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LETTER TO THE EDITOR

Intestinal inflammation and the microbiota: Beyond diversity

Gabriela Gama Freire Alberca, Naiane Samira Souza Cardoso, Rosa Liliana Solis-Castro, Viviane Nakano, Ricardo Wesley Alberca

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Abstract

The recent manuscript entitled "Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis" reported a difference in the intestinal microbiota of patients with ulcerative colitis according to the severity of the colitis. The influence of the intestinal microbiota on the development and progress of gastrointestinal disorders is well established. Besides the diversity in the microbiome, the presence of virulence factors and toxins by commensal bacteria may affect an extensive variety of cellular processes, contributing to the induction of a proinflammatory environment.

Key Words: Inflammation; Microbiota; Toxins; Intestinal; Ulcerative; Colitis; Cancer

Core Tip: The manuscript entitled "Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis" and previous investigations have identified alterations in the intestinal microbiome of patients with inflammatory bowel disease, ulcerative colitis, and colorectal cancer. The microbiota composition impacts the development of inflammatory disorders. Nevertheless, investigations should focus on identifying alterations not only on the diversity of the microbiota but the presence of the toxin-producing bacteria. Further investigations should investigate alterations in the microbiota composition and the production of toxins by commensal bacteria such as *Escherichia coli*, *Clostridium perfringens*, and *Bacteroides fragilis*.

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TO THE EDITOR

We read with great interest the manuscript entitled "Relationship between clinical features and intestinal microbiota in Chinese patients with ulcerative colitis" published by He *et al*[1] in the World Journal Gastroenterology. He *et al*[1] performed an investigation on the microbiota composition on the fecal and mucosa samples from patients with ulcerative colitis. Their work reinforces the importance of the microbiota on the inflammatory process and gastrointestinal disorders. Importantly, the manuscript provided information on the composition of the gastrointestinal microbiota of patients with ulcerative colitis of various severity and patients without ulcerative colitis[1]. We would like to raise a few considerations regarding the microbiota and gastrointestinal inflammatory disorders.

The microbiota is an ecosystem in constant regulation, influenced by the diet, antibiotics, sanitary conditions, environmental stimulus, and the host's immune system[2]. The gastrointestinal tract is the largest reservoir of bacteria in the human body and shapes both the local and systemic immune responses[3-5]. The microbiome influences the maturation and development of the host's immune system[6], regulating the development of food tolerance, response to inflammation, infections, vaccination, and metabolism[7,8]. Importantly, the microbiota directly influences the development of the inflammatory process independent of dietary intake[9], and abrupt alterations in the microbiota composition can result in an inflammatory insult[10]. He *et al*[1] identified an increase in *Escherichia* and *Shigella* in patients with ulcerative colitis in comparison to patients without ulcerative colitis[1]. *Escherichia* and *Shigella* has been implicated in a reduction in the response to anticoagulation therapy and could impact the treatment of patients with gastrointestinal disorders and under anticoagulation therapy such as coronavirus disease 2019 patients[11-14].

Shiga toxin-producing *Shigella* species and *Escherichia coli* are considered pathogenic, associated with diarrhea and colitis[15]. These toxins can induce the activation of the NOD-like receptor protein 3 inflammasome, inducing the production of interleukin (IL)-1β and IL-18 and cellular death by pyroptosis[16]. The virulence of Shiga-toxin-producing *Escherichia coli* can lead to diarrheal sicknesses and death[17,18]. Shiga-toxins can be encapsulated within microvesicles and influence the inflammatory response in other organs, such as the kidneys[19]. Shiga toxin-producing *Escherichia coli* (O26:H11 strain 97-3250 and O145:H28 strain 4865/96) induces a greater production of chemokines and cytokines, such as IL-8 and IL-1β, in comparison to *Escherichia coli* (O9:H4 strain HS)[20].

The complex symbiotic interaction between the microbiota and the host is mediated by an equilibrium in the tolerance and inflammatory response to microbial products in the gut[6]. He *et al*[1] did not identify an increase in other strains in patients with ulcerative colitis. Nevertheless, in addition to the microbiota composition, certain commensal bacteria, such as *Clostridium perfringens* and *Bacteroides fragilis*, can express a wide range of toxins and metabolic compounds to induce inflammation [21-23]. *Clostridium perfringens* is a gram-positive anaerobic bacteria, commonly in the environment and is part of the resident microbiota but can become virulent by the expression of toxin genes[24,25]. *Clostridium perfringens* can produce over 20 toxins including alpha (α), beta (β), epsilon (e), enterotoxins, and hydrolytic enzymes[26-29]. These toxins can damage and kill intestinal cells, disturb the epithelial barrier, and induce proinflammatory and propathogenic milieu[26,30,31].

The alpha toxin produced by *Clostridium perfringens* is a zinc-dependent metalloenzyme, is able to rupture the plasma membrane of the host's cells[25,32], induces an immature profile in the host's innate immune response (neutrophils), and is involved in the formation of myonecrosis in animals, including humans[33,34]. The β toxin is a pore-forming toxin associated with hemorrhagic diarrhea[35]. *Clostridium perfringens* with the expression of α and β toxins is associated with necrotic enteritis in animals and humans[36-38]. The e toxin is also pore-forming and is involved in intestinal and neurological diseases in humans[39-43].

In addition, *Clostridium perfringens* is able to produce several other toxins such as enterotoxins[44-46], NetB[47,48], and TpeL[49,50], which can induce inflammatory responses, biofilm formation, and chronically disrupt the intestinal epithelium[44,47,50]. *Bacteroides fragilis,* another resident bacteria, can produce a zinc-dependent metalloprotease called fragilisyn[51]. Fragilisyn-producing *Bacteroides fragilis* are named *Enterotoxigenic Bacteroides Fragilis* (ETBF)[52]. ETBF toxin is coded by the *bft* gene and is highly correlated with diarrhea in humans[53,54]. ETBF can cleave E-cadherin in the epithelial cells, allowing bacterial translocation[55,56]. ETBF induces an IL-17-mediated immune response with the infiltration of lymphocytes and neutrophils and damages the DNA *via* the formation of microadenoma [4,53,54]. In addition, the inflammatory process may be mediated by several bacteria. For example, in the "driver-passenger" model, the colonization by one bacteria may facilitate the expansion and proinflammatory action of another microorganism[55].

A recent manuscript by Avril and DePaolo[56], identified that the co-colonization of ETBF and *Escherichia coli* strains, harboring the pks island, promotes the development of intestinal cancer. ETBF promotes the degradation of the intestinal mucus and induction of IL-17-mediated inflammation by the host's immune cells. This process enables the adherence of *Escherichia coli* to the intestinal wall, releases colibactin, and promotes cancer development[56]. Therefore, quantitative analyses are important to characterize the composition of the microbiota in several diseases and aid in the design of possible interventions to modulate the immune response of the host in microbiota-mediated inflammatory disorders[1]. Nevertheless, due to the potential pathobiont role of several resident bacteria, investigations on toxin-producing bacteria are crucial for an overall interpretation of the role of the microbiota on gastrointestinal disorders.

FOOTNOTES

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