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REVIEW ARTICLE

Human Intestinal Microbiota: Interaction Between Parasites and the Host Immune Response

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The human gut is a highly complex ecosystem with an extensive microbial community, and the influence of the intestinal microbiota reaches the entire host organism. For example, the microbiome regulates fat storage, stimulates or renews epithelial cells, and influences the development and maturation of the brain and the immune system. Intestinal microbes can protect against infection by pathogenic bacteria, viruses, fungi and parasites. Hence, the maintenance of homeostasis between the gut microbiota and the rest of the body is crucial for health, with dysbiosis affecting disease. This review focuses on intestinal protozoa, especially those still representing a public health problem in Mexico, and their interactions with the microbiome and the host. The decrease in prevalence of intestinal helminthes in humans left a vacant ecological niche that was quickly occupied by protozoa. Although the mechanisms governing the interaction between intestinal microbiota and protozoa are poorly understood, it is known that the composition of the intestinal bacterial populations modulates the progression of protozoan infection and the outcome of parasitic disease. Most reports on the complex interactions between intestinal bacteria, protozoa and the immune system emphasize the protective role of the microbiota against protozoan infection. Insights into such protection may facilitate the manipulation of microbiota components to prevent and treat intestinal protozoan infections. Here we discuss recent findings about the immunoregulatory effect of intestinal microbiota with regards to intestinal colonization by protozoa, focusing on infections by *Entamoeba histolytica*, *Blastocystis* spp, *Giardia duodenalis*, *Toxoplasma gondii* and *Cryptosporidium parvum*. The possible consequences of the microbiota on parasitic, allergic and autoimmune disorders are also considered.

Key Words: Intestinal parasites, Dysbiosis, Protozoa, Immune response, Cell interactions, Inflammation.

Epidemiological Considerations of Parasites

During the 1990's, great efforts were taken to control and reduce infections caused by soil-transmitted helminths in schoolchildren. The most severe consequences of worm infections are seen in young children who can die of acute roundworm obstruction of the gut and severe malnutrition. During the second half of the 20th Century, World Health Organization (WHO) developed effective community-based treatment programs in various developing countries around the world (Sub-Saharan Africa, Asia, Latin America and Caribbean countries). These programs had different results depending on resources available for its implementation. However, reports clearly show the reduction of

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morbidity rates of soil transmitted-helminthes, intestinal nematodes and roundworm parasites worldwide.

This program was also implemented in Mexico. After 1995, when this program began, the incidence rate of nematode infections decreased considerably, and in some geographic areas of Mexico had almost disappeared (http://www.dgepi.gob.mx). The empty ecological niche left by this change has been occupied by other commensal or pathogenic intestinal protozoa (1).

Globally, the most prevalent pathogenic protozoa are (in order of frequency of infection): *Blastocystis* spp (2−70%), *Giardia duodenalis* (5−20%), the *Entamoeba histolytica/E. dispar* complex (2−21%), and *Cryptosporidium* spp (1−17%) (2−4). The latter is a neglected parasite previously considered as opportunistic, affecting only immunocompromised patients. It is now one of the most frequent parasites detected in children under five who suffer from diarrhea. Whereas the prevalence of infection in Mexico of *Cryptosporidium* is around 3%, recent studies in developed countries have found that there might be slight differences in the frequency of intestinal parasitic infections, depending on sociodemographic and cultural characteristics of particular communities (5−8).

In general, intestinal parasitic infections due to protozoa represent a key component of the burden of infectious disease worldwide, constituting an important public health problem in most underdeveloped countries. However, these diseases remain a neglected issue in extended geographic areas. Since the composition of the intestinal bacterial population modulates the progression of protozoan, the regulation of different components of the microbiota could be used to prevent or attenuate intestinal protozoan infection and ultimate outcome of parasitic disease. Parasites and microbes have co-evolved together throughout evolution. For that reason, bacteria and parasites display complex interactions in the human mucosa. Since the underlying mechanisms remain poorly understood, the aim of the present review is to summarize recent findings in this area (9,10).

General Characteristics of Intestinal Microbiota

Fecal and metagenomic studies have revealed that the healthy intestinal microbiota is a complex ecological community of trillions of microorganisms, containing viruses, bacteria, protozoa and fungi. These microorganisms interact with the intestinal mucosa and carry out critical physiological functions for the host (11). The intestinal microbiota has coevolved with the intestinal immune system of the human host, maintaining a mutualistic host-microbial relationship. It has a significant influence on the maturation, development and modulation of the intestinal immune response, regulating the expression of immune mediators as well as the development, recruitment and differentiation of local immune cell populations (12,13).

The intestinal microbiota is highly diverse and varies over time as well as between individuals and regions of the intestine. Despite the large number of distinct bacterial taxa, they belong to a comparatively small number of phyla. Bacteroidetes and Firmicutes are the most abundant taxa in the intestinal microbiota (14). As with other elements of the microbiota, the relative levels of their respective populations are variable between individuals. The structure of the microbial community is a vital factor for host immunity under certain environmental contexts. Disruption of the microbiota from the normal balance and its interaction with the immune system can upset host homeostasis and susceptibility to disease, and thus determine the outcome of infections by intestinal pathogens. An imbalance in the population structure of the intestinal microbiota is called dysbiosis (15−17).

The application of high-throughput approaches, including next generation sequencing of the small subunit ribosomal RNA (16s rRNA), has led to a revolution in the identification of intestinal microbiota components. It is now known that approximately 500−1000 bacterial species inhabit the human adult intestine, the predominant genera being *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Peptococcus*, *Peptostreptococcus*, *Lactobacillus* and *Ruminococcus* (18).

Parasites (particularly intestinal parasites) are ancient in evolution. Although parasites have co-evolved with the human host, there is a relatively small number to which we are exposed. Helminths, for example, show a strong immunoregulatory activity, as do some bacteria of the intestinal microbiota. Thus, these parasites can modify the structure of intestinal microbiota, colonize this organ, and persist among the distinct populations of microorganisms (19−22). On the other hand, certain compositions of the bacterial community of microbiota are able to impede gut colonization by helminths, or prevent their persistence in case of colonization (23).

The interaction of intestinal parasites with the bacterial community of the gut microbiota forms a complex interacting system. Any modification of the microbiota has an effect on the host immune response, in part because these parasites and microbiota metabolize substrates in an interactive fashion and generate products that affect one another. The products of the microbiota may interfere with the survival and physiology of different parasites and consequently with the outcome of many parasitic infections (24). Likewise, intestinal parasites (both helminths and protozoa) continually secrete molecules that may change the environment and therefore cause an alteration in the structure of the gut microbiota (25). It is important to conceptualize the intestinal environment as an ecosystem in which biological and biochemical interactions occur at various organizational levels between the parasites, the microbial communities, and the host immune response (26,27).