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Modulation of Gut Microbiota in Pathological States

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ABSTRACT

The human microbiota is an aggregate of microorganisms residing in the human body, mostly in the gastrointestinal tract (GIT). Our gut microbiota evolves with us and plays a pivotal role in human health and disease. In recent years, the microbiota has gained increasing attention due to its impact on host metabolism, physiology, and immune system development, but also because the perturbation of the microbiota may result in a number of diseases. The gut microbiota may be linked to malignancies such as gastric cancer and colorectal cancer. It may also be linked to disorders such as nonalcoholic fatty liver disease (NAFLD); obesity and diabetes, which are characterized as "lifestyle diseases" of the industrialized world; coronary heart disease; and neurological disorders. Although the revolution in molecular technologies has provided us with the necessary tools to study the gut microbiota more accurately, we need to elucidate the relationships between the gut microbiota and several human pathologies more precisely, as understanding the impact that the microbiota plays in various diseases is fundamental for the development of novel therapeutic strategies. Therefore, the aim of this review is to provide the reader with an updated overview of the importance of the gut microbiota for human health and the potential to manipulate gut microbial composition for purposes such as the treatment of antibiotic-resistant *Clostridium difficile* (*C. difficile*) infections. The concept of altering the gut community by microbial intervention in an effort to improve health is currently in its infancy. However, the therapeutic implications appear to be very great. Thus, the removal of harmful organisms and the enrichment of beneficial microbes may protect our health, and such efforts will pave the way for the development of more rational treatment options in the future.

1. Introduction

Trillions of gut microbes reside in the human body, primarily within the gastrointestinal tract (GIT), where the population of gut microbes increases by approximately eight orders of magnitude from the proximal small intestine (10^3 mL^{-1} luminal content) to the colon (10^{11} g^{-1} content) [1]. Taking a 70 kg man as a reference, the total number of microbes is estimated to be 3.8×10^{13}, with a total weight of 0.2 kg [2]. Metagenomics sequencing is able to detect more than 1000 species of gut microbes, which are dominated by four major phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The genomes of these microbes encompass more than three million genes—approximately 100 times more than the entire human genome [3]. These gut microbes are acquired as early as during fetal development, and there is growing evidence for the presence of gut microbes in the placenta,

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amniotic fluid, and meconium [4–7]. Although gut microbes are phylogenetically conserved [8], the composition of human gut microbes can be affected by the host's personal hygiene, diet, drug intake, and disease status throughout his or her life [9,10]. These effects are more profound during the early life stages, when initial microbial colonization begins; however, the stability and homeostasis of gut microbes are usually established once the host is between 2–5 years of age [11].

In recent years, gut microbes have been gaining increasing attention due to their impact on human health [12]. The composition and function of our gut microbes appear to play an essential role in almost every biological process in the body. It has long been recognized that gut microbes can help their host to defend against pathogens, develop a healthy intestinal structure and immune system, and aid with the digestion of indigestible dietary fibers [13]. More recently, associations have also been recognized between gut microbes and diseases such as fatty liver disease, coronary heart disease, cancer, and obesity and diabetes [14]. In this review, we summarize and provide the most recent facts on the roles of gut microbes in human health, along with the unmet need for and solutions toward modulating the gut microbiota.

2. The function of gut microbes in human health

Gut microbes can coexist symbiotically with a healthy human. Short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, are fermentation products of dietary fibers produced by gut microbes. Although such fibers are otherwise indigestible by humans, their metabolites provide essential nutrients for colonic cells and play an important role in maintaining gut health. *Eubacterium hallii* (*E. hallii*) is considered to be an SCFA-producing microbe, and a recent discovery indicates that *E. hallii* is capable of producing high levels of glycerol/diol dehydratase, a key enzyme in the conversion of glycerol to 3-hydroxypropionaldehyde, a process that also produces cobalamin [15]. Levels of serotonin, a neurotransmitter synthesized in colonic enterochromaffin cells that is known to regulate a wide range of physiological activities such as enteric motor and platelet function, are regulated by the ingestion of spore-forming bacteria, mainly consisting of clostridial species [16]. Other studies have also investigated the relationship between gut microbes and gut metabolites.

Gut microbes are thought to metabolize phenyl-containing amino acids, such as tryptophan. Levels of tryptophan metabolites, such as indoxyl sulfate and indole-3-propionic acid, are highly correlated to the presence of gut microbes [17]. The production of indole-3-propionic acid is dependent on the colonization of the bacterium *Clostridium sporogenes* [17]. Furthermore, variations in *Faecalibacterium prausnitzii* colonies have been associated with levels of urinary metabolites involved in multiple metabolic pathways [18]. One such association has been identified between *Clostridium difficile* (*C. difficile*) and levels of fecal cholesterol and coprostanol, indicating that gut microbes play a crucial role in lipid metabolism [19]. Taken together, these studies highlight the essential role of gut microbes in maintaining normal physiology in humans. A deviation from the normal gut ecosystem could therefore be associated with a range of abnormalities, such as cancer, nonalcoholic fatty liver disease (NAFLD), obesity and diabetes, coronary heart disease, kidney dysfunction, and neurodegenerative diseases (Fig. 1); these associations will be summarized in the forthcoming sections.

2.1. Cancer

Levels of *Helicobacter pylori* are widely associated with an increased risk of gastric [20] and colorectal cancer [21]. A Gram-negative bacterium resides in the human stomach and can cause various diseases including gastritis, peptic ulcer, and gastric cancer [21]. Other resident gut microbes have also been identified as major factors in the increased risk of human colon cancer, including *Streptococcus bovis* [22,23], *Bacteroides fragilis* [24], and *Escherichia coli* (*E. coli*) [25]. These bacteria can cause inflammation and may trigger inflammatory bowel disease, thereby promoting the development of colorectal cancer. The proposed mechanism for this increased risk is recognized as involving Toll-like receptors (TLRs) and triggering downstream signaling pathways such as NF-κB, ERK, JNK, and p38, leading to an up-regulation of the growth factors and inflammatory mediators that promote neoplasia [26].

2.2. Nonalcoholic fatty liver disease

NAFLD is the most common chronic liver condition in both Western [27] and Asian [28] countries, and is considered to be a hepatic manifestation of metabolic syndrome. Due to its close link with obesity, the pathogenesis of NAFLD has been widely accepted to be the result of multiple "hits," including the contribution of the intestinal dysbiosis that is associated with obesity [29,30].

Studies show that a shift in the gut microbe composition is associated with obesity, and correlates closely with the prevalence and progress of NAFLD [31–34]. Zhu et al. [34] have suggested that the connection between gut-derived endogenous alcoholic and nonalcoholic steatohepatitis (NASH) might be involved in the pathogenesis of obesity in children. A significant compositional shift in gut microbes, such as the decrease of some selected members of Firmicutes, has been observed in patients with NAFLD [33]. A decrease in Bacteroidetes has also been found among obese patients with NASH compared with healthy controls [34]. In addition, Wang et al. [30] assessed the fecal microbial composition and its correlation with liver biochemistry in non-obese adult patients with NAFLD. Boursier et al. [35] have suggested that the severity of NAFLD is associated with gut dysbiosis along with a shift in metabolic function of the gut microbiota. Boursier et al. [35] also revealed that *Bacteroides* and *Ruminococcus* are independently associated with NASH and significant fibrosis, respectively. These studies indicate that an alteration in the composition of the gut microbiota is closely associated with the development of NAFLD.

Several different mechanisms have been uncovered that relate to gut microbe composition and the pathogenesis of NAFLD. Firstly, gut microbes have the potential to increase energy extraction from ingested food [36]; alter appetite signaling [37,38]; and enhance the expression of genes involved in *de novo* lipogenesis, β-oxidation, or inflammation-driven liver steatosis [39,40]. Secondly, gut microbes and the translocation of gut-derived bacteria or metabolites are likely to influence the development of hepatic inflammation [41,42]. Small intestinal bacterial overgrowth

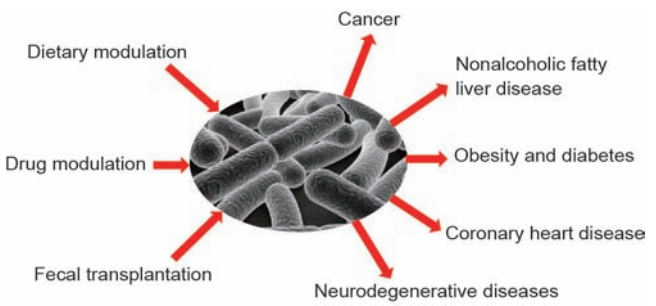

Fig.1. Summary of the role of gut microbes and their modulation in a pathological state.