Journal of the Egyptian Society of Parasitology, Vol. 53, No.1, April 2023
J. Egypt. Soc. Parasitol. (JESP), 53(1), 2023: 101– 110
Online: 2090-2549

INTESTINAL PARASITES-GUT MICROBIOTA INTERACTIONS: A REVIEW

By
HEBAT-ALLAH S. A. YOUSOF
Department of Medical Parasitology, Faculty of Medicine, Cairo University, Cairo, Egypt (Correspondence: drhebasalah@cu.edu.eg; drhebasalah@ kasralainy.edu.eg, https://orcid.org/0000-0001-7214-0991)

Abstract

Healthy gut microbiota is a diverse dynamic biological community comprised of trillions of microorganisms which engage with the intestinal mucosa performing crucial bioactivities for the host and play critical functions in human health**.** Disruption of the gut microbiota from its normal balance, as well as its interaction with the host's immune system, can influence host susceptibility to infection and thus determining the consequence of infections by intestinal microbial agents. Diversity of gut microbiota is linked with several metabolic and immunological conditions, which makes it of great public health concern**.** Protozoa can exert a negative impact on gut microbial ecosystem balance due to niche competition or by influencing the local innate immune response. Helminths, however, can have a positive impact by expanding bacterial populations that produce short-chain fatty acids and thus enhancing host's health status. This review highlights interaction between some intestinal parasites and diversity of gut microbiota ecosystem.

Keywords: Dysbiosis, Gut microbiota, Helminth, Interaction, Intestinal parasites, Protozoa.

Introduction

Healthy gut microbiota is a diverse of biological community comprised of trillions of micro-organisms which engage with the intestinal mucosa performing crucial bioactivities for the host and play critical functions in human health (Ogunrinola *et al,* 2020). Gut microbiota has a considerable impact on human hosts in gaining essential nutrients from food, promoting food digestion, synthesis of essential organic compounds, xenobiotic metabolism, shaping, maturation, improvement and alteration of the innate and adaptive intestinal immunological activities, in addition to protection of their hosts from opportunistic pathogens through regulation of immune mediators' expression along with differentiation and recruitment of gut immune cells (Caballero and Pamer, 2015). Studies showed that gut bacterial microbiota can associate development of or resistance to, obesity, malnourishment, and allergic disorders as well as affection of cognitive function and growth (Fujimura and Lynch, 2015; Million *et al,* 2016).

Review and Discussion

The intestinal microbiota components are extremely varied and fluctuate over time, as well as between individuals and different intestinal parts. In latest years, next generation sequencing of the small subunit ribosomal RNA enabled for a more in-depth understanding of gut microbiota, its genes, and proteins (Morgan and Huttenhower, 2014). The most predominant organisms in gut microbiota belong to *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* (Huttenhower *et al,* 2012). Adult humans gut contains 500-1000 different bacteria species preserving a mutualistic host-microbial interacted with commonest genera were *Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus, Lactobacillus,* and *Ruminococcus* (Gomaa, 2020). Gut microbiota evolve via intrauterine life and that maternal-fetal microbiota occurred during pregnancy (Milani *et al,* 2017). The order in which bacteria invade digestive tract determines product of community assembly as well as individual colonizers' ecological accomplishment. Aside from fetus' genetic determinants, several prenatal factors, such as mother diet, obesity, smoking habits, and antibiotic use during pregnancy, all have a major influence on microbial colonization of digestive tract (Sonnenburg *et al,* 2016). The delivery mode was widely regarded as a crucial determinant of initial colonization (Chu *et al,* 2017). Feeding is a critical aspect in determining gut

microbiota colonization. Because of its high quantity of unique oligosaccharides, breast milk promotes the most balanced microbiota growth for the newborn. Breast feeding is the most substantial factor associated with infant's microbiome structure establishing an early *Bifidobacteria*-dominated gut microbiome. Human milk oligosaccharides raise the proportion of gut microbiota dominated by *Bifidobacteria* spp. (*B. breve* & *B. bifidum*) resulting in plasma immunological marker profiles that reduce morbidity (Azad *et al,* 2018). Formula-fed newborns have a greater diversity of species than breastfed infants with an overrepresentation of *Clostridium difficile* (Lucas *et al,* 2017). The diversity and growth of microbiota during early life influence health risk factors and performs a vital function in immune system development that may alter chronic diseases risk up to and into adulthood (Vandenplas *et al,* 2020).

Diet especially the quantity of animal food, processed food, and dietary fibers (Xu and Knight, 2015), age, stress, geographical location, use of medication especially antibiotic treatment, physiologic and metabolic status (Zhernakova *et al,* 2016), physical damage to the mucosa, infections with invasive intestinal pathogens and host genetic factors (Goodrich *et al,* 2016) can cause rises or reductions in relative abundance and diversity of gut's microbial community resulting in imbalance between the beneficial and harmful bacteria of gut microbiota ecosystem known as dysbiosis (Lynch and Pedersen, 2016; Belizário and Faintuch, 2018). Gut dysbiosis is defined as alterations or imbalance in the gut bacterial diversity and functional capacities of gut microbiota population structure that have a negative impact on the host's health (Levy *et al,* 2017). Disruption of the gut microbiota from its normal balance, as well as its interaction with the host's immune system, can influence host susceptibility to infection and thus determining consequence of infections by intestinal microbial agents (Lin and Zhang, 2017). An impact of dysbiosis was the higher susceptibility to enteric infection, and changes in the commensal microbiota composition (Douglas and Ivey, 2020).

Mucosal barrier formed by gut epithelial cells functions as a protective mechanism, separating pathogens from host immune cells and decreasing intestinal permeability. Disrupting epithelial shield promotes vulnerability to infection and microbial metabolite translocation into the host. Gut dysbiosis, or changes in the microbial makeup of the gut, not only compromises the integrity of the mucosal barrier, but it also deregulates immunological responses, resulting in inflammation and oxidative stress. Chronic gut dysbiosis, as well as bacteria entry and their metabolic products across the mucosal barrier, can raise incidence of a variety of illnesses over time (Yoo *et al,* 2020).

Arumugam *et al.* (2011) introduced the notion of enterotypes of human gut microbiome. They reported that the composition of human bacterial gut microbiota was categorized into three enterotypes. These enterotypes are commonly identified by the most prevalent organism present in a certain individual: Enteroype I (*Bacteroides* spp.), Enteroype II (*Prevotella* spp.), & Enterotype III (*Clostridia* spp.). The human gut microbiota is a complex ecosystem including not only bacteria but also, viruses (mainly bacteriophages), fungi, protozoa and metazoa which work together and compete with each other (Filyk and Osborne, 2016). *Blastocystis* and *Dientamoeba* was far more common than previously assumed, mainly in healthy people, but suggested that the harmless of parasites (Stensvold and van der Giezen, 2018).

Precise underlying mechanisms by which microbiota modulate host immunity are not clearly grasped; however, it's turning abundantly evident that microbiota components can alter both innate as well as adaptive immune cell lines, resulting in a more robust response to subsequent challenge with pathogenic organisms, including parasites (Kogut *et al,* 2020). The processes that link the gut microbiota to human health are still un-

clear, yet healthier people tend to have more microbial diversity (Le Chatelier *et al,* 2013; Hollister *et al,* 2014). Protozoa as *Giardia lamblia*, *Cryptosporidium parvum*, *Entamoeba histolytica/dispar*…etc., and intestinal helminths such as *Ascaris lumbricodes*, *Trichuris trichiura*, *Enerobius vermicularis*, *Strongyloides stercoralis*, hookworms and tapeworms alter the diversity of bacterial gut microbiota (Chabé *et al,* 2017).

Gut protozoa-microbiota interaction: Parasitic protozoan infections are a significant health burden in underdeveloped countries, contributing significantly to mortality as well as morbidity. Enteric protozoa are typically transmitted via fecal-oral route. The intestine is heavily inhabited with commensal bacteria, which are well placed to influence the behavior of the protozoan parasites with which they interact directly (Bär *et al,* 2015). Diarrhea is the second greatest cause of death in children under age of five worldwide, accounted for over 500,000 deaths per year (Murray *et al,* 2014). Although several diseases can cause diarrhea, protozoan infections remain a frequent cause in many cases (Kotloff *et al,* 2013). An estimated 357 million infection episodes caused by at least one of three intestinal protozoa, *Entamoeba*, *Cryptosporidium*, and *Giardia* in 2010 (Torgerson *et al,* 2015). *Cryptosporidium* spp. was among the top diarrhea-associated pathogens in a recent investigation of moderate-to-severe diarrhea in African and Asian children (Liu *et al,* 2016). Protozoan infections such as *Entamoeba, Giardia,* and *Cryptosporidium* could be asymptomatic, despite the considerable health burden they impose elements influence illness severity are yet unknown (Villarino *et al,* 2016). Host genetics and immune response variability contribute to resistance against parasites; nevertheless, it is becoming obvious that the intestinal microbiota may have a considerable impact on the course of disease caused by enteric protozoa. The infecting parasites live in the intestinal mucosa and are so surrounded by the host gut microbiota. Studies showed that the gut bacterial microbiota can alter the virulence of specific pathogens and potentially expand the range of parasitic protozoan infection outcomes. It has been postulated that the dynamic interaction between the protozoan parasite, the host gut microbiota, and the host immune system influences the clinical outcome of enteric infections (Bär *et al,* 2015; Burgess and Petri, 2016).

Entamoeba spp. infection was found to be substantially linked to fecal microbiome diversity. *Prevotellaceae* was one of the most important taxa in predicting *Entamoeba histolytica* infection. *Prevotella copri*, a *Prevotellaceae* species, was discovered to be raised in individuals with diarrheagenic *E. histolytica* infections. *Prevotella copri* and *Prevotella stercorea* were both considerably suppressed in asymptomatic amebiasis (Hofer, 2014; Morton *et al,* 2015). This shows that the composition of the microbiota may have a major impact during *Entamoeba histolytica* infection and emphasizes the probable relevance of inflammation caused by the gut microbiome in modifying parasite infection consequences and suggests the existence of complicated interactions between gut bacteria, eukaryotes, and host (Burgess and Petri, 2016; Gilchrist *et al,* 2016). *Prevotella copri* levels are related to inflammatory responses and a higher risk of colitis and autoimmune diseases indicating that *P. copri* is proinflammatory (Scher *et al,* 2013). Compared to healthy, *E. histolytica* was accompanied by a reduction in *Bacteroides*, *Clostridium*, *Lactobacillus*, *Eubacterium*, *and Ca-mpylobacter* with rise in *Bifidobacterium* spp (Verma *et al,* 2012). In an amoebic colitis murine model, dysbiosis resulting from antibiotic treatment exacerbated the intensity of amoebic colitis and slowed clearance of *E. histolytica* (Watanabe *et al,* 2017). Common human commensal bacteria were co-cultured with *E. histolytica* in an in vitro experiment and it was found that *Lactobacillus casei* and *Enterococcus faecium* cultures alone reduced parasite survival by 71%. Survival was reduced by 80% when both

bacteria were employed together. Furthermore, a study on Indian patients discovered an association between decreased *Lactobacillus* and amebiasis, lending credence to the possibility of an association between these bacteria and resistance to *E. histolytica* infection. It is believed that *Lactobacilli* may influence the susceptibility to *E. histolytica* infection (Verma *et al,* 2012). Existence of *Entamoeba* spp. (other than *histolytica*) was linked to increase gut microbial diversity and microbiome composition. Most gut microbias significantly linked to *Entamoeba* infection was negatively associated with autoimmune diseases and inflammation-related illnesses (Morton, 2015).

Giardia intestinalis, one of the most prevalent water-borne protozoan causes of diarrhea, was also connected with a disrupted intestinal microbiota. The presence of *Giardia* parasites could reshape the gut microbial ecosystem. It has been proposed that *G. intestinalis* infection in humans imposed heavy alterations in gut microbiota enhancing bacterial invasiveness in intestinal mucosa during post-clearance period. In a mouse model, the epithelial barrier disruption causes an unresolved immunological response in the host to its gut microbiome (Chen *et al,* 2013; Iebba *et al,* 2016).

In vitro cultures and in vivo animal experiments are useful tools to study how the gut microbiota affects the intensity and progression of infection, as well as what mechanisms could strongly influence such progression, and they allow for the analysis of interactions between infecting protozoa and individual microbiota components. A study of the in vitro impacts of *Lactobacillus johnsonii* La1 on *Giardia duodenalis* survival found that it greatly reduced *Giardia* trophozoite multiplication (Pérez *et al,* 2001). Furthermore, in vivo testing of *Lactobacillus johnsonii* La1-treated gerbils proved that they were protected against *Giardia* infection and mucosal injury and verified the possible protective role of *Lactobacillus johnssonii* La1 against *Giardia* infection (Humen *et al,* 2005; Berrilli *et al,* 2012).

In an animal model, Infection with *Giardia* was associated with an upsurge in facultative anaerobic and aerobic bacteria (Barash *et al,* 2017). Nevertheless, a rise in *Enterobacteriaceae*, which is typically seen in dysbiosis, was not observed in *Giardia* infections, and strict aerobes belonging to the b-proteobacteria rose instead, indicating that parasite-linked dysbiosis can result in diverse microbiota compositions (Rivera-Chávez *et al,* 2017). Those with *G. intestinalis* infection caused a reduced *Faecalibacterium prausnitzii-Escherichia coli* ratio (Iebba *et al,* 2016). Moreover, the predominance of *Bifidobacterium* increased significantly in *Giardia duodenalis* positive patients (Burgess *et al,* 2017). Individuals infected with *G. intestinalis* were switched to type II enterotype (*Prevotella* spp.) compared to healthy ones with type I enterotype; *Bacteroides* spp. (Toro-Londono *et al,* 2019). Maertens *et al.* (2021) explored that gut microbiota's regulatory effect in the immune response to *Giardia* infection. They highlighted that *Giardia* infection in microbiome-depleted mice not only developed in a chronic way over time, but also increased the parasite load. In absence of gut microbiota, multiple immune effector pathways were weakened. These elements were found in both innate (antimicrobial peptides and intestinal transit) and adaptive (IgA) immune responses. Parasite's induction of IL-17A alone was insufficient for *Giardia* clearance; gut microbiota must also prime the immune system. Moreover, reduction of innate immune system constituents including defensing, angiogenin 4, and intestinal motility may underlie why microbiome-depleted mice are more susceptible to *G. duodenalis* infection (Beer *et al,* 2017). Giardia- induced diarrhea is frequently misdiagnosed, leads to consumption of antibiotics not only ineffective against the parasite but also carrying the potential danger of more severe and long-lasting infection added to the possible development of antibiotic resistance (Maertens *et al,* 2021).

Apicomplexan *Cryptosporidium* spp. was been identified as the fifth commonest pathogen in children (Platts-Mills *et al,* 2015). At least 15 distinct genera are either parasitized or communalized human bowel (Hamad *et al,* 2016). Protozoan parasite induced a minor but considerable disruption in gut microbiota. Ras *et al.* (2015) reported that *C. parvum* disrupts the native gut microbiota of immunocompromised mice. They hypothesize that cryptosporidiosis affects the microbiota indirectly as a consequence of the damage that it induces to the intestinal epithelium since the intracellular *C. parvum* multiplies inside intestinal epithelium cells and the parasite's interaction with gut microbiota colonizing mucus layer and lumen is minimal and transient effect of gut microbiota on *Cryptosporidium* varied and ambiguous. Germ-free, immunodeficient mice acquired severe *C. parvum* infections in few weeks, but immunodeficient mice with a normal microbiome didn't (Bär *et al,* 2015).

Gut microbiota may possibly play a role in *Cryptosporidium* infections in humans. A retrospective study of volunteers investigated the correlation between the diversity of different bacterial populations frequently detected in adults prior to or within 48 hours after *Cryptosporidium* infection and infection outcomes. (Chappell *et al,* 2016) Patients who were not infected had higher levels of *Proteobacteria* and relatively low levels of *Bacteriodetes* and *Verrucomicrobia* than infected individuals. Uninfected subjects had a larger ratio of *Firmicutes* to *Bacteriodetes* than infected subjects. Seven individual species showed at least a 2.5-fold disparity among the two study groups. Uninfected participants had higher relative abundance and distribution of *Bacillus* spp. and the indole-producing bacteria *Escherichia coli* along with *Clostridium* spp. Infected patients, on the other hand, had higher relative abundances of *Bacteroides pyogenes, Bacteroides fragilis*, *Prevotella bryantii*, and also *Akkermansia muciniphila*. The mechanism by which higher indole synthesis may protect against *Cryptosporidium* is still uncertain. Indole may directly harm the parasite or remodel host tissues to improve the innate response by enhancing epithelial integrity (Shimada *et al,* 2013) and/or promoting anti-inflammatory pathways (Chappell *et al,* 2016).

In fact, numerous protozoan parasites clearly alter the composition of the host microbiome, either via local inflammation or through direct effect via resource competition within the host's intestine. The great majority of these research works, however, reveal that the microbiome also has a substantial role in determining host vulnerability to parasitic infection, emphasizing bidirectional relationship between protozoa and the host gut microbiota.

Soil-transmitted helminths-microbiota interaction: More than 1 billion individuals worldwide were infected by soil-transmitted helminths. The most prevalent infections are caused by *A. lumbricoides*, *T. trichiura* and hookworms and others which inhabit in the host's intestines (Peterson and Artis, 2014). The world’s helminthes infections burden is maintained in the developing countries especially among children who are the most vulnerable individuals due to socioeconomic factors such as poor sanitation, and malnutrition that has a synergistic association with gastrointestinal infections due to the decreese of gastrointestinal mucosal integrity (Pullan *et al,* 2014). Complex relationships between intestinal helminths and gut microbiota have been widely studied, with specific microbiota species influencing the consequences of helminthes infection (Zaiss and Harris, 2016). It is currently unclear whether helminthes infections increase or decrease guts microbial diversity (Lee *et al,* 2014; Houlden *et al,* 2015). These indicated that helminthes infection causes alterations in the microbiome. Whether these are useful or not is determined by a variety of circumstances, including the host's susceptibility and concurrent infection with other infections (Britton *et al,* 2012). This could be achieved by

immunological regulation, variations in metabolites, and or nutritional consequences resulting from higher worm loads. Furthermore, various infections break intestinal barrier, eliciting potent innate and adaptive responses. Defenses, which are formed by Paneth cells in the human gut, are among the substances that act against parasites, but they may also affect microbiome, potentially changing its diversity (Cattadori *et al,* 2016).

Helminthic parasite infection causes significant changes in the gut microbiota species. It could cause a rise in the number of *Lactobacillaceae* and *Enterobacteriaceae* spp. in the gut (Rausch *et al,* 2013; Reynolds *et al,* 2014) and a decline in some fecal microbial community, particularly among *Bacteroidetes* spp. (Holm *et al,* 2015). Microbiota modifications during helminthes infection correspond with worm load (Wu *et al,* 2012; Reynolds *et al,* 2014), but return to normal after helminthic clearance, suggesting that the existence of parasites is essential for long-term changes in the bacterial microbiota (Houlden *et al,* 2015). Helminthes infections were associated with increased bacterial microbiota variability, with each helminth associated with distinct changes in microbiota species diversity or prevalence (Kreisinger *et al,* 2015). The faecal microbiota of Malaysians infected by at least one helminth parasite (*Trichuris*, *Ascaris* or hookworms) harbored a more heterogeneous species than those devoid of helminth infection (Lee *et al,* 2014). These interactions are strictly controlled to avoid tissue damage and pathology. Signaling via IL-10R receptors in intestinal immune cells is crucial for controlling these interactions. In the absence of this receptor on intestinal immune cells, whipworms remain in the colon, accompanied by excessive inflammation that damages the mucosal lining. This tissue damage is associated by an abundance of members of the *Enterococcaceae* and *Enterobacteriaceae* bacteria, which behave as enteric pathogens (Duque-Correa *et al,* 2019).

The gut microbiota is responsible for energy extraction from diet, fat deposition, vitamin biosynthesis, and other biological functions. Alteration of these activities can lead to a variety of metabolic disorders. Helminthes may also have an indirect effect on metabolic processes by modifying the microbiota over time. Helminthes can engage with microbiota and promote SCFA production.

SCFAs have a significant impact on metabolic activities, they attach to G protein-coup-led receptors, modulating insulin sensitivity and metabolic activity (den Besten *et al,* 2013). Elevated abundance may impact subsequent insulin sensitivity and fat deposition and imply enhanced energy harvesting capacity, yet they are also linked to anti-inflammatory state, satiety, and good health (Clarke *et al,* 2014).

The elicitation of a Type-2 immune response with a regulatory response is a distinguishing hallmark of helminthiasis, particularly in chronic, asymptomatic cases (Allen and Maizels, 2011). Considering immune system's involvement in maintaining and controlling gut microbiota species, disturbance and readjustment of immunological homeostasis caused alterations in microbiota communities (Hooper *et al,* 2012), via innate and adaptive mechanisms (Reynolds *et al,* 2015).

Helminths secrete many excretory secretory byproducts, such as immunomodulatory peptides, glycoproteins, & miRNAs regulate activity of diverse cell types, included regulatory immune cells significantly impacts on immune system (Sipahi and Baptista, 2017). Immunomodulatory effects attribute to intestinal helminthes and certain bacterial microbiota species, helminth infection changes the nature of bacterial intestinal microbiota, and their composition affects helminth colonization and survival in hosts. Zaiss *et al.* (2015) reported that intestinal helminths are powerful immune system regulators, promoting anti-inflammatory cytokine release and regulatory T cell suppressor activity, and alleviate inflammatory conditions such as allergic respiratory problems. The produ-

ction of suppressive regulatory T cells was a crucial route essential to immune- modulatory capacities of helminthes, especially in the context of allergy prevention (Wilson *et al,* 2005; Grainger *et al,* 2010). Several microbiota species induced suppressive regulatory T cells in parallel, such as *Clostridia* spp. stimulated TGFβ-1 synthesis from intestinal epithelial cells (Round and Mazmanian, 2010; Atarashi *et al,* 2013). Short-chain fatty acids can increase suppressive regulatory T cells development and IL-10 release from suppressive regulatory T cells in the periphery (Arpaia *et al,* 2013), elevated circulating Short-chain fatty acids levels are protective of allergy diseases (Trompette *et al,* 2014). Reynolds *et al.* (2014) found that modifications of gut microbiota in mice with helminthes were induced by: (i) parasite's secretion of antimicrobial elements that effectively reconfigure microbiota, (ii) parasite's disruption of gut epithelial barrier, which modify intestinal ecosystem and facilitates the establishment of selected microbiota, or (iii) parasite's activated certain immunological responses (as suppressive regulatory T cells expansion) that contribute significantly towards a shift in gut microbiota. Whether or not a helminth is involved, altered gut microbiome is a direct outcome. Immunological response triggered by helminths is yet to be confirmed. With surge in helminthic treatment worldwide, economic growth cause major shifts in hygiene, parasitosis, allergy, immunity, and metabolic disorders (Bhattacharjee *et al,* 2017).

Conclusion

Direct relationship between gut microbiota and parasitic diseases is mainly via immunological processes. Relationships are associations with little knowledge of causality, susceptibility to genetic allelic components and/ or environmental factors.

Microbiome modulate parasite virulence, triggering dysbiosis or even favorable alterations in microbiota that increase competition for lumen of gut niche, and modifying host immunity to parasite. Certain components of the microbiota may determine the courses of parasitic infection, and parasite infection can remodel the microbiota in such a way that the distinctive profile can be diagnostic of the parasite's existence.

The author declared that she neither has conflict of interest nor received any funds.

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