Regulation and its consequences

The examples of immunopathological lesions mentioned in the previous section highlight the need for a balanced immune response that effectively eliminates the parasite while minimizing tissue injury. To avoid the development of immunopathologicaly damages, the host utilizes two interconnected anti-inflammatory mechanisms:

- In response to overactive DC and effector T cells, and its mediators IL-12 and IFN-γ, T regulatory cells (Treg cells), and possibly too B regulatory cells, microglia, and alternatively activated macrophages, release regulatory cytokines such as IL-10 and transforming growth factor (TGF-β).[62,63,64,65] IL-10 plays a particular role in regulating Th1 responses; for instance, mouse models lacking IL-10 exhibit elevated levels of IL-12 and IFN-γ, leading to lethal inflammation and necrotic liver lesions, even when parasite burdens are controlled.[66] TGF-β, produced by Treg cells and resident tissue cells, also helps suppress local inflammation and protects sensitive tissues such as neurons and retinal cells.[67]
- The binding of pro-inflammatory cytokines, such as IFN-γ and tumor necrosis factor-α, to epithelial cells, DCs, and macrophages can induce the expression of indoleamine-2,3-dioxygenase (IDO).[65,68,69] IDO is an intracellular enzyme that inhibits *T. gondii* growth.[68]. However, metabolites

from the IDO mediated kynurenine pathway (degradation of tryptophan) have been shown to inhibit immune responses by suppressing CD8+ T cell, NK cell, DC, and macrophage functions, promoting Th2 and T reg cells differentiation, and by this way, inducing the production of the anti-inflammatory cytokine TGF-β.[68]

On the other hand, *T. gondii* can use the first of the aforementioned anti-inflammatory pathways to enhance its persistence. Parasite molecules, including microneme proteins MIC1 and MIC4, have been shown to induce IL-10 production in host cells,[70] promoting a permissive environment that limits immune activation. By boosting IL-10 expression and expanding Treg responses, the parasite tempers host immunity to avoid its totais elimination. This immunomodulatory strategy enables *T. gondii* to establish long-term chronic infections, particularly in immune-privileged tissues, such as the brain and retina.

Evasion of Host Immunity

In addition to the modulation of the immune response of the host, *T. gondii* has developed sophisticated additional strategies to prolong its presence in it. Several works on the topic allow summarizing those mechanisms as follows:

- Virulent strains are protected by the parasitophorous vacuole (PV), which does not fuse with host cell lysosomes, nor does it become acidified to kill the parasite[23,41]
- Some infected macrophages are suboptimal targets for T cell-induced immunity because of reduced expression. of MHC class II and costimulatory molecules[41]
- As described in the previous section, *T. gondii* induces the production of regulatory molecules, such as IL-10 and TGF-β, which both downregulate a potentially pathological host inflammatory response and inhibit macrophage antimicrobial activity[65,66,67]

- *T. gondii* interferes with normal macrophage signaling; for example, infection inhibits DNA binding of signal transducer and activator of transcription 1 (STAT1) and nuclear factor kappa B (NF-κB) activation and promotes anti-inflammatory pathways downstream of the suppressor of cytokine synthesis proteins[41]
- The parasite has several virulence proteins, among them ROP5 and ROP16, which bind to the PV and reduce accumulation of the immunity-related GTPases[41]
- ROP proteins also activate host STAT3 and STAT6, driving an M2 macrophage phenotype that is permissive to infection[23,41]
- The parasite suppresses DC activation through an ROP16 kinase-dependent mechanism[41].

Conclusions

T. gondii is a widespread intracellular protozoan that affects around one-third of the world human population. The clinical expression of toxoplasmosis is closely related to the host immunocompetence. Whereas most immunocompetent persons are asymptomatic after primary acquired infection, immunocompromised patients may develop an array of severe clinical manifestations.

From our perspective, the knowledge about numerous aspects of toxoplasmosis, including immunity to *T. gondii* infection, is insufficient or controversial. A recent work published in the pages of this journal evidenced such deficiencies. In response to that problem, this Opinion-type paper aims to provide a concise and comprehensive overview of the host immune responses to this parasite. *T. gondii* induces a vigorous innate and adaptive immune response characterized by a strong T cell immunity. CD4 and CD8 T cells are protagonists in the control of acute infection and are essential for preventing cyst reactivation during chronic latent infection. This parasite can evade and modulate host innate and adaptive immune responses, and establish long-term niches in immune-privileged areas like the

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From an academic perspective, and considering the limitations of current treatments for toxoplasmosis (relatively high toxicity, restricted efficacy against tissue cysts, and the threat of parasite resistance), the introduction of emerging therapies, including drugs that modulate the host immune response, and the development of safe and effective vaccines, especially those capable of blocking chronic infection or transmission, remains peremptory. In carrying out both objectives, the introduction of emerging therapies and the development of safe and effective vaccines, a deep knowledge of the particular complexities of the host-parasite interaction that *T. gondii* infection represents is essential.

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Conflict of Interest

The authors declare no conflicts of interest.