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Review

The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease

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Food is a primordial need for our survival and well-being. However, diet is not only essential to maintain human growth, reproduction, and health, but it also modulates and supports the symbiotic microbial communities that colonize the digestive tract—the gut microbiota. Type, quality, and origin of our food shape our gut microbes and affect their composition and function, impacting host-microbe interactions. In this review, we will focus on dietary fibers, which interact directly with gut microbes and lead to the production of key metabolites such as short-chain fatty acids, and discuss how dietary fiber impacts gut microbial ecology, host physiology, and health. Hippocrates' notion "Let food be thy medicine and medicine be thy food" remains highly relevant millennia later, but requires consideration of how diet can be used for modulation of gut microbial ecology to promote health.

Introduction

Our gut harbors trillions of microbes representing all kingdoms of life that are essential for host development and physiology. This "gut microbiota" constitutes a complex community that interacts with each other and with the host to modulate biological processes essential for health. Our understanding of the biological roles of the gut microbiome, which include modulating juvenile growth (Schwarzer et al., 2016), maturation of the immune system (Rescigno, 2014), and modulation of glucose and lipid metabolism (Bäckhed et al., 2004), has increased dramatically in the past decade.

The microbiome contributes to homeostatic regulation in different tissues in our body (Schroeder and Bäckhed, 2016). However, although the overall interrelationship of humans with their microbiota can be considered a mutualistic symbiosis (Walter et al., 2011), eubiosis, which refers to a healthy balance of the microbes in the gut, can be disrupted, leading to the development of various chronic diseases with an underlying inflammatory condition (Hand et al., 2016). Most microbiome-linked pathologies have dramatically increased over the past century, suggesting that a change in lifestyle might disrupt gut microbiota symbiosis due to the loss of beneficial, protective microbes (Logan et al., 2016). In fact, Western-style diet, low in microbiota-accessible carbohydrates (MACs), may irreversibly reduce microbial diversity and lead to the disappearance of specific bacterial species in the digestive system (Sonnenburg et al., 2016). Accordingly, the low intake of dietary fibers and the increased amounts of fat and sugar in our food, typical for a Westernized lifestyle and nutrition, may at least in part contribute to depletion of specific bacterial taxa (Sonnenburg and Sonnenburg, 2014). These alterations may result in dysfunctions, contributing to the increase in the development of chronic inflammatory diseases such as intestinal bowel disease (IBD), colorectal cancer (CRC), allergies, autoimmune diseases, and obesity and its associated pathologies. These diseases can, at least in part, be prevented by dietary fiber, arguing for attempts to close the "fiber gap" through adjustment of human diet (Deehan and Walter, 2016). Here we will discuss how dietary fiber impacts gut microbial ecology, host physiology, and health by specifically focusing on mechanisms by which a low-fiber diet disrupts the microbial ecosystem and leads to a predisposition to chronic inflammatory diseases.

Dietary Fibers: Definitions, Characteristics, and Origin

The definition of dietary fiber has been a matter of debate and has evolved over the last decade (Jones, 2014). Most countries adopted the definition of the Codex Alimentarius commission from 2009, which defines dietary fiber as edible carbohydrate polymers with three or more monomeric units that are resistant to the endogenous digestive enzymes and thus neither hydrolyzed nor absorbed in the small intestine, and that belong to the following categories: (1) edible carbohydrate polymers naturally occurring in foods such as fruits, vegetables, legumes, and cereals; (2) edible carbohydrate polymers obtained from food raw materials by physical, enzymatic, and chemical means that have a proven physiological benefit; and (3) synthetic carbohydrate polymers with a proven physiological benefit. Although most national authorities adhere to this definition, some differences are found between dietary fiber definitions, and they mainly concern (1) considering some non-carbohydrates such as lignin and other substances present in cell walls linked to polysaccharides as dietary fibers (Stephen et al., 2017) and (2) the minimum number of carbohydrate monomers to be included.

Dietary fibers are classified according to several parameters, including their primary food source, their chemical structure, their water solubility and viscosity, and their fermentability.

Dietary fibers are subdivided either into polysaccharides (non-starch polysaccharides [NSPs], resistant starch [RS], and resistant oligosaccharides [ROs]) or into insoluble and soluble forms (Deehan et al., 2017). Most insoluble forms such as cellulose and hemi-cellulose have a fecal bulking effect, as they reach the colon and are not, or only slowly, digested by the gut bacteria. Most soluble fibers do not contribute to fecal bulking, but are fermented by the gut bacteria and thus give rise to metabolites such as short-chain fatty acids (SCFAs). In contrast to ROs, most soluble NSPs, especially polymers with high molecular weight such as guar gum, certain pectins, β-glucans, and psyllium, are viscous, meaning that they are able to form a gel structure in the intestinal tract that can delay absorption of glucose and lipids influencing post-prandial metabolism (Deehan et al., 2017).

Soluble and insoluble fibers are found in different food sources such as legumes, vegetables, nuts, seeds, fruits, and cereals in different proportions. However, not all types of fibers are present in the same food categories. RS can only be found in starchy foods such as cereals, legumes, tubers, and non-mature fruits like green bananas, while pectins are more enriched in fruits and some vegetables, whereas β-glucans and arabinoxylans are present in cereals (Lovegrove et al., 2017). Although fibers are present in a wide range of plant-based food sources, consumption is low in Western countries. Fortification of foods with extracted or synthesized non-digestible carbohydrates or their use in dietary supplements therefore constitutes a strategy to increase fiber intake. A wide range of these carbohydrate polymers and oligosaccharides is commercially available (Deehan and Walter, 2016). Some of these compounds are considered "prebiotics" on the premise that they exert health benefits by selectively inducing beneficial bacterial populations in the gut. However, the assignment of only certain fibers as prebiotics based on these criteria is somehow arbitrary (Bindels et al., 2015; Deehan et al., 2017). As we describe in the following sections, virtually all fibers will induce specific shifts in microbiota composition due to competitive interactions, and which of these compositional shifts contribute to health benefits, or if they are even functionally relevant, has not yet been established (Bindels et al., 2015). In contrast, the mechanisms that have been demonstrated to contribute to health benefits do not rely on a selective utilization of the carbohydrate but rather on metabolic compounds (e.g., SCFAs) (Koh et al., 2016), physiological changes (pH lowering), or protection of the mucus layer (Schroeder et al., 2018; Zou et al., 2018). Therefore, it may be worth considering a shift in focus of the prebiotic concept away from the selective effect of specific dietary components on gut microbial communities and instead toward ecological and functional consequences of fiber fermentation, which is more relevant for host physiology (Bindels et al., 2015).

Impact of Dietary Fiber on Microbial Ecology in the Gut

Diet has a major impact on gut microbiota composition, diversity, and richness. Different components of the diet will shape the gut bacterial communities in a time-dependent manner. Long-term dietary patterns, particularly the intake of protein and animal fat (*Bacteroides*) versus carbohydrates or plant-based foods (*Prevotella*), are associated with so-called enterotypes (Wu et al., 2011). This dichotomy in the *Prevotella*/*Bacteroides* ratio was also observed between industrialized and non-industrialized human populations, suggesting that these bacterial populations are driven by long-term differences in diet, e.g., meat (drives *Bacteroides* in the West) and dietary fiber (drives *Prevotella* in non-Westernized populations). Comparing gut microbiota of children from rural (Burkina Faso [BF]) versus urban (Italy) communities reflected the impact of diet on the microbiome. De Filippo et al. found a significant difference within the gut microbiota composition in both groups after weaning. A significant increase in the abundance of bacteria from the genera *Prevotella* and *Xylanibacter* associated with higher levels of fecal SCFAs was observed in BF children, thus reflecting the ability of these individuals to degrade complex carbohydrates (De Filippo et al., 2010). These differences are independent of ethnicity as the gut bacterial communities of BF children living in urban, as opposed to rural, areas of BF became more similar to the Italian children. When people move to urban areas, they are exposed to a Westernized lifestyle, including access to food rich in fat and simple sugars. Accordingly, the microbiota of children living in the urbanized areas of BF have bacteria that are more suited to metabolize animal protein, fat, and sugar-rich foods, while children living in rural zones have a bacterial reservoir (enrichment in *Prevotella*, *Treponema*, and *Succinivibrio*) adapted for fiber and carbohydrate fermentation from vegetables. Interestingly, the microbial communities of BF children living in urban areas were comparable to those of Italian children, highlighting the important impact of the diet independent of host genetic (De Filippo et al., 2017).

These findings are supported by a study from Schnorr et al. that showed that the Hadza hunter-gatherer individuals possess higher levels of microbial richness and biodiversity compared to Italian urban controls. The gut microbiota of these individuals had increased Bacteroidetes and decreased Firmicutes abundances, and unexpectedly they almost lack the Actinobacteria phylum, including low levels of *Bifidobacterium*. Interestingly, SCFA production in Hadza was characterized by increased propionate concentrations, while the Italian cohort had more butyrate (Schnorr et al., 2014). This segregation in SCFA production may reflect differences in dietary variation related to the amount and type of fiber and carbohydrates consumed by both communities. Similarly, analysis of the microbiome of Malawian, Venezuelan, and American populations from infants to adults showed significant differences, which were associated with diet and culture (Yatsunenko et al., 2012). The microbiome of Malawian and Venezuelan infants was characterized by the enrichment of bacterial genes implicated in vitamin B12 biosynthesis, host glycan utilization, and urea catabolism, while increased ability to metabolize fucose was observed in US infants. In the same study, significant differences in microbial functions between US versus Malawian and Venezuelan adults were shown that corresponded to carnivorous (protein consumption) versus herbivorous (dietary fiber consumption) profiles, respectively.

Consistent with these observations, environmental lifestyle changes rather than host genetics influence gut microbiota diversity, and industrialization leads to a significant depletion of species (Smits et al., 2017). The underlying mechanisms for reduced diversity are proposed to include antibiotic utilization, clinical practices (e.g., cesarean sections), and sanitation (Sonnenburg and Sonnenburg, 2014). In agreement with this notion,

the most diverse microbiome to date is observed in the Yanomami, an indigenous population with limited contact to the industrialized world (Clemente et al., 2015; Smits et al., 2017). However, even in non-industrialized human populations with access to antibiotics, such as rural Papua New Guineans, diversity is higher than in the West (Martínez et al., 2015). Thus, other environmental factors that differentiate Western and non-Western human populations such as diet may be more important. The non-Western populations consume far less refined diets and significantly higher proportions of dietary fibers, suggesting that this dietary component contributes to microbiota richness. In fact, Sonnenburg et al. investigated the consequences of the lack of fiber (referred to as MACs) intake in mice colonized with a human microbiota and showed that a low-MAC diet led to dramatically reduced microbial diversity in just three generations, which could not be restored when mice were moved to a normal-MAC diet (Sonnenburg et al., 2016). Interestingly, they also observed seasonal reductions in microbiome diversity in Hadza hunter-gatherer individuals of Tanzania. The microbiota composition and function of this community varied according to seasonal changes and reflected dietary habit as well as the type of food eaten (Smits et al., 2017). During the wet season, the representation of CAZymes in the metagenome that are specific for plant carbohydrates was reduced and was associated with a disappearance-reappearance cycle of specific OTUs (operational taxonomic units) such as *Prevotellaceae*, which are lost in industrialized populations. Similar seasonal observations were found in hibernating free-ranging brown bears in which microbes associated with fiber utilization were increased during the late spring and depleted during hibernation. The enrichment of these bacteria led to increased efficiency in calorie harvest from a fiber-rich diet (Sommer et al., 2016). Thus, periodic reduction in fiber intake does not appear to have long-lasting effects on the microbiome (Smits et al., 2017), whereas long-term reduction in fiber intake, like in the Western world, may lead to permanent extinction of important microbial taxa, similar to the findings in mice (Sonnenburg et al., 2016).

In addition to the long-term effects of the diet on the microbiome as outlined above, gut microbial communities respond within 24 hr to dramatic changes in macronutrient composition (David et al., 2014). In particular, taxa with fiber-degrading capacity increased when humans were fed a plant-based diet. In agreement, a dramatic and rapid rearrangement in the human microbiome within 24 hr after reduction of carbohydrate (including fiber) intake to 30 g/day was observed in a recent human cohort study (Mardinoglu et al., 2018). As expected, the loss in carbohydrates dramatically reduced the abundance of fiber-degrading bacteria, while the abundance of *Lactococcus*, *Eggerrthella*, and *Streptococcus* increased, resulting in reduced levels of SCFAs (Mardinoglu et al., 2018).

Fiber Forms the Food Webs for Bacteria

Dietary administration of fiber alters the niche environment in the gut by providing substrates for microbial growth, allowing microbial species that are able to utilize these substrates to expand their populations (Deehan et al., 2017). Together, the gut microbiome harbors 130 glycoside hydrolase, 22 polysaccharide lyase, and 16 carbohydrate esterase families, which provide the microbiome flexibility to switch between different energy sources of fibers depending on availability (Flint et al., 2012). Species belonging to Firmicutes and Actinobacteria are the main responders to dietary fiber (Deehan et al., 2017), although they contain relatively few fiber-metabolizing enzymes per organism. However, they generally have more specialized roles such as the initiation of complex substrate degradation. For example, administration of RS has been shown to enrich *Bifidobacterium adolescentis*, *Ruminoccocus bromii*, *Eubacterium rectale*, and *Parabacteroides distasonis* in a subset of individuals dependent on RS (Martínez et al., 2010; Walker et al., 2011). In contrast, the consumption of galactooligosaccharides mainly induces *Bifidobacterium* species that possess the enzymatic machinery to efficiently utilize this substrate (Davis et al., 2011). It is not only the enzymatic capacity (as a primary fiber degrader) that determines the ability of a microbe to benefit from a dietary fiber, but also its ability to "adhere" to a substrate, tolerate the environmental conditions changed through the fiber (e.g., increased acidity through fermentation), and benefit from carbohydrate breakdown products (secondary fiber degraders) and metabolites (through cross-feeding) (Deehan et al., 2017). Primary fiber degraders can hereby function as "keystone" species that initiate the utilization of a complex fiber through what can be considered a "guild" of species (Zhao et al., 2018). For example, *R. bromii* is considered a keystone species for the degradation of RS and contributes significantly to butyrate production in the colon, although the species itself does not produce butyrate. Similar keystone species are likely to exist for other dietary fiber types but have not yet been identified.

The impact of dietary fiber on microbiota composition displays several consistent characteristics. First, the observed shifts induced by non-digestible carbohydrates in humans, regardless if they are accepted prebiotics or not, are restricted to a limited number of taxa (Davis et al., 2011; Martínez et al., 2010; Walker et al., 2011). Second, the magnitude of the induced changes can be substantial, with specific species constituting more than 30% of the total sequences obtained by amplicon sequencing of the fecal microbiota (Davis et al., 2011; Martínez et al., 2010; Walker et al., 2011). However, these changes are only maintained so long as the substrate is consumed. Third, the microbial response to dietary fiber is highly individualized (Davis et al., 2011; Martínez et al., 2010). The reason for this individuality is not yet understood. Individuals may lack keystone species (Ze et al., 2012) or lack strains that possess the enzymatic capacity to utilize a specific substrate (Zhao et al., 2018).

Microbial Metabolism of Dietary Fibers and Functional Implications

Dietary fibers are important energy sources for cecum and colon-residing microbiota. Anaerobic bacteria under specific intestinal conditions activate their machinery, constituted of key enzymes and metabolic pathways, which can metabolize complex carbohydrates, thus leading to the production of metabolites such as SCFAs.

SCFAs are organic products mainly composed of acetate, propionate, and butyrate. SCFAs possess key roles in regulating host metabolism, immune system, and cell proliferation (Koh et al., 2016). SCFAs are found at high concentration in the cecum and proximal colon, where they are used as energy sources in colonocytes (especially butyrate), but can also be transported

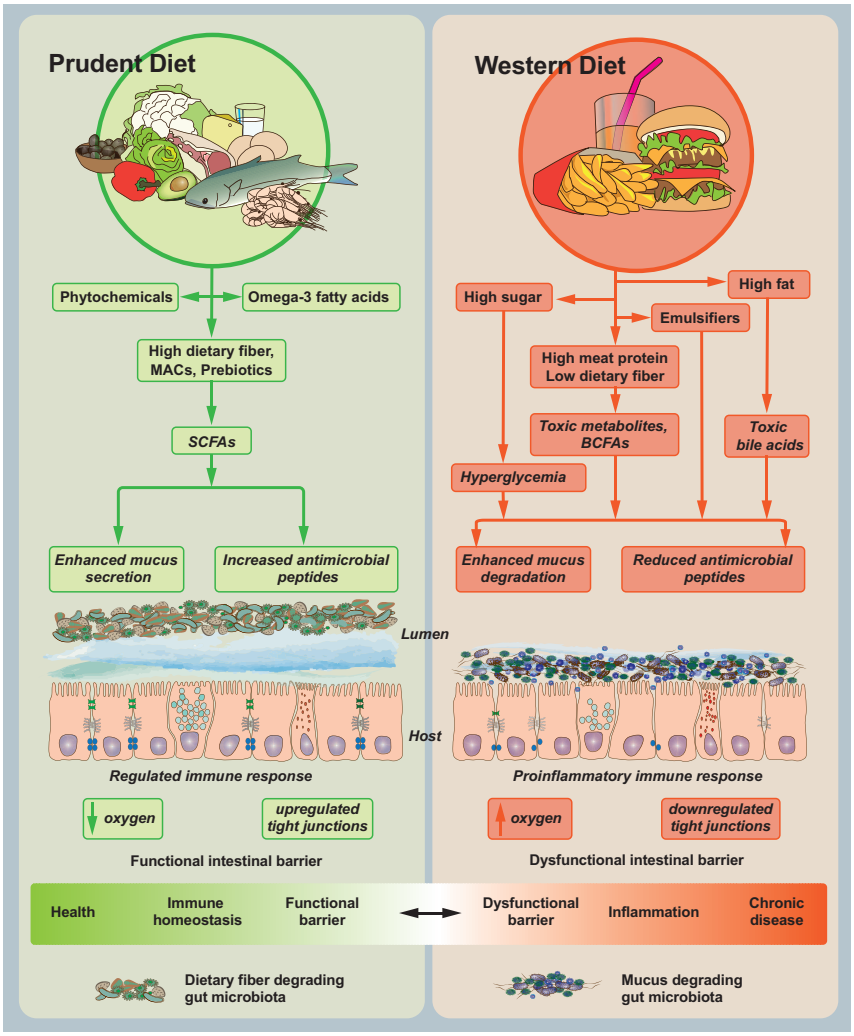

Figure 1. Effect of Low- and High-Fiber Diet on Gut Microbiota Composition, Diversity, and Function in Host Physiology

A diet rich in fiber contributes to the maintenance of a healthy gut microbiota associated with increased diversity and functions such as the production of short-chain fatty acids (SCFAs). With the industrialization of the diet, low fiber intake, and high protein and sugar consumption, the diversity of the gut bacteria is reduced and their function is altered, including significant reduction in their ability to produce SCFAs, and associated with the appearance of chronic inflammatory diseases. High fiber intake and the production of SCFAs by the gut bacteria enhance mucus and anti-microbial peptide production, and increase expression of tight junction proteins. In addition, SCFAs reduce oxygen levels and maintain a functional immune system. These biological processes are disrupted when the diet is shifted toward a Western lifestyle and may lead to increased susceptibility to infections and IBD, and to impaired physiology.

to the peripheral circulation via the portal vein to act on the liver and peripheral tissues. Although the levels of SCFAs are low in the peripheral circulation, it is now well accepted that they act as signaling molecules and regulate different biological processes in the host (Koh et al., 2016).

A low intake of dietary fiber does not only lead to reduced microbial diversity and SCFA production, but also shifts the gut microbial metabolism toward the utilization of less favorable substrates, particularly dietary and endogenously supplied proteins (Cummings and Macfarlane, 1991) and host mucins (Desai et al., 2016; Schroeder et al., 2018; Zou et al., 2018), which may be detrimental to the host. Supplying human volunteers with a high-protein, low-carbohydrate diet did not only significantly reduce the production of total SCFAs and butyrate (Duncan et al., 2007), but also led to an increase in potentially detrimental metabolites derived from the fermentation of amino acids, including branched-chain fatty acids, ammonia, amines, N-nitroso compounds, phenolic compounds including *p*-Cresol, sulphides, indolic compounds, and hydrogen sulfide. The cytotoxic and pro-inflammatory nature of these metabolites contributes to the development of chronic diseases, particularly CRC (Windey et al., 2012). Given the trade-off between saccharolytic and proteolytic fermentation, a high-fiber diet is likely to inhibit protein fermentation counteracting many of the detrimental effects of meat and fat, making these food components less detrimental.

Effect of Dietary Fibers and SCFAs on Host

Mucus Production and Luminal Oxygen Levels

The gut epithelium is covered and protected by a mucus layer, thus keeping bacteria separated from the mucosa (Johansson et al., 2008). One of the mechanisms used by the host to prevent microbe invasions and susceptibility to infections is to maintain a well-structured and intact mucus layer. The gut microbiota and diet are two important components to maintain a normal structure and production of the intestinal mucus. An altered gut microbiota resulting from a diet low in fibers leads to a severe deterioration of the mucus layer and can enhance the susceptibility to infections and the development of chronic inflammatory diseases (Figure 1) (Desai et al., 2016; Johansson et al., 2008; Schroeder et al., 2018; Zou et al., 2018).

Dietary fibers and SCFAs stimulate mucus production and secretion. Both acetate and butyrate maintain a balance for mucus production and secretion. *Bacteroides thetaiotaomicron*, an acetate and propionate producer, promotes goblet cell differentiation and expression of mucin-related genes. In contrast, *Faecalibacterium prausnitzii*, a consumer of acetate and a butyrate producer, reduces the effect of acetate on mucus and prevents overproduction of mucus, thus maintaining an appropriate structure and composition of the gut epithelium (Wrzosek et al., 2013). Furthermore, dietary fibers can also mechanically stimulate the intestinal epithelium to secrete mucus (McRorie and McKeown, 2017).

Prolonged lack of dietary fibers damages the mucus barrier and is associated with increased abundance of mucin-degrading bacteria such as *Akkermansia muciniphila* (Desai et al., 2016). Furthermore, when the diet is devoid of dietary fibers some gut bacteria switch their metabolism to use mucin glycans by inducing gene expression of mucin-degrading enzymes (Sonnenburg et al., 2005). Consistent with this, Western-diet feeding (very low fiber content) of mice increases the penetrability of the inner mucus layer and lowers growth rate, rendering the mucus penetrable, and may thus increase the susceptibility to infections (Schroeder et al., 2018). Interestingly, low amount of inulin (1%), a prebiotic with bifidogenic effect, or *Bifidobacterium longum* administration prevented mucus defects. Inulin supplementation corrected the penetrability of the inner mucus layer, while *B. longum* supplementation restored the mucus growth rate defect, suggesting that those two parameters are independent and might be regulated by different factors. Neither 1% inulin nor *B. longum* administration improved metabolic features of obese animals. In contrast, high inulin intake (20%) prevented microbiota encroachment, improved gut health, and led to a resolution of the low-grade inflammation associated with improvement in metabolic parameters of obese mice (Zou et al., 2018). Thus, it appears that although low levels of inulin are sufficient for restoring local effects in the gut, including protection against enteric infections (Desai et al., 2016), higher concentrations are required for achieving metabolic benefits, suggesting separate and dose-dependent mechanisms. However, such high doses of inulin would most likely not be tolerated in humans (Figure 1).

An important recent discovery from the Bäumler lab demonstrated that beta-oxidation of butyrate by colonocytes consumes oxygen and results in an anaerobic milieu in the gut (Byndloss et al., 2017). Since butyrate-producing bacteria are very sensitive to oxygen, their abundance is reduced further, lowering the amount of butyrate production. This feedforward loop results in increased luminal oxygen levels, allowing Proteobacteria such as *Escherichia coli* and *S. enterica* serovar Typhimurium to bloom. This novel mechanism provides not only an explanation for many of the pathologies associated with a low-fiber diet, but also a mechanistic understanding for why reduced microbial diversity is observed in both humans and mice on a low-fiber diet.

The Immune System

A healthy gut microbiota contributes to the maturation and the development of the immune system (Rescigno, 2014). One such mechanism is through SCFAs, which are known to promote generation of colonic regulatory T cells (Tregs) in a GPR43-dependent manner as well as by inducing histone H3 acetylation (Furusawa et al., 2013; Smith et al., 2013). Accordingly, maternal high-fiber feeding during pregnancy and lactation modulate thymic microenvironment and induced autoimmune regulator (Aire) expression, a factor expressed in the thymus, a primary lymphoid tissue, which is essential for the maturation of T cells. The maternal fiber intake increased butyrate levels in the blood of the offspring and contributed to the enhancement of peripheral and thymic Treg counts of the animals in a GPR41-dependent manner (Nakajima et al., 2017). In contrast, high-fat diet induces premature thymic involution reflected by the reduced thymocyte counts and the increased apoptosis of developing T cell populations (Yang et al., 2009). These phenotypes may help explain why obese people have accelerated thymic aging and alteration of primary lymphoid tissue architecture (Andersen et al., 2016).

Taken together, these observations emphasize the important role of SCFAs in regulating and maintaining a normal function of the innate and adaptive immune system, and although we have limited the discussion to a few examples, there are several links between fiber intake, immune system, and diseases as illustrated below (Figure 1).

The Local Beneficial Effect of Fiber Intake

IBD and CRC

The incidence of IBD is increasing in occidental countries, and the Westernization of the diet and lower gut bacterial diversity, especially reduction in butyrate-producing bacteria, have been suggested to contribute to increased IBD prevalence (Ott and Schreiber, 2006). In agreement, low fiber intake is correlated with increased incidence of Crohn's disease (Hou et al., 2011) and exacerbates colitis in mice. By investigating the effect of 40 defined diets in mice, Llewellyn et al. demonstrated that dietary protein and fibers had negative and beneficial effects on colitis development, respectively. Similarly, mice developed DSS-induced colitis proportional to the amount of fibers in the diet (Macia et al., 2015). The preventive effect of fibers may be due to increased cecal SCFA levels, especially butyrate, which is known to have anti-inflammatory properties, potentially through GPR43 (Maslowski et al., 2009).

IBD can lead to CRC (Beaugerie and Itzkowitz, 2015), which is the third most common cancer (Johnson et al., 2013). CRC is associated with genetic and environmental factors such as dietary habits, smoking, and physical activity (Johnson et al., 2013), and butyrate-producing bacteria are reduced in CRC patients compared to healthy volunteers (Wang et al., 2012). Reduced dietary fiber intake is associated with increased incidence of CRC (Aune et al., 2016). Thus, it is not surprising that diets low in fat and high in fiber-containing grain products, vegetables, and fruits have health claims, approved by the FDA, for a potential reduction of the incidence of developing some types of cancer. In agreement, a dietary intervention increasing dietary fibers in African Americans changed the microbiome and increased butyrogenesis, resulting in reduction of biomarkers of cancer risk (O'Keefe et al., 2015).

The Systemic Beneficial Effect of Fiber Intake

Lung COPD and Asthma

Fiber intake and SCFAs not only act locally but can also affect lung physiology. Patients suffering from severe persistent asthma consumed more fat and less fiber compared with healthy controls (Berthon et al., 2013). Similarly, a prospective study showed an inverse relationship between cereal fiber intake and the risk of chronic obstructive pulmonary disease (COPD) (Raffatellu et al., 2008). In mice, prolonged low-fiber feeding aggravated allergic airway disease in mice (Trompette et al., 2014), which could be corrected by administration of the SCFA propionate (Trompette et al., 2014). Thus, it appears that the increase in different airway disease may be coupled to microbial fermentation of dietary fibers.

Obesity and Diabetes

The epidemic of obesity is occurring in both developing and industrialized countries. Obesity is influenced by several factors

such as specific dietary and lifestyle behaviors and is associated with reduced microbial diversity, which may reflect reduced fiber intake. In agreement, a prospective study on 120,877 non-obese individuals demonstrated that long-term weight gain was inversely correlated with intake of dietary fibers, suggesting their role in limiting long-term body weight gain (Mozaffarian et al., 2011). Similarly, high fiber intake is associated with increased gut microbial diversity and lower long-term weight gain (Menni et al., 2017). A recent intervention study with oligofructose-enriched inulin for 16 weeks in overweight and obese children reduced their fat mass, suggesting that increased intake of fermentable fibers may have beneficial effects on obesity (Nicolucci et al., 2017).

Obesity is associated with type 2 diabetes (T2D). In contrast to obesity, T2D is associated with reduced abundance of fiber-degrading bacteria (Karlsson et al., 2013; Qin et al., 2012). Accordingly, diets with high glucose index (high in digestible starch and low in fiber) are associated with an increased diabetes risk (Sluijs et al., 2012). Administration of soluble fibers, such as oligofructose and long-chain inulin, corrected gut dysbiosis, reduced body weight gain and low-grade inflammation, and improved glucose metabolism, which was at least attributed to decreased intestinal permeability and endotoxemia (Cani et al., 2007, 2008). Furthermore, providing healthy human volunteers with barley kernel-based bread (BKB), rich in β-glucans, improved glucose metabolism (Nilsson et al., 2015). Thus, it is tempting to speculate that whereas the reduced diversity in obesity is caused by reduced fiber intake, lack of fiber-degrading and butyrate-producing bacteria may predispose to T2D.

SCFA-Independent Effect of Dietary Fibers

Thus far, this review has focused mainly on the fermentation of fibers to SCFAs, but it is important to mention that microbial metabolism of fibers also has additional effects. Ferulic acid (FA) is a phenolic compound that can be found in plant cell wall and serves to enhance its rigidity and strength. Microbial metabolism of dietary fibers, for example those found in cereal bran, leads to the release of FA by bacteria such as *L. fermentum* NCIMB 5221 harboring the FA esterase gene (Tomaro-Duchesneau et al., 2012). In the digestive tract, FA can either act locally to modulate gut physiology or be transported in its free form into the bloodstream to influence systemic health. FA has antioxidant and anti-inflammatory properties and could be considered as a potential therapeutic treatment for various chronic pathologies such as neurodegeneration, obesity, diabetes, and cancer. FA administration stimulates neurogenesis in corticosterone-treated mice and was shown to prevent Aβ-related toxicity in Alzheimer disease models (Mori et al., 2013). In a model of ulcerative colitis, FA treatment showed anti-inflammatory properties reflected by the reduction of pro-inflammatory cytokine and the upregulation of IL-10 (Sadar et al., 2016). In addition, FA can prevent development of diet-induced obesity (de Melo et al., 2017) and has anti-diabetic effects: diabetic rats treated with this compound normalized glucose and serum insulin levels (Narasimhan et al., 2015).

Dietary fibers can also bind different micro- and macronutrients including ions such as copper, calcium, and zinc and transport them to the distal gut, where they are released when the fiber is metabolized by the colonic bacteria (Bergman et al., 1997). Acidification through the production of SCFAs further increases mineral solubility and absorption by the colon (Baye et al., 2017; Trinidad et al., 1997). Some of these ions possess anti-microbial action under specific conditions and help in the prevention from gut infections. Thus, we hypothesize that the capacity of different dietary fibers to bind ions in the gut may serve to establish important local reservoirs. Accordingly, zinc has been shown to promote the metabolic activity of gut microbiota of weaned piglets (Højberg et al., 2005), resulting in improved metabolic health parameters. In parallel, a recent study in chickens demonstrated that zinc-deficient diet results in lower gut microbiota diversity associated with reduced SCFA production (Reed et al., 2015). These observations suggest that dietary fibers could participate in preserving a healthy intestinal ecology by providing micronutrients to bacteria and the host in the distal gut. However, some studies suggested that mineral binding to dietary fibers may lower their availability for the host, which may lead to mineral deficiency (Baye et al., 2017). It is thus important to determine the mineral binding capacity and effects on homeostasis for different fibers.

In addition to regulating bioavailability to nutrients as suggested above, fibers may also form platforms for bringing bacteria and biomolecules into close proximity. For example, conjugated bile acids in the small intestine can bind to fibers before they are deconjugated by *Bacteroides* and *Lacotobacillus* species (Kahlon and Woodruff, 2003). Deconjugation is a prerequisite for further biotransformation to secondary bile acids by low abundant bacteria such as *Clostridium scindens* (Reddy et al., 1992). We thus suggest that binding of both bile acids and specific bacteria to the same fiber, which serves as a platform, can explain how low abundant bacteria can serve as efficient transformers of biomolecules and thus increase production of secondary bile acids. Secondary bile acids, such as deoxycholic acids, have a number of physiologically important effects and have been positively associated with both CRC (Bernstein et al., 2005) and improved metabolism (Li and Chiang, 2015) (Figure 2). This platform concept can perhaps be extended to additional bacteria and biomolecules.

One Size Does Not Fit All: Fiber Quantity and Personalization

The role of dietary fibers in preventing and alleviating chronic inflammatory diseases in humans has been widely studied during the past years, although findings from intervention trials are often inconsistent (Buyken et al., 2014). Studies performed on animal models usually have more dramatic effects, but also use higher amount of fibers compared to levels used in human clinical trials, especially for prebiotics, whose dose is often 40-fold higher on a body weight basis (Schaafsma and Slavin, 2014). In fact, the dose of dietary fiber used in animal studies more closely resembles the estimated amount of fiber consumed by our ancestors before the advent of agriculture (>100 g/day) (Eaton et al., 1997). Therefore, even fiber doses that meet the dietary recommendations of today (~30 g/day) (Jones, 2014) are still far below the fiber amounts ingested when the symbiosis between us and the microbes was formed (Deehan and Walter, 2016). Non-industrialized human populations that consume fiber amounts of more than 50 g/day, such as rural South Africans and rural Ugandans, are known to be

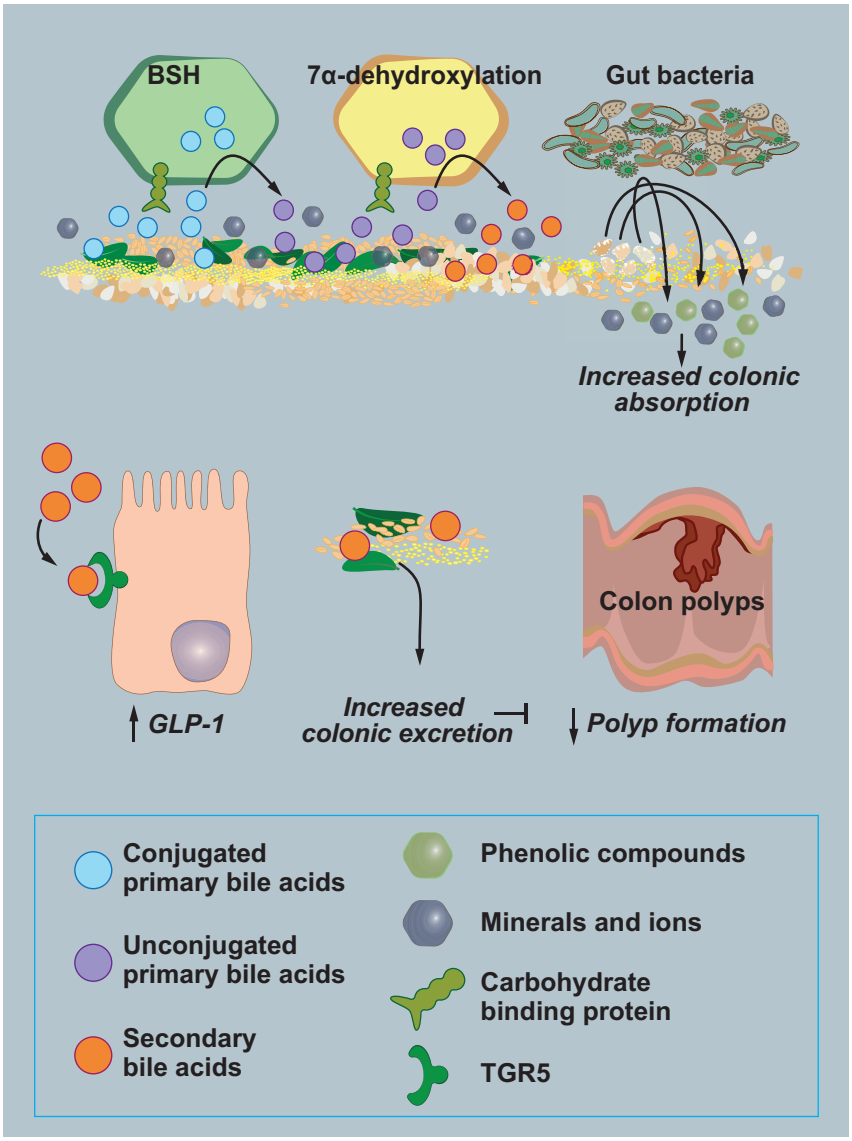

Figure 2. SCFA-Independent Effect of Dietary Fibers in Colon

Dietary fibers bind conjugated primary bile acids (BAs) and may serve as a platform for gut bacteria that possess the bile salt hydrolase (*Bsh*), leading to the production of non-conjugated BAs. These can also bind to dietary fibers and be further metabolized by specific bacteria with 7-alpha dehydroxylation activity, thus generating secondary BAs. The fact that dietary fibers can bind secondary BAs suggests that they may play a role in regulating BA levels within the gut. This structural interaction may modulate host physiology either by preventing the accumulation of toxic BAs that can lead to the development of polyps and colorectal cancer (CRC) or by increasing the disposal of BAs that can activate TGR5 to increase glucagon-like peptide 1 (GLP-1) secretion. In addition, bacterial degradation of dietary fibers leads to the release of minerals and phenolic compounds, which can be absorbed by the distal gut.

largely free from chronic inflammatory diseases. Most importantly, moving African Americans to an "African-style" diet with 55 g fiber reversed risk markers of CRC within only 2 weeks (O'Keefe et al., 2015). Therefore, it is plausible that dietary fiber supplementation below these doses, which are used in virtually all human intervention trials today, are too low and physiologically irrelevant. Recent suggestions postulate daily fiber amounts of greater than 50 g to achieve health benefits linked to fiber (Deehan et al., 2017; O'Keefe, 2018), and accordingly, human interventions with greater than 50 g/day of fiber observed significant improvements in the assessed health markers (Jenkins et al., 2001; O'Keefe et al., 2015; Pedersen et al., 2013; Zhao et al., 2018). However, high fiber amounts will be challenging to achieve with regular food items but could be achieved by systematically supplementing the food supply with dietary fiber sources (Deehan and Walter, 2016).

There are concerns, however, that modern humans may have problems tolerating such high doses of fiber as its intake can lead to undesirable side effects, such as flatulence, bloating, stomachaches, diarrhea, and constipation (Grabitske and Slavin, 2009), and may thus be negative for individuals with irritable bowel syndrome. In addition, a few recent studies using animal models suggest that fiber intake and/or their derived metabolites may have a negative impact on host health in specific conditions such as colitis (Miles et al., 2017) and/or CRC (Belcheva et al., 2014). Although the overwhelming data suggest beneficial effects of fibers, there may be instances in which caution in making generalizable recommendations is warranted. It should be noted that tolerance to fiber is dependent on the individual and often improves over time as the gastrointestinal tract and microbiota adapt to higher doses of dietary fiber (Mego et al., 2017). It is therefore realistic to have the diet of modern humans enriched with fiber beyond 50 g daily, especially with sufficient acclimatization and if slower fermenting polysaccharides, such as RS, arabinoxylan, acacia gum, and resistant maltodextrin, are consumed since these fiber types are better tolerated at higher doses than faster fermenting oligosaccharides like oligofructose or galactooligosaccharides (Deehan and Walter, 2016). For future applications, one could use specific fiber types in a personalized fashion (matched with microbiota profile) to reduce the severity of side effects while enhancing the physiologic benefit to the host.

Inconsistencies in human intervention trials could also result from the response of the human gut microbiota to dietary fiber being highly individualized (Davis et al., 2011; Martínez et al., 2010). Missing keystone species in individuals, the absence of functional "guilds" able to assess a fiber, and/or the absence of strains that can utilize specific fiber sources could explain why some studies show segregation in response profiles of

patients during dietary intervention (Deehan et al., 2017). Matching of fibers to the microbiota may produce more beneficial effects on the host, especially if the subject's lack of keystone species leads to a non-response profile. This was exemplified in a recent study showing that supplementation of BKB did not result in metabolic improvement in all healthy subjects. Individuals who exhibited improved metabolic profile after 3 days of BKB consumption had a higher *Prevotella*/*Bacteriodes* ratio with an enrichment of *Prevotella copri*, reflecting the ability to degrade complex carbohydrates (Kovatcheva-Datchary et al., 2015). Interestingly, the capacity for using fibers varies between *Prevotella*- versus *Bacteroides*-dominated gut microbiota. *Prevotella*-dominated bacteria produce higher levels and different proportions of SCFAs compared to *Bacteroides*-dominated microbiota (Chen et al., 2017). In parallel, a very elegant study performed on 800 individuals, representative of an adult non-prediabetic population, showed that post-prandial glucose response (PPGR) was highly variable between individuals who consumed the same standardized meal. The PPGR correlated with some microbiota features, highlighting the importance of the diet-microbiota interaction and its impact on host metabolism. An algorithm using clinical and microbiota profiles as input demonstrated that the PPGR of each individual can be predicted and that a personalized dietary intervention based on their predictor can lead to an improvement in glucose metabolism including lower PPGR (Zeevi et al., 2015).

Concluding Remarks

In conclusion, dietary fibers can be considered key ancestral compounds that preserve gut ecology, especially regulating macronutrients and host physiology. Screening novel fibers, both extracted and purified from food as well as those selectively modified or synthesized, for their potential as the next-generation prebiotics, and defining efficient strategies to reintroduce high amount of fibers aiming at replenishing the gut microbiome with essential missing microbes, will be the next challenge to significantly impact gut microbiota-associated human diseases. Finally, a better understanding of diet-microbiota interactions will help to develop a personalized nutrition approach that would target and reduce more efficiently the incidence of chronic inflammatory diseases.

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DECLARATION OF INTERESTS

J.W. has received research funding from industry sources involved in the manufacture and marketing of prebiotics and dietary fibers, and is a co-owner of Synbiotics Solutions, a developer of synbiotic products. F.B. is founder and shareholder of Metabogen AB.

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