Review Article

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INTESTINAL BACTERIA AND BOWEL DISEASE: ROLE OF PROBIOTICS

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Abstract

The gut of a healthy adult harbours a myriad of different microbial species (approximately 10^{14} colony forming units). In healthy adults, the main control of intestinal bacterial colonization occurs through the gastric acidity. Moreover, other factors can influence the intestinal microenvironment, as pH, temperature, competition among different bacterial strains, peristalsis, drugs, radiotherapy, and much more. It was found that, when you have an impaired microbial homeostasis, the intestinal microsystem becomes unstable, so that leads to an alteration of the permeability of tissues, together with the activation of the intestinal immune system (MALT). These microenvironmental changes thus provide the substrate for the etiopathogenetic outbreak of numerous pathologies of gastro-intestinal tract, together with a miscellany of extraintestinal disorders. From the foregoing, we understand the real importance of maintaining a correct homeostasis of the intestinal microenvironment, in order to prevent the onset of specific disease of the digestive system.

Keywords: intestinal disorders, intestinal microflora, probiotics.

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Introduction

This study reviews the latest international bibliography to underline the close causal relationship that exists between the intestinal microbial flora and inflammatory bowel diseases (IBD, i.e.: Crohn's disease and Ulcerative Colitis), in conjunction with other extra-intestinal diseases (1). Various morbid conditions of the digestive and extra-intestinal tract find their origin in a change in the bacterial microenvironment (2,3). According to the latest clinical trials this could result from a pathogenic effect linked to the presence of pathogenic bacteria.
Finally, in the present study, we analyzed the benefical role of probiotics and in particular Lactobacilli. Among these, the *"Rhamnosus"* one, in its various strains, has shown to have a therapeutic role, in preventing miscellaneous intestinal diseases (1).

The human gut flora

In the human gut harbour globally about 100 trillions of bacteria and more than 500 different species in the colon that can reach a concentration or density of $9x10^{13}$ units (3).
To date, how can such a large number of bacteria, with different microbiological characteristics, lodge and coexist in our intestine without damage to the host organism remains a mystery. Even mucus, plays an important role in protecting the intestinal mucosa. It is responsible for the integrity of the mucosa, helping to maintain stable solution in the submucosal glands secretions (secretory IgA), and maintaining a healthy mucosal tissue tropism (4).

Regulation and role of intestinal microbial flora

The commensal intestinal microflora plays both

directly and indirectly effective action on the intestinal mucosa (2). The complex symbiotic relationship between microflora and host leads sure benefits to both parties (2). From this interaction comes a regular modulation of numerous physiological functions throughout the digestive system (3).
In healthy individuals, the major control of bacterial colonization in the digestive tract occurs thorough the gastric acidity, because it neutralizes the transit of unwanted bacteria.
Among other factors deputies to the control of bacterial flora, we recall pH, temperature, interaction between different bacterial strains, peristalsis, drugs (especially antibiotics), and the effect of radiotherapy.
The competitive interaction between intestinal microflora and the environment triggers biological fermentation processes leading to the production of putrefactive gas together with nitrogen compounds, performing a noxious action on the mucous membrane (3). These biochemical processes are the basis of a rich parade of symptoms characterized by abdominal bloating, flatulence, borborygm, abdominal distension, feeling of discomfort. Many authors define this disorders as "gas-related syndrome" (3).

Microbiological imbalance and intestinal diseases.
It seems now well established the close interaction between commensal bacterial flora and intestinal immune system. This interaction plays an essential role in the onset and development of several diseases such us IBD (Crohn's disease and Ulcerative Colitis) and beyond (5).
Among the various etiopathogenetic hypothesis the most striking sees a change in the microbial saprophytic flora as "primum movens" which conducts to mucosal damage (6,7). Specifically, the microbiological imbalance leads to modifications of intercellular junctions deputies to cement the layer of epithelial line. This inevitably leads to a worsening of mucosal permeability (1,2,5). Consequently, an effective penetration of antigens within the intercellular space, and the activation of the intestinal lymphatic system (MALT), with recruitment and transition of the inflammatory cascade elements (leukocytes, cytokines, TNF- *α)* and tissue damage occurs (6).
For this reason, the maintenance of a proper homeostasis of saprophytic microbial element appears essential in order to eliminate the etiologic substrate for inflammatory bowel disease, extraintestinal (autoimmune) diseases and cancer (8,9); indeed, it is known that 1-2% of all colorectal cancers develop from a background of inflammatory bowel disease such us Crohn's disease and Ulcerative Colitis (10).

Use of probiotics in the intestinal diseases.
To date, numerous clinical trials have already been developed and are in progress, to understand the preventive and therapeutic use of probiotics in diseases of the digestive tract (5,10). But what is meant by probiotics?
For a long time the so-called "official medicine" ignored this topic, leaving the therapy of intestinal diseases to the "official drugs" consisting of intestinal disinfectants, antibiotics and anti-inflammatory molecules.
It is known nowadays as the indiscriminate use of broad spectrum antibiotics, immunosuppressive therapy and/or radiotherapy may cause also important changes in bacterial intestinal microflora, that almost always lead to particularly severe symptoms (11).
The term "probiotics" has been used for the first time in 1965 by Lilly and Stilwell (11). They reported the observation that certain substances extrapolated by segments of intestine, if placed in vitro with organic tissue, continued their growth. Subsequently, further studies have better defined these substances, identifying them as commensal intestinal bacteria.
Today, we tend to identify with the term of probiotics a pool of microrganisms producing beneficial effects on a health bowel. They are part of the normal intestinal microbial flora as the commensal batteroides. This distinguishes them from pathogenic bacteria, both exogenous (e.g. *Salmonella*) and residents *(Bacilli, Clostridia, Klebsiella, Proteus, etc.).* However, they are not part of the normal flora colonies unless outnumbered (0.02 % of total) (12).
It was noted how the administration of certain live bacteria can have beneficial effects for the host organism, so that restoring the microflora intestinal balance has become a viable strategy for therapeutic action. The aim is of preventing and

treating many diseases of the digestive system (11).
Nowadays, the pharmaceutical industry, sensing the safe therapeutic potential of probiotics, has studied and marketed preparations of probiotic bacteria acting synergistically. These generally include various types of bacteria, among which stand out *Lactobacilli*, *Bifidobacteria* and *Enterococci* (11).
These formulations have been marketed for several years with variables related to bacteria and the composition that includes different bacterial species or the same species, but with different strains.
These preparations are increasingly used in clinical practice and engaged in a myriad of intestinal and extraintestinal diseases.
Among the number of diseases in which it is suggested the use of probiotics, we include: diarrheal syndromes (including those from antibiotics), necrotizing enterocolitis, *Clostridium difficile* colitis, *rotavirus* enteritis; now this has spread to infection by *Helicobacter Pylori*, as well as urogenital infections (especially in women), chronic inflammatory diseases (Crohn's and Ulcerative Colitis), up to find also a rationale for their use in prevention of cancers of the digestive tract (5, 11-13).
The *Lactobacillus Rhamnosus GG*, for example, can be used in traveller's diarrhoea, but also in "milk-induced" food allergy, and also in particular respiratory syndromes in children (12,13). Some clinical trials propose *Lactobacillus Rhamnosus GG* in prostate cancer, diabetes and rheumatoid arthritis therapy (13).
In focusing on colic disease, *Lactobacillus Rhamnosus GG* it is now found to have beneficial effect on the intestinal immune system. Particularly, it has been proved that an increasing number of IgA and other Immunoglobulin are secreted by the intestinal glands (11). Therefore the *Lactobacillus Rhamnosus GG* tends to modulate the antigen recognition by the intestinal lymphoid tissue – i.e. Peyer's patches (11). It was also highlighted its regulatory action on the constituent parts of the inflammatory cascade. It shows a clear beneficial effect of inflammatory mediators down-regulation, for example modulating the action of cytokines as *TNF-α* (5).
In our experience, we have also studied the effects of *Lactobacillus Rhamnosus GG* in improving the function of the intestinal barrier and the permeability between cells (5), while others proposed their anti-carcinogenic role. Particularly, a Finnish double-blind study by Hatakka et al. (14) tends to highlight the protective role of *Lactobacillus Rhamnosus GG* in colon tumors. This study stems from the observation that specific enzymes produced by pathogenetic bacteria in the large intestine, such as beta-glucosidase, beta-glucuronodase and urease, are considered to be carcinogenic factors for colorectal cancer. The biological inactivation of these metabolic products is done by enzymes produced by other types of bacteria (so-called "good bacteria") such as those included in probiotics.
The same study also analyzed the presence of beta-glucosidase, beta-glucuronidase and urease in faeces of patients in which they administered *Lactobacillus Rhamnosus GG* for a period of 4 weeks. The presence of these faecal enzymes was significantly lower (statistical significance, $p = 0.16$) in patients treated with *Lactobacillus Rhamnosus GG* as compared to the placebo group (14).
Further controlled trials are better define and validate the beneficial and protective role of probiotics on various gastrointestinal diseases (13). At the end, what emerges from the current analysis is that to achieve a therapeutic effect, probiotics should be selected, assembled and marketed in correct therapeutic formulations, keeping in mind the different topographical locations that the microbial flora has along the various intestinal segments (5).

Conclusion

The "*primum movens*" of a number of digestive tract diseases is the alteration of intestinal microflora. Functional disorders, such as "gas-related syndrome", or organic diseases, such as IBD (Crohn's and Ulcerative Colitis) may find etiologic substrate in an alteration of gut microenvironment that leads to inflammation of the mucosa. The beneficial role of probiotics seems to extend their effects to the prevention of neoplastic diseases.
In this regard, controlled clinical trial demonstrating the contribution of specific enzymes produced by "bad bacteria" in the carcinogenic evolution began to appear in

scientific literature. In this sense, the anti-tumor effect of *Lactobacillus Rhamnosus GG* in its various strains is particularly studied. This probiotic has been shown to have beneficial effects also as protective anticancer agent on the colonic mucosa. The scenario is exciting, the expectations are attractive, the involvement of researchers in this field is necessary.

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BATTERI E MALATTIE INTESTINALI: RUOLO DEI PROBIOTICI

L'intestino di un adulto sano ospita differenti specie microbiche (all'incirca 10^{14} unità formanti colonie). In un adulto sano il maggior controllo della colonizzazione batterica avviene attraverso l'acidità gastrica. Altri fattori possono influenzare il microambiente batterico: pH, temperatura, competizione tra differenti specie batteriche, peristalsi, farmaci, radioterapia e molto altro. Si è scoperto che quando l'omeostasi microbica viene compromessa, il microambiente intestinale diviene instabile, con alterazione della permeabilità dei tessuti ed attivazione del sistema immunitario intestinale (MALT). Queste alterazioni del micro-ambiente rappresentano il substrato eziopatogenetico per lo sviluppo di numerose patologie gastro-intestinali e svariati altri disordini extra -intestinali. Da quanto detto, si comprende la reale importanza del mantenimento di una corretta omeostasi del microambiente intestinale, al fine di prevenire l'insorgenza di specifiche patologie del tratto digerente.

Parole chiave: disordini intestinali, microflora intestinali, probiotici

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