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The Human Microbiota in Health and Disease

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ABSTRACT

Trillions of microbes have evolved with and continue to live on and within human beings. A variety of environmental factors can affect intestinal microbial imbalance, which has a close relationship with human health and disease. Here, we focus on the interactions between the human microbiota and the host in order to provide an overview of the microbial role in basic biological processes and in the development and progression of major human diseases such as infectious diseases, liver diseases, gastrointestinal cancers, metabolic diseases, respiratory diseases, mental or psychological diseases, and autoimmune diseases. We also review important advances in techniques associated with microbial research, such as DNA sequencing, metabonomics, and proteomics combined with computation-based bioinformatics. Current research on the human microbiota has become much more sophisticated and more comprehensive. Therefore, we propose that research should focus on the host-microbe interaction and on cause-effect mechanisms, which could pave the way to an understanding of the role of gut microbiota in health and disease, and provide new therapeutic targets and treatment approaches in clinical practice.

1. Introduction

More than 100 trillion symbiotic microorganisms live on and within human beings and play an important role in human health and disease. The human microbiota, especially the gut microbiota, has even been considered to be an "essential organ" [1], carrying approximately 150 times more genes than are found in the entire human genome [2]. Important advances have shown that the gut microbiota is involved in basic human biological processes, including modulating the metabolic phenotype, regulating epithelial development, and influencing innate immunity [3–6]. Chronic diseases such as obesity, inflammatory bowel disease (IBD), diabetes mellitus, metabolic syndrome, atherosclerosis, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma have been associated with the human microbiota [7,8] (Fig.1).

In recent decades, a tremendous amount of evidence has strongly suggested a crucial role of the human microbiota in human health and disease [7,9–23] via several mechanisms. First, the microbiota has the potential to increase energy extraction from food [24], increase nutrient harvest [9,10], and alter appetite signaling [25,26]. The microbiota contains far more versatile metabolic genes than are found in the human genome, and provides humans with unique and specific enzymes and biochemical pathways [9]. In addition, a large proportion of the metabolic microbiotic processes that are beneficial to the host are involved in either nutrient acquisition or xenobiotic processing, including the metabolism of undigested carbohydrates and the biosynthesis of vitamins [10]. Second, the human microbiota also provides a physical barrier, protecting its host against foreign pathogens through competitive exclusion and the production of antimicrobial substances [11–13]. Finally, the microbiota is essential in the development of the intestinal mucosa and immune system of the host [14,16]. For example, germ-free (GF) animals have abnormal numbers of several immune cell types, deficits in local and systemic lymphoid structures, poorly formed spleens and lymph

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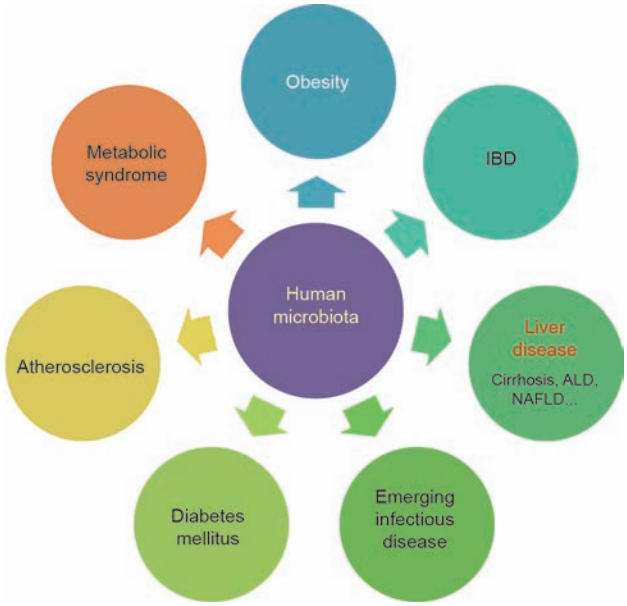

Fig. 1. Human microbial symbiosis has a close relationship with diseases of different systems.

nodes, and perturbed cytokine levels [16]. Studies on GF animals have suggested that the immune modulation functions of the microbiota are primarily involved in promoting the maturation of immune cells and the normal development of immune functions [14]. In addition, studies have revealed the central role of microbial symbiosis in the development of many diseases [17], such as infection [18], liver diseases [19], gastrointestinal (GI) malignancy [20], metabolic disorders [7], respiratory diseases [21], mental or psychological diseases [22], and autoimmune diseases [23].

In this article, we provide an overview of the role of the human microbiota in health and disease, the advent of microbiome-wide association studies, and potential and important advances in the development of clinical applications to prevent and treat human disease.

2. The human microbiota in health

The human microbiota affects host physiology to a great extent. Trillions of microbes colonize the human body, including bacteria, archaea, viruses, and eukaryotic microbes. The body contains at least 1000 different species of known bacteria and carries 150 times more microbial genes than are found in the entire human genome [2]. Microbiotic composition and function differ according to different locations, ages, sexes, races, and diets of the host [27].

Commensal bacteria colonize the host shortly after birth. This simple community gradually develops into a highly diverse ecosystem during host growth [28]. Over time, host-bacterial associations have developed into beneficial relationships. Symbiotic bacteria metabolize indigestible compounds, supply essential nutrients, defend against colonization by opportunistic pathogens, and contribute to the formation of intestinal architecture [29]. For example, the intestinal microbiota is involved in the digestion of certain foods that cannot be digested by the stomach and small intestine, and plays a key role in maintaining energy homeostasis. These foods are primarily dietary fibers such as xyloglucans, which are commonly found in vegetables and can be digested by a specific species of *Bacteroides* [30]. Other non-digestible fibers, such as fructooligosaccharides and oligosaccharides, can be utilized by beneficial microbes, such as *Lactobacillus* and *Bifidobacterium* [31]. Studies have clarified the role of the gut microbiota in lipid and protein homeostasis as well as in the microbial synthesis of essential nutrient vitamins [32]. The normal gut microbiome produces 50–100 mmol·L^{-1} per day of short-chain fatty acids (SCFAs), such as acetic, propionic, and butyric acids, and serves as an energy source to the host intestinal epithelium [33]. These SCFAs can be quickly absorbed in the colon and serve many diverse roles in regulating gut motility, inflammation, glucose homeostasis, and energy harvesting [34,35]. Furthermore, the gut microbiota has been shown to deliver vitamins to the host, such as folates, vitamin K, biotin, riboflavin (B_2), cobalamin (B_{12}), and possibly other B vitamins. A previous study demonstrated that B_{12} can be produced from delta-aminolevulinate (ALA) as a precursor [36].

In addition, gut-colonizing bacteria stimulate the normal development of the humoral and cellular mucosal immune systems [37]. The signals and metabolites of microorganisms can be sensed by the hematopoietic and non-hematopoietic cells of the innate immune system and translated into physiological responses [38]. Studies comparing normal mice with GF mice have found that GF mice show extensive defects in the development of gut-associated lymphoid tissue and antibody production [29,39]. A report has also demonstrated that the gut microbiota generates a tolerogenic response that acts on gut dendritic cells and inhibits the type 17 T-helper cell (Th17) anti-inflammatory pathway [40]. However, not all microbiota lead to health benefits. Some induce inflammation under certain conditions.

3. The human microbiota in disease

3.1. The human microbiota and infectious diseases

Infection is one of the most common diseases caused by dysbiosis of the microbiota. Importantly, infectious disease and its treatment have a profound impact on the human microbiota, which in turn determines the outcome of the infectious disease in the human host (Fig. 2). Offending pathogens colonize the intestinal mucosa, thus resulting in the induction of a strong inflammatory response, followed by the translocation of the intestinal bacteria [41,42]. Numerous studies have demonstrated the intimate relationship between infection and dysbiosis of the microbiota, and have shown that infection is associated not only with the microbiome, but also with viruses [43,44]. For example, the intestinal microbiota of patients with *Clostridium difficile* (*C. difficile*) infection (CDI) is significantly altered [45,46]. Disturbance of the microbiota is also associated with the progression of human immunodeficiency virus (HIV) [44,47], hepatitis B virus (HBV) [48], and other diseases [49,50].

3.1.1. *Infection with* Clostridium difficile

The pathological overgrowth of *C. difficile* is usually related to antibiotic-associated diarrhea, which is one of the most frequent complications following antibiotic administration and which is now a growing public health threat [45]. *C. difficile* is an anaerobic, gram-positive, spore-forming bacillus that is a component of the human gut microbiota. Antibiotics disturb intestinal mucosa homeostasis, thus decreasing resistance against toxin-producing *C. difficile* and promoting the progression of CDI [45]. Gu et al. [45] found that fecal bacterial diversity is reduced and the microbial composition dramatically shifts in patients following antibiotic administration, whether or not CDI is present. A decrease in putative butyrate-producing anaerobic bacteria and an increase in endotoxin-producing opportunistic pathogens and lactate-producing phylotypes have been detected in patients following antibiotic administration, whether or not CDI is present [45]. Putative butyrate-producing anaerobic bacteria are significantly depleted