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Microbiota: the missing link in the etiology of inflammatory bowel disease

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ABSTRACT

Within its twisted and tight walls, where a hostile and arid environment prevails, the lumen of the digestive tract nests a true microuniverse called the microbiota. The existing relationship between humans and these microorganisms is one in which both benefit, creating a condition called Eubiosis.

The dynamic relationship existing between the microbiota and the human body can be affected at various times, leading to an imbalance that may have important implications on health and generating a condition called Disbiosis.

Recent studies have highlighted possible links between several diseases with incompletely elucidated etiology and disturbances of the microbiota. In this review we aim to analyze the existing relationship between the imbalances of the gastrointestinal flora and the etiopathogeny inflammatory bowel diseases, a group of diseases whose incidence has increased considerably in recent years.

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Introduction

There are over 100 trillion microorganisms at the level of the gastrointestinal tract (GI), which make up a complex biosystem called the microbiota. The composition of the microbiota is vast, containing entities belonging to all domains of life: Eukarya Bacteria and Archaea. Broadly, the main components that make up the structure of this microuniverse belong to the bacteria group and are represented by species from four major phyla: Actinobacteria, Proteobacteria, Bacteroidetes, and Firmicutes [1].

Between the human body and the microbiota is established a dynamic and very complex relationship, alteration of this biosystem sometimes causing adverse consequences on the health status. The functions of the GI flora depend on its composition/ biocharacteristics of the species, having implications for the following processes: modulation of the digestion process, regulation of immunity, biosynthesis of vitamins, and harvesting energy [2-6].

Alteration of the structure - and thus of the function- of the microbiota bears the name of dysbiosis, a condition linked to numerous pathological conditions such as type 2 diabetes, obesity, cancer, autoimmune disorders, and allergies [7-13].

Inflammatory bowel diseases (IBD) represent a set of gastrointestinal disorders with incompletely elucidated etiology, which includes two distinct clinical and pathological entities: Crohn's disease (CD) and Ulcerative Colitis (UC). IBD are characterized by inflammatory impairment of the digestive tract, which present an undulating evolution consisting of periods of remission and relapse [14].

Discussions

IBD: Overview

IBD usually refers to two chronic pathological conditions, represented by Crohn's Disease and Ulcerative Colitis. The main feature of IBD consists of inflammation, which can be localized at any level of the digestive tract.

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The clinical manifestations of these conditions are dominated by gastrointestinal symptoms, ranging from diarrhea to malabsorption, loss of nutrients as well as digestive bleeding due to inflammation. These symptoms are often accompanied by abdominal pain, severity ranging from mild to severe (life-threatening) according to the degree of the local/ intestinal inflammatory process. The inflammation has generally a chronic clinical evolution, marked by an alternation of remissions and exacerbations [15].

The incidence and prevalence of these diseases are globally increasing, the countries with the highest values being those that are highly developed and industrialized, such as North America and Northern Europe. Recent investigations show that the incidence is stabilising or slightly decreasing in developed countries, being conversely rapidly increasing in countries that are in the full process of industrialization, urbanization, and westernization, such as in Asia, South America, and Africa [16,17].

Microbiota and IBD

The etiology and pathophysiology of IBD are not completely elucidated. IBD results from the complex interaction of environmental and intestinal microbial factors within a organism that has a genetic susceptibility, which ultimately results in an abnormal immune response partly disconnected from its own regulatory mechanisms (Figure 1) [18].

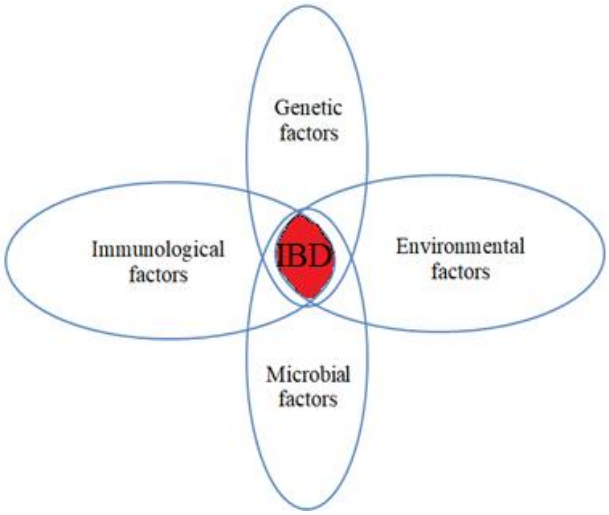

Figure 1. Interaction of factors that are contributing to IBD occurrence.

Recently, more emphasis has been placed on the interaction between the intestinal flora and the host's immune system, the presence of microorganisms at intestinal level being a key element (if not mandatory) in the genesis of this pathology [19]. The loss of tolerance for intestinal bacteria (which triggers an immune response) may be one of the main explanations for pathogenesis of these diseases [20]. This pathological process may be strongly influenced by alteration in the composition, structure, and function of the gut microbiota, a condition referred to as dysbiosis. These assumptions are indirectly supported by the positive results (good control of intestinal inflammation) obtained after administration of gut flora regulators such as probiotics, prebiotics, and antibiotics [21].

An important quantitative change found in the intestinal flora of IBD patients is reduction of the bacterial load and reduction of its diversity [22], the reduction of diversity being described within the same individual, in the same digestive segment, and between the areas affected by the inflammatory process and the healthy ones [23].

The main qualitative changes in the composition of the microbiota are represented in IBD patients by increases and decreases of certain bacterial populations. An important change in this balance is represented by an increase of the harmful bacteria and a reduction in the population of bacteria with a protective role on the digestive tract.

The reduction of protective bacterial species is usually related to the following populations: gram-positive bacterias (species from phyla Firmicutes), butyrate-producing bacterias (Roseburia, Faecalibacterium prausnitzii), and general protective species (from the genus Bifidobacterium) [24, 25]. These changes are significant because all of these species play an important role in maintaining the intestinal homeostasis through a range of functions, such as: production of short chain fatty acids, strengthening the intestinal barrier, reduction of local and systemic inflamation, and protection from pathogenic species of bacteria. The protective role of these microorganisms in the pathophysiology of IBD is supported by multiple research studies. As an example, some studies have shown that chemically induced intestinal inflammation induces clinical manifestations that are more pronounced in mice with a sterile gut, than in conventional mice having a digestive tract populated with microorganisms [26].

The populations of harmfull bacterial species found to be increased in IBD patients are represented by several gram-negative bacteria (such as Proteobacteria, Pasteurellaceae) and various opportunistic pathogens (Escherichia coli, Fusobacteria, etc.), all these species having as the main characteristic a proinflammatory effect that is present both locally and systemically [27].

The manner in which the altered bacterial population interacts with the internal environment (leading thus to pathogenesis of IBD) is incompletely elucidated, but their presence is quite well documented. In support of this, a recent study proved that mice with a sterile gut do not develop colitis, and this is possible only through insertion of fecal matter containing bacteria [28].

Several mechanisms have been proposed to explain the role of an altered intestinal microbiota in the development of

the inflammatory process that is associated with inflammatory bowel diseases. Such mechanisms are represented by an increase in intestinal permeability leading to bacterial translocation, synthesis of toxic products that migrate into the internal environment due to increased intestinal permeability (generating thus endotoxinemia), disturbance of intestinal cell's endoplasmic reticulum homeostasis, and oxidative stress.

The increase in intestinal permeability could be a consequence of reduction of the population of short-chain fatty acid-producing bacteria. Endotoxinemia is caused by production of toxic substances by bacteria (such as Escherichia coli, Proteobacteria, Pasteurellaceae), migration of toxic compounds being favored by the deficient intestinal barrier. The functional alteration of the endoplasmic reticulum can be induced by different bacterial species' production of various toxic substances, which enter the intestinal epithelial cells and are able to interfere with the functionality of the endoplasmic reticulum (e.g. Escherichia coli). Some species of bacterias (Escherichia coli, Helicobacter pylori) can produce reactive oxygen, causing oxidative stress in the digestive tract and thus contributing to the maintenance of the inflammatory process [29].

In addition to bacterial abnormalities described for IBD, it appears that intestinal viral and fungal populations also exhibit a number of alterations, even if they represent an extremely small part of the microbiota composition.

Regarding the changes found in the fungal population, species belonging to the classes Basidiomycota, Candida albicans, and Ascomycota have been found to be increased, while the Saccharomyces cerevisiae population seems to be decreased. The role of the fungal implication in pathophysiology of IBD is incompletely elucidated, literature data showing that molecules present on the fungal wall surface (beta-glucans, chitin) are able to trigger the innate immune response and thus to contribute to maintenance of the inflammatory process [30].

The intestinal viral population of IBD patients is characterized by a greater variability, with the expansion of the bacteriophage-type population [31]. A recent study revealed an increased bacteriophages class from the order Caudovirales. At the level of the digestive tract, the bacteriophages contribute not only to the maintenance of bacterial homeostasis but also to the modulation of the immune response. Even so, there is currently not enough evidence to suggest that intestinal viral microbiota play an essential role in the development and evolution of IBD [32].

Highlights

At the level of the gastrointestinal tract there are over 100 trillion microorganisms that make up the microbiota.

Alteration of the structure and the function of the microbiota, known as dysbiosis, has been linked to numerous pathological conditions such as type 2 diabetes, obesity, cancer, autoimmune disorders, and allergies.

Inflammatory bowel diseases result from the complex interaction of environmental and intestinal microbial factors, within an organism that generally has a genetic susceptibility.

The loss of tolerance for intestinal bacteria (which often triggers an immune response) may be one of the main explanations in the pathogenesis of this disease.

Some changes encountered in composition of the microbiota are characterised by an increase/ abundance of the harmful bacteria, and a reduction in the population of bacteria with a protective role on the digestive tract.

Conclusions

IBD is a group of diseases whose incidence is still increasing. With multiple complications and comorbidities, and often debilitating clinical manifestations, IBD causes a marked decrease in patients' quality of life. The etiology and pathogenesis of these diseases are incompletely elucidated, the new researches emphasizing an important role of the gut microbiota in the occurrence and progression of such inflammatory diseases. Modulation of the composition and structure of the commensal flora through multiple therapeutic pathways (like probiotics, prebiotics, antibiotics, and fecal transplantation) can determine positive results and provide a better perspective for these digestive conditions.

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