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Minireview

GUT MICROBIOTA IN METABOLIC AND INFLAMMATORY DISEASES

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Abstract

Human body is colonized by more than 5000 different bacteria species living in symbiosis with the host. Most of them, however, inhabit intestinal tract and perform vital functions for the host, as metabolism, differentiation of gut epithelium, modulation of immune system. Many factors can influence equilibrium of normal flora and, among these, host genetic features, nutrients, lifestyle. Pathogenesis of several bowel and metabolic disorders is not well elucidated. Application of omics sciences for molecular characterization of gut microbiota is proving the high impact of gastrointestinal bacteria in development of inflammatory bowel diseases, as Crohn disease, and metabolic disorders, like diabetes mellitus and obesity. Here we focused on the main pathological conditions, with particular attention to the role of microbiota.

Keywords

gut microbiota, inflammatory bowel diseases, metabolic diseases, bacterial molecular characterization

The Human Gut Microbiota

Human gut microbiota comprises bacteria but also fungi, viruses, bacteriophages and helminths that are essential for the regular digestive functions. Clearly, the most well characterized are the bacterial species. About 1,000 bacterial species were found to colonize human bowel and, of these, each person carries about 160 species, with no uniform distribution among the different tracts, for a total of 3.8×10^{13} bacteria. This distribution tends to remain constant during life. However, several factors can alter this equilibrium and they include genetic factors, like some loci of the Major Histocompatibility Complex, drugs, as antibiotics, and sudden dietary changes. Four phyla are mainly represented and they are *Bacteroidetes, Firmicutes, Proteobacteria* and *Actinobacteria* although a high rate of interindividual variability was observed. Only less of 50 species are common to the individuals [1]. Molecular characterization of bacterial species is highly performing conducted by high throughput sequencing technologies that allow to sequence the entire pool of bacteria colonizing human gut. Differential analysis is based on 16S rRNA sequence comparison and metagenomics is the term used to indicate the analytical workflow, form the experimental to the data elaboration phases. This approach is based on the evidence that bacterial genes encoding for 16S rRNA differ also among strains belonging to the same species. Two big projects aim to collect data generated from high throughput sequencing and these are the Human Microbiome Project (HMP) consortium funded by The United States National Institutes of Health (NIH), and the MetaHIT (Metagenomics of the Human Intestinal Tract) consortium funded by the European Commission. Gut bacteria catalyze many enzymatic reactions making digestible lots of metabolites introduced with diet. They act anaerobic fermentation of fiber carbohydrates, producing short chain fatty acids and provide to their oxidation, metabolize choline and other molecules. Moreover, microbiota is involved in synthesis of several vitamins, as B12 and K [2]. Surprisingly, a role in immunoglobulin chain rearrangements and in early development of B

cells was reported. Spectacularly, existence of a gut-brain axis was described and this link is mediated by gut microbiota and it consists of several biochemical signals transmitted from the gut to the brain and they are essential for the healthiness of the brain [3]. Since gut bacteria are involved in metabolic transformations and energy harvest, they have been reported as a biotic factor regulating body weight, potentially linked to a risk of obesity and other metabolic disorders, also of autoimmune ones [4]. Alteration in microbial community is called "microbiota dysbiosis" and it is involved in development of both intestinal and systemic diseases, as cardiovascular and neurodegenerative diseases, and cancers.

Microbiota dysbiosis

The term dysbiosis indicates the imbalance condition that comes from alteration of normal gut bacterial flora. Association between dysbiosis and bowel inflammation is today well known. Among all pathological condition affecting intestinal tract, certainly irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease, obesity and colorectal cancer are tightly linked to alteration of microbiota [5].

Irritable Bowel Syndrome

IBS is a multifactorial condition characterized by an increased growth of *Enterobacteriaceae* and a reduction of *Bifidobacteria* and *Lactobacillus*. Dysbiosis can result by nervous disorders as anxiety that induce the gastrointestinal epithelium to releases inflammatory cytokines [6]. In this context, gut – brain axis play essential role and intestinal symptoms result from somatisation of psychic disorders [7].

Inflammatory Bowel Disease

IBD comprises all pathological conditions characterized by chronic inflammation status, as Crohn's disease and ulcerative colitis. Their incidence is increasing growing and in Europe affected patients reach 2.2 million. IBD usually causes relapsing diarrhoea and abdominal pain. Microbiota of the patients shows an increased growth of *Proteobacteria*, *Actinobacteria* and *Enterobacteriaceae*, while *Faecalibacteria* result reduced. This switch is probably due to microenvironment caused by phlogosis [8]. Dysbiosis probably results from excessive response of immune host defence against gut bacteria, as consequence of the presence of genetic risk factors, and causes impairment of intestinal barrier. Moreover, inflammatory cytokines contribute to damage gut epithelium [9]. While little is known about genetic risk factors that predispose to ulcerative colitis, Crohn's disease is known that arises due to mutations at *NOD2* gene. *NOD2* encodes for a protein involved in the immune response to intracellular bacterial lipopolysaccharides by recognizing the muramyl dipeptide derived from them, activation of the NFKB protein with consequent alteration of intraepithelial autophagy. Alteration of cytokine expression patterns resulted by the translocation of enteric bacteria into the lamina propria, following *NOD2* mutations [10]. Other loci potentially involved in Crohn's disease development include interleukin 23 (*IL-23*), the autophagy related protein 16-like 1 (*ATG16L1*), the immunity-related GTPase family M (*IRGM*) and the Toll-like receptors *TLR-3* and *TLR-4* [11]. TLRs are expressed on neurons of enteric nervous system and interact with bacteria acting as signalling transmitter from bacteria to brain. Although several aspects of IBD are clarifying, is not yet defined if dysbiosis is a cause or a consequence of phlogosis status.

Obesity and Diabetes Mellitus Type 1 and 2

Obesity is a metabolic disorder caused by the imbalance between introduced and consumed calories and affects more than 600 million individuals. The data is provided by the World Health Organization (WHO) and its frequency is estimated to grow. WHO defines obese an individual having a Body Mass Index ≥ 30kg/m2. Clearly, the main risk factors for develop obesity are the unhealthy diet and the sedentary lifestyle. However, also hormonal imbalance, genetic factors as genes encoding for enzymes involved in metabolism, and microbiota can contribute such fatty acids and carbohydrates and dysbiosis is often guilty of insulin resistance in obese patients [12]. Insulin-resistance, moreover, is often observed in patients affected by diabetes mellitus type 2 (T2D) [13]. Diabetes mellitus type 1 (T1D) and 2 (T2D) are the most common metabolic disorders. Their pathogenesis differs, being type 1 an autoimmune condition with well-known genetic bases, while type 2 characterized by insulin resistance. The two different diabetes types show distinct microbiota alterations. In T1D a reduction of the normal flora is observed at the early stage of the disease and it leads to a leaky

gut most permeable, with consequent increase of phlogosis rate. In contrast, T2D patients show an increased presence of Gram-negative opportunistic pathogens that activate TLR-4 receptors, leading to the insulin-resistance [14].

Celiac Disease

Celiac disease is an autoimmune chronic disorder that leads to damage of the small intestine, after ingestion of gluten. Celiac disease is hereditary and people with a first-degree relative with celiac disease have a 1 in 10 risk of developing celiac disease. Its worldwide incidence is more than 1%. Although genetic bases are well confirmed, also microbiota can contribute to disease onset. Dysbiosis is frequent in patients harbouring genetic rick factors and causes sensitization to gluten. Genetic risk factors include specific alleles of Histocompatibility Major Complex, like HLA-DQ2 and/or HLA-DQ8 [15]. In celiac patients, ingestion of gluten causes activation of T cells with consequent release of cytokine that damage intestinal epithelial villi. Following these events, Gram-positive bacteria decrease while the number of Gram-negative increases, contributing to further epithelial damage.

Colorectal Cancer

Colorectal cancer is the most frequent neoplastic disease and is the 4th cause of mortality in developed countries. Although genetic syndromes are reported, the most cases arise sporadically. While there are several evidences that show association of infection by *Helicobacter pylori* with development of gastric carcinoma, role of gut microbiota in colorectal cancer pathogenesis is to date not clear [16]. However, an increased rate of *Fusobacteria* is recurrent in microbiota of affected patients and it is probably due to microenvironment created by malignant cells. A pathogenic role was attributed to fragilis enterotoxin (BFT), secreted by *Bacteroides fragilis*, also increased in patients [17].

Conclusions

As briefly reported, gut microbiota perform essential functions for maintaining the host healthy. Bacterial equilibrium, however, is easy to perturb. Chronic inflammation stimuli, together with genetic predisposing factors, can lead to the development of intestinal inflammation conditions that, prolonged in time, may culminate in real pathological conditions. Therefore, intestinal inflammatory diseases are the result of interaction of the host with environment and gut micro-environment. To determinate gut micro-environment can contribute the diet, the assumption of drugs such as antibiotics. An excess of antibiotics assumption was related to a drastic reduction of microbiota population [18]. However, if microbiota participates to pathogenesis or its alteration is a consequence of phlogosis status needs to be clarified in order to better manage patient care. Moreover, the wide knowledge of affected bacterial species can help to direct the therapy with specific probiotics.

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