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The Interaction Between Giardiasis and Host Mucosal Immune System: A Review

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Abstract

Giardia spp. is an intestinal protozoal parasite that infect humans and many different other mammalian hosts. The most significant clinical features of giardia infection are malabsorption and diarrhea. *Giardia lamblia* possesses the remarkable ability to continually alter its dominant surface antigen, known as the variant surface protein (VSP), allowing it to evade host immune detection. Infection with this protozoan trigger a strong adaptive immune response in both humans and animal models. It has long been established that significant amounts of parasite-specific IgA are produced following infection, with CD4+ T lymphocytes playing a pivotal role in stimulating IgA synthesis and contributing to the regulation of the infection. Although anti-VSP IgA antibodies in the gut have been demonstrated to influence the parasite's antigenic switching, the extent to which local intestinal antibodies directly control *Giardia* colonization remains a subject of debate. The interface between the intestinal lumen and the epithelial lining serves as the primary attachment site for *Giardia* trophozoites, making it a critical zone for both the establishment of the parasite and the initiation of host immune defenses. This area thus represents a central battleground where host-pathogen interactions dictate the outcome of infection. This review will therefore focus on innate immune mechanisms and barrier integrity in giardiasis. The specific aims of this review are centered on elucidating the multifaceted interactions between *Giardia* and the host intestinal environment. First, the review seeks to characterize how *Giardia* disrupts epithelial junctional complexes and alters the cytoskeletal architecture, compromising intestinal barrier integrity. Second, it aims to examine the innate immune responses initiated by various cell types, including epithelial cells, macrophages, dendritic cells, and Paneth cells, in reaction to *Giardia* infection and its secreted molecules. Third, the review intends to analyze how these host–parasite interactions contribute to persistent barrier dysfunction and facilitate microbial translocation, which may exacerbate inflammatory outcomes. Finally, it explores potential therapeutic strategies that strengthen epithelial barrier function and modulate innate immune mechanisms to mitigate the pathological effects of giardiasis and promote mucosal homeostasis.

Keywords: Giardiasis, Host Mucosal Immune, parasite-specific IgA

Introduction

Gastrointestinal infections still an important wolrdwide health concern, that contributes substantially to morbidity, nutritional deficits, and reduced quality of life, especially among young children in low- and middle-income countries. Among protozoan pathogens, *Giardia lamblia* (also known as *G. duodenalis*) is one of the most well-known causes of non-viral diarrheal disease globally, estimated to affect hundreds of millions annually (Klimczak et al., 2024). Unlike many enteropathogens, *Giardia* typically occupies the lumen of the small intestine and does not invade tissues, yet its presence frequently leads to malabsorption, barrier dysfunction, and long-term gastrointestinal disturbances (Fink & Singer, 2017; Klimczak et al., 2024).

The mucosal immune system of the gastrointestinal tract plays an indispensable role in maintaining gut homeostasis, distinguishing harmful pathogens from commensal microbes, and mounting responses that eradicate pathogens while limiting damage to host tissue. Diverse cell types (epithelial cells, goblet cells, dendritic cells, macrophages, T-cells), secreted mucins, antimicrobial peptides, immunoglobulin A (IgA), and cytokine networks jointly constitute the first line of defense. Disruption of any component of this system may lead to increased susceptibility to infection, inflammation, or chronic gut dysfunction (Al-Rashidi & El-Wakil, 2024; Fink & Singer, 2017).

In the case of giardiasis, host-parasite interactions are complex: *Giardia* triggers modifications in barrier function, mucin production, immune cell recruitment, and cytokine secretion. The disturbance of epithelial cytoskeletal components and tight junctional proteins leads to a weakening of the barrier's structural integrity. As a result, epithelial permeability becomes elevated, a condition that may persist even after the elimination of the parasite. This compromised state is believed to precede—and in some cases sustain—the activation of mucosal immune responses (Serradell et al., 2018). In addition, *Giardia* also influences the composition of commensal microbiota, which in turn affects immune responses—a bidirectional relationship that can modulate disease severity and contribute to either resolution or persistence of infection (Al-Rashidi & El-Wakil, 2024; Klimczak et al., 2024).

It has long been recognized that infection with *Giardia* stimulates the production of substantial quantities of parasite-specific IgA, with CD4+ T cells playing a crucial role in driving this IgA response and in regulating the course of the infection. Recent studies reveal that *Giardia* infection often shifts the mucosal cytokine milieu. Early infection may provoke a mixed inflammatory response (TNF-α, IL-1β, Th17, Th1), accompanied by specific antibody (IgA, IgG) responses, but over time there frequently emerges a regulatory or Type 2 biased profile characterized by cytokines such as IL-25, IL-5, IL-4, increased IL-10 production and expansion of goblet cell numbers, which appear to both favor parasite persistence and protect against excessive mucosal damage or inflammation (Serradell et al., 2018; Sardinha-Silva et al., 2025). For example, Serradell et al. (2018) observed in animal models that after an initial surge of pro-inflammatory cytokines, a shift towards Th2 responses was seen, likely acting as a counterbalance to limit tissue injury.

Additionally, insights into molecular and cellular mechanisms are becoming more precise. *T*he trophozoite surface of *Giardia,* including its flagella and ventral disc, is enveloped by variant-specific surface proteins (VSPs), a group of structurally related yet remarkably diverse molecules. In the Giardia genome, nearly 200 distinct VSP genes have been identified; however, only a single VSP is typically presented on the surface of an individual trophozoite at any given moment. During the encystation process, in contrast, multiple VSPs are expressed concurrently, reflecting a stage-dependent regulatory mechanism. These proteins generally exhibit a heterogeneous N-terminal domain, a conserved transmembrane segment, and a short intracellular tail containing the CRGKA motif—a structural signature shared among this protein family. Approximately every 6 to 13 cell divisions, the dominant VSP expressed on a trophozoite surface is replaced through a spontaneous switching event. This antigenic variation is believed to represent a sophisticated survival strategy, allowing Giardia to evade recognition and clearance by the host's immune defenses. Rather than being an induced process, this periodic transformation occurs inherently within the parasite's life cycle, ensuring continuous alteration of surface antigens and thereby enhancing persistence within the intestinal environment. (Liu et al., 2021).

Innate Immunity and Barrier Integrity Giardiasis

The gastrointestinal system is persistently subjected to a wide spectrum of dietary antigens, environmental contaminants, and microbial populations. Maintaining homeostasis within this dynamic environment relies fundamentally on the mucosal barrier—a complex, multilayered defense structure. This barrier is composed of the epithelial cell lining that provides physical separation, the mucus layer inhabited by commensal microorganisms that contribute to immune regulation, and numerous innate immune effectors that collectively safeguard intestinal integrity and balance immune responsiveness. This barrier fulfills multiple roles: preventing pathogen invasion, limiting translocation of luminal microbes, and orchestrating early immune signaling (Buret, 2019). Disruption of barrier integrity is implicated in many enteric diseases, metabolic disorders, and growth deficits in children, particularly in areas with poor sanitation (Klimczak et al., 2024).

Giardia species are non-invasive protozoan parasites that cause giardiasis, a leading contributor to diarrheal disease globally. Infections range from asymptomatic carriage to severe diarrhea and malnutrition. Even after parasite clearance, many individuals experience prolonged symptoms, including malabsorption and intestinal discomfort (Maloney, et al., 2017).

Innate immunity represents the first line of defense against Giardia, including physical barriers, chemical secretions, resident innate immune cells (such as macrophages, dendritic cells, Paneth cells), antimicrobial molecules, and pattern recognition receptors (Klimczak et al., 2024). Epithelial cells are not passive; they respond to Giardia by producing chemokines, antimicrobial peptides, and nitric oxide, and engage in crosstalk with immune cells. The integrity of tight junctions, adherens junctions, and the cytoskeleton is often compromised during infection, increasing paracellular permeability and allowing passage of luminal contents that activate immune responses (Liu, et al., 2018).

Recent studies have reported the way by which Giardia disturbs barrier integrity. For example, cysteine proteases secreted by Giardia intestinalis can degrade key junctional proteins like claudin-1, claudin-4, occludin, JAM-1, β-catenin, and E-cadherin, and can mislocalize them within epithelial cell monolayers. This disruption extends beyond the infection period: in murine models, tight junction damage and bacterial influx persist even after parasites are cleared, with elevated pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β) associated with ongoing mucosal inflammation (Liu et al., 2018).

Studies also show that Giardia's secreted extracellular vesicles (EVs) play an immunomodulatory role. In vitro experiments demonstrate that G. duodenalis EVs stimulate macrophages to release pro-inflammatory cytokines via activation of MAPK, AKT, and NF-κB pathways, acting as early signals that alert the innate immune system (Parasites & Vectors, 2021). Another recent work reveals that Giardia-derived PPIB (peptidyl-prolyl isomerase B) triggers inflammasome activation in macrophages via TLR4-induced ROS and regulation of NLRP3 through A20-mediated deubiquitination. The result is secretion of IL-1β and IL-18, two cytokines important for early inflammation and possible recruitment of further immune effectors (Liu et al., 2021).

Cytokine Networks in Giardiasis

Cytokines constitute the chemical language of the immune system, coordinating immediate innate defenses and shaping subsequent adaptive responses at mucosal surfaces. In the intestine, cytokine networks integrate signals from epithelial cells, resident innate cells, recruited leukocytes, and the microbiota to determine whether an encounter with a microbe will result in exclusion, controlled inflammation, tolerance, or chronic dysfunction (Fink & Singer, 2017). The balance and timing of cytokine production are therefore critical: early proinflammatory mediators promote pathogen containment, whereas anti-inflammatory and regulatory cytokines limit tissue damage and restore homeostasis (Klimczak et al., 2024).

Giardiasis presents a distinctive case in mucosal immunology because the parasite inhabits the intestinal lumen without true tissue invasion, yet it elicits complex cytokine responses that influence both parasite clearance and host pathology (Allain et al., 2017). Studies in animal models and human cohorts reveal that *Giardia* infection can provoke a mixed cytokine milieu that includes Th1-associated interferon-gamma (IFN-γ), Th17 cytokines (notably interleukin-17A), and regulatory mediators such as interleukin-10 (Serradell et al., 2018; Paerewijck et al., 2019).

Interleukin-17A (IL-17A) is recognized as a key mediator of mucosal immunity, contributing significantly to

inflammatory responses and antimicrobial defense against bacterial infections at epithelial surfaces. In the present investigation, its pivotal role in protecting the host from *Giardia* infection was established. Using murine models infected with *G. muris* and *G. lamblia*, a pronounced and selective increase in intestinal IL-17A expression was detected, reaching its highest levels approximately two weeks post-infection. Both Th17 lymphocytes within the lamina propria and innate immune populations located in the intestinal epithelium were identified as major sources of IL-17A production. Studies employing genetically modified mice further demonstrated that IL-17A and its receptor, IL-17RA, are indispensable for effective parasite clearance. The cytokine's protective effects were exerted through hematopoietic cells and were found to be essential for the translocation of IgA into the intestinal lumen. In IL-17A-deficient mice, a significant decline in fecal IgA levels was observed, accompanied by reduced intestinal expression of antimicrobial molecules such as β-defensin 1 and resistin-like molecule β. Conversely, intestinal hypermotility—another critical host defense mechanism against *Giardia*—remained unaffected by the absence of IL-17A (Paerewijck et al., 2019). Reaction with commensal microorganisms may result in opposing immunological effects: in some contexts, these interactions strengthen host defense by stimulating Th17 activity and IgA-mediated pathways, while in others, they suppress such responses through activation of regulatory networks. This bidirectional influence helps explain the broad variability in clinical manifestations of giardiasis, ranging from symptom-free colonization to pronounced diarrheal illness. (Fekete et al., 2021

Earlier research demonstrated that interferon-gamma (IFN-γ) and transforming growth factor-beta (TGF-β) contribute positively to host defense by stimulating mononuclear (MN) cells to act against *Entamoeba histolytica*. Nevertheless, the precise effector mechanisms through which these cytokines mediate cellular activation, as well as their functional roles during interactions with *Giardia lamblia*, have not been fully elucidated. Cytokines like IFN-γ primarily target monocytes and macrophages, enhancing their phagocytic capacity and microbicidal activity. Evidence from *in vitro* experiments further indicates that MN cells exhibit increased antimicrobial potency once activated by cytokines such as IFN-γ, highlighting their potential importance in the innate immune response to parasitic infections (Fink & Singer, 2017; Serradell et al., 2018).

During giardiasis, cytokine production predominantly originates from $CD4^+$ T cells located within Peyer's patches or from other components of the mucosa-associated lymphoid tissue (MALT). This response typically arises following prolonged antigenic exposure to the trophozoite or cystic stages of *Giardia lamblia*. The profile and magnitude of these cytokine responses are influenced by characteristics of the infecting strain, particularly whether it exhibits invasive or noninvasive behavior. Experimental observations by Jung and colleagues revealed that colon epithelial cells exposed to noninvasive *G. lamblia* did not express mRNA for cytokines such as IL-2, IL-4, IL-6, IL-12, or IFN-γ. Instead, these cells exhibited marked expression of IL-1 and IL-10, a pattern considered characteristic of colonic epithelial immune responses. (Liu et al., 2021; Pu et al., 2021).

Giardia intestinalis functions as an extracellular parasite that attaches firmly to the surface of enterocytes without penetrating them. The organism secretes multiple types of extracellular vesicles (EVs), which are taken up by human immature dendritic cells and contribute to the adhesion of *G. duodenalis* to intestinal epithelial cells. The parasite's secretome—comprising a range of enzymes and proteins—includes high cysteine-rich membrane proteins (HCMPs), ornithine carbamoyl transferases (OCTs), tenascins, proteases, variant surface proteins (VSPs), giardins, elongation factors (EFs), arginine deaminase (ADI), and carbamate kinase (CK). A substantial portion of these virulence molecules is believed to be enclosed within Giardia-derived microvesicles, which can be internalized by immature dendritic cells and subsequently trigger immune activation. Moreover, macrophages are also capable of capturing Giardia EVs, which in turn promote immune signaling and enhance the production of proinflammatory cytokines (Liu et al., 2021).

Immunomodulation and Microbiota Interaction with Giardia

The gastrointestinal (GI) tract represents the body's most extensive interface with the external environment, responsible for processing ingested food and maintaining the coexistence of symbiotic commensal microorganisms while excluding harmful pathogens. Serving as a crucial defensive frontier, the GI tract relies on epithelial cells that form a physical shield and

collaborate with stromal and immune components to restrict pathogen access and minimize epithelial contact (Maertens et al., 2021; Fekete et al., 2021). Perturbations in the gut microbiota—such as those caused by antibiotic treatment—can reshape microbial communities and diminish colonization resistance. As a result, the host becomes more vulnerable to pathogen establishment. This issue is especially significant in hospital environments, where both antibiotic usage and exposure to antibiotic-resistant microorganisms are common, leading to a considerable proportion of hospital-acquired infections that originate from gastrointestinal colonization. (Peruzzo et al., 2023).

The colonization and multiplication of *Giardia* within the host's small intestine can disturb the ecological equilibrium of resident gut microbiota, thereby contributing to the diarrheal manifestations commonly associated with giardiasis. Current evidence indicates that the intestinal microbial community serves as a crucial intermediary in the parasite–host dynamic—not only by engaging in direct interactions with the protozoan but also by modulating the host's immune responses. Each microbial species within the intestinal ecosystem introduces potential points of interaction along the host–parasite–microbe continuum, which may destabilize homeostatic balance and modify the course of parasitic pathogenicity. (Gomes et al., 2023; Peruzzo et al., 2023).

Giardia interacts with both the gut microbiota and the host immune system through several interconnected mechanisms. One primary route involves the modification of mucus composition and the alteration of mucin glycosylation patterns. When mucins are excessively degraded, the protective barrier function of the intestinal lining may be compromised, leading to heightened permeability and disrupted epithelial integrity. Concurrently, the parasite's competition with commensal microbes for mucin-derived nutrients during infection can disturb the microbial equilibrium, fostering dysbiosis. Changes in mucin glycosylation profiles are often detected in contexts of infection, microbial imbalance, and intestinal inflammation; however, the exact causal relationships among these phenomena remain insufficiently defined and continue to be an area of active investigation. (Zhao et al., 2021; Liu et al., 2021).

Third, interactions are indirect and microbiota-mediated. Dysbiosis induced by *Giardia* can alter short-chain fatty acid (SCFA) profiles, bile acid metabolism, and production of other immunomodulatory metabolites, all of which affect epithelial barrier integrity and innate immune tone (Fekete et al., 2021; Maertens et al., 2021). Experimental depletion of the microbiota (e.g., antibiotics) blunts certain protective Th17/IL-17 responses against *Giardia*, demonstrating that commensals are instrumental in mounting effective anti-parasite immunity (Maertens et al., 2021). Conversely, particular bacterial taxa may favor regulatory responses (IL-10, TGF-β) that permit parasite persistence but reduce inflammatory damage—this trade-off likely contributes to the broad spectrum of clinical outcomes observed across populations (Klimczak et al., 2024).

The immunological consequences of these interactions are multifaceted. Studies have shown that peritoneal macrophages in mice release substantial levels of proinflammatory cytokines upon infection with *G. duodenalis*. However, the role of TLR9 in this process remains unclear. It is not yet determined whether TLR9 contributes to the promotion of cytokine secretion, offers a protective effect, or exacerbates disease progression. Additionally, the potential differential effects of TLR9 in macrophages infected with GLV-free versus GLV-containing *Giardia* trophozoites have not been fully elucidated. (Sardinha-Silva et al., 2024).

From a clinical perspective, these ecological and immunoregulatory dynamics provide potential explanations for several puzzling observations: the high prevalence of asymptomatic infections in endemic areas, variability in treatment responses, and the development of post-infectious conditions characterized by ongoing intestinal dysfunction. Changes in gut microbiota composition and disrupted mucosal immune responses following *Giardia* infection have been linked to symptoms resembling post-infectious irritable bowel syndrome and to reduced nutrient absorption, even after successful parasitic clearance. (Barash et al., 2017; Peruzzo et al., 2023). Furthermore, the microbial profile present at the time of infection appears to be a critical determinant of immune trajectory—dictating whether the host elicits a protective IL-17/IgA-mediated defense or instead transitions toward a regulatory state—an observation that holds considerable promise for the

development of targeted preventive and therapeutic interventions. (Maertens et al., 2021).

It has been found that probiotics and microbiota-directed dietary interventions have shown variable benefit in experimental and limited clinical studies, likely because timing, strain selection, and host context matter (Fekete et al., 2021; Peruzzo et al., 2023). Targeting EV production or specific secreted effectors might attenuate immunosuppressive signaling and improve clearance, but such approaches remain experimental (Zhao et al., 2021). Vaccination strategies that prime mucosal Th17/IgA responses could potentially counteract *Giardia*'s immunomodulatory tactics—but would need to account for microbiota-dependent adjuvant effects (Nguyen et al., 2024).

Conclusion

Understanding cytokine networks in giardiasis thus has translational relevance. Modulating cytokine responses—either by enhancing early protective signals or by tempering excessive regulation when it impairs clearance—could inform vaccine adjuvant design and adjunct therapies. Yet therapeutic manipulation requires nuance: promoting one pathway may unintentionally exacerbate pathology or disrupt homeostasis. Future research should emphasize longitudinal human studies that track cytokine trajectories from acute infection through recovery, and mechanistic work that dissects how parasite molecules differentially engage host receptors to bias cytokine outcomes. The threshold and duration of junctional protein disruption needed to trigger downstream innate immune cascades are not well quantitated. Also unclear are the roles of epithelial cell death, autophagy, and repair mechanisms post infection; how microbiota composition influences early innate responses; and how nutritional status, coinfections, or host genetics alter the acute vs. persistent deficits in barrier function (Chen et al., 2013). Furthermore, few human studies have longitudinally tracked barrier integrity and innate immune markers beyond acute giardiasis. Critical gaps remain. Longitudinal human studies that couple microbiome profiling with immune phenotyping before, during, and after infection are scarce. The causal pathways linking specific bacterial taxa, metabolite signatures, and immune outcomes need experimental validation. Finally, heterogeneity among human populations—driven by diet, coinfections, genetics, and environmental exposures—complicates translation of animal model findings. Addressing these gaps will require integrated, multidisciplinary approaches combining microbiology, immunology, metabolomics, and carefully designed clinical cohorts.

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