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THE MOLECULAR MECHANISMS OF TOXOPLASMA GONDII, A PROTOZOAN THREAT TO HUMAN HEALTH

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ABSTRACT

Toxoplasmosis is an infection caused by the *Toxoplasma gondii* parasite which can lead to serious complications in immunocompromised individuals and during pregnancy. The relationship between *T. gondii*, immunity, and inflammation is complex and infection depends on the host's immune response and the parasite's ability to evade immune defenses. *T. gondii* is usually transmitted to humans by ingestion cysts, directly from mother to fetus during pregnancy, or through organ transplantation or blood transfusion. *T. gondii* induces a strong innate and adaptive immune response with the activation of macrophages and T and B cells, respectively. *T. gondii* secretes proteins from micronemes (MICs) and rhoptries, and these proteins facilitate cell attachment, entry, and the formation of vacuole parasitopophore. MIC2 and MIC6, interact with the surface membrane of host cells to start the invasion, while the rhoptry proteins (ROPs) are injected into the host cytoplasm. The dense granules proteins of the parasite, such as GRA15 and GRA24, are secreted into the host cell to modulate the inflammatory responses. *T. gondii* uses lipids for cell membrane synthesis and replication and tryptophan from the host cell for its vital growth. In this article, the biochemical and mechanical mechanisms of action of *T. gondii* in the host cell and the immune and inflammatory responses it induces are discussed.

KEYWORDS: *Toxoplasma gondii, protozoa, parasite, toxoplasmosis, infection, immunity*

INTRODUCTION

Protozoa are single-celled eukaryotic organisms that live in a variety of environments, including soil, water, and inside other organisms (1). Some protozoa are parasites that live at the expense of their host, causing disease in humans and animals (2) Among the most well-known protozoan parasites is *T. gondii*, which is an intracellular protozoan that infects the host through the oral route (3). This parasite can infect a variety of animal species, including mammals, and causes the disease toxoplasmosis, which can be asymptomatic, but can also be severe or potentially fatal if it affects immunosuppressed individuals or during pregnancy (4).

T. gondii can be found as undeveloped and/or developed oocysts, and cysts. This parasite prefers to reproduce in cats; however, it can infect many different animals, including humans. Toxoplasmosis is often transmitted through contact with infected cat feces or undercooked meat.

In healthy people, toxoplasmosis is often asymptomatic but can be serious for pregnant women or immunocompromised individuals. During pregnancy in women who are infected with *T. gondii* for the first time, the parasite can cross the placenta and infect the fetus, which has the potential to cause congenital toxoplasmosis that may

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produce serious developmental problems or miscarriage (5). Additionally, infection may cause neurological or ocular damage to the fetus.

The pathogenesis of this ubiquitous disease is still quite obscure, and it is important to clarify it given that it afflicts both industrialized and non-industrialized countries. The parasite's ability to establish a latent infection and evade immune responses still presents a challenge to overcome.

DISCUSSION

The pathogenic process of *T. gondii* which leads to infection and dissemination within the host occurs in several stages (6). *T. gondii* is usually transmitted to humans through ingestion of tissue cysts from undercooked meat or water contaminated with oocysts, through direct transmission from mother to fetus during pregnancy, or by organ transplantation or blood transfusion.

After ingestion, the parasite passes through the stomach and reaches the intestine, where sporozoites or bradyzoites are released from cysts (7). These forms differentiate into tachyzoites, which replicate rapidly and are responsible for acute infection. Tachyzoites invade host cells, particularly macrophages, fibroblasts, neurons, and muscle cells, by actively penetrating the plasma membrane. During active invasion, *T. gondii* enters host cells through a specialized process known as gliding motility (8). The parasite's actin-myosin motor complex drives this process, allowing it to rapidly invade cells without damaging the host membrane (9).

In humans, toxoplasmosis can initially cause mild flu-like symptoms and psychiatric disorders, including bipolar disorder (10). In immunocompromised individuals, *T. gondii* primarily affects the central nervous system (CNS) and can be lethal (11). Live but non-activated cysts (controlled by the immune system) that form within muscles and neurons can remain in the host throughout their entire lifespan.

The life cycle of *T. gondii* has a sexual component in the non-domestic cat and an asexual component that can occur in all warm-blooded animals, including humans (12). The definitive host of *T. gondii* is the cat, where it reproduces, while all other animals are intermediate hosts where only asexual reproduction can occur.

The surface of *T. gondii* includes a family of proteins regulated by glycosylphosphatidylinositol (GPI)-linked proteins (SRS) of which SAG1 (P30) is the prototypical member (13). *T. gondii* cysts develop in muscles, neurons, and other tissues and infect intermediate host animals which go on to infect the definitive host animal. The intermediate hosts include many species (over 200) such as horses, pigs, dogs, rabbits, and rats.

T. gondii infection typically occurs when a cat ingests an infected mouse containing the cysts of the parasite, which pass through the stomach and infect the epithelial cells of the animal's intestine (14). In intestinal cells, parasites undergo sexual reproduction and produce millions of walled cysts containing zygotes called oocysts. The cat is the definitive host as, not having the delta-6-desaturase enzyme in the intestine, it cannot convert linoleic acid which is important for the sexual reproduction of *T. gondii* (15). Infected epithelial cells eventually rupture and release oocysts into the intestine which shed in the feces. Oocysts can survive in soil at very cold temperatures and cause infection if they are eaten by humans and other animals, which in turn become intermediate hosts (12). Cysts containing sporozoans are released inside the animal and the sporozoans implant into the muscles where they form adult cysts (16).

The immune response to *T. gondii* is robust and involves both innate and adaptive mechanisms. This can have significant impacts on human health, especially in immunocompromised individuals or pregnant women (17). Individuals with weakened immunity are at increased risk of severe toxoplasmosis or reactivation, as the immune system may not be able to suppress latent stages of the parasite.

At the beginning of *T. gondii* infection, innate immune cells are activated, such as macrophages and T cells which produce IL-2 and interferon-gamma (IFN-γ). T cells such as CD4+ and CD8+ play an important role in immunity against toxoplasmosis (17). Major histocompatibility complex (MHC) presents *T. gondii* antigens to T cells, which determines the severity of the infection (18). CD4+ T cells are essential for orchestrating the immune response, secreting cytokines like IFN-γ and helping to maintain control over chronic infection (19). CD8+ T cells are cytotoxic T cells which recognize infected cells and kill them to limit the spread of the parasite. They also produce IFN-γ, which further enhances immune defenses (20).

IFN-γ is a cytokine that is very important in the immune defense against *T. gondii*. It activates macrophages to produce reactive nitrogen and oxygen species, which can kill the parasite inside cells. IFN-γ also stimulates the production of indoleamine 2,3-dioxygenase (IDO), an enzyme that deprives *T. gondii* of tryptophan, a vital nutrient for its survival (21). B cells produce antibodies (IgG and IgM) specific to *T. gondii*. These antibodies help neutralize extracellular parasites and mark them for destruction by immune cells like macrophages (22).

The pathogenic effect of *T. gondii* is carried out in different phases with the diffusion and infection of the host. The transmission of the parasite can occur through different mechanisms, such as ingestion of cysts with raw or undercooked

meat, or with contaminated water. Toxoplasmosis can also be congenital when it happens during pregnancy with fetal transmission from the mother (6). In addition, infection can occur in the event of blood transfusion or organ transplantation (23).

After the ingestion, the parasite passes through the stomach and reaches the intestine, where sporozoites or bradyzoites from the cysts are released. These are different forms of tachizoites that invade host cells such as macrophages, fibroblasts, muscle cells, and neurons. The parasite's actin-myosin motor complex allows it to quickly invade the cells. After invasion, *T. gondii* lies in a vacuole parasitophore that derives from the guest cell membrane but is modified by the parasite to avoid melting with lysosomes and subsequent degradation (24). The parasite replicates inside the cell and releases tachizoites which infect new cells.

The infection spreads throughout the body through the blood and lymphatic system, arriving to the brain and muscles, where chronic cysts are formed. At this point, the tachizoites differ into bradyzoites, which persist in tissue cysts (particularly in muscle and neural tissues) and lead to chronic infections (25). The cysts demonstrate a useful process in immunosuppression by escaping the immune system while also activating it.

T. gondii release proteins from specialized secretory organelles called micronemes (MICs) and rhoptries (18). These proteins facilitate cell attachment, entry, and formation of vacuole parasitopophores. MICs, such as MIC2 and MIC6, interact with the surface membrane of the host cells to initiate the invasion, while the rhoptries are injected into the host cytoplasm, where the reporting routes of the host cells manipulate, modulate immune responses, and promote survival (26). The kinases ROP18 and ROP5 interfere with the immuno-related GTPasi of the host which causes the interruption of the vacuole parasitophore (27). By interrupting these mechanisms, the host cell is unable to attack the parasite.

The parasitic dense granule proteins, such as GRA15 and GRA24, are secreted into the host cell to modulate inflammatory responses, including the alteration of the NF-kB signaling routes and MAPK with disruption of the host's immune response, for the benefit of the survival of the parasite (28).

T. gondii has efficient systems to obtain essential amino acids from the host, such as tryptophan, which is vital for parasitic growth. Host cells often deplete tryptophan as an immune defense (29). *T. gondii* uses host lipids, for cell membrane synthesis and replication. The parasite can modulate host lipid metabolism by altering key pathways involved in fatty acid and sterol synthesis.

T. gondii also employs glycolysis, which is crucial for its survival and replication, and for maintaining chronic infection (30). Glycolysis is essential during the tachyzoite phase, where rapid energy demands are met by breaking down glucose into pyruvate. During chronic infection, bradyzoites switch to more efficient oxidative phosphorylation to conserve energy. Additionally, *T. gondii* relies on *de novo* fatty acid synthesis for membrane production during its replication phase. It uses a unique type II fatty acid synthesis (FAS II) pathway that is different from that found in humans, making it a potential drug target (31).

Other biochemical pathways include the methylerythritol phosphate (MEP) pathway in the apicoplast, which is responsible for the synthesis of isoprenoid precursors that are essential for cellular functions such as membrane maintenance and protein prenylation (32). The apicoplast also plays a role in the FAS II pathway, which is crucial for the synthesis of fatty acids used in membrane generation.

T. gondii can utilize various nutrients from its host, including purines and lipids. The parasite does not have the ability to synthesize purines *de novo*, so it relies on scavenging them from the host cell for DNA and RNA synthesis (33). Furthermore, *T. gondii* has sophisticated transporters to take up amino acids from the host. Arginine metabolism is particularly important, as arginine deprivation can suppress the host immune response by limiting nitric oxide production (34).

CONCLUSIONS

Toxoplasmosis is caused by infection with the *T. gondii* protozoan. It is a parasitic infection that can lead to serious complications in immuno-compromised individuals and during pregnancy *T. gondii* elicits an innate immune response that activates TH1 and TH2 cells. Macrophages and cytotoxic T cells produce inflammatory cytokines and generate IFN-γ, which are essential for controlling the infection. Inflammation is a key factor in the pathogenesis of toxoplasmosis, with a balance required between effective parasitic control and limiting tissue damage.

The interaction of the parasite with the host leads to complex molecular and biochemical mechanisms, as well as immune evasion strategies that allow the parasite to survive. Prevention of *T. gondii* infections is mainly based on hygienic measures, such as avoiding contaminated water, cooking food properly, taking preventive measures during pregnancy, and, in some regions, employing protection from insect bites. Treatment usually involves the use of *T. gondii*-specific antiparasitic drugs.

Research on human vaccines is ongoing, and therefore, no approved human vaccine against *T. gondii* exists as to date. Studies are also focusing on vaccines that enhance T cell and IFN-γ-mediated responses, which are central to strengthen the immune response against the parasite. Future studies on these topics should continue to shed light on the parasite-host reaction and immune and inflammatory activation.

Conflict of interest

The authors declare that they have no conflict of interest.

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