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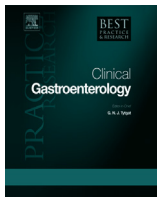

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Function of the microbiota

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A B S T R A C T

The gut microbiota of humans is complex but stable in composition and function. Metabolic conversions performed by the members of the microbiota yield both beneficial and hazardous compounds, and have a systematic impact on human health. Comparative studies have shown that the microbiota of patients, suffering from a number of diseases, is in dysbiosis, which is characterized by a distinct composition. Compositional differences have also been noted between members of geographically distant healthy populations. To be able to identify which compositional changes promote compromised health, it is of interest to identify members of the microbiota that perform essential metabolic transformations. This review provides an insight into the microbial contribution to the metabolism of carbohydrates, proteins and bile acids, and focuses on the link between diversity and function.

Introduction and general remarks

Gastrointestinal tract provides a home for 'a microbial world within us' that is composed of several hundreds of different species [1]. These bacteria, archaea, fungi and yeasts are utilizing indigestible food components and host derived substrates such as mucus, enzymes and epithelial cells, and convert them into various metabolites. The living conditions in the gastrointestinal tract are very dynamic, given the difference in day to day diet, fast nutrient flux (particularly in the upper parts of the tract), presence of immune system, presence of other microbes, occasional infections and usage of antibiotics. Even under such dynamic conditions, the microbiota is an exceptionally stable ecosystem [2,3]. The ability to resist significant environmental challenges illustrates the flexibility of the ecosystem, which

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is enabled through its diverse metabolic potential. The gut microbiota's collective genome – metagenome – contains at least 100 fold more genes than its human host [4]. All functions encoded by these microbial genes are relevant to their survival, but much of the microbial activity is highly relevant to human physiology. The effects of microbial metabolites can be, on one hand, health-promoting and include improved digestion, vitamin synthesis, inhibition of the pathogenic growth, lowering of the gas distension and immuno-stimulation. On the other hand, microbiota can synthesize carcinogenic compounds and toxins, can contribute to the development of diarrhoea, constipation and intestinal infections.

The beneficial role of some intestinal inhabitants has been acknowledged already for over a century. In particular, this stands for lactic acid bacteria belonging to the genera *Bifidobacterium* and *Lactobacillus*. Application of these bacteria as probiotics is health-promoting, although probiotics success depends on the applied bacterial strain(s), and on the targeted disease. Mechanisms by which lactic acid bacteria promote health of the host include stimulation of the immune system, anti-allergic effects, suppression of pathogens, and vitamin synthesis (for more detail see review [5]).

In recent years a whole range of high throughput techniques for studying human and microbiota's DNA, RNA, proteins or metabolites has been developed [6]. Application of these techniques has made a significant progress in understanding the impact of the gut microbiota. The ultimate goal of these studies is to identify key microbial players for different functions of the ecosystem and to provide links between the microbiota's composition, activity and health. This task is challenging since many functions of the ecosystem are shared among microbes that are phylogenetically distant – this represents the functional redundancy of the ecosystem. Furthermore, each subject contains a unique consortium of microbes and attempts to identify core microbiota – the microbiota that is shared among (most of) humans – have not reached a consensus [7,8]. As an alternative to the presence of universal core, three types of the microbiota – enterotypes [9] have been proposed. The concept of eneterotypes is in line with the observation that not all humans excrete methane [10], which is accompanied with different microbiota composition [11]. However, this concept was also challenged [12], and it remains to be seen if the proposed concept should be tuned or abandoned. A recent study of the microbiota of the largest cohort reported up to date, showed that the concept of enterotypes certainly cannot be applied on the microbiota of infants and young children [13].

Although it is still not clear what represents normal intestinal microbiota, it has been shown that the microbiota composition of healthy subjects differs from that of patients suffering from a number of different diseases. Significantly different microbiota composition related to a disease is called dysbiosis, and specific dysbiosis has been determined for obese subjects [14], patients suffering from type 2 diabetes [15], as well as for adolescents with high risk for type 1 diabetes development [16]. Furthermore, a specific microbiota dysbiosis is present in patients suffering from irritable bowel syndrome (IBS) [17,18], inflammatory bowel diseases (IBD) [19–22], *Clostridium difficile* associated diarrhoea (CDAD) [23], and colorectal cancer (CRC) [24] (summarized in Fig. 1). Such widely disturbed and reproducibly detected dysbiosis suggests that a change in abundance or the loss of particular microbiota constituents leads to the loss of the normal microbiota function. The essential role of the microbiota for some of these diseases is confirmed in faecal transplantation experiments (also called bacteriotherapy), where the faecal microbiota from a healthy donor inoculated in patients significantly improves symptoms of the disease, as has been shown for CDAD [25], and, more recently, for metabolic syndrome [26].

It should be noted that differences in the microbiota composition have also been detected between groups of healthy human subjects. Such differences were noted when comparing the microbiotas of subjects of a different cultural groups including comparison of the Japanese and the Canadians [27], the Chinese and the Americans [28], rural African and European children [29] and subjects from the Amazonas, rural Malawi and the USA [13]. Although different in composition, the microbiota of these healthy subjects performs similar functions, and the major driver of the observed differences is most likely different diets. It is of interest to define the type of changes in the microbiota composition that do not disturb its function and those that lead to the development of diseases. This review provides a platform for identification of key microbial players for particular microbiota functions by summarizing results of this dynamic research field and by putting particular attention on discoveries that link the diversity and function.