ACTA MICROBIOLOGICA BULGARICA Volume 33 / 2 (2017)

Review

Gut Microbiome: Probable Relations to Human Health*

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Abstract

Humans co-evolve with their microbiota. It is becoming better understood today that health and disease are determined by microbiota in many cases. The gut microbiota constitutes the main part of the current research on the subject and is already found to be related to many disorders in humans. Diet and gut microbiota seem to have a stable relation.

Key words: Gut microbiota, microbiome, health, disease, diet.

Резюме

Хората са еволюирали успоредно с техния микробиом. Днес все по-добре разбираме, че в много случаи здравето и болестите са свързани с микробиома. Съществена част от сегашните изследвания по въпроса са посветени на чревния микробиом. Изглежда, че между чревния микробиом и диетата има стабилна връзка.

Microbiota and Microbiome

Microbiota is the community of microrganisms including bacteria, viruses, archaea, and some unicellular eukaryotes, living in a specific environment; therefore, Human Microbiota is a whole collection of microorganisms living on the surfaces and internal parts of the human body. Microbiome is the entire collection of all genomic elements of a specific microbiota (D'Argenio and Salvatore, 2015).

Approximately, the total number of human cells is 10^{13} and that of the microbial cells is 10^{14} in an adult, meaning that the microbe cells are 10-fold the number of the human cells in an adult body.

This same microbiota encodes five million microbial genes to make up the human microbiome, meaning that the microbial genes are 150-fold the number of the human genes in a human body. The microbiota makes up 1-2 kilograms of an average adult body weight and performs some vital functions which the human body cannot manage by itself; and this is why the microbiota has recently been called the "forgotten organ" in the body of human beings (Clemente *et al*., 2012).

Multiple factors such as the immune system, genetic variations, racial origin or ethnic roots, local environment, hygienic factors, socioeconomic status, lifestyle and diet, determine the human microbiota and microbiome (Findley *et al.*, 2016). In 2007, the US National Institute of Health (NIH) launched the Human Microbiome Project (HMP) for "exploring the microbial parts of ourselves", in order to understand how these microorganisms contribute to our normal and abnormal states, namely, to human health and diseases. HMP was considered a global interdisciplinary study to break down the artificial barriers between medical and environmental microbiology (Turnbaugh *et al*., 2007).

Since most of the human microbiota is in the gut, the European Commission, in collaboration with China, initiated the Metagenomics Project of the Human Intestinal Tract (MetaHIT), for analyzing our intestinal microbiota with a final aim to explain the evolution of human chronic diseases. Until now, the MetaHIT Project has produced a catalogue of more than three million bacterial genes present in the gut and discovered that most humans belong to one of the four enterotypes. As preliminary outcomes of the MetaHIT, new clues have emerged for early diagnosis of chronic diseases, personalized medicine and more healthful food (http://www.metahit.eu/).

* *The paper was presented at the FOOD-3 Conference, 2017, Sofia, Bulgaria*

Therefore, the new gut microbiota/microbiome research has been focussed now onto three main questions: 1. Who is in there and what is it doing? 2. What are the relations to health and disease? 3. How is it possible to modify the gut microbiome to maintain health and treat disease? (Owyang and Wu, 2014).

Gut Microbiota

In general, the gut microbiota consists of microorganisms which are either harmless or are of benefit to the human-host. It protects against enteric pathogens, provides the body with nutrients and energy from ingested food, produces essential vitamins (such as B_3, B_5, B_6, B_{12}, K), performs vital functions (such as encoding some proteins which cannot be encoded by the human genome although they are necessary for human survival), contributes to immune functions (providing signals to promote the maturation of immune cells and functions) and secretes some neurotransmitters which are necessary for mental well-being (Kau *et al*. 2011; Clemente *et al.* 2012; Owyang and Wu, 2014).

Gut microbiota is highly variable. It varies between individuals and fluctuates over time in the same individual. The majority of gut bacteria consists of only a few bacterial phyla: *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia.* Sharp changes in lifestyles change the microbial ecology (Turnbaugh *et al*., 2007). Gut microbiota of most individuals can be categorized into some enterotypes and all enterotypes are driven mainly by diet. Different enterotypes show different saccharolytic, proteolytic and lipolytic profiles (Turnbaugh *et al*., 2007; Clemente *et al.*, 2012).

Gut Microbiota, Dysbiosis and Disease

Disturbance of the normal balance between the gut microbiota and the human-host is called dysbiosis and it is assumed to lead to many disorders such as obesity, malnutrition, inflammatory bowel disease, neurological disorders, coronary vascular disease, alcoholic and nonalcoholic fatty liver disease and cirrhosis, insulin resistance and diabetes, and colorectal cancer. In the dysbiosis state, the intestinal barrier function is disturbed, bacteria and their products are translocated, and immune activation takes place. Microbiome-related internal alterations work together with external factors, such as the Western-type diet, to provoke the development of disease (Owyang and Wu, 2014).

It is now much better understood that even some infectious diseases might result from dysbiosis, rather than a single pathogen. Microbial-dysbiosis-related diseases include mainly the autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, etc.), allergic diseases, and obesity. The autoimmune diseases result from inappropriate action of the immune system with the dysbiotic gut microbiota. Children with a high risk of diabetes have a distinct gut microbiota composition with decreased diversity and relative abundance of some specific bacteria. Animal models of multiple sclerosis and rheumatoid arthritis suggest influence of the gut microbiota. Autoimmune diseases do not develop in germ-free mice, and multiple sclerosis is restored when germ-free mice are colonized by specific bacterial taxa. Obesity is related with the Western-type diet, which brings some shifts in microbiota. (Clemente *et al.,* 2012).

The gut microbiota also communicates with the central nervous system through neural, endocrine and immune pathways, and influences the brain function and behavior. Studies suggest that the gut–brain axis even regulates the psychological states in humans, including anxiety, mood, cognition and pain (Cryan and Dinan, 2012).

Genome and Microbiome

It is well known now that humans have two genomes: the first is inherited from parents, and the second is acquired from microbes (microbiome). The inherited genome is stable over the lifetime. The microbiome also has two parts: (a) the core gut microbiome which is stable, and whose composition and structure are determined by the human-host genetics, (b) the variable gut microbiome which changes with age, hormonal cycles, therapies, illness, travel and diet (Owyang and Wu, 2014; D'Argenio and Salvatore, 2015). Changes in the gut microbiome lead to pathological dysbiosis, which itself leads to intestinal and extra-intestinal diseases (Turnbaugh *et al*., 2007).

Diet and Biodiversity

Each adult develops a personalized diet pattern and therefore a unique gut microbiome. Diverse diet leads to diverse and rich gut microbiome, which results in good adaptation to disturbances. A greater range of signals enhances greater ability to maintain homeostasis and health. Microbial richness in gut microbiota is therefore, considered to correlate with good health. During the past 50 years, the prevalence of obesity, type 2 diabetes,

and inflammatory bowel diseases has sharply increased. The shared finding for all these diseases is reduced biodiversity in the gut microbiome (Heiman and Greenway, 2016).

Obese subjects with increased adiposity have less microbial diversity and have some gut bacteria with inflammatory effects. Lean subjects have more diverse microbiota that contains higher proportions of different microbes which are correlated with anti-inflammatory responses (Ursell *et al*., 2014).

In gut microbiota, two bacterial phyla dominate in general: Firmicutes and Bacteroidetes. A high Firmicutes/Bacteroidetes ratio is observed to be associated with obesity with or without increased food intake. Gut microbiota regulates the expression of genes that affect fat deposition in adipocytes. Germ-free mice are resistant to diet-induced obesity (Kau *et al*., 2011).

Diet is recognized as a key factor in shaping the gut microbiota composition and in promoting either the intestinal homeostasis or the inflammation-associated intestinal dysbiosis. Nondegradable food elements such as starch or vegetal fibers are degraded and fermented only in the large intestine by the resident microbiota. Fiber fermentation end products are short-chain-fatty-acids (acetate, propionate and butyrate), which are used by the host colonocytes as an energy source. Short-chain-fatty-acids have a role in the prevention of colon cancer and promotion of immune tolerance, among many more. In a comparative study, microbial richness and short chain fatty acid production were shown to be high in the agrarian diet, which is rich in non-animal protein and vegetal fiber, while both parameters were found seriously low in the Western diet, which is rich in animal protein, sugar, starch and fat, and low in fiber (Albenberg and Wu, 2014).

Manipulation of the Gut Microbiome

Forcing a change in gut microbiota by fecal microbiota transplantation is shown to be very efficient in treating refractory Clostridium difficile infections, inferring that intestinal microbiota would be a therapeutic target in humans, particularly to treat metabolic diseases (Owyang and Wu, 2014).

Diet is a major issue in non-invasive manipulation of the gut microbiota and its metabolic functions. Diet may influence the whole set of microbial metabolites (metabolome), which in turn may affect the host physiology and immune functions (Owyang and Wu, 2014).

The sensitivity of the microbiota to external factors, such as diet, is a clue on how to shape strategies for treating microbiome-linked diseases. Clinical applications are expected to lead to personalized medicine, hopefully in the near future (Lozupone *et al*., 2012; Owyang and Wu, 2014).

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