Diet and Gut Microbiota in Health and Disease

Ting-Chin David Shen
Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract
Gut microbiota plays an important role in host health maintenance and disease pathogenesis. The development of a stable and diverse gut microbiota is essential to various host physiologic functions such as immunoregulation, pathogen prevention, energy harvest, and metabolism. At the same time, a dysbiotic gut microbiota associated with disease is altered in structure and function, and often characterized by a decrease in species richness and proliferation of pathogenic bacterial taxa. As a shared substrate between the host and the gut microbiota, diet significantly impacts the health and disease states of the host both directly and through gut microbial metabolite production. This is demonstrated in the examples of short-chain fatty acid and trimethylamine production via bacterial metabolism of dietary complex carbohydrates and choline, respectively. In disorders related to mucosal immune dysregulation such as inflammatory bowel disease, the dysbiotic gut microbiota and diet contribute to its pathogenesis. Reversal of dysbiosis through fecal microbiota transplantation and dietary interventions may thus represent important strategies to modify the gut microbiota and its metabolite production for health maintenance as well as disease prevention and management.

Introduction
We coexist with trillions of microorganisms that reside on our various mucosal surfaces, including the skin and respiratory, genitourinary, and gastrointestinal (GI) tracts. These microorganisms comprise bacteria, fungi, viruses, and archaea, and are collectively known as our microbiota. They have evolved with our
body to help us to maintain health in various ways such as immunoregulation, pathogen prevention, energy harvest, and metabolism [1, 2]. At the same time, the microbiota can become altered in structure and function by host and/or environmental factors. In the setting of disease, this is known as dysbiosis. Dysbiosis has been associated with various diseases, including diabetes, atherosclerosis, asthma, cancer, and inflammatory bowel disease (IBD) [3]. In this review, we will focus on the microbiota that inhabits our GI tract, otherwise known as the gut microbiota, and its interactions with diet. We will examine how the intricate and dynamic interplay between diet and gut microbiota affects both the health and disease states of the host.

**Early Gut Microbiota Development**

From birth, we are exposed to various microorganisms in our environment that gradually colonize our GI tract and become part of our gut microbiota. Various substances enter the body through the mouth and interact with the gut microbiota. These include food, antibiotics, and xenobiotics, each of which can exert strong and direct effects on the body and the gut microbiota, which in turn mediate downstream effects on the host. For example, the use of antibiotics can deplete certain endogenous microbial populations within the GI tract, allowing opportunistic pathogens to proliferate, as in the case of *Clostridium difficile* infection [4]. This infection results in severe diarrhea and abdominal pain that is frequently relapsing and refractory to conventional medical treatment. The use of fecal microbiota transplantation (FMT) from healthy donors has been shown to dramatically induce remission and prevent relapse [5]. The use of antibiotics early in life has also been linked to the development of obesity [6]. One study showed that low-dose antibiotic treatment (i.e. penicillin) of preweaning murine pups led to increased and lasting adiposity [7]. The metabolic consequences are likely secondary to altered gut microbiota rather than the effects of the antibiotic itself, as the obese phenotype is transferred to germ-free mice that received FMT from antibiotic-treated mice but not from control mice. These findings point to the critical time in infancy during which changes that affect either the host or the gut microbiota can have lasting metabolic effects on the other. For example, the cessation of breastfeeding correlates with the transition of microbiota to a more “adult-like” microbiome state with increased diversity and stability that may be critical for health with long-term consequences on growth and development. One recent study found that Malawian mothers with stunted infants have decreased levels of sialylated milk oligosaccharides compared to those with healthy infants [8]. Furthermore, the transfer of fecal microbiota from a
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The gut microbiota interacts with diet to affect host physiology and metabolism. Differences in the composition of the gut microbiota among individuals may explain the interindividual variations in response to the same dietary modifications. In a recent study, investigators compared the microbiota of participants that demonstrated improved glucose metabolism after administration of a short-term supplementation of barley kernel-based bread to those that did not respond [9]. They found a higher *Prevotella/Bacteroides* ratio in the responders, consistent with metagenomic analysis results showing an increased potential to ferment complex carbohydrates. This supports a personalized approach to improve metabolism based on analyses of gut microbial composition and function as well as dietary interventions. Another study found that there is high variability in postprandial glycemic response (PPGR) among an 800-person cohort after consuming standardized meals [10]. By collecting clinical and microbiota metagenomic data and integrating them into an algorithm, the investigators were able to accurately predict PPGR in a second independent cohort as well as personalize dietary interventions to reduce PPGR with consistent changes in gut microbiota composition. Other studies have quantified and accurately predicted fecal and blood metabolomics data using mathematical modeling of the human gut microbiome and its interactions with diet and the host [11].

The typical high-fat, high-sugar “Western” diet has been associated with decreases in gut microbial diversity, whereas an agrarian diet, rich in fruits and vegetables with high fiber content, is associated with increased bacterial gene richness [12]. Diet may affect the composition of the gut microbiota, although the extent of this effect remains controversial. Prior studies have suggested that different human populations may be grouped into distinct clusters based on the predominant bacterial taxa associated with different dietary patterns. For example, agrarian-based cultures that consume a plant-based diet generally have higher relative abundance of *Prevotella*, whereas industrialized populations that consume more animal proteins and fats generally have higher relative abundance of *Bacteroides* [12]. Other studies have demonstrated that the impact of diet on the gut microbiota composition may be less prominent. In a study that examined the gut microbiota of omnivores and vegans residing in an urban environment in the United States, differences in the gut microbiota between both...

**Diet and Microbial Metabolites**

As a shared substrate between the host and the gut microbiota, diet affects the host via both direct intestinal absorption and microbial metabolite production with downstream effects (Fig. 1). One prime example is the fermentation of dietary complex carbohydrates by gut microbiota to produce short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate. Certain bacterial species, including *Bacteroides thetaiotaomicron* and *B. ovatus*, contain more glycosidases and lyases than humans and thereby are able to metabolize nearly all the glycans in dietary fibers [2]. SCFAs perform a variety of functions. Butyrate serves as an important energy substrate for the colonic epithelium, where it can also affect proliferation, differentiation, and modulation of gene expression by inhibiting histone deacetylase [2]. Acetate and propionate can reach various organs through the bloodstream and serve as substrates for lipogenesis and gluconeogenesis as well as regulate different gene expressions by binding to G protein-coupled receptors GPR41 and GPR43 [1]. The end-organ effects of SCFAs through these receptors depend on the cell type. For example, SCFAs can modulate secretion of the hormone glucagon-like peptide-1 (GLP-1) through effects on enteroendocrine L cells in the distal small intestine and colon, thereby improving insulin
secretion [1]. On the other hand, SCFAs suppress inflammation in neutrophils via GPR43 signaling. SCFAs have also been shown to play a role in mucosal immune tolerance through regulation of colonic regulatory T cells [15].

**Risk of Cardiovascular Disease**

Another dietary component that strongly impacts upon the health of the host via gut microbial metabolism is choline. Choline is predominantly obtained from the diet in foods such as red meat and eggs, although it can also be synthesized by the host [2]. Choline is primarily metabolized in the liver, where it plays a role in lipid metabolism and the synthesis of very-low-density lipoprotein. The gut microbiota can also metabolize dietary choline to produce trimethylamine (TMA) through the enzymatic activity of choline TMA-lyase, which is encoded by the CutC gene carried by both human commensal and pathogenic bacteria [16]. TMA is further metabolized in the liver by the flavin monooxygenase system to produce TMA-N-oxide (TMAO), which has shown to be associated with the development of atherosclerosis and cardiovascular diseases [17]. Strategies to reduce the risk of cardiovascular disease from dietary choline consumption and microbial TMA production include interventions that reduce the representation of CutC-expressing gut bacteria and/or inhibit microbial TMA-lyase activity. As proof of concept, one study demonstrated that a structural analog of choline, 3,3-dimethyl-1-butanol (DMB), can nonlethally inhibit microbial TMA-lyase and TMA production to reduce TMAO levels in mice fed a high-choline diet [18]. DMB further inhibited choline diet-enhanced endogenous macrophage foam cell formation and atherosclerotic lesion development in mice. By compiling clinical, metagenomic, and metabolomic data, one can develop a comprehensive and individualized plan to not only prognosticate the risk of cardiovascular disease in association with choline consumption and gut microbial TMA production, but also prevent and manage disease risk via modulation of the gut microbiota.

**Effect of Chronic Kidney Disease**

Microbial metabolites such as TMA cross the intestinal epithelium to enter the body and circulate in the plasma. A steady state of the microbial metabolites in the host is then determined by a balance between input (from dietary substrate intake and subsequent microbial metabolism) and output (primarily via renal excretion). Changes in either can alter the plasma metabolome equilibrium. Patients with chronic kidney disease and decreased glomerular filtration rate may not be able to properly and efficiently excrete toxic metabolites that can lead to disease. Indeed, it has been shown that the age-adjusted risks of death and cardiovascular events vary inversely with the estimated glomerular filtration rate [19]. Also, TMA and TMAO levels were found to be elevated in patients with
end-stage renal disease [20]. These findings suggest that the determination of renal excretion of microbial metabolites may be important in cardiovascular disease prevention and management. Researchers who examine and characterize the abundance of additional metabolites that vary between healthy subjects and chronic kidney disease patients may reveal novel associations between microbial metabolites and host metabolic pathways linked to disease.

**Inflammatory Bowel Disease**

In addition to its role in cardiovascular disease, the gut microbiota impacts the development of inflammatory bowel disease (IBD). IBD represents a group of inflammatory disorders that primarily affect the GI tract, and Crohn disease (CD) and ulcerative colitis (UC) are the two most common types. CD presents with ulcerations anywhere along the GI tract from the mouth to the anus, whereas UC is restricted to the colon, but both can have extraintestinal manifestations that involve the skin, joints, and eyes. Over the past few decades, the incidence of IBD has risen globally [21], which may be related to improved diagnosis rates but also to potential changes to our diet and/or gut microbiota. The pathogenesis of IBD is multifactorial and incompletely elucidated. Genetic predisposition, immune system dysregulation, and environmental triggers all play a role (Fig. 2). The genetic contribution to the development of CD is found to be at most 30–40%, where the total contribution of all 163 IBD-associated genetic loci account for only 13% of CD variance [22]. This suggests that environmental factors likely represent the greatest contributor to the pathogenesis of IBD.
Current approaches to IBD treatment focus primarily on immunosuppression through medications such as biologics, immunomodulators, and corticosteroids. These therapies reduce intestinal inflammation without modifying its triggers, which may be related to luminal antigens in the diet and/or gut microbiota but remain incompletely characterized. At the same time, intestinal inflammation contributes to a dysbiotic microbiota in IBD, marked by a decrease in species richness as well as the proliferation of certain pathogenic bacterial taxa [22]. Studies have shown that the abundance of Bacteroidetes and Firmicutes, two dominant phyla in the human gut microbiota, decrease in IBD, whereas Proteobacteria such as Enterobacteriaceae increase in abundance. However, it is unclear if intestinal inflammation and changes in the redox potential of the intestinal milieu lead to the development of a dysbiotic microbiota with increased facultative anaerobes, or whether dysbiosis promotes the persistence of intestinal inflammation [23].

**Fecal Microbiota Transplantation**

Reversing dysbiosis through FMT represents a novel approach to IBD treatment. Two randomized clinical trials have investigated the use of FMT in UC with conflicting results. Moayyedi et al. [24] performed FMT via enema using stool from healthy unrelated donors given weekly for 6 weeks and found significantly higher remission rates at week 7 compared to the use of water enema as placebo (24 vs. 5%; \( p = 0.03 \)). Subgroup analyses revealed that the efficacy of FMT in UC may be donor dependent, and remission rates may be higher if FMT is performed early in the disease course. On the other hand, Rossen et al. [25] found that UC patients who received FMT by nasoduodenal tube at weeks 0 and 3 using stool from healthy donors showed no difference in remission rates at week 12 compared to those that received autologous FMT as placebo (30.4 vs. 20%; \( p = 0.51 \)). The major differences between both studies include the route and frequency of FMT administration. In the case of CD, no randomized clinical trials have been completed to date, although 4 case series involving 38 patients with CD showed a clinical response to FMT in 60.5% (95% CI 28–86%) [26]. In short, additional large-scale randomized controlled studies are needed before FMT can be recommended as a therapy for IBD.

**Exclusive Enteral Nutrition**

The use of defined formula diets has been investigated extensively for the treatment of IBD, in particular CD. Numerous studies in IBD patients as well as in murine models of colitis have shown that exclusive enteral nutrition (EEN), whether it is elemental, semi-elemental, or polymeric, can induce remission in CD and promote mucosal healing. In particular, one study demonstrated that EEN was as effective in inducing clinical remission and more effective than cor-
corticosteroids in mucosal healing [27], potentially sparing the adverse effects of corticosteroids on the development of and bone growth in children. However, studies have demonstrated less efficacy of EEN in treating UC or CD primarily involving the colon. Interestingly, the efficacy of EEN may not be dependent on the composition of the formula. A Cochrane review found no significant difference in efficacy among different formulations of EEN based on protein or fat content [28]. The exact mechanisms by which EEN ameliorates CD remain unclear and may include improved nutrition, exclusion or reduction in luminal antigens derived from food, direct anti-inflammatory effects of the formula, or changes in the gut microbiota [22]. Indeed, it is possible that EEN may eliminate some harmful substances in processed foods, as 2 recent studies showed that artificial sweeteners and dietary emulsifiers can affect the gut microbiota leading to metabolic disturbances and inflammation [29, 30].

Conclusion

In conclusion, both our gut microbiota and diet can strongly impact our health, with the effects of one mediated by the availability and property of the other. Dietary substrates can have beneficial and/or adverse effects on our body through direct absorption across the intestinal epithelium upon food passage through the GI tract. At the same time, the effects of various dietary components may not be fully realized without the metabolic capacity of the gut microbiota. The development of a rich and stable gut microbiota is crucial for the proper development of many host physiologic functions. In the setting of disease, the dysbiotic gut microbiota is characterized by decreased diversity and the predominance of a few pathogenic taxa which can adversely affect host health. Gut microbiota affects host health primarily through the metabolites they produce, which is strongly dependent upon the substrates available through dietary intake. Furthermore, diet can shape both the structure and the function of gut microbiota. The future of gut microbial medicine lies in an individualized approach based on a comprehensive analysis of the unique gut microbiomes different individuals possess and their dietary intake, taking into account their genetic and epigenetic predispositions. A better understanding of the intricate and dynamic relationship between diet, the gut microbiota, and the host is crucial for enhancing health and preventing disease.

Disclosure Statement

Conflict of interest: none.
References