

## Parasitic Infections and Intestinal Microbiota: A Review

G. I. Izvekova\*

*Papanin Institute for Biology of Inland Waters, Russian Academy of Sciences, Borok 109, Yaroslavl oblast, 152742 Russia*  
\*e-mail: [izvekova@ibiw.ru](mailto:izvekova@ibiw.ru)

Received April 23, 2021; revised May 29, 2021; accepted December 20, 2021

**Abstract**—Articles devoted to the relationships between parasites inhabiting vertebrate intestines and the host microbiota, as well as the influence of these members of the intestinal ecosystem on the host, are analyzed in this review. The effect of helminths on the composition of the microbiota and immunity of the host, some autoimmune disorders, and inflammatory bowel diseases are considered, and the antimicrobial activity of helminths is noted. Understanding the complex three-way interactions between the host, its microbiota, and parasites is a fundamental parasitological problem underlying the search for new approaches to the improvement of animal and human health.

**Keywords:** parasitic worms, intestinal microbiota, host–parasite–microbiota relationships

**DOI:** 10.1134/S1062359022040070

### INTRODUCTION

Thus far it has been proven that the higher organisms cannot exist without continuous interactions with microorganisms, and many physiological processes in humans, animals and plants are inextricably intertwined with the respective processes in resident bacteria (Rowland et al., 2018). Various groups of parasites, including helminths, protozoa, and arthropods, interact directly or indirectly with each other and with microorganisms. These interactions can be either useful or harmful for one or both pathogenic species. For hosts, these interactions can also be either deleterious or beneficial. Elucidation of the scale and significance of this interaction, as well as assessment of the nature of relationships between parasites and bacteria, can be highly important for preventing quite a number of infectious diseases (Ashour and Othman, 2020).

The symbiotic relationship between animals and microorganisms inhabiting the digestive tract is one of the most important characteristics of the digestive system. The animal host and its intestinal microbiota are a complex ecological system with a significant effect of microbiota on the host and the components of microbiocenosis on each other. The normal microbiota of the digestive tract plays a key role in the formation of host immunity, the synthesis of some enzymes and vitamins, and the utilization of food substrates with production of essential amino acids (Izvekova, 2008; Berrilli et al., 2012; Rowland et al., 2018). There is an extensive literature devoted to the quantitative and qualitative composition of enteric microbiota in different vertebrate species (Austin, 2006; Gomaa, 2020). Studies in this field have been conducted for quite a long time, and the concepts of the intestinal

ecosystem are extensive and specified with the development of metagenomic techniques.

Interest in the study of human intestinal microbiota has significantly increased in recent years, especially due to the development of metagenomic analysis. The intestinal microbiota is highly diverse and contains trillions of microorganisms. The formation and improvement of the diversity of the intestinal microbiome begin at birth, while changes in its composition depend on various factors. The changes in the composition and functions of intestinal microbiota influence intestinal permeability, digestion and metabolism, and immune responses. An altered balance of intestinal microbiota leads to metabolic disorders and development of many gastrointestinal diseases, as well as immunological and psychoneurological disorders. Therefore, studies of the interrelationship between intestinal microbiota and the host have become increasingly important (Gomaa, 2020).

Microorganisms in the gastrointestinal tract often share the environment with parasitic worms, which leads to physical and physiological interactions between these two groups. Such associations can affect the host health, as well as the populations of bacteria and helminths. The studies of interactions between a microbiome and parasitic helminths are at different stages (Glendinning et al., 2014; Zais and Harris, 2016). At the same time, the problem of relationships between a parasite and its host is one of the fundamental problems of parasitology. In order to establish close specific relationships after getting into a host organism, a parasite is fully adapted to life under these conditions. A host, a parasite, and a symbiotic microbiota make up the microbiocenosis with close

interrelationships established during their joint evolution, which should be studied to understand the processes occurring therein (Izvekova, 2008; Zaiss and Harris, 2016). It is known that intestinal helminths affect physiological processes in the bowel, first of all, mucus secretion and production of antimicrobial peptides, which, in turn, can influence the survival rate and spatial organization of bacteria (Dezfuli et al., 2016). A parasite and its host interact mainly through secreted proteins, generally referred to as “secretome.” The proteins secreted by a parasite are able to modify the host’s environment and to modulate its immune system. The compositions and functions of these proteins vary depending on the ecology, lifestyle, and environment (Cuesta-Astroz et al., 2017). It is known that the excretory/secretory proteins from parasites play an important role in various infections and host–pathogen interactions (Ranganathan and Garg, 2009; Huang et al., 2019); they regulate the balance between a parasite and the host and, as a result, a parasite can exist within a host for quite a long time (Huang et al., 2019). Intestinal parasites encounter not immune responses but rather the problem of increasing resistance to host proteolytic enzymes, which have a permanent destructive effect on gut inhabitants. Helminths secrete various proteins including proteases, protease inhibitors, allergens, glycolytic enzymes, and lectins. However, the relative amount of each protein varies in different parasites and at different stages of their lifecycle (Hewitson et al., 2009).

Some researchers believe that helminths are an important component of the biome in vertebrates, which has largely influenced the evolution of their genes. For example, it is believed that the absence of these macroscopic organisms at the early stage of development and life of people in the western culture probably leads to the appearance of different immunological human diseases (McKenney et al., 2015). However, the interaction between a microbiome and helminths has been poorly studied.

The intestinal microbiota is vitally important for the host health, and, therefore, different authors have made numerous attempts to elucidate the mechanisms affecting the modification of its composition and diversity. The host–helminth and host–microbiota interactions are rather well-studied, in contrast to the microbiota–helminth relationships, where studies are usually focused on experimental infection of laboratory animals by a single helminth species (Kreisinger et al., 2015). Helminths underwent evolution together with intestinal microbiota and hosts. Recently, studies of this three-way interaction have been started, making it possible to develop new therapeutic strategies for treating some metabolic and inflammatory diseases (Loke and Lim, 2015).

It would be interesting to see the differences in life strategies between the symbiotic species of microbiota and parasitic or pathogenic organisms. The symbiotic

species of the microbiota influence the habitat with minimal damage to the host. On the contrary, most parasites and pathogenic bacteria impair the mucosal barrier, exhaust nutrient reserves, and have a more profound effect on the immune system of the host, which is functionally much more difficult. According to some authors, it can explain why there is a great number of species of commensal and symbiotic bacteria colonizing the gastrointestinal tract, while the number of helminths and pathogenic bacteria that can do it is limited (Reynolds et al., 2015).

Mammalian intestines contain various commensal and pathogenic organisms playing a key role in the formation of the immune system. The data being accumulated confirm the opinion that helminths can change the relative composition of microorganisms in the host intestines and, as a result, that parasites affect the immune homeostasis. It is emphasized that the intestinal microbiome and helminths exert a profound effect on health and pathologies, and it partially sheds light on the causes of various inflammatory bowel diseases (Giacomin et al., 2016).

This review analyzes the works devoted to some aspects of interaction between parasites inhabiting vertebrate animal intestines and the host microbiota, as well as the effects of these members of the intestinal ecosystem on the host.

#### THE EFFECTS OF HELMINTHIC INVASIONS ON THE COMPOSITION OF THE INTESTINAL MICROBIOTA OF THE HOST

The intestinal microbiota (both present in the chyme and associated with the intestinal mucous membrane and parasitizing helminths) plays an important multifunctional role in the life of macroorganisms. The role of microorganisms in the bowel is ambiguous and varies depending on different factors of the ambient and internal medium. It is known that the qualitative and quantitative composition of intestinal microbiota varies under the influence of different endogenous (the structure of the digestive tract, pH of intestinal contents, anaerobic conditions, intestinal enzymes, osmotic pressure, host immunity) and exogenous (abiotic and biotic factors of the environment, including nutrients) factors (Izvekova, 2006, 2008; Austin, 2006). It has been supposed that helminth infections are accompanied by considerable changes in the number and composition of microbiota in the gastrointestinal tract (Eckburg et al., 2005). Though the competition between helminths for nutrient resources, the secretion of bacterial growth inhibitors by some species (Hewitson et al., 2011), and the host age and diet (Berrilli et al., 2012; Glendinning et al., 2014) have been proposed as factors influencing the composition of intestinal microbiota, the interaction between a host, helminths, and the microbiota attracts great attention due to the ability of helminths to

induce direct or indirect changes in the composition of the microbiota (Glendinning et al., 2014).

Soil-transmitted helminths infect more than 1.5 billion people worldwide; however, little is known about their interaction with the intestinal microbiota. These parasites infect mostly people in developing countries, which can account for the differences in the quantitative and qualitative composition of intestinal microbiota compared to people from developed countries (Lee et al., 2014). Most such works are devoted to studies of interactions in the host–parasite–microbiota system, where parasites are different species of nematodes. Most often, they represent the genera *Ascaris*, *Trichuris*, and *Necator*. For example, it was shown that patients infected by *Trichuris* nematodes had a wider range of species of intestinal microbiota, demonstrating the effects of helminths on the diversity and structure of bacterial communities and on the functions of intestinal microbiota (Lee et al., 2014).

Due to anatomical, physiological, and immunological similarities between the species, pigs are widely used as a model in studies of human diseases. Moreover, the biological diversity of intestinal microbiota in pigs and humans is comparable (Li et al., 2012). Helminthic invasions are widespread in pig breeding systems worldwide and among people from regions with limited resources. *Trichuris suis* nematodes in pigs are an example of widespread helminthosis causing diarrhea, anorexia, and growth retardation, which can be controlled by administration of anthelmintics. The study of *T. suis* infection in pigs is highly important for human health, because it can contribute to elucidation of the mechanisms of interactions between a host, a parasite, and the microbiota. The effect of *T. suis* infection on the composition of intestinal microbiota in pigs (Li et al., 2012) and the relationship between the state of the mucous membrane, immune response, infection rate, and changes in the composition of microbiota (Wu et al., 2012) have been studied. Infected animals were shown to have a great number of *Mucispirillum* bacteria and a decreased number of cellulolytic bacteria *Ruminococcus* colonizing the mucus (Li et al., 2012). It has been noted that a 21-day *T. suis* infection in pigs caused profound changes, both in the composition of microbiota and in the metabolic potential, in the lumen of the proximal part of the colon. The changes in the amounts of *Succinivibrio* and *Mucispirillum* were associated with parasite-induced changes in carbohydrate and amino acid metabolism and habitat disturbance in the case of mucosal pathologies (Li et al., 2012). In addition, it was shown that the populations of intestinal microbiota changed after the pigs had been infected by the *T. suis* nematode, and the authors suppose associated with different nutrient sources for bacteria as a result of parasite-induced intestinal epithelial damage (Wu et al., 2012).

There are not many studies using the meta-taxonomic approach to investigate the relationship between gastrointestinal helminths and the composition/diversity of microbiota in mammals (Walk et al., 2010; Rausch et al., 2013; Cooper et al., 2013; Cantacessi et al., 2014). Experimental infection of laboratory mice by the nematode *Heligmosomoides polygyrus bakeri* was conducted, which resulted in an increased number of bacteria at the place of helminth colonization both in the ileum/small intestine (Walk et al., 2010) and in the blind gut and the colon (Rausch et al., 2013). At the same time, experimental removal of the whipworm *Trichurus trichuria* in humans or infection by the hookworm *Necator americanus* had no effect on the diversity and composition of the host fecal microbiota. However, experimental infection by helminths can increase the microbial diversity; e.g., in laboratory animals (Kreisinger et al., 2015; Zaiss and Harris, 2016).

The nematode *Trichuris trichiura* exhibited no effect on the composition of the fecal microbiota in children compared to uninfected children, and infection treatment did not affect the composition of the microbiota. However, co-invasion by *A. lumbricoides* and *T. trichiura* led to a decrease in the total diversity of bacteria, in particular, in the relative number of some members of the class Clostridia (Cooper et al., 2013).

It has been shown that, although infection by the hookworm *Necator americanus* leads to a minor increase in the compositional diversity of microorganisms, there is no significant effect on the community structure, the diversity, or the relative abundance of individual bacterial species. It has been supposed that hookworms and other helminths trigger changes in the composition of microbiota at the place of infection (e.g., the duodenal mucosa for hookworm), which do not affect the composition of fecal microbial communities (Cantacessi et al., 2014).

It has been shown that nematode infection by *Ostertagia ostertagi* in cattle results in dysfunction of the gastrointestinal tract (Li et al., 2011). An abomasal microbiota in response to reinfection by the parasite was characterized. It was shown that reinfection did not trigger any significant changes in the microbial community of animals. The infection seemed to exert minimal effects on the genus-level microbial diversity in the abomasum of immunized animals. The authors believe that the results demonstrate the ability of immunized animals to develop and maintain the proper stability of the abomasal microbial ecosystem, and minimal disruption of the abomasal microbiota in cattle as a result of reinfection can equally contribute to the recovery of gastric function in immunized animals (Li et al., 2011). During evolution, a host and its microbiota have established a mutualistic relationship. The abomasal microbiota contains bacteria that produce a powerful inhibitor of gastrin secretion in the

host organism, which leads to a decrease in the level of gastrin by approximately 90% and has a direct effect on the physiology of the host. The abomasal microbiota has been shown to produce a considerable number of serpins, the large class of protease inhibitors involved in the regulation of a broad range of physiological processes. Serpins produced by the abomasal microbiota prevent the attachment of host proteases, playing a key role in the interaction between the abomasal microbiota and the host. Most likely, parasitic infection alters the composition of the gut microbiota and thereby reduces the production of essential amino acids by the microbiota (Li et al., 2011).

Some authors assume that the composition of the microbiota in the mouse duodenum influences the survival of *Heligmosomoides polygyrus* within the host, while the nematode, in turn, can actively modify the microbiota to promote its own survival (Reynolds et al., 2014). These data are in agreement with the previous data obtained from the study of another parasitic nematode of pigs, *Trichuris muris*, the survival of which was shown to depend on the presence of intestinal microbiota. It allowed the authors to assume the existence of richer and more interactive relationships between the microbiota and helminths in the gastrointestinal tract of mammals (Reynolds et al., 2014).

Controlled laboratory experiments in animals have demonstrated that helminthic infection leads to essential changes in the composition of the intestinal microbiota. Chronic infection by *Heligmosomoides polygyrus* in the mouse duodenum induces an increase in the species abundance of Lactobacillaceae and Enterobacteriaceae in the small intestine (Walk et al., 2010; Rausch et al., 2013; Reynolds et al., 2014). Similarly, the chronic infection of mice by the nematodes *Trichuris muris* colonizing the blind gut leads to a decrease in bacterial diversity within the scope of *Bacteroidetes* phyla in the host feces, as well as to an increase in the abundance of representatives of the family Lactobacillaceae (Houlden et al., 2015). These data confirm the hypothesis that parasites trigger changes in the number and relative distribution of bacteria in the gastrointestinal tract.

Along with the effects on the composition and function of commensal and symbiotic species of the microbiota, helminthic infection can also change the host response to infection by pathogenic species of bacteria. For example, co-infection by the nematodes *H. polygyrus* or *Nippostrongylus brasiliensis* and the pathogenic bacteria *Salmonella enterica* serovar *typhimurium* (*S. typhimurium*) in mice leads to an increased mortality of mice, intestinal edema, erythro-erosions, and bowel wall thickening, compared to *S. typhimurium* mono-infection in these mammals (Reynolds et al., 2015).

There are only a few analogous studies associated with cestodes. It has been shown that infection of rats by the cestode *Hymenolepis diminuta* triggers changes

in the microbiome of the host blind gut. Most of the changes occur in Firmicutes representatives: in the presence of helminths, the number of Bacilli species decreases, while the number of Clostridia species increases, which may be evidence of the existence of mechanisms enabling this helminth to exert a therapeutic effect (McKenney et al., 2015). In general, the presence of helminths is associated with a high diversity of the microbiota, which, in the opinion of some authors, may have a positive effect on the host health (Ramanan et al., 2016; Giacomini et al., 2016). In the system of wild rodents, variations in the composition and number of taxa of helminth-associated intestinal microorganisms were specific to each helminth species and observed both above and below the helminth position within the intestines. The most marked association between helminths and the microbiota was found for the presence of tapeworms in the small intestine and an increased number of Bacteroidetes in the stomach (Kreisinger et al., 2015). The authors believe that helminths can change the intestinal homeostasis, and free-living rodents with a diverse community of helminths can be a useful model for elucidating the relationships between helminths and microbiota.

Thus, the study of the effects of helminths on the composition and diversity of host microbiota deserves close attention.

#### PARASITE–MICROBIOTA RELATIONSHIP AND HOST IMMUNITY

It is known that the intestinal microbiota is important for the development of a mature immune system in vertebrates, as well as for the maintenance of immunological homeostasis in the bowel (Zaiss and Harris, 2016). Though there are many hundreds of bacterial species colonizing mammalian intestines, the balance between these species varies within a broad range among people in a population.

Helminthic infection can also change the host metabolism, which in turn affects the host immune response (Zaiss and Harris, 2016). The interactions between the intestinal microbiota, the immune system, and pathogens describe the bowel as a complex ecosystem, where all components interact with each other to maintain homeostasis (Berrilli et al., 2012). The intestinal microbiota has a great effect on the development of the metabolic and immunological status of mammalian hosts. Both microorganisms and helminths must resist the host immune system. For example, experimental infection by the nematode *Trichuris muris* in mice decreased the fecal levels of metabolites such as vitamin D2/D3 derivatives, fatty acids and related metabolites, glycerophospholipids, carbohydrates of plant origin, and the intermediate products of amino acid synthesis (Houlden et al., 2015). Hamsters infected by the hookworm *Necator americanus* also demonstrated a considerable change

in the urine levels of metabolites, probably due to the changes in the composition of the intestinal microbiota (Reynolds et al., 2015). In pigs infected by the nematode *Trichuris suis*, the changes in the composition of the colon microbiota are accompanied by a metabolic shift; at the same time, the infection induces a reduction in the level of cofactors of carbohydrate metabolism and amino acid biosynthesis (Li et al., 2012; Wu et al., 2012).

Intestinal helminths and some bacterial species of the microbiota are considered as having potent immunomodulatory properties. For example, it has been shown that helminths alter the composition of intestinal microbiota and, on the contrary, the presence and composition of the microbiota influence helminth colonization in mammalian hosts. There is the opinion that understanding the complex multidirectional interactions between intestinal microorganisms, helminths, and host immunity will make it possible to use a more integral approach to the application of pro-, pre-, and synbiotics, antibiotics, and anthelmintics, as well as the development of therapeutic techniques for autoimmune and allergic disease states (Reynolds et al., 2015).

#### PARASITE–MICROBIOTA RELATIONSHIP AND INFLAMMATORY BOWEL DISEASES

As was mentioned above, intestinal parasites interact with the microbial community, changing the balance between the host and the commensal microbiota, which is crucial for organismal health. As a result, there is increasing interest in the study of possible interactions between microbiota, parasites, the host immune response to infection, and inflammatory processes in the bowel (Berrilli et al., 2012).

It has been demonstrated in mice and humans that gastrointestinal helminth infections can protect against some inflammatory bowel diseases (IBDs), causing immune responses that change the balance between commensal and pathogenic bacteria in the intestines (Ramanan et al., 2016). A scheme of interaction between helminths and bacteria during inflammatory bowel disease has been proposed (Giacomin et al., 2016). According to this scheme, IBD is associated with limited bacterial diversity and impaired barrier function of the epithelium, as well as with the impaired formation of tight cell–cell junctions and mucus production. As a result, bacteria such as Bacteroidales can attach to the epithelial wall or overcome the epithelial barrier. Intestinal helminths induce an immune response protecting the epithelial barrier, including the secretion of type 2 cytokines and interleukin IL22, which together intensify the production of mucus by goblet cells and the expression of antimicrobial peptides, thereby preventing bacterial attachment. Enhanced barrier function promotes the development of various bacteria (e.g., Clostridiales) influencing the recovery; together with the induction of

regulatory T cells by worms and their secretory products, it helps stop the inflammatory process in the bowel, thereby mitigating the severity of IBD (Ramanan et al., 2016; Giacomin et al., 2016).

With a view to the revealed effect of parasites on the composition of intestinal microbiota, it was proposed to investigate the possibility of using parasites and parasite components or products as therapeutic agents for inflammatory processes in the bowel (Chen et al., 2005) and to assess helminths as a therapeutic agent for some immune-mediated disorders, including particular types of inflammatory bowel diseases (Summers et al., 2005). The authors believe that the findings will provide a basis for understanding the immunomodulatory effect of helminths. This, in turn, will make it possible to develop more efficient methods for the treatment of immune-mediated diseases and intestinal vaccines for the prevention and therapy of diseases caused by microorganisms in regions with multiple infections (Weng et al., 2007).

It has been shown in animal models that helminthoses improve the state of patients with some inflammatory diseases. Helminths can cause serious damage to host tissues during their maturation, migration, and nutrition inside the host. These parasites can remain in a host organism for many years. In this case, the host immune response should be well-adapted for eradication of large multicellular pathogens, wound healing and tissue repair, and mitigation of inflammatory pathology related to chronic infection. It has been suggested that the immune response triggered for the expulsion of gastrointestinal parasites includes the enhanced production of mucus, changes in its composition, and increased epithelial cell turnover. All the above can have a positive effect on restoration of the mucosal barrier function in the case of inflammatory bowel disease and reduce the inflammation caused by pathogenic intestinal bacteria. Study of protective mechanisms of the host activated during intestinal helminthic infection can reveal new ways for maintaining the mucosal barrier function (Wolff et al., 2012).

At the same time, it has been reported that infection by the nematode *Heligmosomoides polygyrus* aggravates colitis caused by the Gram-negative bacterium *Citrobacter rodentium*. The severity of the disease in co-infected mice correlated with a high load of *Citrobacter* in the bowel. These results demonstrate that helminthic infection can impair host protection from concurrent enteric bacterial infection and promote bacteria-induced damage in the bowel (Weng et al., 2007).

The studies of episodes with *Giardia lamblia*, parasitic flagellated protozoa, have shown that 40–80% of infected patients suffer from long-term functional gastrointestinal disorders after eradication of these parasites. These data demonstrate that the immune responses of a host to its own microbiota as a result of

epithelial barrier injury can partially promote the development of postinfectious intestinal disorders. Understanding postinfectious mechanisms may contribute to the development of new therapeutic approaches to the treatment of chronic bowel diseases (Chen et al., 2013).

#### PARASITE–MICROBIOTA RELATIONSHIP AND AUTOIMMUNE DISEASES

As was mentioned above, it is well known that intestinal helminths have potent immunomodulatory properties. Hence, the effects of helminthic invasions on some autoimmune diseases are being studied. For example, it has been demonstrated in mice that helminthosis alters the composition of the bacterial microbiota and increases the concentration of short-chain fatty acids, which mitigate the clinical course of allergic asthma (Zaiss et al., 2015). A tentative scheme of the effects of nematode invasion resulting in the mitigation of allergic airway inflammation has been proposed (Reynolds et al., 2015). The mechanisms of action of helminths on various diseases of hosts such as allergies, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, and autism are under study (Wu et al., 2012).

Helminth infections were shown to be accompanied by a total decrease in proinflammatory cytokines related to chronic inflammation. In addition, autoimmune disorders are less frequent in geographical regions with a higher prevalence of parasitic infections (Sewell et al., 2002). The view has been expressed that a reduction in the number of helminthic invasions in developed countries may be a cause of the increased incidence of autoimmune and allergic diseases in human populations (Reddy, 2010). Several studies performed in developing countries have presented evidence of the role of intestinal nematodes in prevention of allergic reactions (Summers et al., 2005). This phenomenon is known as the “hygienic hypothesis” (Berrilli et al., 2012). There are data on the applications of live helminths in clinical trials in an effort to mitigate allergic and autoimmune disorders (Khan and Fallon, 2013). Though positive clinical results have been recorded in many studies, therapy with the involvement of the nematode *Trichuris suis* nevertheless draws criticism because of the danger of worm invasion for human physiology (Van Kruiningen and West, 2005), as well as potential adverse effects on the gastrointestinal tract (Bager et al., 2011). Such studies have both pros and cons. The pros are the potent immunogenic properties of the live parasite, its low cost, and the good results of this therapy. At the same time, there are many more cons. They include, first of all, the ethical aspect of using live worms. In addition, a patient is exposed to the effects of the entire spectrum of excretory–secretory products of helminths; the intestinal mucosa is damaged in the case of helminthic therapy; recurrence of symptoms is observed after the expulsion of parasites; there are difficulties

with the correct use of placebo controls and the proinflammatory activity of live worms (Maruszczyńska-Cheruiyot et al., 2018).

#### ANTIMICROBIAL ACTIVITY OF INTESTINAL HELMINTHS

One of the mechanisms of action of intestinal helminths on the host microbiota is the secretion of antimicrobial peptides by these parasites (Ashour and Othman, 2020). Antimicrobial peptides are natural antibiotics produced by all living organisms. In multicellular animals, they act as host protective factors against bacterial pathogens (Bruno et al., 2019). For example, nematodes were shown to produce four groups of antimicrobial peptides. These studies are generally confined to the species *Caenorhabditis elegans* and *Ascaris suum*. Though there is no comprehensive information about the genome for the most nematode species, it is clear that none of the antimicrobial peptide groups is expressed universally by all nematodes. On the contrary, none of the species produces all types of antimicrobial peptides (Tarr, 2012).

With the purpose of studying the relationship between parasitic nematodes and the vertebrate host microbiota, the excretory–secretory products and the biological fluid of *A. suum* were analyzed to determine the antimicrobial activity in these samples (Midha et al., 2018). The excretory–secretory products from different stages of *A. suum* and the biological fluids from adult males were analyzed by mass spectrometry. The samples were shown to contain the antibacterial factors of *A. suum* and antimicrobial peptides, lysozyme, as well as proteins containing C-type lectin-like domains. The secretory products of nematodes from L4 stage larvae and adult worms exhibited broad-spectrum antibacterial activity. In addition, the excretory–secretory products of adult *A. suum* interfered with the formation of *Escherichia coli* biofilm and caused bacterial agglutination. In the opinion of the authors, these results show that *A. suum* produces numerous factors with broad-spectrum antibacterial activity for interaction with the microbiological environment in the bowel (Midha et al., 2018). The formation of intestinal microbiota is affected both by host immunity and by helminth metabolites, though the latter have been little studied. Taking into account that nematodes alter the composition of host intestinal microbiota without any noticeable damage to the host, some authors believe that investigation of the development of parasitic nematodes and their effects on the ambient microbiota can give an idea how the latter can be changed for therapeutic purposes (Midha et al., 2018). It has been shown that *A. suum* at the life cycle stages in the intestines uses different antimicrobial strategies to influence the composition of the host microbiota. At the same time, the antimicrobial potential of the excretory–secretory products of nematodes varies depending on the stage of the life cycle of the parasite

and habitat composition. The effects of helminths will be more marked in the case of severe infestation, because the local concentration of antimicrobial agents will probably be higher. These factors allow nematodes to allocate a niche for survival in the microbial environment and, at the same time, be partially responsible for the changes in the intestinal microbiome during parasitic infection (Midha et al., 2018).

It has been shown that the excretory–secretory products of the nematode *Heligmosomoides polygyrus* exhibit antimicrobial activity against various bacteria (Reynolds et al., 2014, Rausch et al., 2018). It has been supposed that nematodes alter the microbial environment and have developed factors limiting the growth of particular microorganisms. It has been demonstrated that *H. polygyrus* can actively form the composition of the host microbiota by releasing antimicrobial substances and impair the adaptability of nematodes in the absence of host bacteria (Rausch et al., 2018). Other researchers have shown that the species abundance of *Lactobacillus* in the duodenum positively correlates with the susceptibility to *H. polygyrus* (Reynolds et al., 2014). The authors have postulated the two main hypotheses to explain the changes in the microbiota composition after an infection by *H. polygyrus*. They believe that, firstly, *H. polygyrus* can actively modify the microbiota using secretory antimicrobial products, e.g., lysozyme. Secondly, the inflammatory response caused by helminthic invasion, or both the former and the latter, or destruction of the epithelial barrier by parasites, can modify the intestinal niche in favor of particular commensal microorganisms (Reynolds et al., 2014).

#### THE HOST, PARASITE, AND INTESTINAL MICROBIOTA IN FISH

In contrast to mammals, very few works are devoted to study of the host–parasite–gut microbiota relationships in fish. At the same time, fish are a very interesting object in the context of the host–parasite–gut microbiota relationship. The bowel is one of the main pathways for infecting fish, because they are always in close contact with the environment, water, being continuously exposed to bacteria, including pathogens. It is known that the intestinal microbiota of fish plays an important role in stimulation of the development of the host gastrointestinal tract, promotes digestive function, maintains mucosal tolerance, stimulates the host immune response, and provides a certain level of protection against infections (Ghosh et al., 2020). Hence, the few works related to the study of the host–parasite–gut microbiota relationships in fish deserve particular attention.

The methods of scanning and transmission electron microscopy were used to study the symbiotic microflora associated with the surface of the following intestinal parasites: *Eubothrium rugosum* cestodes in

burbot (Poddubnaya, 2005), *Caryophyllaeus laticeps* in bream and *Khawia armeniaca* in khramulya (*Varicorinus capoeta sevangi*) (Poddubnaya and Izvekova, 2005), several species of cestodes of the genus *Proteocephalus* in different host fish species (Korneva and Plotnikov, 2006a), and *Triaenophorus nodulosus* cestodes in pike (Korneva and Plotnikov, 2006b). These works presented convincing evidence of a tight association between bacteria and the digestive–transport surfaces of cestodes. Localization between microtrichia and close adherence of bacteria with thin cell walls may be indicative of their involvement in the processes of digestion and absorption occurring on the tegumental surface (Poddubnaya, 2005). The absence of evident damage to the tegument by the cells of microorganisms makes it possible to consider the detected bacteria as symbionts. Based on the findings, the authors state the presence in cestodes of normal symbiotic microflora inhabiting the tegumental surface and having specific morphological features (Korneva and Plotnikov, 2006a, 2006b). The peculiarities of interaction between symbiotic microbiota and cestodes demonstrate the mutual adaptation of bacteria and parasites. It manifests itself, in particular, in the presence of specialized cell–cell contacts and the absence of ultrastructural signs of pathogenic effects of bacteria on the tegument of cestodes. Other evidence for the symbiotic relationship between cestodes and microbiota is the specificity of the morphological composition of bacteria in different species of cestodes (Korneva and Plotnikov, 2006a). The analysis of bacterial diversity in the gastrointestinal tract of perch and on the surface of *Proteocephalus* sp. cestodes parasitizing the latter showed considerable similarity in its composition between the host and the parasite (Kashinskaya et al., 2020). In order to understand the relationships in the host–parasite–gut microbiota system, the authors recommend taking into account the presence of endoparasites and their bacterial load in the study of the fish microbiome. The study of the composition and diversity of the intestinal microbiota of the common carp infected by two species of tapeworms, *Khawia japonensis* and *Atractolytocestus tenuicollis*, showed that the infection by two cestode species had no considerable effect on the microbial diversity or abundance but altered the microbial composition at the generic level. *K. japonensis* had a greater effect on the composition of intestinal microbiota (Fu et al., 2019).

In addition, it has been shown that bacteria are associated with the mucosa of fish intestines and the tegument of cestodes with varying degrees of strength. The total number and biomass of these bacteria were determined (Izvekova and Lapteva, 2002). It has been shown that the bacteria associated with the digestive–transport surfaces of the intestines of fish (pike, burbot, and bream) and the tegument of cestodes inhabiting them (*T. nodulosus*, *E. rugosum*, and *C. laticeps*, respectively) are able to secrete enzymes hydrolyzing

the major nutrient substrates: proteins and carbohydrates (Izvekova, 2005, 2006). Microorganisms make a substantial contribution to degradation of these substances by intestinal enzymes. It has been suggested that the intestines of fish and the teguments of its parasites are colonized by the same groups of bacteria and the parasite can use the microbiota hydrolases allowing its successful competition with the host for nutrient sources (Izvekova, 2008).

## CONCLUSIONS

For the sake of understanding the evolutionary basis of helminth–microbiota associations, it is highly important to investigate natural systems with undisturbed communities of microorganisms and helminths. Some authors believe that the work should be focused on the study of certain mechanisms involved in the three-way interaction between the microbiota, the host, and helminths (Kreisinger et al., 2015).

Microorganisms inhabiting host intestines become pathogenic under certain conditions and can be a source of pathogens of different diseases (Llewellyn et al., 2017). The establishment of such community dynamics in the development of diseases or susceptibility to transmitted infections is an important goal of further research. The maintenance of stability of microbial communities using pre- or pro-synbiotics can be a powerful tool for mitigating parasitic diseases. The authors emphasize the importance of an integral approach including observations of the changes in the physiological parameters of the host, the parasite, and the microbiome in order to assess their relative roles in changing the disease outcome. The interactions between a parasite, the host, and the host-associated microbiota are increasingly considered to be decisive for disease progression and incidence (Llewellyn et al., 2017).

According to some authors, understanding the interaction between the microbiota and intestinal parasites is interesting in terms of the development of alternative therapeutic methods, which are not based on chemotherapy and do not lead to the development of drug resistance (Ras et al., 2015). In addition, it has been shown that the autochthonous microbiota influences colonization by bacterial, viral, and fungal pathogens. Determination of the mechanisms of these interactions will probably reveal new therapeutic approaches to controlling infectious diseases. At the same time, taking into consideration the current clinical trials using helminths and helminth products, as well as the ability to modulate the function of microbiota using pro-, pre-, and synbiotics, it is important to determine the contribution of microbiota to the interaction with helminths in order to provide synergistic pathways aimed at the treatment for immune dysregulation (Reynolds et al., 2015).

It can be supposed that a holistic understanding of the complex three-way interaction between a host, its

microbiota, and parasites will result in the improvement of animal and human health.

## FUNDING

This work was supported by a State Assignment (topic no. 121051100100-8).

## COMPLIANCE WITH ETHICAL STANDARDS

The author declares that she has no conflicts of interest. This article does not contain any studies involving animals or human participants performed by the author.

## REFERENCES

- Ashour, D.S. and Othman, A.A., Parasite–bacteria interrelationship, *Parasitol. Res.*, 2020, vol. 119, pp. 3145–3164.
- Austin, B., The bacterial microflora of fish, revised. Review article, *Sci. World J.*, 2006, vol. 6, pp. 931–945.
- Bager, P., Kapel, C., Roepstorff, A., Thamsborg, S., Arneved, J., Ronborg, S., Kristensen, B., Poulsen, L.K., Wohlfahrt, J., and Melbye, M., Symptoms after ingestion of pig whipworm *Trichuris suis* eggs in a randomized placebo-controlled double-blind clinical trial, *PLoS One*, 2011, vol. 6, no. 8, article ID e22346, pp. 1–11.
- Berrilli, F., Di Cave, D., Cavallero, S., and D’Amelio, S., Interactions between parasites and microbial communities in the human gut, *Front. Cell. Infect. Microbiol.*, 2012, vol. 2, article ID 141, pp. 1–6.
- Bruno, R., Maresca, M., Canaan, S., Cavalier, J.-F., Mabrouk, K., Boidin-Wichlacz, C., Olleik, H., Zeppilli, D., Brodin, P., Massol, F., Jollivet, D., Jung, S., and Tasiemski, A., Worms’ antimicrobial peptides, *Mar. Drugs*, 2019, vol. 17, no. 9, pp. 1–22.
- Cantacessi, C., Giacomini, P., Croese, J., Zakrzewski, M., Sotillo, J., McCann, L., Nolan, M.J., Mitreva, M., Krause, L., and Loukas, A., Impact of experimental hookworm infection on the human gut microbiota, *J. Infect. Dis.*, 2014, vol. 10, pp. 1431–1434.
- Chen, C.C., Louie, S., McCormick, B.W., Walker, A., and Shi, H.N., Concurrent infection with an intestinal helminth parasite impairs host resistance to enteric *Citrobacter rodentium* and enhances *Citrobacter*-induced colitis in mice, *Infect. Immun.*, 2005, vol. 73, pp. 5468–5481.
- Chen, T.-L., Chen, S., Wu, H.-W., Lee, T.-C., Lu, Y.-Z., Wu, L.-L., Ni, Y.-H., Sun, C.-H., Yu, W.-H., Buret, A.G., and Yu, L.C.-H., Persistent gut barrier damage and commensal bacterial influx following eradication of *Giardia* infection in mice, *Gut Pathogens*, 2013, vol. 5, article ID 26, pp. 1–12.
- Cooper, P., Walker, A.W., Reyes, J., Chico, M., Salter, S.J., Vaca, M., and Parkhill, J., Patent human infections with the whipworm, *Trichuris trichiura*, are not associated with alterations in the faecal microbiota, *PLoS One*, 2013, vol. 8, article ID e76573, pp. 1–12.
- Cuesta-Astroz, Y., de Oliveira, F., Nahum, L.A., and Oliveira, G., Helminth secretomes reflect different lifestyles and parasitized hosts, *Int. J. Parasitol.*, 2017, vol. 47, pp. 529–544.



- Dezfuli, B.S., Bosi, G., DePasquale, J.A., Manera, M., and Giari, L., Fish innate immunity against intestinal helminths, *Fish Shellfish Immunol.*, 2016, vol. 50, pp. 274–287.
- Eckburg, P.B., Bik, E.M., Bernstein, C.N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S.R., Nelson, K.E., and Relman, D.A., Diversity of the human intestinal microbial flora, *Science*, 2005, vol. 308, pp. 1635–1638.
- Fu, P.P., Xiong, F., Feng, W.W., Zou, H., Wu, S.G., Li, M., Wang, G.T., and Li, W.X., Effect of intestinal tapeworms on the gut microbiota of the common carp, *Cyprinus carpio*, *Parasites Vectors*, 2019, vol. 12, article ID 252, pp. 1–11.
- Ghosh, K., Mukherjee, A., Dutta, D., Banerjee, S., Breines, E.M., Hareide, E., and Ringø, E., Endosymbiotic pathogen-inhibitory gut bacteria in three Indian Major Carps under polyculture system: a step toward making a probiotics consortium, *Aquacult. Fish.*, 2020, vol. 6, pp. 192–204.
- Giacomin, P., Agha, Z., and Loukas, A., Helminths and intestinal flora team up to improve gut health, *Trends Parasitol.*, 2016, vol. 32, pp. 664–666.
- Glendinning, L., Nausch, N., Free, A., Taylor, D.W., and Mutapi, F., The microbiota and helminths: sharing the same niche in the human host, *Parasitology*, 2014, vol. 141, pp. 1255–1271.
- Gomaa, E.Z., Human gut microbiota/microbiome in health and diseases: a review, *Antonie Leeuwenhoek*, 2020, vol. 113, pp. 2019–2040.
- Hewitson, J.P., Grainger, J.R., and Maizels, R.M., Review helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity, *Mol. Biochem. Parasitol.*, 2009, vol. 167, pp. 1–11.
- Hewitson, J.P., Harcus, Y., Murray, J., van Agtmaal, M., Filbey, K.J., Grainger, J.R., Bridgett, S., Blaxter, M.L., Ashton, P.D., Ashford, D.A., Curwen, R.S., Wilson, R.A., Dowe, A.A., and Maizels, R.M., Proteomic analysis of secretory products from the model gastrointestinal nematode *Heligmosomoides polygyrus* reveals dominance of venom allergen-like (VAL) proteins, *J. Proteom.*, 2011, vol. 74, pp. 1573–1594.
- Houlden, A., Hayes, K.S., Bancroft, A.J., Worthington, J.J., Wang, P., Grecnis, R.K., and Roberts, I.S., Chronic *Trichuris muris* infection in C57BL/6 mice causes significant changes in host microbiota and metabolome: effects reversed by pathogen clearance, *PLoS One*, 2015, vol. 10, article ID e0125945, pp. 1–25.
- Huang, S.-Y., Yue, D.-M., Hou, J.-L., Zhang, X.-X., Zhang, F., Wang, C.-R., and Zhu, X.-Q., Proteomic analysis of *Fasciola gigantica* excretory and secretory products (FgESPs) interacting with buffalo serum of different infection periods by shotgun LC-MS/MS, *Parasitol. Res.*, 2019, vol. 118, pp. 453–460.
- Izvekova, G.I., Activity of carbohydrases of symbiotic microflora and their role in the processes of digestion in fishes and cestodes parasitizing them (by the example of pike and *Triaenophorus nodulosus*), *Zh. Evol. Biokhim. Fiziol.*, 2005, vol. 41, no. 4, pp. 325–331.
- Izvekova, G.I., Nutritional adaptations in lower cestodes, parasites of fishes, *Usp. Sovrem. Biol.*, 2006, vol. 126, no. 6, pp. 630–642.
- Izvekova, G.I., Functional significance of the intestinal microflora for fishes and cestodes, *Usp. Sovrem. Biol.*, 2008, vol. 128, no. 5, pp. 507–517.
- Izvekova, G.I. and Lapteva, N.A., Microflora of the digestive-transport surfaces of the intestines of the pike and its parasite *Triaenophorus nodulosus* (Pallas, 1781) (Cestoda, Pseudophyllidea), *Biol. Vnutr. Vod*, 2002, no. 4, pp. 75–79.
- Kashinskaya, E.N., Simonov, E.P., Izvekova, G.I., Parshukov, A.N., Andree, K.B., and Solovyev, M.M., Composition of the microbial communities in the gastrointestinal tract of perch (*Perca fluviatilis* L. 1758) and cestodes parasitizing the perch digestive tract, *J. Fish Dis.*, 2020, vol. 43, no. 1, pp. 23–38.
- Khan, A.R. and Fallon, P.G., Helminth therapies: translating the unknown unknowns to known knowns, *Int. J. Parasitol.*, 2013, vol. 43, pp. 293–299.
- Korneva, Zh.V. and Plotnikov, A.O., Symbiotic microflora colonizing the tegument of proteocephalid cestodes and the intestines of their fish hosts, *Parazitologiya*, 2006a, vol. 40, no. 4, pp. 313–327.
- Korneva, Zh.V. and Plotnikov, A.O., Symbiotic microflora colonizing the tegument of *Triaenophorus nodulosus* (Cestoda) and the intestines of its host, pike, *Parazitologiya*, 2006b, vol. 40, no. 6, pp. 535–546.
- Kreisinger, J., Bastien, G., Haufler, H.C., Marchesi, J., and Perkins, S.E., Interactions between multiple helminths and the gut microbiota in wild rodents, *Philos. Trans. R. Soc. London B*, 2015, vol. 370, article ID 20140295, pp. 1–13.
- Van Kruiningen, H.J. and West, A.B., Potential danger in the medical use of *Trichuris suis* for the treatment of inflammatory bowel disease, *Inflamm. Bowel Dis.*, 2005, vol. 11, p. 515.
- Lee, S.C., Tang, M.S., Lim, Y.A.L., Choy, S.H., Kurtz, Z.D., Cox, L.M., Gundra, U.M., Cho, I., Bonneau, R., Blaser, M.J., Chua, K.H., and Loke, P., Helminth colonization is associated with increased diversity of the gut microbiota, *PLoS Negl. Trop. Dis.*, 2014, vol. 8, no. 5, article ID e2880, pp. 1–15.
- Li, R.W., Wu, S., Li, W., Huang, Y., and Gasbarre, L.C., Metagenome plasticity of the bovine abomasal microbiota in immune animals in response to *Ostertagia ostertagi* infection, *PLoS One*, 2011, vol. 6, article ID e24417, pp. 1–10.
- Li, R.W., Wu, S., Li, W., Navarro, K., Couch, R.D., Hill, D., and Urban, J.F., Alterations in the porcine colon microbiota induced by the gastrointestinal nematode *Trichuris suis*, *Infect. Immun.*, 2012, vol. 80, pp. 2150–2157.
- Llewellyn, M.S., Leadbeater, S., Garcia, C., Sylvain, F.E., Custodio, M., Ang, K.P., Powell, F., Carvalho, G.R., Creer, S., Elliot, J., and Derome, N., Parasitism perturbs the mucosal microbiome of Atlantic salmon, *Sci. Rep.*, 2017, vol. 7, article ID 43465, pp. 1–10.
- Loke, P. and Lim, Y.A.L., Helminths and the microbiota: parts of the hygiene hypothesis, *Parasite Immunol.*, 2015, vol. 37, pp. 314–323.
- Maruszewska-Cheruiyot, M., Donskow-Lysoniewska, K., and Doligalska, M., Helminth therapy: advances in the use of parasitic worms against inflammatory bowel diseases and its challenges. Review, *Helminthologia*, 2018, vol. 55, pp. 1–11.
- McKenney, E.A., Williamson, L., Yoder, A.D., Rawls, J.F., Bilbo, S.D., and Parker, W., Alteration of the rat cecal microbiome during colonization with the helminth *Hymenolepis diminuta*, *Gut Microbes*, 2015, vol. 6, pp. 182–193.
- Midha, A., Janek, K., Niewienda, A., Henklein, P., Guenther, S., Serra, D.O., Schlosser, J., Hengge, R., and Hartmann, S., The intestinal roundworm *Ascaris suum* releases antimicrobial factors which interfere with bacterial growth

- and biofilm formation, *Front. Cell. Infect. Microbiol.*, 2018, vol. 8, article ID 271, pp. 1–13.
- Poddubnaya, L.G., Electron microscopic study of the microflora associated with the tegument of the cestode *Eubothrium rugosum*, an intestinal parasite of burbot, *Parazitologiya*, 2005, vol. 39, no. 4, pp. 293–298.
- Poddubnaya, L.G. and Izvekova, G.I., Detection of bacteria associated with the tegument of caryophyllidean cestodes, *Helminthologia*, 2005, vol. 42, no. 1, pp. 9–14.
- Ramanan, D., Bowcutt, R., Lee, S.C., Tang, M.S., Kurtz, Z.D., Ding, Y., Honda, K., Gause, W.C., Blaser, M.J., Bonneau, R.A., Lim, Y.A.L., Loke, P., and Cadwell, K., Helminth infection promotes colonization resistance via type 2 immunity, *Science*, 2016, vol. 352, pp. 608–612.
- Ranganathan, S. and Garg, G., Review secretome: clues into pathogen infection and clinical applications, *Genome Med.*, 2009, vol. 1, article ID 113, pp. 1–7.
- Ras, R., Huynh, K., Desoky, E., Badawy, A., and Widmer, G., Perturbation of the intestinal microbiota of mice infected with *Cryptosporidium parvum*, *Int. J. Parasitol.*, 2015, vol. 45, pp. 567–573.
- Rausch, S., Held, J., Fischer, A., Heimesaat, M.M., Kuhl, A.A., Bereswill, S., and Hartmann, S., Small intestinal nematode infection of mice is associated with increased enterobacterial loads alongside the intestinal tract, *PLoS One*, 2013, vol. 8, pp. 1–13.
- Rausch, S., Midha, A., Kuhring, M., Affinass, N., Radonic, A., Kuhl, A.A., Bleich, A., Renard, B.Y., and Hartmann, S., Parasitic nematodes exert antimicrobial activity and benefit from microbiota-driven support for host immune regulation, *Front. Immunol.*, 2018, article ID 92282, pp. 1–12.
- Reddy, M.V.R., Immunomodulators of helminthes: promising therapeutics for autoimmune disorders and allergic diseases, *Indian J. Clin. Biochem.*, 2010, vol. 25, pp. 109–110.
- Reynolds, L.A., Smith, K.A., Filbey, K.J., Harcus, Y., Hewitson, J.P., Redpath, S.A., Valdez, Y., Yebra, M.J., Finlay, B.B., and Maizels, R.M., Commensal-pathogen interactions in the intestinal tract lactobacilli promote infection with, and are promoted by, helminth parasites, *Gut Microbes*, 2014, vol. 5, pp. 522–532.
- Reynolds, L.A., Finlay, B.B., and Maizels, R.M., Cohabitation in the intestine: interactions among helminth parasites, bacterial microbiota, and host immunity, *J. Immunol.*, 2015, vol. 195, pp. 4059–4066.
- Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I., and Tuohy, K., Gut microbiota functions: metabolism of nutrients and other food components, *Eur. J. Nutr.*, 2018, vol. 57, pp. 1–24.
- Sewell, D.L., Reinke, E.K., Hogan, L.H., Sandor, M., and Fabry, Z., Immunoregulation of CNS autoimmunity by helminth and mycobacterial infections, *Immunol. Lett.*, 2002, vol. 82, pp. 101–110.
- Summers, R.W., Elliott, D.E., Urban, J.F., Thompson, R.A., and Weinstock, J.V., *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial, *Gastroenterology*, 2005, vol. 128, pp. 825–832.
- Tarr, D.E.K., Nematode antimicrobial peptides, *Invertebr. Surv. J.*, 2012, vol. 9, pp. 122–133.
- Walk, S.T., Blum, A.M., Ewing, A.-S., Weinstock, J.V., and Young, V.B., Alteration of the murine gut microbiota during infection with the parasitic helminth *Heligmosomoides polygyrus*, *Inflamm. Bowel. Dis.*, 2010, vol. 16, pp. 1841–1849.
- Weng, M., Huntley, D., Huang, I.F., Foye-Jackson, O., Wang, L., Sarkissian, A., Zhou, Q., Walker, W.A., Cherayil, B.J., and Shi, H.N., Alternatively activated macrophages in intestinal helminth infection: effects on concurrent bacterial colitis, *J. Immunol.*, 2007, vol. 179, pp. 4721–4731.
- Wolff, M.J., Broadhurst, M.J., and Loke, P., Helminthic therapy: improving mucosal barrier function, *Trends Parasitol.*, 2012, vol. 28, pp. 187–194.
- Wu, S., Li, R.W., Li, W., Beshah, E., Beshah, E., Dawson, H.D., and Urban, J.F., Jr., Worm burden-dependent disruption of the porcine colon microbiota by *Trichuris suis* infection, *PLoS One*, 2012, vol. 7, no. 4, article ID e35470, pp. 1–9.
- Zaiss, M.M. and Harris, N.L., Interactions between the intestinal microbiome and helminth parasites, *Parasite Immunol.*, 2016, vol. 38, pp. 5–11.
- Zaiss, M.M., Rapin, A., Lebon, L., Dubey, L.K., Mosconi, I., Sarter, K., Piersigilli, A., Menin, L., Walker, A.W., Rougemont, J., Paerewijck, O., Geldhof, P., McCoy, K.D., Macpherson, A.J., Croese, J., Giacomini, P.R., Loukas, A., Junt, T., Marsland, B.J., and Harris, N.L., The intestinal microbiota contributes to the ability of helminths to modulate allergic inflammation, *Immunity*, 2015, vol. 43, pp. 998–1010.

Translated by E.V. Makeeva