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Review

Interactions between Parasites and Human Microbiota

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ABSTRACT

Parasitic infections are threatening millions of people, particularly in developing countries. These infections are usually associated with significant variability in clinical presentation from asymptomatic infection to chronic disease. It is suggested that the intestinal microbiota may help to explain the differences in disease expression. Recent studies reported that microbiota effect to parasite colonization and persistence in the host and the presence of parasitic infection may also alter the intestinal bacterial community. Microbiota plays an important role in protecting against pathogens and maintaining immune and metabolic homeostasis. The alteration of microbiota composition (dysbiosis) has been associated with the pathogenesis of many infections and inflammatory diseases. Understanding the interactions among microbiota, human parasites, and the host immune system may allow us for designing new treatment options for parasitic infections. The objective of this review was to summarize the recent development in this field.

Keywords: Helminth, intestinal microbiota, parasite, protozoa

INTRODUCTION

Humans are colonized by a variety of bacteria, fungi, viruses, and eukaryotic parasites in their intestines, mucosae, and skins. The term microbiota represents an ecological community of commensal microbes that live within the human body, and the term microbiome represents a total genome of the microbiota (1). Our gut microbiota contains approximately 10^{12} organisms/g at least 1000 different species of bacteria with nearly 3 million genes that are 150 times larger than human genes (1). Microbiota compositions can vary from one person to another (2). Human microbiota studies suggested that healthy or asymptomatic conditions areassociated with increased microbial diversity, and disease states are often linked to decreased bacterial diversity (3).

Microbiota is also well known for its role in the development and education of the immune system. These microbes not only modulate immune defense but also provide a variety of metabolic impact that usually is unfavor of colonization and invasion of pathogens. However, its interactions with diseases are still not well known. Environmental factors, such as diet, antibiotic usage, and lifestyle,may cause dysbiosis that is frequently associated with increased susceptibility to infections and non-infectious diseases (obesity, diabetes, allergy, and autoimmune and inflammatory diseases) (1, 3).

Globally, diarrhea is currently the second leading cause of death in children, and a large proportion of cases are caused by parasitic protozoans and helminths (4). *Entamoeba*, *Cryptosporidium*, and *Giardia* caused 357 million cases and resulted in almost 34,000 deaths annually (5). Malaria kills approximately 660,000 people/year, and most of them are young children under the age of five years (6). Recent estimates indicate that approximately two billion people currently suffer from infections with intestinal helminths in developing countries (7).

Despite the significant health burden that parasites cause, infections could be asymptomatic or show wide variations in clinical presentation, especially in protozoan parasites (8). Factors that affect disease severity remain poorly understood (8). Immune response contributes to protection from parasites; however, an increasing number of studies show that it is increasingly clear that the intestinal microbiota may have a significant influence on disease progression (8, 9).

Parasites usually enter the body through the oral fecal route and directly interact with the commensal bacteria of the intestine (8). Microbiota may increase resistance to parasitic infections at mucosal sites via changes in the composition of intestinal bacteria, and it may also alter systemic immunity to these parasites. Microbiota might also influence extraintestinal disease via many pathways, such as by the alteration of adaptive immunity and the development of T and B cell-mediated responses and bytheenhancement of innate immune pathways via trained immunity (10). Mechanisms underlying these extraintestinal effects are poorly understood. The focus of this review is the interactions between human microbiota and human parasites thatinfect the intestine and vagina or cause systemic infections.

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Intestinal Protozoan Parasites and Microbiota Interactions in Humans

Entamoeba histolytica, *Giardia intestinalis*, *Cryptosporidium* spp.,and *Blastocystis* spp. are the most common enteric protozoans that inhabit the intestinal mucosa and surround the intestinal microbiota. An increasing number of studies proposed that the clinical outcome of these parasitic infections could be shaped by host microbiota and host immune system (8).

The referenced human studies so far suggest that there is a strong interaction between the composition of the intestinal microbiota and mucosa-associated protozoan parasites. In a previous study, increased numbers of *Prevotella copri* were found in infants with *E. histolytica* infections (11). It is also observed that both *P. copri* and *Prevotella stercorea* were significantly decreased in asymptomatic infected adults (12). Another previous study suggested that elevated levels of *P. copri* might also be associated with severe inflammation and an increased risk of autoimmune disease and colitis (8).

In a similar study, it is reported that the patients who were protected from *Cryptosporidium* infection had an increased level of indole-producing bacteria, such as *Escherichia coli*, *Bacillus* spp., and *Clostridium* spp. In contrast, infected patients had an increased level of *Bacteroides fragilis*, *Bacteroides pyogenes*, *Prevotella bryantii*, and *Akkermansia muciniphila* (13).

A previous study of intestinal parasite infection in individuals from a rural area showed that there was a significant increase in the relative number of *Bifidobacterium* spp. in *G. intestinalis*-positive patients (14). Increased Clostridia levels but lower Enterobacteriaceae levels were observed in *Blastocystis*-positive subjects (15). All these studies suggested that the tested intestinal parasites may induce significant bacterial changes in the microbiota, and gut microbiota has also a potential influence on parasite infection outcome.

Trichomonas vaginalis, a mucosal protozoan parasite, which is the causative agent of trichomoniasis, is the most common non-viral sexually transmitted infection globally. It has been shown that variation in the clinical presentation of the disease is impacted by the composition of the vaginal microbiota consisting of low proportions of lactobacilli but a higher level of *Mycoplasma* spp., *Parvimonas* spp., and *Sneathia* spp. (16). It is also shown in another previous study that *Lactobacillus* species inhibit parasite interactions with human cells (17).

An emerging study suggests that protozoa may also alter host immunity to subsequent exposures (8). It is suggested that *Giardia* infection has been associated with protection from diarrhea. During this prospective study, it was observed that acute diarrhea occurred less often among *Giardia*-positive children than among children who were not infected with *G.intestinalis* (18).

A recent study in murine models provides a demonstration of how protozoan infection might provide protection from subsequent infections. *Tritrichomonas musculis* is a common murine commensal that has been shown to cause the expansion of adaptive T helper (Th) 1 cells and Th17 effector cells in the colonic mucosa. This expansion required the production of interleukin (IL)-18 by epithelial cells. *T. musculis* colonization showed significant protection from *Salmonella* infection-driven enteritis in an IL-18-dependent manner. However, colonization with *T. musculis* exacerbated the development of Tcell-driven colitis and resulted in the development of sporadic colorectal tumors in colonized mice (19). Combined, these studies revealed novel host–protozoan interactions that led to increased mucosal host defenses while also increasing the risk of inflammatory disease (8, 19).

***Plasmodium spp*. and Microbiota Interactions in Humans**

It is shown that not only intestinal parasites but also blood and tissue parasites can be affected by gut microbiota (8, 20). Researchers are investigating the effects of bacterial microbiota on the clinical variability of *Plasmodium* spp. infection. Approximately 60% of the population worldwide is at risk of infection with *Plasmodium* spp., which is the causative agent of malaria disease (21). Malaria kills approximately 660,000 people/year. However, the distribution of clinical malaria is also highly heterogeneous. Genetic differences, variation in exposure, and variance in immune response may not completely explain clinical variation (8, 21).

A recent study showed that the intestinal microbiota of a patient who became infected with *Plasmodium falciparum* had a significantly lower level of *Bifidobacterium* and *Streptococcus* species than that of subjects who did not become infected (22). This suggests that the alteration of the intestinal microbiota composition by probiotics may decrease the risk of *P. falciparum* infection in endemic areas.

Recently, the influence of the microbiota on *Plasmodium* infection was explored by Villorino et al., and significant differences in parasitemia level were observed between the genetically identical mice infected with *Plasmodium yoelii* from different vendors. Resistant mice exhibited higher numbers of *Lactobacillus* spp. and *Bifidobacterium* spp. than susceptible mice. After cecal transplants to germ-free mice from resistant or susceptible mice, low and high parasite burdens were observed, respectively (23). Resistant mice exhibited higher antibody profile and higher CD4 T cells and B cells than susceptible mice. These findings suggest that the intestinal microbiota may shape the severity of malaria, and the composition of the gut microbiota may be an unidentified risk factor for severe malaria. The alteration of the gut microbiota might affect the host response to extraintestinal parasites (23).

It has also been shown that the gut microbiota has a systemic influence on serum metabolites in humans (8). These findings suggest that blood-stage parasites might also be influenced by serum metabolite changes induced by the microbiota. It is recently demonstrated that anti-α-gal antibodies confer protection against *Plasmodium* spp. infection in humans. Both *Plasmodium* spp. and *E. coli* O86:B7 (normally a member of an intestinal microbiome) express α-gal that produces protective anti-α-gal antibodies. Anti-α-gal antibodies, immediately after inoculation by *Anopheles* mosquitoes, target *Plasmodium* sporozoites for com-

plement-mediated cytotoxicity in the skin. Experiments showed that vaccination against α-gal antigen confers sterile protection against malaria in mice, suggesting that a similar approach may reduce malaria transmission in humans (24). This study is a very good example that gut microbiota has a systemic influence on serum metabolites in humans, and that probiotics-based malaria vaccines might be used in the near future.

Alteration of Gut Microbiota as a Therapy for Protozoan Infections

In the near future, microbiota studies will establish a more complete understanding of the variation in clinical presentations of parasitic protozoa infection and the effects of the microbiota on parasite survival and proliferation. These studies suggest that the alteration of individual components of the microbiota might provide cost-effective prophylactic treatment for parasite infection without using antiparasite agents (25). The alteration of the intestinal microbiota in model systems may also help to understand the role of immune factors in a clinical variation of parasitic disease.

Murine models provide a useful tool to explore host–microbiota–pathogen interactions (8). Currently, few in vitro and in vivo disease models provide us with a useful tool to understand interactions between infecting agents and components of the microbiota. For example, an invitro study demonstrated that the proliferation of *Giardia* trophozoites was significantly inhibited by *Lactobacillus johnsonii* La1 strain. The protective role of *L. johnsonii* La1 was confirmed by in vivo experiments with La1-treated gerbils (26). In another in vitro study, *Lactobacillus casei* and *Enterococcus faecium* were cocultured with *E.histolytica* and reduced parasite survival by 80%. An in vivo study demonstrated a link between decreased *Lactobacillus* spp. and amebiasis in humans (27).

It was previously described that lactobacilli may impact susceptibility to *T. vaginalis* infection (8). Even though the mechanisms underlying this effect are still unknown, protection might be explained by the inhibition of adhesion by the parasite to epithelial cells (17). In an in vitro study, *T.vaginalis* trophozoites and *Lactobacillus gasseri* ATCC 9857 were incubated in vaginal epithelial cells, and significant parasite adhesion inhibition was observed (17).

In another previous study, it is demonstrated that segmented filamentous bacteria (Gram-positive, spore-forming bacteria that were originally identified in the ilia of mice and rats) colonized mice are protected from experimental *E. histolytica* infection (28). It was also discovered that bone marrow-derived dendritic cells from segmented filamentous bacteria-colonized mice produced significantly higher levels of IL-23. This ILis responsible for induction of IL-17A and neutrophils, which are both important in immunity to the ameba (29). Transfer of bone marrow-derived dendritic cells from segmented filamentous bacteria-colonized mice provided protection from *E. histolytica* infection (28). This important study suggested that gut microbiota might alter the responsiveness of bone marrow-derived cells to the inflammatory response.

In an animal model of *Giardia* infection,theantibiotic alteration of the microbiota was shown to prevent CD8 T cell activation by *Giardia duodenalis* (20). One potential mechanism is that during infection, the parasite promotes the breakdown of the intestinal barrier. Translocation of luminal bacteria into the mucosa leads to the activation of CD8 T cells; therefore, reducing the bacterial load by antibiotic treatment may reduce this and prevent pathological CD8 T cell activation (20).

Intestinal Helminth Parasites and Microbiota Interactions in Humans

Helminth parasites usually live in adult form in the human intestine for a prolonged time. Helminths suppress host immunity to establish chronic infections and may impact on host responses against other pathogens (8). It is well known that both helminths and bacterial species had strong immunomodulatory effects. Our immune system has co-evolved together with large numbers of intestinal bacteria and helminths. Helminths were also described as themain selective force for selection of human genes associated with autoimmunity (30). Especially, chronic intestinal helminth infections have been documented to lower the severity of allergic and autoimmune disorders in humans (31). Interestingly, a study suggests that the eradication of helminths might be the reason for increasing number of chronic inflammatory diseases in Western countries.

Intestinal helminths can alter intestinal physiology, permeability, and mucous secretion that may impact to the microbiota. Currently, few studies have specifically addressed the impact of helminth infection on the microbiota. Conversely, the presence and composition of bacterial microbiota affect helminth colonization and persistence as well.

There are few reported microbiota studies from humans who were infected with helminths. In human populations, studies about the influence of helminth infection on microbiota composition and function have been only recently performed. A cross-sectional study was performed on 51 individuals who were infected by helminths from an endemic region (32). It is found that the helminth-colonized individuals had greater species richness in their stool sample than the uninfected individuals.

In a cohort study, *Schistosoma haematobium* infection-positive Zimbabwean children were found to have a significantly higher number of genus *Provetella* (33). In these subjects, microbiota composition did not revert even after helminth clearance with praziquantel treatment. This study suggested that childhood helminth exposure may have long-term effects on microbiota composition (33).

In another previous study, bacterial communities in stool samples of children living in a rural part of Ecuador were compared. A decreased in overall bacterial diversity was noted in helminth-infected children, especially in those coinfected with *Trichuris trichiura* and *Ascaris lumbricoides* (34). In an Australian study, stool samples from helminth-infected and non-infected individuals were compared (35). The authors reported a significant increase in bacterial diversity among individuals infected with any helminth species. In the same study, an increased number

of bacterial species belonging to the Paraprevotellaceae family was observed in subjects who were infected with *T. trichiura*. In another previous study, the impact of experimental infection with *Necator americanus* on intestinal bacterial communities in patients suffering from coeliac disease was observed (36). Stool samples from patients with coeliac disease both before and after infection with a low dose of *N. americanus* were compared, and increased bacterial diversity was noted in infected individuals (36). All these studies indicate that helminth infection may promote bacterial diversity.

Murine model experiments have clearly demonstrated that infection with helminth parasites may impact on the intestinal microbiota species composition. An increased number of Lactobacillaceae and Enterobacteriaceae species in the small intestine was observed during experimental chronic *Heligmosomoides polygyrus bakeri* infection in the duodenum of mice (37).

In a similar study, chronic infection with *Trichuris muris* (a mouse whipworm) leads to a reduced diversity of fecal bacterial species particularly within the *Bacteroides* spp., as well as an increase in the number of *Lactobacillus* spp. in the mice caecum (38).

In vitro animal studies showed that the presence and composition of bacterial microbiota may affect helminth colonization and persistence. A study showed that a murine nematode *H. polygyrus bakeri* (formerly named *Nematospiroides dubius*) caused mortality in germ-free mice but not in normal raised commercial mice (39). *L.casei* was shown to reduce adult worm burdens of *Trichinella spiralis* in murine models (40). Similarly, *Bifidobacterium* spp. strains provided protection against the helminth *Strongyloides venezuelensis* infection (9). These findings may suggest that intestinal bacteria prevent infection against parasitic helminths. However, it is still unclear whether direct interactions are occurring only between bacteria and helminths or indirectly via the host immunity. It is well known that the microbiota can modulate host immunity, and it may also impact on the host immune response against helminths. Germ-free mice exhibit smaller lymphoid tissues, decreased IgA levels but increasedIgE levels, and increased numbers of basophils and natural killer T cells (9, 41). Although the exact mechanisms still remain unclear, experimental studies needed to understand how microbiota and host immunity impact helminth infection.

A recent study has suggested that helminth infections have also an indirect effect on the modulation of mood and behavior in children via its effects on the alteration of the normal gut microbiota. Factors supporting this hypothesis are as follows: (1) gut microbiota playsa role on cognitive development (2), helminth infections can change gut microbiota composition and diversity, and (3) observed effect of helminth infection on cognitive development indicators (42).

Helminth infection can also have dramatic impacts on intestinal physiology, including increased fluid secretion, altered mucous production, and the infiltration of host immune cells that impact on bacterial communities via alterations to their habitat (9). Alterations in mucous cause dramatic consequences for bacterial growth and metabolism as many species use the mucous as an energy source (9).

Some studies indicated that helminth infection can also modify host metabolism (9). Bacterial-derived short-chain fatty acids (SCFAs) are well known to impact on host health by modulating immune function (43). Both helminth and protozoan parasites can also produce the SCFA acetate (44). Hamsters infected with the human hookworm *N.americanus* also showed extensively altered urinary metabolite levels that could be explained by changes in the intestinal microflora (45).

Helminths as a Therapeutic Agent for Infections?

Clinical studies and animal models have shown both human intestinal microbiota and helminths to be responsible for shaping human immunological responses. The alteration of the microbiota and using helminths to treat diseases could be a possible way to lower treatment cost (46). However, it is still unclear whether the immunemodulatory potential of helminths involves alterations of the microbiota via helminths providing the treatment.

Fecal transplantation from a healthy donor to diseased humans has been successfully used as a treatment for inflammatory bowel disease and *Clostridium difficile*-associated diarrhea (47). It is expected that helminth-induced alterations to intestinal bacterial communities may result in alterations to the severity of immune and metabolic diseases in humans. Helminth-based therapeutics, including infection with *Trichuris suis* or with *N. americanus*, has been used in allergy and inflammatory bowel disease (48). *N. americanus* was also used for treatment of coeliac disease, but no difference in symptoms was observed (49).

A couple of studies reported that helminth infection may provide protection against *Helicobacter*-induced gastric adenocarcinomas via preventing bacterial colonization of the stomach and reducing the number of neoplasticlesions (50). The experimental infection of *T. trichiura* in Macaques monkeys was reported to improve clinical symptoms in monkeys suffering from idiopathic chronic diarrhea (46). Mouse models and human studies have shown that chronic helminth infection regulates the host immune response and provides a beneficial action on allergic, autoimmune, and inflammatory disorders in humans (9).

CONCLUSION

The microbiota and parasites may interact with each other in different ways; microbiota may alternate parasite virulence, parasites may cause dysbiosis, and both parasites and microbiota may modulate host immunity. Recent studies have shown that the intestinal microbiotacan impact on clinical variation in parasitic infections. On the other hand, both human and animal studies indicate that both protozoa and helminth infections can impact on the intestinal microbiota. The exact mechanisms underlying the microbiota modulation of host immunity are not yet fully understood; however, it is becoming increasingly apparent that components of the microbiota may alter both innate and adaptive immune cell populations. The study of parasite interactions with the microbiota and the host immune system will help us to better understand the fundamental mechanisms of human

immunology. The exploration of interactions between the gut microbiota and parasites will provide additional information that will help with the diagnosis, treatment, and prevention of parasitic infections. It may also help with the treatment of inflammatory and autoimmune diseases.

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