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Review

Digestive disorders and Intestinal microbiota

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Summary. In the last decade, a barge body of scientific literature has suggested that specific alterations of the gut microbiota may be associated with ther development and clinical course of several gastrointestinal diseases, including irritable bowel syndrome, inflammatory bowel disease, celiac disease, gastrointestinal cancer and *Clostridium difficile* infection. These alterations are often referred to as "dysbiosis", a generic term designing reduction of gut microbiota biodiversity and alterations in its composition. Here, we provide a synthetic overview of the key concepts on the relationship between intestinal microbiota and gastrointestinal diseases, focusing on the translation of these concepts into clinical practice. (www.actabiomedica.it)

Key words: dysbiosis, microbiome, IBD, celiac disease, *Clostridium difficile*

Dysbiosis

Alongside the definition of the "normal" human intestinal microbiota and the factors that may condition its composition, in recent years biomedical research has made an enormous effort to try to identify any "abnormality" of the microbiota composition associated with various acute and chronic diseases, and to establish possible cause-effect links (1). In some cases, a clinically significant contribution of the microbiota to the pathogenesis and clinical progress of a disease has been demonstrated. While this is fairly intuitive for diseases that primarily involve the bowel, such as intestinal inflammatory diseases (IBD) and *Clostridium difficile* enterocolitis, on the other hand, it is certainly less for diseases that they involve organs anatomically very far from the intestine. However, this has allowed to hypothesize and, in some cases, to demonstrate the presence of metabolic, endocrine and systemic mechanisms through which the microbiota can, through the GI tract, influence the pathophysiology of the whole body (1-2).

The pathological changes of the human intestinal microbiota can be generalized, when they concern the balance of the microbial population as a whole, or limited to a single or a small group of minor players, which, thanks to particular metabolic activities or a high pathogenic potential, may alone to influence the onset of a disease, either in a negative (absence of a bacterium with protective activity) or positive (presence of a pathogenic bacterium or with harmful activity) way (1-2).

When the alteration of the intestinal microbiota is generalized, we generally speak of dysbiosis, meaning a generic variation in the global composition of the microbial population, with an increase in the relative abundance of some taxa and reduction of the relative abundance of others. In many cases, dysbiosis is associated with increased representation of pathobionts, that is, taxa with potential pathogenic activity such as *Escherichia* and *Klebsiella* spp, at the expense of a reduced representation of taxa with possible beneficial metabolic activity, including lactobacilli and bifidobacteria. Dysbiosis is also associated with reduced biodi-

versity, that is, number of microbial species present in the microbiome and lower complexity of the microbial community (3-4). However, this concept is not uniformly shared by the entire scientific community, and its clinical implications are still unclear. From a medical point of view, the dysbiosis is neither a disease nor a symptom, but a condition that is associated with certain diseases or that can increase the risk. Moreover, the boundaries between dysbiosis and normal individual variability in the composition of the microbiota are still undefined, and therefore it is sometimes particularly difficult to determine whether a given microbiota profile is affected by dysbiosis or not (3-4).

The intestinal microbiota can therefore influence the human pathology at different levels and its alterations can be both cause and consequence of a state of illness. In recent years, many studies have tried to identify the main abnormalities of the intestinal microbiota associated with a long series of acute and chronic human diseases, and to clarify how these anomalies can be linked to the pathogenesis of the diseases themselves. The following is an overview, far from being exhaustive, on the main results of these studies focused on gastrointestinal diseases (1).

Inflammatory Bowel Disease

In IBD there is generally a reduction of the *Firmicutes*, in particular of the species with anti-inflammatory activity *Faecalibacterium prausnitzii*, and an increase in the relative abundance of the *Bacteroidetes*, in particular of the species *Bacteroides fragilis* (5-6). There is also an increase in *Proteobacteria*, and namely a blooming of *Enterobacteriaceae*, including the opportunistic pathogens *Escherichia coli* and *Klebsiella pneumoniae*, which help to support inflammation of the mucosa and increase the risk of infections (7). Overall, this framework leads to strong dysbiosis, with a reduction in microbial diversity, the number of bacteria and their metabolic activity (8). Microbiota manipulation techniques, such as the administration of probiotics and the fecal microbiota transplantation can determine beneficial clinical consequences on the progress of the disease (9-10).

Irritable Bowel Syndrome

Although the pathogenesis of IBS is not fully understood, the role of the microbiota appears to be relevant. In fact, a significant percentage of patients shows intestinal bacterial overgrowth (SIBO). Many studies have shown a reduction of *Bifidobacteria* and *Lactobacilli* and an increase in *Enterobacter* especially in patients with IBS and diarrhea (IBS-D). Other studies have also documented an increase in *Veillonella* in patients with IBS and constipation (IBS-C). Other authors associate IBS and *Campylobacter, Yersinia, Salmonella, Shigella* and *E. Coli*. The great heterogeneity of results is also due to the multiple methods used to determine the microbiota and to the different patient inclusion criteria. Finally, there is also evidence that viruses, parasites and fungi may also play a primary role in the pathophysiology of IBS (11).

Celiac disease

The faecal microbiota of subjects with active celiac disease is associated with a greater microbial diversity compared to the healthy subject, with the expansion of *taxa Bacteroides*, *Prevotella*, *Clostridium* and *Staphylococcus* and a significant decline of bacteria with anti-inflammatory and mucosa protection activities such as *Bifidobacterium* and *Lactobacillus*. It has been proposed that this dysbiosis may play a role in sensitization to gluten and subsequent inflammation (12).

Clostridium difficile infection

The susceptibility to *Clostridium difficile* infection generally depends on a very pronounced dysbiosis, with a reduction in the number of microbiota species and microbial complexity and profound changes in the overall composition of the same (13-15). There is generally a depletion of both the bacteria that are part of the *core microbiota* and of *minor players* like bacteria producing short-chain fatty acids, non-pathogenic clostridia, *Alistipes* and *Bilophila*, which can play a central role in preventing the colonization of intestine by *C. difficile* (13-15). Moreover, *Clostridium difficile*

colitis is associated with a reduced representation of bacteria able to metabolize biliary acids, resulting in a misregulation of the entero-hepatic circle of these substances (13-15). The resulting alterations of gastrointestinal lumen milieu favour the expansion of toxinogenic *Clostridium difficile* populations. These changes are generally caused by prolonged antibiotic therapies and are more pronounced in the elderly subject with multimorbidity (13,16). An additional role could be played by non-antibiotic drugs, such as proton pump inhibitors (PPI), that have a recognized effect of modification of gut microbiota composition and are linked to increased risk of *Clostridium difficile* colitis in some studies (17). The fecal microbiota transplatation, counteracting the extreme intestinal dysbiosis associated with infection and contributing to restore a favorable biochemical milieu in the enteric lumen, is able to clinically prevent recurrences and to significantly modify the natural history of the infection (18).

Colon cancer

Alterations of the intestinal microbiota could play a role in promoting tumorigenesis at the level of the colon (19). However, these alterations probably involve only minor modifications, confined to some species with pathogenic properties and ability to locally invade the intestinal mucosa, without causing acute infectious diseases. Among these modifications, the expansion of *Enterococcus faecalis*, *Bacteroides fragilis* and *Streptococcus gallolyticus* could have the greatest relevance (20). Some metabolic products of the *genus Salmonella* are also able to activate the intracellular signaling of β-catenin which promotes epithelial proliferation (21). Furthermore, the depletion bacteria able to produce butyric acid (22) and the interaction between dietary variations and *Prevotella* enterotype (23) could promote the accumulation of metabolites with oncogenic potential in the intestinal lumen. However, at the current literature state-of-art, the role of the microbiome in gastrointestinal tumorigenesis is far from understood, and the microbiota probably represents only a cofactor in the complex pathogenic pathway, rather than a direct oncogenic player.

Esophageal cancer

There are few studies on the effects of microbiota in the development of esophageal cancer. However, it is plausible that alterations of gastric microbiota near the gastro-esophageal junction may contribute to an increased risk of cancer of the esophagus. Moreover, some studies have shown that the esophageal microbiota of patients with Barrett's esophagus is significantly different from healthy subjects (11). However, more research is needed in this field before definitive conclusions can be made.

Gastric cancer

The inflammatory cascade (Correa's cascade), that causes the progression from chronic gastritis to metaplasia to atrophy to gastric cancer, is known to be triggered by *Helicobacter Pylori* infection. However, it is noteworthy that only a minority of patients infected with *Helicobacter Pylori* develop cancer and the bacterium is often absent or present in minimal concentrations in neoplastic lesions. Some studies have shown significant differences in gastric microbiota with *H. pylori* or without *H. Pylori*. Some authors propose a modification of the current model of gastric carcinogenesis focusing the attention on the interactions between microorganisms and gastric mucosa with possible modifications of the gastric microbiota, whose alterations could determine *per se* gastric atrophy. It is possible that the "new" microbiota developing in the stomach in response to low acidity takes part to gastric carcinogenesis with a complementary (or alternative) role to the more virulent strains of *H. Pylori* (e.g. Cag A) (11).

Liver disease

The liver function is strongly influenced by the metabolism of the intestinal microbiota and of the phenomena of endotoxinemia, namely the absorption by the intestinal mucosa of the lipopolysaccharide produced by the microbiota (24-25). In non-alcoholic fatty liver disease a certain degree of gut microbiota

dysbiosis has been demonstrated, with reduced representation of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, *Anaerotruncus colihominis* and *Butyrivibrio crossotus*, and increased representation of bacteria such as *Ruminococcus*, *Campylobacter* and *Shigella*, some of which produce the metabolite acetate, which is a lipogenic substrate (26). In alcoholic liver disease, however, a deeper dysbiosis is observed, with depletion of *Bacteroidetes* and increase of *Enterobacteriaceae*. This is linked to the effect of alcohol on the intestinal mucosa, with increased permeability and perturbation of immune function resulting in an altered equilibrium between gut bacteria and immune system (24). Similar alterations of the intestinal microbiota also occur in non-alcoholic cirrhosis of the liver, where an intestinal colonization by bacteria normally present in the oral cavity microbiota is also observed (27). Moreover, in the phases of decompensation of cirrhosis, most complications (spontaneous bacterial peritonitis, hepatic encephalopathy) are related to the intestinal microbiota and to the alteration of intestinal mucosal permeability (24).

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