Chapter 20

The Interactive Effects between Toxoplasma Gondii and the Gut Microbiota

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ABSTRACT

Parasites, gut microbiota, and the host exist in a complex and intricate interplay. Infection with *Toxoplasma gondii* can lead to alterations, dysbiosis, and inflammatory diseases in the gut microbiome; concurrently, the gut microbiota influences the colonization, proliferation, and virulence of *T. gondii* within the host. Recent research on the interactions between intestinal parasites and the microbiota has revealed that the gut microbiota can either promote or inhibit the pathogenic effects of *T. gondii* on the host, and probiotics have shown specific preventive or therapeutic effects on intestinal *T. gondii* infections. Current research on the interaction between *T. gondii* and the microbiota is still in its infancy, and the mechanisms of their interaction are not yet fully understood. Elucidating the mutual influences and mechanisms of action between *T. gondii* and the gut microbiota is crucial for a deeper understanding of the relationships among *T. gondii*, the gut microbiota, and the host, as well as for developing effective anti-*T. gondii* microbiome preparations and the safeguarding of public health. This article reviews recent advances in research on the interaction between *T. gondii* and the microbiota. It provides perspectives on future research directions in this field, aiming to offer new strategies and theoretical foundations for preventing and controlling Toxoplasmosis.

KEYWORDS
Toxoplasma gondii; Gut microbiota; Public health; Prevention and control

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INTRODUCTION

Toxoplasma gondii and Toxoplasmosis

Toxoplasma gondii, a protozoan parasite belonging to the phylum Apicomplexa, is recognized as one of the most successful parasites on Earth. It is an important zoonotic pathogen capable of infecting all warm-blooded vertebrates, leading to abortions and stillbirths (Sanchez et al., 2021). This parasite significantly threatens livestock and public health safety, resulting in substantial economic losses. *T. gondii* exhibits a complex life cycle with five distinct stages of development: as tachyzoites and cysts within intermediate hosts, which include a range of mammals and birds, and as schizonts, gametocytes, and oocysts within definitive hosts, such as cats and other members of the Felidae family (Matta et al., 2021). Tachyzoites, known for their rapid replication within the host, are widespread throughout the body and are commonly found in acute cases. In contrast, cysts are often detected in chronic or asymptomatic cases within tissues such as the brain, skeletal muscle, heart, lungs, liver, and kidneys. Schizonts and gametocytes are typically found within the intestinal epithelial cells of definitive hosts. At the same time, oocysts are formed in the intestinal epithelial cells and released into the environment with the feces of the definitive host, exhibiting strong infectivity (Freppel et al., 2018). Although pyrimethamine and sulfonamide drugs are significantly effective in treating Toxoplasmosis, their hepato-renal toxicity and the issue of drug resistance cannot be overlooked (Montazeri et al., 2018; ShanShan Hu et al., 2024).

Recent research has highlighted the crucial role of the gut microbiota in various infectious diseases. However, studies on the impact of *T. gondii* infection on the gut microbiota are relatively limited. Understanding the link between Toxoplasmosis and the gut microbiota can aid in developing new strategies for preventing and treating *T. gondii* infection, safeguarding public health and animal welfare.

Gut Microbiota

The gut microbiota is vertebrate animals' most abundant and complex microbial ecosystem. It is an integral part of the immune system, closely related to the host's health status. Thousands of microbial communities form a dynamic and stable gut microbiome structure, including over 1500 species across more than 50 different phyla, with bacteria accounting for 90% of the total gut microbial population. Recent research advancements have rapidly expanded our understanding of the

gut microbiota, encompassing disease pathogenesis, immune modulation, and parasite interactions. The complex interplay between gut microbiota and health implicates multiple pathways, including immune function, energy metabolism, lipid, and glucose metabolism (de Vos et al., 2022). Studies have demonstrated a link between gut microbiota dysbiosis and conditions such as obesity, type 2 diabetes, hepatic steatosis, inflammatory bowel diseases (IBDs), and certain types of cancer (Sepich-Poore et al., 2021). Parasitic infections can alter the composition and diversity of the gut microbiota, impacting the host's health (Méthot and Alizon, 2014; Hauck, 2017; Benson et al., 2009). Concurrently, the gut microbiota influences parasites' colonization, proliferation, and virulence (Tierney et al., 2004; Pérez et al., 2001; Foster et al., 2003; Matthew et al., 2004). Research has revealed that microbial agents such as probiotics, prebiotics, and synbiotics can modulate gut microbiota balance, enhance intestinal defense mechanisms, and positively affect the treatment of diseases like diarrhea, constipation, and indigestion (Sorbara et al., 2022). In recent years, breakthroughs in technologies such as high-throughput metagenomics analysis and artificial intelligence have facilitated a deeper understanding of the complexity of gut microbial communities and the exploration of their mechanisms of action, providing a foundation for developing new therapies. Modulating the balance of the gut microbiota is of significant importance for preventing and treating related diseases.

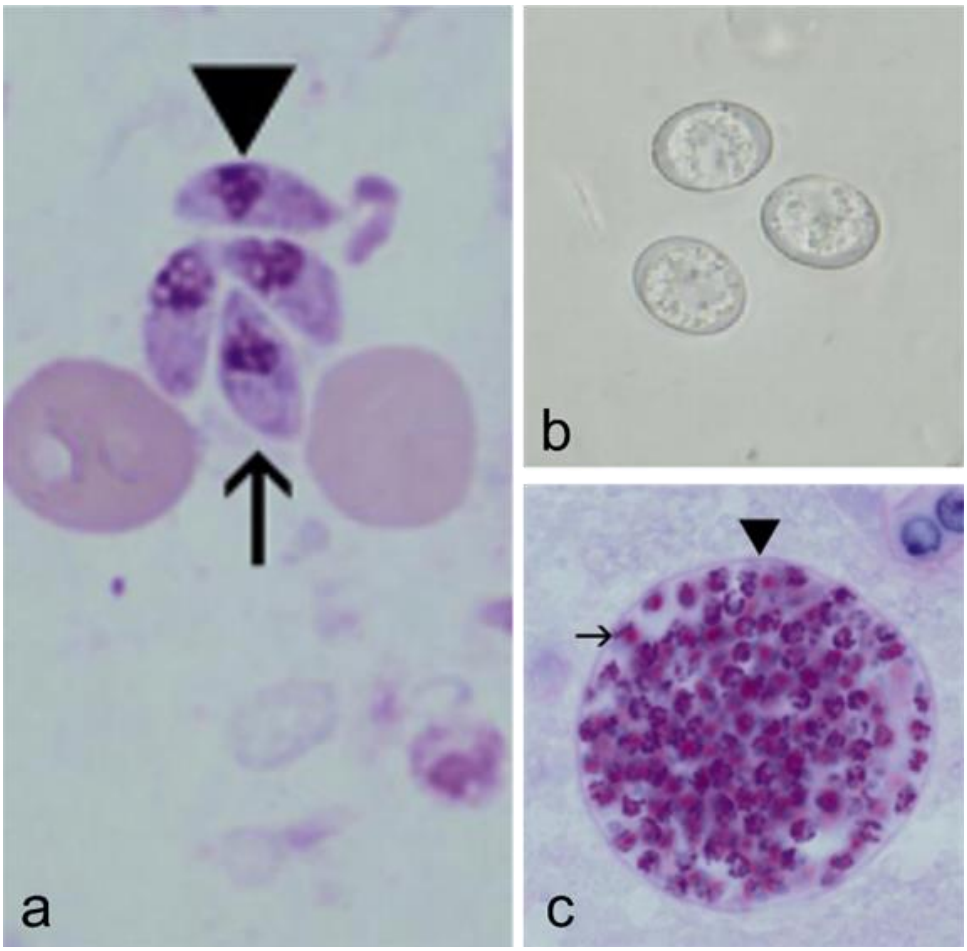

Fig. 1: The different developmental stages of *Toxoplasma gondii* (a. Tachyzoites, b. Oocysts, c. Tissue Cysts).

Interaction between Toxoplasma Infection and Gut Microbiota

Disruption of Intestinal Homeostasis by Toxoplasma Infection

Toxoplasma infection triggers intestinal inflammatory responses associated with changes in the gut microbiota composition. This study elucidates the shifts in gut microbiota composition during Toxoplasma infection and their implications for intestinal health. In healthy mice, the ileum is predominantly occupied by *Firmicutes* and *Bacteroidetes*, constituting 67% and 28% of the total microbiota, respectively. *Lactobacillus*, a probiotic, is essential for maintaining gut microbiota balance, preventing diseases, and promoting health. However, during Toxoplasma infection, there is a significant decrease in probiotics like *Lactobacillus*, while the numbers of *Enterobacteriaceae* from *Proteobacteria* and *Enterococcus* from *Firmicutes* increase, exhibiting a trend of initial rise followed by a decline. Conversely, the overall number of *Bacteroidetes* slightly increases compared to uninfected controls (Heimesaat et al., 2018; 2019). Molecular analyses reveal that the development of immunopathology is accompanied by profound changes in bacterial flora, with *Escherichia coli*, *Bacteroides*, and *Prevotella* dominating in acute ileitis. The total bacterial load in the ileum increases dramatically during inflammation, with significant increases in aerobic and anaerobic bacteria (Markus et al., 2006). Acute Toxoplasma infection activates the Th1 immune response, secreting many cytokines with anti-parasitic effects. However, an overactive immune response can decrease Paneth cells, which are vital for the intestinal epithelial barrier. The depletion of

Paneth cells and their antimicrobial secretions results in diminished expression and secretion of α-defensins, loss of gut microbiota diversity, and a pronounced expansion of *E. coli,* thereby exacerbating intestinal dysbiosis (Eriguchi et al., 2012; Raetz et al., 2013; Lu et al., 2018). In our experiments, high-throughput sequencing of the 16S rDNA of the gut microbiota in chickens yielded the following results, as shown in Fig. 2. After analyzing the sequencing results of the control group and the Toxoplasma gondii-inoculated group (from now on referred to as the infected group) in the 7-day-old group, the control group had 16 unique operational taxonomic units (OTUs). In contrast, the infected group had 69 unique OTUs. In the analysis of the sequencing results for the 28-day-old group, the control group had 26 unique OTUs, and the infected group had 50 unique OTUs. This indicates that the shared bacterial communities in the gut of the infected group are generally more diverse than those in the control group. At the phylum level (Fig. 3), the abundance of *Proteobacteria* and *Actinobacteria* was slightly lower in the infected group. In comparison, the abundance of *Bacteroidetes* and *Firmicutes* was slightly higher, with the most significant increase in abundance observed in *Bacteroidetes*.

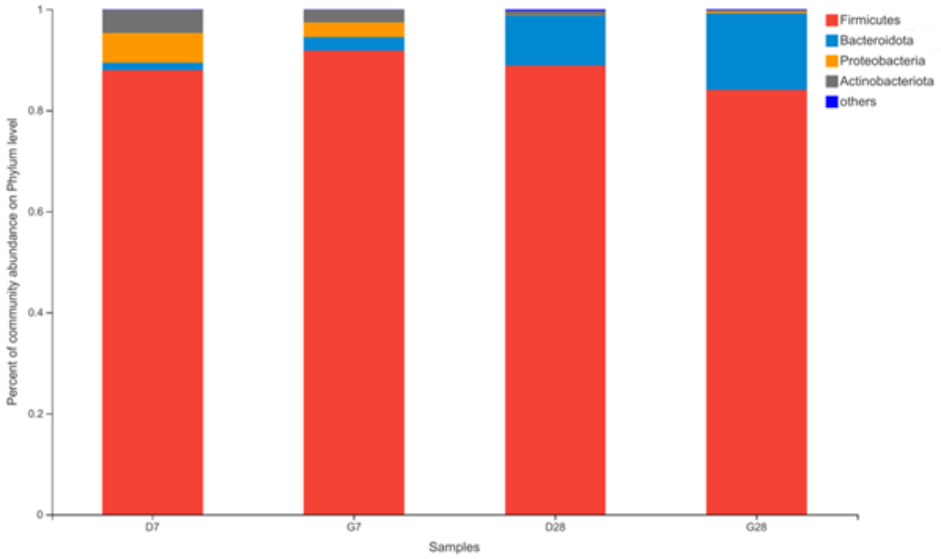

Fig. 2: Differences in species composition among samples. A) shows the comparison between the 7-day-old infected group and the control group; B) compares the 28-day-old infected group with the control group; and C) compares the 7-day-old infected group with the 28-day-old infected group.

Intestinal Dysbiosis and the Co-occurrence of *Toxoplasma gondii* Enteritis

The gut microbiota is an integral part of the immune system in humans and animals, contributing to the proper functioning of the host's immune defenses. The gut microbiota plays a crucial role in the immune system of humans and animals, influencing the development and function of both innate and adaptive immunity. The presence of gut microbiota facilitates the development of delicate structures in gut-associated lymphoid tissues and peripheral lymphoid organs, such as Peyer's patches and the spleen (Macpherson et al., 2006). The gut microbiota protects the host from pathogenic infections through various mechanisms, including competition for adhesion receptors and nutrients and stimulation of mucosal production of mucus and antimicrobial substances (Stecher et al., 2008). Gut microbiota expresses pathogen-associated molecular patterns (PAMPs) antigens that directly stimulate innate immune receptors, activating surface receptors on intestinal epithelial cells, dendritic cells, and macrophages. This leads to the production of antimicrobial substances such as COX-2, KGF-1, KGF-2, and angiogenin-4, and modifiable TGF-β1 through MyD88-dependent and TLR-dependent immune stimulation pathways, thereby maintaining intestinal homeostasis (Rakoff-Nahoum et al., 2004; Iwasaki et al., 2007). Under normal conditions, the gut maintains immune tolerance to commensal bacteria. However, during oral infection with *T. gondii*, the host loses immune tolerance to intestinal commensal bacteria (Hand et al. 2012), which facilitates the invasion of *T. gondii*.

Under normal conditions, the intestinal commensal bacteria can work with the mucosal immune system to produce beneficial effects for the host. However, in the case of dysbiosis, the overgrown gut microbiota can translocate to organs such as the mesenteric lymph nodes, liver, lungs, and blood, leading to secondary inflammation. An excessive increase in pro-inflammatory cytokines in the serum, including IFN-γ, TNF, MCP-1, IL-12, IL-6, and IL-10, triggers a cytokine storm. The host then exhibits symptoms such as weight loss, bloody diarrhea, and acute transmural enteritis, including apoptosis and necrosis of the small intestinal epithelial cells (Von Klitzing et al., 2017; Dos Santos et al., 2020). Current research suggests that Toxoplasmosis involves complex tripartite interactions between *T. gondii,* the mucosal immune system, and the host's gut microbiota (Cohen et al., 2014).

Toxoplasmosis can induce the formation of inflammatory bowel disease (IBD), and the intestinal state during acute *T. gondii* infection is similar to that of Crohn's disease (CD) patients (Egan et al., 2012). By orally infecting mice, the pathological process of CD can be simulated. The results show that germ-free (GF) mice have lower levels of IFN, IL-22, TIMP1, KC, and MPO in the intestine and higher levels of IL-1 compared to specific pathogen-free (SPF) mice, indicating that GF mice have better resistance to *T. gondii*-induced mucosal inflammation (Nascimento et al., 2017)). At the same time, the parasite load in GF mice is also significantly lower than that in SPF mice. Therefore, in normal gut microbiota, the microbiota can exacerbate the small intestinal inflammation caused by *T. gondii*.

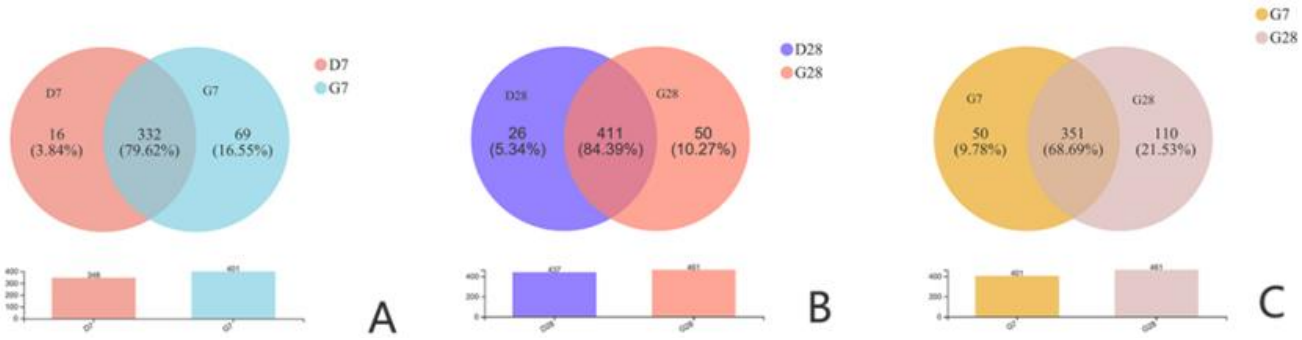

Fig. 3: Gut microbiota relative abundance at the phylum level.

The Treatment Effect of Probiotic Metabolites on *Toxoplasma Gondii* Infection

Indole-3-Propionic Acid (ILA) is a metabolite produced by bacteria of the *Lactobacillus genus*, which has a potential positive role in treating *Toxoplasma gondii* infection. Following infection with *T. gondii*, there is a significant decrease in the levels of ILA in the serum. ILA can activate the aryl hydrocarbon receptor signaling pathway in intestinal epithelial cells, promoting the activation of CD8+ T cells and the secretion of interferon-γ, thereby helping to suppress inflammation caused by *T. gondii* infection (Chen et al., 2024). This suggests that ILA, as a gut microbiota-related metabolite, may positively impact the treatment of *T. gondii* infection by regulating the host's immune response. According to existing studies, *T. gondii* infection leads to an imbalance in the gut microbiota, particularly reducing the abundance of probiotics, such as *lactobacilli* (Meng et al., 2023). This imbalance exacerbates damage to the intestinal and brain barriers. Research has found that the administration of *Lactobacillus murinus* and *Lactobacillus gasseri* can restore the balance of the gut microbiota, significantly inhibit the burden of *T. gondii* in the intestines, liver, and brain, and improve intestinal barrier damage, reducing central nervous system inflammation and neuronal apoptosis (Chen et al., 2024). Therefore, the supplementation of ILA and its producing bacteria, *Lactobacillus*, may become a potential strategy for treating *T. gondii* infection.

In addition, Alpha-Linolenic Acid (ALA), a gut microbiota-related metabolite, has been found to alleviate intestinal inflammation caused by *T. gondii* (Yang et al., 2023). Specifically, the study pointed out that oral administration of ALA and fecal microbiota transplantation (FMT) can both reduce the expression of pro-inflammatory cytokines and inhibit the MyD88/NF-κB signaling pathway, which helps to alleviate colitis and improve the survival rate of the host. Furthermore, the microbiota in the feces of mice treated with ALA can restructure the colonization of beneficial bacterial groups, such as *Enterobacteriaceae*, *Proteobacteria*, *Shigella*, *Lactobacillus*, and *Enterococcus*.

Summary and Prospects

Current research indicates a tripartite interaction between *Toxoplasma gondii*, the mucosal immune system, and the host's gut microbiota during *T. gondii* infection. During acute infection, the mucosal immune system is compromised, and the homeostasis of the gut microbiota is disrupted, exacerbating the occurrence of *T. gondii* enteritis. Previous studies have elucidated the molecular mechanisms related to *T. gondii*, gut microbiota, and immunity. These findings have revealed the connection between *T. gondii*-induced apoptosis and inflammatory responses and the gut microbiota, providing new directions for preventing and treating Toxoplasmosis.

High-throughput sequencing technology currently provides a platform for studying the interactions between parasites and the gut microbiota. The sequencing results can reveal extensive taxonomic changes in the gut microbiota, providing a basis for further exploration of the mechanisms of parasite-microbiota interactions. Metabolites of the gut microbiota, such as indole-3-lactic acid (ILA) and alpha-linolenic acid (ALA), have been found to inhibit the occurrence of *T. gondii* enteritis by regulating the host's immune system, providing a basis for the development and application of anti-*T—gondii* microbial preparations.

Furthermore, research on the interactions between intestinal parasites and microbiota in their natural state will help translate laboratory findings into clinical applications. Since the gut microbiota can affect the survival and infection outcomes of various parasites, understanding the interactions and mechanisms between parasites and the gut microbiota can lead to the design of prebiotics that stimulate the growth of specific microbes, suppress or reduce the virulence, colonization, or reproduction of parasites. This approach is expected to provide new directions and technologies for preventing and controlling parasitic diseases, which is of great significance for reducing the use of anti-parasitic drugs, promoting the development of animal husbandry, and ensuring public health security.

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