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Intestinal microbiota and its host: harmony or discord?

Physiological role of the intestinal microbiota and interactions with the host

Doctor Nadine CERF-BENSUSSAN (Paris)
INSERM, UMR1163, Laboratoire Immunité Intestinale and Institut Imagine, F-75015 Paris, France.
Université Paris Descartes-Université de Paris F-75015 Paris, France

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INTRODUCTION

It is now established that microbes make up more than 95% of the living mass on the planet and colonize all its ecosystems. Notably, bacteria have colonized the digestive tract of animals, forming communities of various complexities, that is maximal in the distal part of the mammals' gut. Because of this important microbial community, the human colon is described as the most ecologically dense site of bacteria on earth, with a total of bacteria estimated at around 10^{13}, comparable with the total number of cells in the human body.

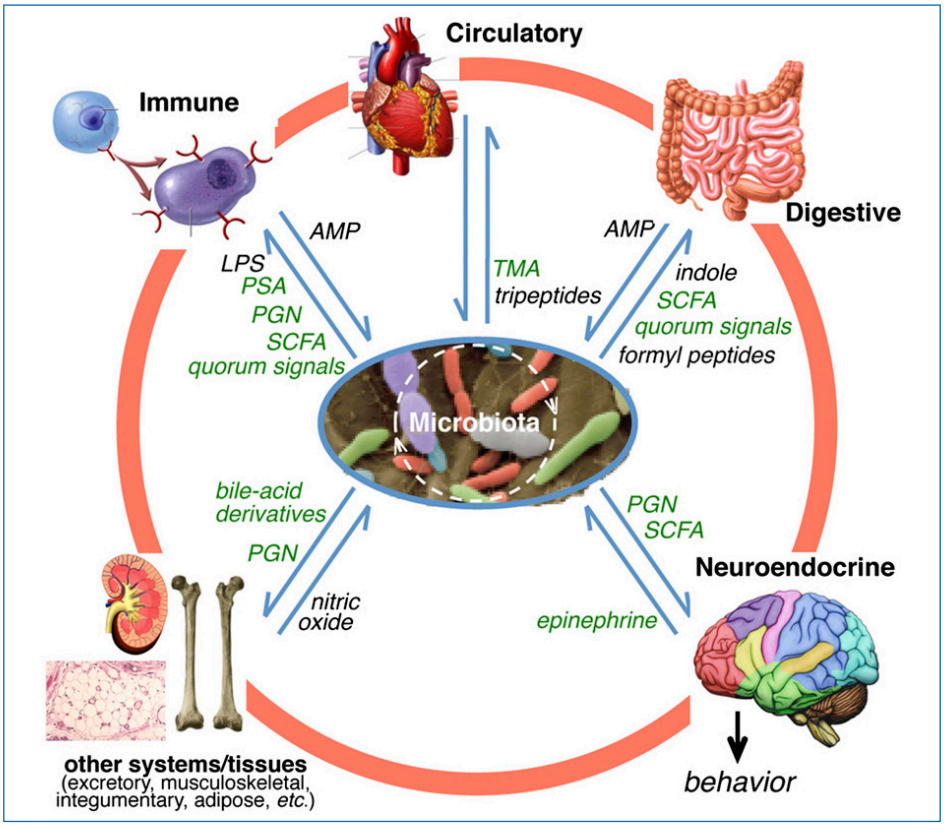
Since the beginning of the 20th century, intestinal bacteria have been the subject of great interest both for their physiological (barrier effect against enteropathogens) and pathological role at the origin of various gastrointestinal diseases. However, the study of intestinal bacteria has long been hampered by the difficulties in culturing them. High throughput genome sequencing techniques have overcome this difficulty, to establish a catalog of the species present in the microbiota first, and then to establish a catalog of all the bacterial genes encoded by the microbiota. The number of bacterial genes is estimated at 600,000 in each individual and more than 10 million for all human microbiotas already studied. Comparison between the amounts of bacterial genes encoded by the microbiota and the much lower number of genes present in the human genome, estimated at 22,000, led researchers to propose the concept of a "superorganism" constituted by the host and its microbiota. In fact, while some of the bacterial genes allow bacteria to grow in the intestinal ecosystem, many of them seem to be able to enhance the metabolic capabilities of their host and to modulate many of its functions.

EFFECTS OF THE INTESTINAL MICROBIOTA ON ITS HOST

Proven effects on the host

The key role of the microbiota in physiology and pathology has been shown in numerous studies conducted over the past 15 years. These studies have established correlations between the composition of microbiota and health status, either healthy or diseased, of the human or animal host. A growing body of work has demonstrated cause-and-effect relationships, and has, more recently, identified the mechanisms involved in this relationship. The effects of the microbiota on its host have mostly been demonstrated in animal studies, in which the microbiota is eliminated by oral administration of broad-spectrum antibiotics, or when animals, most often mice, are reared sterile and then colonized in a controlled manner by individual bacterial species, by more or less complex microbiota, or by transfer of feces of murine or human origin. These experiments have revealed the diversity of microbiota effects, in the intestinal tract where the bacteria are located, but also remotely on many other organs (Figure 1).[1] The microbiota behaves like a bioreactor, releasing multiple metabolites able to diffuse into the blood and to modulate many of the host functions.

Figure 1. The multiple effects of the intestinal microbiota on its host and the mechanisms involved.[1]



Barrier effect against enteropathogens

Resistance to colonization by enteropathogenic bacteria is a first major benefit conferred by the establishment of a complex community of symbiotic bacteria in the intestine. The protective effect of the microbiota against enteric pathogens, called the barrier effect, was first demonstrated in the 1950s, by comparing the mortality induced by *Salmonella typhimurium* in mice treated or not with streptomycin.[2] While oral administration of more than 10^6 salmonella was required to induce the death of untreated mice, a hundred salmonellae were sufficient to induce lethal infection in the treated mice, showing that partial elimination of the microbiota by streptomycin promoted colonization by pathogenic bacteria.[2]

The onset of severe intestinal infections by pathogens such as *Clostridium difficile* in patients treated with antibiotics in humans demonstrates the importance of the barrier role of the microbiota. Many studies, as reviewed by Schnupf and colleagues,[3] emphasize the complexity of the mechanisms contributing to this protective effect. These mechanisms include the competition between bacteria for nutrients, the production of antibiotic-like substances (such as bacteriocins or siderophores) by resident bacteria that capture iron and can impair, in the case of inflammation, the proliferation of pathogenic proteobacteria.[3] Another mechanism more recently discovered is similar to niche construction. Production of butyrate from non-digestible dietary carbohydrates (fibers) allows the anaerobic symbiotic bacteria that predominate in the normal colon (Firmicutes and Bacteroidetes) to direct colonocyte metabolism towards the oxidative degradation of fatty acids, a process that is highly oxygen consuming. These bacteria maintain anaerobic conditions that favor their own growth but are less favorable to that of proteobacteria, a large family of facultative anaerobic bacteria, many of which can exert pro-inflammatory or pathogenic effects in the colon. A fourth mechanism by which symbiotic bacteria protect their host from enteropathogenic bacteria involves the stimulation of the host's immune defenses. These different mechanisms contribute to creating and maintaining a digestive ecosystem that promotes colonization by resident species (symbionts) and resists invasion by pathogenic bacteria.[3] Nevertheless, because of the very rapid bacterial growth, even minor changes in the intestinal ecosystem can modify the balance between bacteria and favor the emergence and multiplication of pathogenic species that are more able to survive and

multiply in these new conditions. Colon inflammation is thus appropriate to the expansion of proteobacteria over the firmicutes.

A better understanding of the mechanisms that control the intestinal ecosystem should improve strategies able to fight pathogenic bacteria and the multidrug-resistant bacteria that have become a public health problem with the massive use of antibiotics.[3] In fact, by reducing the diversity and the number of microbiota bacteria, antibiotics open niches accessible to colonization by resistant and/or pathogenic bacteria. Alterations of the microbiota vary, dependent on the antibiotic, the duration of the treatment and its repetition. Nevertheless, it is important to emphasize that even short-term treatments can induce compositional changes that are not completely reversible. The use of antibiotics is likely to contribute to the reduction of microbiota diversity and the emergence of more pro-inflammatory strains such as *Escherichia coli* B2 in industrialized countries. However, it must be emphasized that while bacteria protect the gut against enteropathogenic bacteria, they do not protect against all pathogens. Some viruses use intestinal bacteria to colonize their host.[4]

Role of the microbiota in the physiological activation of the immune system

Role of the microbiota in the activation of intestinal immune responses

A very dynamic dialogue between the microbiota and the immune system of the host is established during intestinal colonization after birth and continues throughout life. This dialogue is particularly active in the gut where, either through direct contact with the epithelium or through metabolites, bacteria can modulate the properties of the epithelial barrier and induce the recruitment of a large number of immune cells of hematopoietic origin that reinforce this barrier. The dialogue between the host and its bacteria thus contributes to creating a state of physiological inflammation essential for the formation of an effective intestinal barrier, able to circumscribe microbiota bacteria in the intestinal lumen and prevent their systemic dissemination. Very precise regulation makes it possible to prevent excessive inflammation, which would be deleterious for both the host and the resident microbiota bacteria. In the gut, colonization by the microbiota thus induces a wide range of innate responses such as the production by the epithelium of mucus, microbicidal peptides and free radicals (reactive oxygen species). It also promotes the recruitment of macrophages, polynuclear and innate lymphoid cells. At the same time, colonization induces adaptive responses and activates the expansion and differentiation of intestinal plasma cells producing secretory IgA and many regulating and proinflammatory T lymphocytes (in particular TH17).[5, 6]

Role of the microbiota in the activation of intestinal immune responses remote from the gut

In a healthy immunocompetent individual, very few bacteria can cross the intestinal barrier, and the few bacteria that cross it are stopped in the mesenteric lymph nodes. When the intestinal barrier is altered, more bacteria can translocate, but most are destroyed in the liver. The entry of bacteria into the systemic bloodstream is limited. However, many products of bacterial origin can cross the intestinal barrier and enter into the blood. Metabolites are derived either from the bacteria themselves or from food products transformed by the bacteria. Through the blood, these metabolites can come into contact with the immune cells that are present in the bone marrow, liver or spleen, and modulate the functions of the immune system away from the gut. Studies in mice notably show that the presence of the microbiota has a powerful adjuvant effect on the anti-infectious defenses and tends to inhibit allergic responses. This effect of the microbiota on systemic responses is influenced by diet. A fiber-rich diet allows microbiota production of short-chain fatty acids whose modulatory effects on pulmonary allergic responses have recently been demonstrated.

Effects of the microbiota on the host metabolism

A growing number of studies have demonstrated a considerable impact of microbiota metabolism on host metabolism, both in the intestine and in other organs.

As mentioned above, butyrate produced by resident colonic bacteria capable of digesting dietary fiber, stimulates the oxidative degradation of fatty acids, promoting anaerobic conditions in the colic lumen.[7, 8]

At the systemic level, the microbiota notably modulates glucido-lipid metabolism and the storage of fats in adipose tissue. Bäckhed and colleagues[9] were the first to report that axenic mice were thinner than mice raised in conventional conditions. They also showed that the colonization of these mice by a complex microbiota or by certain bacteria was accompanied with a 60% increase in their fat mass, independent of an increase in food intake. These authors also showed that the microbiota, by favoring **1)** the digestion of carbohydrates of vegetable origin, **2)** the glucose transport in the enterocyte, and **3)** the intestinal angiogenesis, increased the concentration of glucose in the portal vein.[9] This resulted in an increased synthesis of triglycerides in the liver and their accumulation in the adipose tissue. These effects were associated with an increased insulin resistance. The microbiota can thus promote energy savings in its host. Such an effect is likely to be favorable when the host has limited access to food resources and when these are non-digestible sugars of vegetable origin (fiber), a situation that has largely prevailed during evolution. Conversely, in the context of the overconsumption of food, which is frequent in Western countries, this effect can favor metabolic syndrome and obesity. Moreover, the high fat and high sugar diets prevalent in these countries may also favor the selection of proinflammatory bacteria likely to worsen metabolic disorders.

The mechanisms through which the microbiota modulates its host's metabolism are being examined in a growing number of studies. Elegant work recently published in *Cell* by Koh and colleagues[10] showed that imidazole propionate, derived from the transformation of dietary histidine by some bacteria, was responsible for the increase in insulin resistance observed in colonized mice compared with germ-free mice, an effect that is due to the activation of the mTORC1 pathway. Interestingly, imidazole propionate is present at higher concentrations in the blood of patients with type 2 diabetes compared with non-diabetic controls. In addition, the fecal microbiota of patients with type 2 diabetes is enriched with strains harbouring the enzyme that allows the conversion of histidine to imidazole propionate.[10] These results establish a first precise mechanism through which the composition of the microbiota can promote the development of type 2 diabetes.

SUMMARY AND CONCLUSION

The interactions between the host and its microbiota can be considered a symbiosis, in which each of the two partners gain advantages, especially metabolic benefits, which increases their respective "fitness". The compromise established during the long coevolution between bacteria and their hosts is based on the development of an efficient and finely regulated immune system capable of protecting the host against the invasion of bacteria while preserving tissue homeostasis, which is essential to digestion and absorption functions of the gut.

Today, there are significant changes in the composition of the microbiota in individuals living in industrialized societies. These have been attributed to the transformation of lifestyle, and more particularly to changes in human nutrition (depleted in fiber, enriched in fat and high-glycemic index sugars), antibiotic consumption, and exposure to various pollutants. These alterations are characterized by a reduction in bacterial diversity and the loss of symbiotic bacteria that exert favorable effects on the metabolism or the immune system, in favor of so-called "pathobionts", bacteria with often proinflammatory properties. Fast bacterial replication allows microbial populations to adapt quickly to changes in their gut environment. Thus, changes in the composition of the microbiota are observed in the months following the arrival in an industrialized country of migrants from a society with a traditional way of life. Conversely, it is more difficult for the hosts to adapt their metabolism and immune system, and it is now strongly suspected that recent changes in the microbiota create an imbalance of immune and metabolic responses favoring the epidemics of chronic metabolic and inflammatory diseases that accompany industrialization. A thorough knowledge of the mechanisms underlying the effects of the microbiota, as well as of those controlling its composition, is essential today to understand precisely its role in these disabling pathologies, and to define therapeutic or preventive strategies capable to restore a composition of the microbiota favorable to human health.

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