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Toxoplasma gondii: Cellular aspects of parasite

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Abstract
Objective: *Toxoplasma gondii* is an obligate intracellular protozoan of significant veterinary and medical concern, as it causes toxoplasmosis, a disease that is easily transmissible and presents in various infectious forms. This review aims to explore the complexities of *T. gondii* transmission and pathogenesis, as well as the challenges in developing effective vaccines. Methodology: To produce the article, a literature review was carried out based on books and experimental papers through searches in Google, academic databases and PubMed. Impact: Toxoplasmosis remains a widespread public health and veterinary issue, particularly in immunocompromised individuals, where the disease can lead to more severe outcomes. We highlight comprehensive analysis of *T. gondii's* life cycle, transmission routes, and mechanisms of host infection is presented. The review focuses on the parasite's ability to invade nucleated cells in the intermediate host, such as macrophages, epithelial cells, and neural and muscle cells, ultimately leading to the formation of cysts that contribute to chronic infection. Despite numerous studies on the parasite, the lack of an effective vaccine continues to hinder progress in disease prevention and control. Findings and Unique Contributions: This review highlights the sophisticated mechanisms by which *T. gondii* infects host cells and the chronicity of the disease through cyst formation. It emphasizes the ongoing gap in vaccine development, underscoring the urgent need for innovative approaches to vaccine design. The study offers a critical perspective on the current understanding of *T. gondii* biology and challenges in creating lasting immunity against toxoplasmosis, making it a valuable contribution to the field.
Keywords: Toxoplasmosis; Pathogenesis; Molecular characterization; Immunological response.

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Resumo

Objetivo: *O Toxoplasma gondii* é um protozoário intracelular obrigatório de significativa preocupação veterinária e médica, pois causa toxoplasmose, uma doença facilmente transmissível e que se apresenta em várias formas infecciosas. Esta revisão tem como objetivo explorar as complexidades da *transmissão e patogênese de T. gondii*, bem como os desafios no desenvolvimento de vacinas eficazes. Metodologia: Para a produção do artigo, foi realizada uma revisão bibliográfica com base em livros e artigos experimentais por meio de buscas no Google, bases de dados acadêmicas e PubMed. Impacto: A toxoplasmose continua sendo um problema veterinário e de saúde pública generalizado, particularmente em indivíduos imunocomprometidos, onde a doença pode levar a resultados mais graves. Destacamos a análise abrangente do ciclo de vida de *T. gondii*, rotas de transmissão e mecanismos de infecção do hospedeiro. A revisão enfoca a capacidade do parasita de invadir células nucleadas no hospedeiro intermediário, como macrófagos, células epiteliais e células neurais e musculares, levando à formação de cistos que contribuem para a infecção crônica. Apesar de inúmeros estudos sobre o parasita, a falta de uma vacina eficaz continua a dificultar o progresso na prevenção e controle da doença. Descobertas e contribuições únicas: Esta revisão destaca os mecanismos sofisticados pelos quais T. *gondii* infecta as células hospedeiras e a cronicidade da doença por meio da formação de cistos. Ele enfatiza a lacuna contínua no desenvolvimento de vacinas, ressaltando a necessidade urgente de abordagens inovadoras para o design de vacinas. O estudo oferece uma perspectiva crítica sobre a compreensão atual da biologia do *T. gondii* e os desafios na criação de imunidade duradoura contra a toxoplasmose, tornando-se uma contribuição valiosa para o campo.
Palavras-chave: Toxoplasmose; Patogénese; Caracterização molecular; Resposta imunológica.

Resumen

Objetivo: *Toxoplasma gondii* es un protozoo intracelular obligado de gran preocupación veterinaria y médica, ya que causa toxoplasmosis, una enfermedad fácilmente transmisible que se presenta en diversas formas infecciosas. Esta revisión tiene como objetivo explorar las complejidades de la transmisión y patogénesis de *T. gondii*, así como los desafíos en el desarrollo de vacunas efectivas. Metodología: Para la elaboración del artículo se realizó una revisión bibliográfica basada en libros y trabajos experimentales a través de búsquedas en Google, bases de datos académicas y PubMed. Impacto: La toxoplasmosis sigue siendo un problema generalizado de salud pública y veterinaria, especialmente en personas inmunodeprimidas, donde la enfermedad puede provocar resultados más graves. Se presenta un análisis exhaustivo del ciclo de vida de *T. gondii*, las vías de transmisión y los mecanismos de infección del huésped. La revisión se centra en la capacidad del parásito para invadir las células nucleadas del huésped intermediario, como los macrófagos, las células epiteliales y las células neurales y musculares, lo que en última instancia conduce a la formación de quistes que contribuyen a la infección crónica. A pesar de los numerosos estudios sobre el parásito, la falta de una vacuna eficaz sigue obstaculizando el progreso en la prevención y el control de la enfermedad. Hallazgos y contribuciones únicas: Esta revisión destaca los sofisticados mecanismos por los cuales *T. gondii* infecta las células huésped y la cronicidad de la enfermedad a través de la formación de quistes. Hace hincapié en la actual brecha en el desarrollo de vacunas, subrayando la necesidad urgente de enfoques innovadores para el diseño de vacunas. El estudio ofrece una perspectiva crítica sobre la comprensión actual de la biología de *T. gondii* y los desafíos en la creación de inmunidad duradera contra la toxoplasmosis, lo que lo convierte en una valiosa contribución al campo.
Palabras clave: Toxoplasmosis; Patogénesis; Caracterización molecular; Respuesta inmunológica.

1. Introduction

Toxoplasma gondii (T. gondii), the etiological agent of toxoplasmosis, is an obligate intracellular protozoan belonging to the phylum Apicomplexa, where species that have an organelle called apicoplast are grouped and which is related to biochemical processes of *T. gondii* (mler et al., 1987; Waller et al., 1998; Köhler, 2005; Nishi et al., 2008; Souza and Pinto, 2023). Toxoplasmosis is a disease of medical and veterinary importance that can be transmitted mainly by the oral and congenital routes, influenced by environmental and dietary conditions (Dubey and Beattie, 1998; Attias et al., 2020). This etiological agent has its nomenclature based on its morphology since, in Greek, *toxo* means bow and *plasma* denotes mold and/or life (Kim and Weiss, 2008; Ferguson, 2009).

Presumably, the term *gondii* refers to the rodent in which the parasite was first found, known as gundi (*Ctenodactylus gundi*), in 1908 by Nicolle and Manceaux during a study on leishmaniasis, a disease caused by *Leishmania* sp. (Nicolle, 1908; Dubey, 2007). Initially, they related *T. gondii* to Leishman corpuscles or similar organisms. In addition to this discovery, also in 1908 Splendore observed the same parasite in a rabbit in Brazil, classifying it as a new parasite (Cardoso et al., 1956). In 1923, Janku reported human toxoplasmosis for the first time, and later, in 1927, Margarino Torres described, in Rio de Janeiro, a new human disease, also revealing congenital toxoplasmosis (Cardoso et al., 1956).

Some organelles help the parasite enter the host cell, through the secretion of some proteins. One of the organelles, the micronem, helps with parasite mobility and cell adhesion; roptria secretes important proteins in the formation of the parasitophore vacuole, aiding in parasite maintenance in the host cell, and dense granules assist in immune response escape mechanisms (Boothroyd & Dubremetz, 2008; Zhang et al., 2019). However, further studies are needed to identify and elucidate the role of other organelles present, which do not yet have well-defined functions.

Due to the relevance of toxoplasmosis as a disease of worldwide concern, the present study aims to carry out a survey about the life cycle, cellular aspects, forms of infection and susceptibility to the T. *gondii* parasite, as well as cell replication and differentiation. The form of transmission and the ease of the protozoan in infecting humans and other animals also make research extremely important, since the ways of prevention reduce the infection rate.

2. Methodology

The present study is an integrative review (Mattos, 2015; Anima, 2014; Crossetti, 2012; Pereira et al., 2018) based on books, experimental and epidemiological articles to gather relevant information about the protozoan *Toxoplasma gondii*. The terms searched were: "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis pathogenesis", "*Toxoplasma gondii* interconversion", "immunosuppressed toxoplasmosis", "congenital toxoplasmosis", "*Toxoplasma gondii* immune system", "toxoplasmosis symptoms", through the query in Google Scholar and PubMed databases. The selected articles were published between 1908 and 2023. The approach is quantitative-qualitative of the descriptive type involving *Toxoplasma gondii.* The terms mentioned above, in English and Portuguese, were inserted into the search bar of the Google Scholar and PubMed platforms. The number of articles found for each term were presented by the platforms. Through the data obtained, a relation was made between the terms searched and the number of articles found, using the Google Sheets to create the graphics.

3. Results

3.1 Life cycle

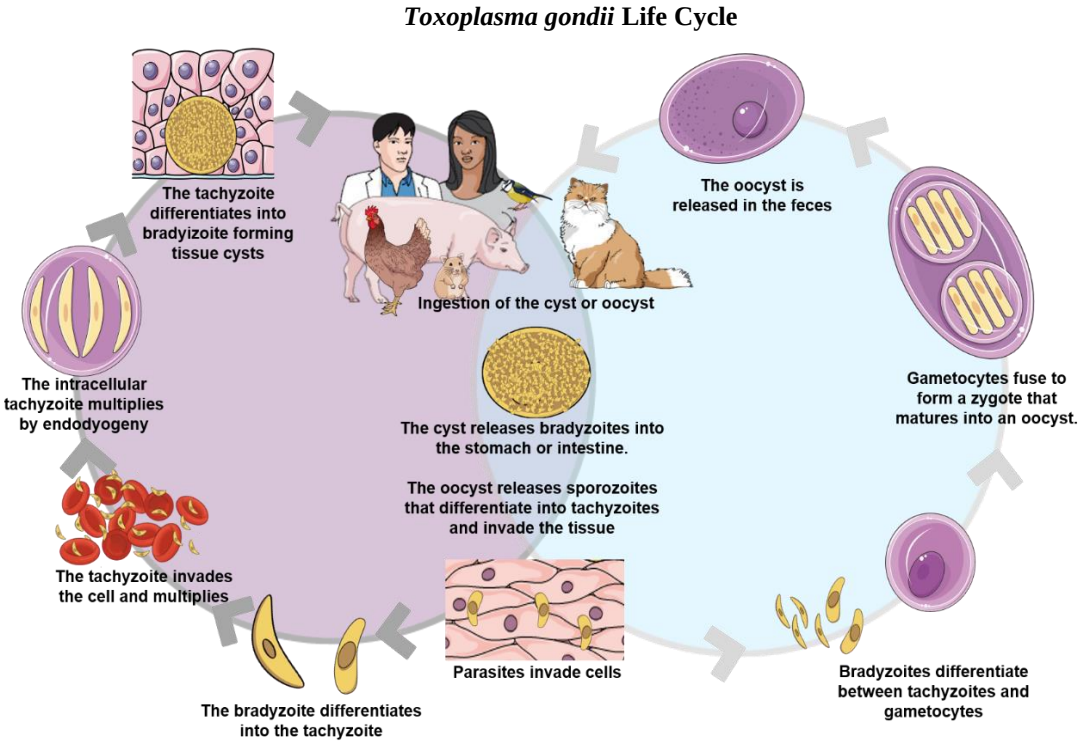
Infection by *Toxoplasma gondii* can become a public health concern, especially with regard to the development of neurological conditions in fetuses infected during pregnancy (Abrantes et al., 1999; Sponchiado & Da Silva, 2023). Toxoplasmosis can be transmitted orally, by eating raw or undercooked meat contaminated with cysts, one of the infectious forms of the parasite, mainly pork and sheep, which are available in a large part of the diet of the population around the world (Dubey et al., 1986; Attias et al., 2020). In addition to the oocysts that contain sporozoites and are eliminated in the feces of the definitive host, the infectious forms of *Toxoplasma gondii* are tachyzoites, found in the acute phase of the disease, mainly in body fluids, with a potential for rapid multiplication, and bradyzoites, with slow metabolism and present in the chronic phase of the disease, which can form tissue cysts present in the flesh of infected organisms (Dubey et al., 1998*;* Attias et al., 2020).

Infectious forms of *T. gondii* develop from the primary infection of a feline (definitive host), from the ingestion of a previously infected prey, containing tissue cysts or oocysts that have been excreted by another feline. In felines, the parasite reproduces sexually, with the wall of the oocyst or cyst ruptured by the action of enzymes and low pH in the host's stomach, causing sporozoites or bradyzoites to be released, respectively (Dubey et al., 1998*;* Attias et al., 2020).

When moving through the digestive system of the definitive host, the first target cells infected by *T. gondii* are those of the intestinal epithelium, where the protozoan reproduces by schizogony before the individualization of the cells and becomes schizont, a form that is characterized by several nuclei (Souza, 1974). Schizogony occurs in the epithelial cells of felines during the sexual phase and will then give rise to merozoites that, after maturation, will give rise to microgametes (male gametes) and macrogametes (female gametes). This type of reproduction is characterized by the formation of several nuclei without

cytoplasmic division (Souza, 1974; Esteves, 2022). Once the gametes are formed, fusion occurs between them and immature oocysts originate, which are released into the intestinal lumen of the definitive host, following the flow of the digestive system and being excreted by the feline in the environment. After being released, the oocyst contained in the feces will mature by sporulation, generating two sporocysts with four sporozoites each (Frenkel et al., 1970; Esteves, 2022). Sporulated oocysts are resistant to dry or wet weather and can survive in the environment for months (Figure 1) (Dubey et al., 1998; Attias et al., 2020).

Figure 1 - Schematic organization describing the life cycle of *Toxoplasma gondii.* (Laboratory of Cellular and Molecular Therapy and Physiology Prof. Antonio Carlos Campos de Carvalho Collection).



Source: Authors.

3.2 Forms of Transmission

In the 1950s, many scientists sought to explain how *Toxoplasma gondii* infection occurred in humans and animals. When observing the existence of different infectious forms, such as tachyzoites and, especially, tissue cysts containing bradyzoites, the main hypothesis raised was related to the exclusive consumption of meat, also known as carnivorism. This hypothesis was based on the studies of Jacobs, Remington and Melton, who, in 1960, identified that the bradyzoites present in these tissue cysts contained in undercooked meats were resistant to high temperatures, thus being an explanation for the high incidence of toxoplasmosis (JACOBS, 1960). On the other hand, there was a considerable occurrence of the same disease in vegetarians, that is, those who did not consume any type of meat. In 1965, Hutchinson uncovered another infective stage of *T. gondii*, the sporozoite-containing oocysts. This discovery explained the significant incidence of the disease among vegetarians, taking into account that the oocysts released in the cat's feces can contaminate the soil or even the water and vegetables, also contaminating those people who do not consume meat (Azevedo et al., 1983; Barbosa et al., 2014).

There are different forms of transmission defined by the infective forms of *T. gondii.* Transmission can occur vertically, that is, when transplacental infection of tachyzoites occurs, a situation in which the mother transmits the disease to the baby during pregnancy, and it is also perceived that transmission through milk can occur in various hosts, although sometimes

antibodies against *Toxoplasma gondii are not detected* in the milk of infected animals (Chiari & Neves, 1984; Cook et al., 2000; Barbosa et al., 2014); horizontally, through the ingestion of water and vegetables contaminated with oocysts with sporozoites present in the cat's feces; or even through blood transfusion.

Another mode of transmission is through organ transplantation and, in this case, it can occur in two main ways: when organ implantation occurs in a patient who is not immunocompromised or when transplantation occurs in a patient who is already immunocompromised (Dubey & Beattie, 1988; Abreu Guimarães et al., 2022). In addition to these ways, horizontal transmission can also occur through the ingestion of raw or undercooked meat. In this case, contamination occurs by tissue cysts that contain bradyzoites. It is perceived that the infection of the definitive hosts can occur by ingestion of contaminated meat or through contact with the contaminated feces of another animal, thus showing that the cats most susceptible to contamination are wild cats and not domestic cats, as these generally do not consume contaminated prey (Uggla et al., 1990; Attias et al., 2020).

3.3 Pathogenesis: organelles, proteins, and mechanisms

Any endothermic animal can be infected by *T. gondii.* In relation to exothermic animals, it is known that fish is one of the animals that can be infected by this parasite (Fayer et al., 2004; Marino et al., 2019). *T. gondii* has the ability to infect any nucleated cell of birds, reptiles, amphibians and mammals, including humans, with macrophage, epithelial, muscular and neuronal cells being more susceptible (Duarte & Andrade Júnior, 1994; Feitosa et al., 2018; Attias et al., 2020). Initially, the multiplication of *Toxoplasma gondii* occurs in the epithelial cells of different parts of the intestine, such as the jejunum, ileum, and colon (Jacobs, 1974; Briceno, 2023). The development and degree of virulence of the parasite also depends on the host's immune system. It is noticed that immunocompromised hosts tend to have an exacerbated form of the disease. Another aggravating factor for the proliferation of *T. gondii* in the host organism refers to the parasitic strain (Girdwood, 1989; Artigas et al., 2020).

Toxoplasma gondii has an apical complex formed by organelles and cytoskeletal elements that are involved in the process of adhesion and entry into the host cell. Infection begins with the ingestion of oocysts previously eliminated by the definitive host or tissue cysts of animals that have been previously infected (Martins et al., 1990; Attias et al., 2020).

Entry into the host cell occurs through the secretion of proteins from the organelles of the protozoan, which results in a complex formed between the parasitic cell and the host cell (Duarte & Andrade Júnior, 1994; Shen et al., 2014). Different proteins are secreted during the infection process, including the proteins released by the structures: microneme (MICs), rhoptries (ROPs), which are divided into two subclasses (proteins of the basal portion of the organelle and proteins of the apical end (RONs)), and dense granules (GRAs) (Duarte and Andrade Júnior, 1994; Hakimi et al., 2017). Respectively, these proteins play an important role in parasite mobility and cell adhesion, parasitophore vacuole formation, and regulation of the host immune system, impacting the virulence of different strains of *T. gondii* (Boothroyd & Dubremetz, 2008; Zhang et al., 2019).

Microneme proteins are the first to be secreted and are responsible for the parasite's adhesion and motility (Garcia-Reguet et al., 2000; Attias et al., 2020). The sliding of *T. gondii* is the result of the anchoring of these proteins to a myosin, TgMyoA, through another protein, aldolase, which connects to the N-terminal portion of the MICs (Jewett & Sibley, 2003; Attias et al., 2020). Myosin promotes actin glide, resulting in the "forward" movement of *T. gondii.* Also in relation to MICs, there is an interruption in the permeability of the host cell membrane, allowing the influx of parasite molecules, also inciting an increase in the influx of Ca^{++}, which helps the tachyzoite to leave the cell at the end of the cycle (Endo et al., 1982; Vella et al., 2021). At this time, rhoptries proteins are also secreted, which move to where there is contact between the host cell and the parasitic cell, where the mobile junction occurs (Michel et al., 1980; Sharif & Yahaya, 2023).

The formation of mobile junctions allows *T. gondii* to internalize in the parasitophore vacuole, formed mainly by ROPs (Lingelbach & Joiner, 1998; Zhang et al., 2019). Initially, the binding between the parasite and host occurs through a complex

formed by MIC1, MIC4 and MIC6, while MIC2 is associated with a carrier protein and MIC3 accompanies MIC8. The interaction between MICs and neck rhoptries proteins, especially between apical membrane 1 and RON2, is responsible for structuring the motile junctions (Alexander et al., 2005; Zhang et al., 2019). These neck rhoptries proteins are mainly responsible for the parasite's invasion of host cells (Hiramoto, 1998; Attias et al., 2014). Through the secretion of these proteins and the formation of mobile junctions, it becomes possible to internalize the parasite and form the parasitophore vacuole, and this step is essential for the development of *Toxoplasma gondii*, since the parasitophore vacuole has the ideal conditions for replication and nutrition (Jones et al., 1972; Battaglini, 2023).

The parasitophore vacuole (VP) is the result of the invagination of the host membrane and occurs simultaneously with the entry of *T. gondii* into the cell, having lipids and proteins in its membrane originating from the host's own membrane and only 20% synthesized by the parasite (Suss-Toby et al., 1996; Vommaro et al., 2014). The VP formed has characteristics that prevent the fusion of the host cell's lysosome with its membrane, preventing its degradation and removal (Mordue et al., 1999; Attias et al., 2020). ROPs are involved in the formation of VP and some of them are strictly related to blocking the recruitment of immune system cells and molecules, such as $ROP18_{I}$, which blocks the recruitment of IRGs (immunity-related GTPases), preventing the elimination of the parasite (Fentress et al., 2010; Zhang et al., 2019). The non-phosphorylation of IRGs by $ROP18_{III}$ proteins is also responsible for the establishment of chronic infection (Hunter and Sibley, 2012; Zhang et al., 2019).

Another important protein is ROP2, which has a sequence of amino acids similar to the mitochondrial import signal, bringing the host organelle into an association with the VP membrane, facilitating lipid acquisition (Beckers et al., 1994; Souza et al., 2010). The dense granules also play an important role in the structure of the VP, since they are responsible for the assembly of tubules and filaments, which form the intravacuolar network, whose function, according to Magno et al. (2005), is to support and form rosettes as endodiogenic cycles occur (Souza et al., 2010).

3.4 Replication and Differentiation of *T. gondii*

Previously, it was thought that *Toxoplasma gondii* carried out its division process by binary fission (Paraense, 1948; Souza, 1974), but it is currently known that this replication process occurs by endodyogeny (Souza, 1974; Attias et al., 2020). Endodiogenic is a division process carried out by tachyzoites. In this form of asexual reproduction, two daughter cells are formed inside the mother cell (Souza, 1974; Attias et al., 2020). With each endodiogenic cycle, a tachyzoite is able to give rise to two new daughter cells that remain connected to the residual body. This cycle can be repeated several times, resulting in the formation of rosettes that can occupy a vacuole larger than the VP at the beginning. As the host cell can be invaded by more than one parasite, the result of endodiogeny in relation to replication depends mainly on the number of parasitophore vacuoles formed and the size of the host cell (Attias et al., 2014). During the endodiogenic process, several structural changes are observed in the parasite, such as the emergence of two Golgi zones near the nucleus, a structure close to the Golgi Complex, called the Golgi adjunct, which is surrounded by several membranes, and is later divided transversely, and at the poles of the nucleus region, two electrodense bodies composed of DNA can be seen. Possibly these bodies are the inducers of the endodiogeny process, constituting new nuclei in the future (Sheffield & Melton, 1968; Unzaga, 2023). During the process, the invagination of the nuclear membrane occurs and the formation of a thick membrane that will be the inner membrane of the endozoite that is being formed. Thus, after all these changes, the two daughter cells are already completely formed (Souza, 1974; Oliveira, 2013).

After the occurrence of these division cycles, it is noticed that the tachyzoites complete their lytic cycle and different stimuli, such as the influx of Ca^{++}, are responsible for the exit of the tachyzoites, which are able to break the membrane of the host cell reaching the extracellular medium. These new tachyzoites then spread, infecting new cells both lymphatically and hematogenously, reaching other tissues, especially with the help of cells of the immune system itself, such as monocytes found in the intestinal epithelium (Mondragon & Frixione, 1996; Attias et al., 2020).

After several cell divisions, the endodiogeny process occurs more slowly, giving rise to the differentiation of tachyzoites into bradyzoites, generating chronic disease (Frenkel, 1973; Dubey et al., 1998; Radke et al., 2013; Barbosa et al., 2014; Araújo, 2023). This change is caused by different factors, such as the host's immune response, type of *Toxoplasma gondii* strain, protein secretion, and specific kinases (Appleford & Smith, 2000; Barbosa et al., 2014) and the transcriptional expression of certain genes (Walker et al., 2013; You et al., 2018).

It is perceived that the production of pro-inflammatory cytokines by the host's immune system regulates this change in the speed of replication. The main cytokines related to this differentiation process are interleukin 10 (IL-10), transforming growth factor Beta (TGF-β), interleukin 12 (IL-12) and interleukin 27 (IL-27) (Gazzinelli et al., 1994; Barbosa et al., 2014). The production of IL-12, especially, plays a fundamental role in the control of parasite replication, since, according to Gaddi and Yap (2007), mice deficient in IL-12 p35/p40 were more likely to develop the severe pathology of toxoplasmosis, also presenting a higher parasite load (GADDI, 2007). In addition, it is verified that different strains of the parasite have a higher or lower replication rate, since type 1 strains tend to have a faster replication and, on the other hand, type 2 and 3 strains have a slower replication rate, with a tendency to occur in a chronic state of the disease earlier (Howe and Sibley, 1995; Barbosa et al., 2014).

The secretion of proteins and kinases is also involved in the transformation of tachyzoite into bradyzoite. The Apetala 2 (AP2) gene is part of the family of transcription factors and is related to the differentiation of tachyzoites into bradyzoites because they act by regulating the genes of bradyzoites, with the upregulation of several microRNAs of the AP2 gene (Tu et al., 2018). It is noteworthy that some AP2 proteins, such as AP2XI-4 and AP2IV-3, act to induce differentiation into bradyzoites, while the AP2IX-9, AP2IX-4 and AP2IV-4 proteins act by repressing this differentiation (Radke et al., 2013; Tu et al., 2018). In addition, the catalytic subunit 3 of protein kinase A (TgPKAc3) has a regulatory role in the process of cell division and, consequently, in the differentiation of bradyzoites, considering that if there is a deletion of TgPKAc3, there is an increase in the differentiation of tachyzoite into bradyzoite (Sugi et al., 2016; Tu et al., 2018).

With the differentiation of tachyzoites into bradyzoites, it is possible to observe several morphological and structural changes in the parasite, such as conformational change of the parasitophore vacuole matrix and membrane. These changes seen in bradyzoites give rise to the cystic wall, which is responsible for structuring tissue cysts and possibly protecting against the host's immune system responses. The tissue cysts formed can vary in size and are located in different organs, with a predominance in skeletal and cardiac muscle tissue and nervous tissue, reaching organs of vital importance, such as the brain (Weiss and Kim, 2000; Souza and Belfort Jr., 2014). Tissue cysts, containing bradyzoites, may remain latent or rupture. If there is a rupture, there is the conversion of bradyzoites into tachyzoites, resulting in a process of reinfection of the host cells and again the transformation of tachyzoites into bradyzoites, a process that is known as interconversion (Soete et al, 1993; Souza and Belfort Jr., 2014).

3.5 Toxoplasmosis in Immunosuppressed Individuals

Tissue cysts are long-lasting and essential for maintaining the longevity of the infection, but they have no association with the disease, except in immunosuppressed people or in people who are congenitally infected, where cyst rupture can cause reactivation of the disease (Lyons et al., 2002; Daher et al., 2021). Toxoplasmosis in immunocompetent individuals is, in most cases, asymptomatic, depending on the genotype of the parasite (Howe; Summers; Sibley, 1996; Zhang et al., 2019). In immunocompromised individuals, whose cellular immunity may have been influenced by HIV infection or immunosuppressive treatments, there is a higher risk of disease reactivation, since the immune system would not be able to control the replication of tachyzoites and their conversion into bradyzoites, with slower metabolism, after cyst rupture (Khan et al., 1999; Zanna, 2017). The lack of ability to contain the disease in immunosuppressed patients is associated with alterations in T lymphocytes and, consequently, with lower production of IFN-y and Th1 cytokines (T helper cell type 1) (Deckert-Schluter, 1995; Zanna, 2017). In transplanted people, toxoplasmosis can be reactivated if there is a latent infection of the recipient, or an organ from an HIV-

positive donor can be passed on to the patient, where heart transplants are the most prone to such occurrence (Ryning, 1979; Zanna, 2017).

3.6 Congenital Toxoplasmosis

One of the forms of transmission of toxoplasmosis is transplacental, establishing a congenital disease when the mother is infected for the first-time during pregnancy, due to reactivation of a previous infection in immunosuppressed women, or even due to a new infection with a different strain of *T. gondii* (Ducournau et al., 2020; Falcão et al., 2021). The severity of the clinical manifestations and sequelae is closely linked to the gestational age as well as to the immunological status of the pregnant woman, the strain of the parasite and the parasite load acquired (Desmonts & Couvreur, 1986; Carter & Frank, 1986; Falcão et al., 2021). Infection of the fetus is more common in the acute phase of maternal disease, due to the high number of parasites in the bloodstream, and late infection by parasites remaining in the placenta is also possible, and therefore treatment is recommended throughout pregnancy (Duarte & Andrade Júnior, 1994; Bichara et al., 2014). It is known that the clinical manifestations of toxoplasmosis are directly dependent on the host's immune response, and in congenital toxoplasmosis, the same happens. It has been observed, during some studies, that there is a lower response to parasitic antigens. However, other studies have resulted in a preservation of the response against these same antigens (Yamamoto et al., 2000; Bichara et al., 2014).

That said, it is important to note that less than 10% of newborns have abnormalities in physical examinations and, of these 10%, only one third have a clinical picture characteristic of congenital infections, such as hepatomegaly, jaundice and systemic alterations associated with neurological abnormalities (Wilson et al., 1980; Sponchiado & Da Silva, 2023). In the other two-thirds, the alterations are related to the central nervous system and the eyes, including microcephaly or hydrocephalus, seizures and cataracts (Mussi-Pinhata & Yamamoto, 1999; Sponchiado & Da Silva, 2023). Complementary tests also reveal brain calcifications and retinochoroiditis (Bahia et al., 1993; Sponchiado & Da Silva, 2023). A study conducted in Tocantins by Falcão de Sousa et al. (2023) highlighted the importance of treating toxoplasmosis by pregnant women throughout pregnancy (Falcão de Sousa et al., 2023). Mothers who underwent treatment only for two months after diagnosis had their children with some sequelae, such as chorioretinitis (80%), delayed motor development (53%), hearing (47%) and speech (33%). On the other hand, newborns born to mothers who underwent complete treatment, with the use of spiramycin, did not have any sequelae (Falcão de Sousa et al., 2023). Thus, the importance of a brief diagnosis and appropriate treatment, as well as prenatal care, is observed.

3.7 Modulation of the Immune Response by *Toxoplasma gondii*

The secretory organelles of *Toxoplasma gondii* are also capable of generating changes in the host's immune system through important escape mechanisms from immune system responses (Lüder & Gross, 2005; Ahmadpour et al., 2023). The proteins secreted by roptria not only act in the process of penetration of the parasite into the host cell, but are also capable of generating the evasion of the immune system. Roptria protein 16 (ROP16) acts in conjunction with signal transducers and activators of STAT3 transcription and STAT6 phosphorylation. Through this phosphorylation, arginine-1 stimulation occurs, which can generate the hydrolysis of L-arginine (El Kasmi et al., 2008; Ahmadpour et al., 2023). L-arginine, a precursor used by several cells in the production of nitric oxide (Wu & Morris Jr., 1998; Rodríguez, 2022), is not able to generate nitric oxide when it is catabolized (Krishnan and Soldati-Favre, 2021). It should be noted that nitric oxide produced in large quantities works as a mechanism in the fight against invading pathogens; thus, through the hydrolysis of L-arginine, this mechanism of combating the parasite is inhibited (Vincendeau et al., 2003; Ahmadpour et al., 2023).

Programmed cell death (RCD) is an important mechanism mainly related to cell homeostasis and can be modulated by *T. gondii* through gene transcription (Kerr et al., 1972; Ahmadpour et al., 2023). By secreting the apoptosis inhibitor protein

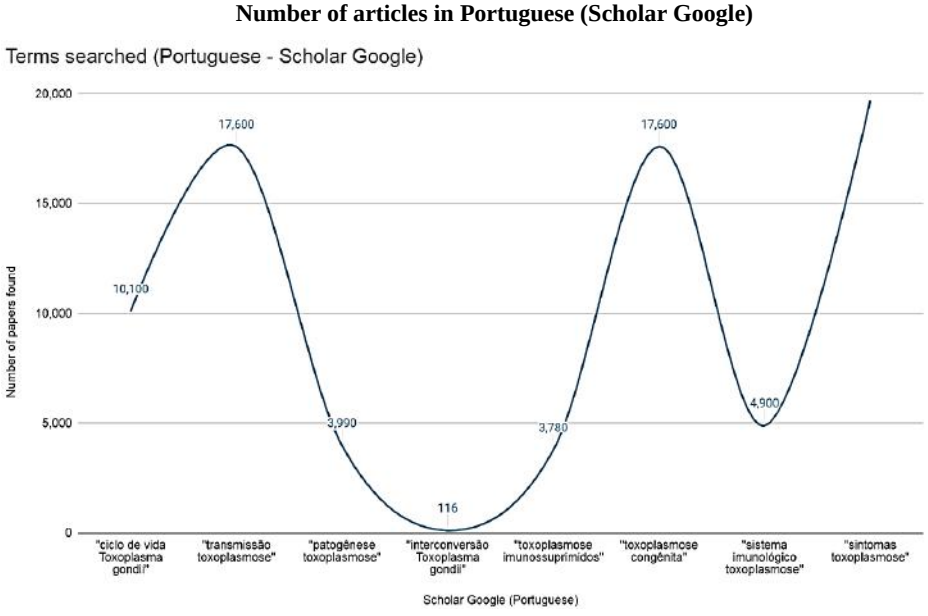
(IAP), *T. gondii* is able to inhibit apoptosis, one of the mechanisms of RCD. In addition, this parasite is capable of regulating intrinsic and extrinsic signaling pathways related to apoptosis (Nash et al., 1998; Ahmadpour et al., 2023). Another mechanism used by *Toxoplasma gondii* in the inhibition of RCD is through the inhibition of the activation of caspases, particularly caspase 3 (Heussler et al., 2001; Ahmadpour et al., 2023). Caspase are proteins that act in the cleavage of important cell substrates, a process that leads to cell death (Cohen, 1997; Luchs & Pantaleão, 2010), i.e., through the inhibition of caspases, *T. gondii* prevents RCD. All these mechanisms allow the proliferation of the parasite intracellularly, which can cause an exacerbated infectious process (Dos Santos et al., 2011; Guirelli, 2014).

The response of the host immune system during infection by *Toxoplasma gondii* is mediated by Th1, acting mainly in resistance against infection (Hsieh et al., 1993; Ratkevicius, 2021). *T. gondii* is able to reduce this response through the stimulation of regulatory interleukins, such as Interleukin 4 (IL-4) and Interleukin 10 (IL-10) (Chaves et al. 2001; Ahmadpour et al., 2023). IL-4 is responsible for differentiating Th0 cells into Th2, inhibiting Th1 cells. In addition, IL-10 is an inhibitory interleukin, as it acts by inhibiting the production of Interferon gamma (IFN-ÿ) (Mayer, 1998; Oliveira, 2017). The production of IFN-ÿ is one of the response mechanisms of the host immune system, as it is capable of inducing enzymes acting on the suppression of *T. gondii*, such as indoleamine 2-3 dioxygenase, thus, by inhibiting the production of IFN-ÿ, *T. gondii* inhibits the responses of the Immune System. According to Lu et al. (2003), IL-10 deficient mice had a higher rate of ocular necrosis, while mice with IL-10 overexpression showed a decrease in ocular tissue destruction (Lu et al., 2003); Thus, it can be seen that IL-10 is also capable of reducing the apoptosis process (Gaddi & Yap, 2007; Batista Jr. et al., 2009wa).

3.8 Graphic Analysis

A total of 77,786 articles were found referring to the terms described in the methodology for the preparation of the article. In the figures below (2-4), it is possible to observe the number of articles found for each term and the respective platforms used.

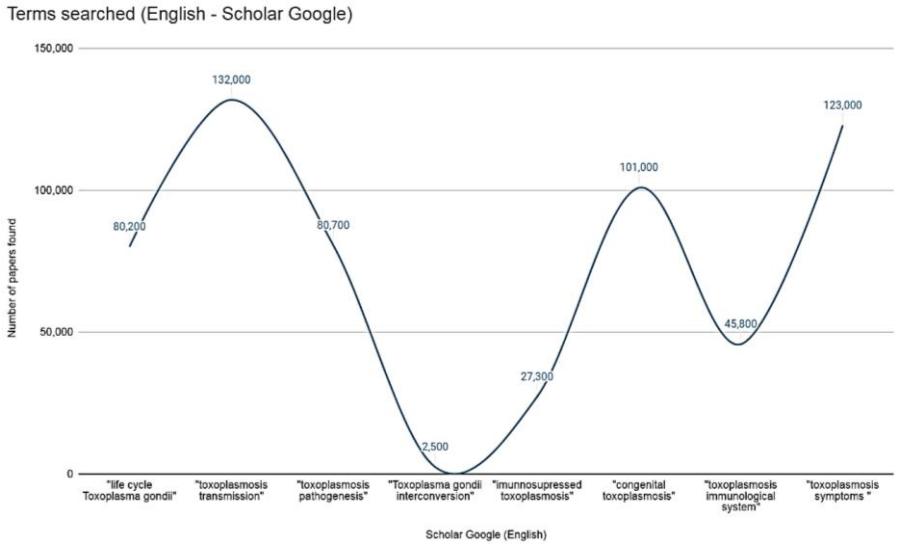
Figure 2 - Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis pathogenesis", "*Toxoplasma gondii* interconversion", "immunosuppressed toxoplasmosis", "congenital toxoplasmosis", "toxoplasmosis immune system", "toxoplasmosis symptoms", in Portuguese. A quantitative analysis was carried out on the articles found on the "Google Scholar" platform, having been searched on 03/13/2024 at 14:23h. Total: 77,786.



Source: Created by the authors.

Figure 3 - Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis pathogenesis", "*Toxoplasma gondii* interconversion", "immunosuppressed toxoplasmosis", "congenital toxoplasmosis", "toxoplasmosis immune system", "toxoplasmosis symptoms", in English. A quantitative analysis was carried out on the articles found on the "Google Scholar" platform, having been searched on 03/13/2024 at 14:28h. Total: 592,500.

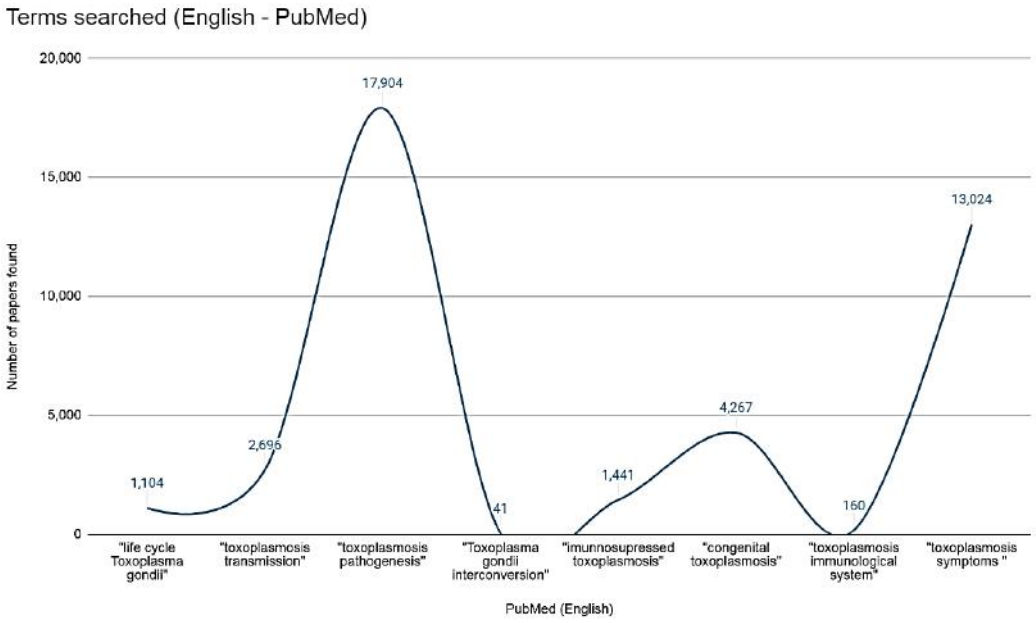
Number of articles in English (Scholar Google)



Source: Created by the authors.

Figure 4 - Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis pathogenesis", "*Toxoplasma gondii* interconversion", "immunosuppressed toxoplasmosis", "congenital toxoplasmosis", "toxoplasmosis immune system", "toxoplasmosis symptoms", in English. A quantitative analysis was carried out on the articles found on the "*PubMed*" platform, and they were searched on 03/13/2024 at 2:32 pm. Total: 40,637.

Number of articles in English (PubMed)



Source: Created by the authors.

4. Discussion

As shown in Figures 1, 2 and 3, it can be seen that the mechanisms of pathogenesis, transmission, as well as issues related to congenital toxoplasmosis are well described and elucidated in the literature. With regard to the terms "*Toxoplasma gondii* interconversion", "toxoplasmosis and immunosuppressed" and "toxoplasmosis immune system", it is noted that there is a low number of articles published in the two languages researched. This difference may demonstrate that certain aspects related to the study of this protozoan and the respective disease associated with it are not yet fully established.

Regarding the well-elucidated mechanisms of *Toxoplasma gondii*, it is observed that the formation of parasitophore vacuoles allows the maintenance of the protozoan in the host organism, culminating in its pathogenic success. The immune system's ability to modulate, through proteins secreted by *T. gondii*, also provides the longevity characteristic of the disease. In addition, this modulation may result in the worsening of the clinical condition in immunosuppressed patients and in cases of congenital toxoplasmosis. Another form of aggravation of the disease is related to organ transplantation, as they can contain cysts, compromising patients, who need to use immunosuppressants.

5. Conclusion

It is concluded that *Toxoplasma gondii* is a protozoan that has developed very efficient mechanisms for its longevity in the host's body, secreting proteins that play important roles in pathogenesis, modulating the immune system in its favor. However, there needs to be more studies on the disease caused by it, since, in certain situations, there may be a worsening of clinical manifestations. There should also be more dissemination about the ways in which the disease is transmitted as well as its forms of prevention, thus reducing the complications caused by the parasite and increasing the quality of life of the population.

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