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Diet, Microbiota, and Metabolic Health: Trade-Off Between Saccharolytic and Proteolytic Fermentation

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Abstract

The intestinal microbiota have emerged as a central regulator of host metabolism and immune function, mediating the effects of diet on host health. However, the large diversity and individuality of the gut microbiota have made it difficult to draw conclusions about microbiota responses to dietary interventions. In the light of recent research, certain general patterns are emerging, revealing how the ecology of the gut microbiota profoundly depends on the quality and quantity of dietary carbohydrates and proteins. In this review, I provide an overview of the dependence of microbial ecology in the human colon on diet and how the effects of diet on host health depend partially on the microbiota. Understanding how the individual-specific microbiota respond to short- and long-term dietary changes and how they influence host energy homeostasis will enable targeted interventions to achieve specific outcomes, such as weight loss in obesity or weight gain in malnutrition.

THE GUT MICROBIOTA AND THEIR FERMENTATION PRODUCTS

Humans permanently carry approximately 100–200 bacterial species in the gastrointestinal tract. Each species harbors a unique genome, resulting in an estimate of approximately 500,000 microbial genes being present in an individual (Qin et al. 2010). Considering that the human genome consists of only approximately 20,000 protein-coding genes (Ezkurdia et al. 2014), it is understandable that the gut microbiota contributes essential metabolic capacities to the host. Indeed, a low number of microbial genes is associated with metabolic dysfunctions in the host (Le Chatelier et al. 2013). The contribution of microbial genetic capacity is particularly pronounced in terms of carbohydrate degradation: The human host produces only 17 carbohydrate-active enzymes, whereas some bacterial species in the gut have more than 200 carbohydrate-active enzymes (Cantarel et al. 2012). Indeed, one of the most prominent tasks of the gut microbiota is aiding the host with the digestion of food. Healthy Western individuals have been reported to obtain 2.8 kcal/g of fiber via microbial fermentation (Behall & Howe 1996), yielding up to 10% of a person's daily calories (McNeil 1984). This figure is likely much greater in individuals consuming traditional diets rich in complex plant polysaccharides from fruits, vegetables, legumes, tubers, and whole grains. In pigs, which have a similar gut morphology to humans, the proportion of energy obtained from microbial fermentation is more than 20% (Yen et al. 1991).

Most of the gut microbiota reside in the colon, the main location of bacterial fermentation. The dominant members of the colonic microbiota are specialized degraders of complex polysaccharides, releasing short-chain fatty acids (SCFAs), also known as volatile fatty acids, as well as lactate, carbon dioxide, methane, hydrogen, and ethanol. Acetate, propionate, and butyrate are the most abundantly produced SCFAs and are present at approximately a 60:20:20 ratio in the human colon (Cummings et al. 1987). SCFAs are actively absorbed into the gut epithelium and partly utilized by colonocytes (Cummings et al. 1987). Acetate produced in the gut eventually enters the liver and can be used for cholesterol synthesis; however, a large fraction passes the liver and becomes available to peripheral tissues as an energy source (Wolever et al. 1991). Propionate is used for gluconeogenesis in the liver and inhibits cholesterol synthesis from acetate (Wolever et al. 1991). Propionate thus represents a source of glucose for the host. Most of the butyrate that is absorbed is utilized by colonocytes (Cummings et al. 1987), as butyrate represents their main energy source. Relatively little butyrate reaches the circulatory system (Cummings et al. 1987).

The Gram-positive phylum Firmicutes often dominates the colonic bacterial community in healthy Western adults (Falony et al. 2016, Zhernakova et al. 2016). This phylum consists of very different types of species, including anaerobic and aerobic and Gram-positive and Gram-negative organisms, with various habitat and substrate preferences, and metabolic capacities and products. The total abundance of Firmicutes is therefore not a meaningful indicator of microbiota composition. The most abundant Firmicute group in fecal samples of Western adults is usually the class Clostridia, including the families Lachnospiraceae and Ruminococcaceae (Jalanka-Tuovinen et al. 2011). These taxa are specialized fiber degraders adapted to the gut environment. Many species in these classes, such as *Eubacterium* spp., *Roseburia* spp., *Subdoligranulum variabile*, and *Faecalibacterium prausnitzii*, produce butyrate (Louis & Flint 2009), either directly from dietary polysaccharides or from acetate, lactate, and degraded polysaccharides produced by other members of the community (Belenguer et al. 2006). Some of the species in these classes, including *Roseburia inulinivorans* and *Coprococcus catus*, switch between butyrate and propionate production depending on the fermentation substrates (Reichardt et al. 2014). Clostridia are fairly acid tolerant (Walker et al. 2005), reflecting their adaptation to conditions of high fermentative activity.

The other Gram-positive phylum, Actinobacteria, mainly consists of the genus *Bifidobacterium* in the human gut. Bifidobacteria ferment various oligosaccharides, including those produced by

the host in intestinal mucus (Ruas-Madiedo et al. 2008) and breast milk (Ward et al. 2007), as well as starch (Belenguer et al. 2006), forming lactate and acetate. *Bifidobacterium* is usually the dominant genus in breastfed infants but its levels decline after weaning to become a minor but important component of the adult microbiota (Bäckhed et al. 2015). Bifidobacteria grow well in acidic conditions (Walker et al. 2005). Although bifidobacteria do not produce butyrate, they can promote butyrogenesis in the gut by producing lactate, which is utilized by butyrate-producing species (Belenguer et al. 2006). Bifidobacteria are widely used as probiotics and have long been recognized for their health-promoting effects (reviewed in Hidalgo-Cantabrana et al. 2017).

The most abundant Gram-negative phylum in the human gut is Bacteroidetes, which reaches more than 50% relative abundance in some individuals and includes the genera *Bacteroides*, *Parabacteroides*, *Alistipes*, and *Prevotella.* Members of Bacteroidetes have the largest repertoire of carbohydrate-active enzymes of all gut inhabitants (El Kaoutari et al. 2013), which gives them tremendous substrate flexibility. *Bacteroides* spp., especially, can be considered generalists because of their ability to degrade various types of substrates, including dietary carbohydrates and proteins as well as host-derived glycans (Macfarlane et al. 1986, Salyers et al. 1977). Indeed, *Bacteroides* is an abundant genus at all ages, from infants to adults (Bäckhed et al. 2015). *Bacteroides* is the main producer of propionate in the gut (Reichardt et al. 2014), and the abundance of propionate in feces correlates strongly with the abundance of *Bacteroides* (Salonen et al. 2014). *Bacteroides* spp. prefer close to neutral pH and grow poorly in acidic conditions (Walker et al. 2005). *Prevotella* is an abundant genus in some individuals but nearly absent in others. Most of the host-associated *Prevotella* species inhabit the oral cavity, and only *Prevotella copri* is considered primarily a human gut symbiont (Shah et al. 2015).

Members of the Gram-negative phylum Proteobacteria normally form a minor part of the gut microbiota. Many members of Proteobacteria, such as *Escherichia*, *Enterobacter*, and *Klebsiella*, are opportunistic pathogens, capable of causing infection and inflammation if the ecological balance in the gut is disturbed. All Gram-negative bacteria produce the endotoxin lipopolysaccharide (LPS), a component of the Gram-negative bacterial cell wall. However, the form of LPS produced by members of Proteobacteria is more inflammatory than that produced by members of Bacteroidetes (Vatanen et al. 2016). Thus, although their abundance is normally low, members of Proteobacteria can potentially have a strong impact on the host via their powerful immunogenicity.

Akkermansia muciniphila is the only gut-associated member of the phylum Verrucomicrobia and has a special role in the gut ecosystem (reviewed in Derrien et al. 2017). Rather than relying on dietary substrates, *Akkermansia* grows in the mucus layer, degrading host-derived mucins and producing propionate and acetate, which can be further utilized by other bacteria (Derrien et al. 2017). Mucus is a constantly available substrate in the gut, whereas the supply of dietary components may vary, and an organism capable of unlocking this abundant source of carbohydrates and nitrogen likely has a key role in maintaining gut homeostasis (Derrien et al. 2017). Indeed, *Akkermansia* adheres to enterocytes and stimulates the gut barrier (Reunanen et al. 2015), protecting the host during excessive calorie consumption from diet-induced metabolic dysfunction (Everard et al. 2013). *Akkermansia* thus appears to be a keystone species in the gut ecosystem, enabling the microbiota and the host to withstand alternating periods of food scarcity and abundance.

Among Europeans, individuals tend to have a high abundance of one of the four major taxa: the genera *Bacteroides* and *Prevotella*, and the families Ruminococcaceae and Lachnospiraceae, which thus represent the main gradients of interindividual differences in microbiota composition (Falony et al. 2016). Earlier, it was suggested that humans could be classified based on three of these main organisms, *Bacteroides*, *Prevotella*, and *Ruminococcus*, into so-called enterotypes (Arumugam et al. 2011). The same taxa are distinctive between populations of people consuming different types of

diets (De Filippo et al. 2010, Gomez et al. 2016, Lin et al. 2013, Obregon-Tito et al. 2015, Ou et al. 2013, Schnorr et al. 2014), suggesting that a habitual diet could have an important effect on the overall gut microbiota composition.

EFFECTS OF DIETARY COMPONENTS ON THE GUT MICROBIOTA

Fiber

The main sources of fermentation substrates to the colonic microbiota are dietary oligosaccharides, undigested (resistant) starch, and plant cell wall components such as cellulose, hemicellulose (xylan), and pectin. The general term for carbohydrates that are not digested and absorbed in the small intestine is dietary fiber, a term that encompasses a variety of substances, including (possibly) various types of oligosaccharides, resistant starch, and plant cell wall components (AACC 2001).

The most active location of carbohydrate fermentation is the proximal colon, where the abundance of available carbohydrates is high and, owing to the production of organic acids, the pH is low (Cummings et al. 1987, Macfarlane et al. 1992). The Gram-positive, acid-tolerant bifidobacteria, Ruminococcaceae, and Lachnospiraceae are likely the most active groups in the proximal colon owing to the acidic pH found there. Indeed, various sources of dietary indigestible carbohydrates, including vegetables, oligosaccharides, bran, and whole grains, generally have a positive influence on bifidobacteria and the butyrate-producing clostridia (Carvalho-Wells et al. 2010; David et al. 2014; Gibson et al. 1995; Martínez et al. 2010, 2013; O'Keefe et al. 2015; Salonen et al. 2014), whereas a reduction in dietary polysaccharides causes a reduction in butyrate producers (David et al. 2014, Duncan et al. 2007, O'Keefe et al. 2015, Russell et al. 2011). High habitual carbohydrate and fiber intake are associated with increased abundances of Lachnospiraceae, Ruminococcaceae, and bifidobacteria (Ou et al. 2013, Wu et al. 2011, Zhernakova et al. 2016). Vegetarians have a higher abundance of butyrate producers than omnivores (Hippe et al. 2011) but only if they consume more fiber than omnivores (Kabeerdoss et al. 2012). This indicates that it is the amount of fermentable carbohydrates rather than the absence of meat in the diet that is important for the butyrate producers.

Fiber degradation likely occurs via cooperation between several bifidobacteria and clostridia (Belenguer et al. 2006), and there appears to be a division of labor between the fiber-degrading organisms. Oligosaccharides are highly bifidogenic (Bouhnik et al. 2004, Gibson et al. 1995, Mitsuoka et al. 1987) and are widely used as prebiotic supplements to increase the abundance of bifidobacteria. Resistant starch can also elicit an increase in bifidobacteria (Martínez et al. 2010, Salonen et al. 2014), but resistant starch seems to most strongly stimulate ruminococci (Abell et al. 2008, Martínez et al. 2010, Salonen et al. 2014, Walker et al. 2011). Non-starch polysaccharides promote mainly Lachnospiraceae (Salonen et al. 2014). These results correspond to observations in vitro demonstrating that ruminococci attach to starch particles and Lachnospiraceae to bran (Leitch et al. 2007). *Ruminococcus bromii* may be a particularly important organism for resistant-starch degradation, as individuals with a low abundance of *R. bromii* show incomplete fermentation of resistant starch (Walker et al. 2011). However, different types of resistant starch may have different effects on the microbiota: It appears that ruminococci may not degrade starch that is rendered indigestible via chemical modification (Martínez et al. 2010). *R. bromii* does not produce butyrate but enhances starch degradation by other bacteria, including butyrate producers (Ze et al. 2012). Indeed, starch has been shown to be the most butyrogenic carbohydrate (Englyst et al. 1987).

Bacteroides spp. are capable of degrading various plant polysaccharides (El Kaoutari et al. 2013) but do not generally increase in response to fiber supplementation in humans (Carvalho-Wells et al. 2010; David et al. 2014; Gibson et al. 1995; Martínez et al. 2010, 2013; O'Keefe et al.

2015; Salonen et al. 2014) and are usually at a low abundance in individuals consuming high-fiber diets (Ou et al. 2013, Wu et al. 2011). Blocking starch digestion medically and thus increasing the amount of starch reaching the colon directs the gut microbiota toward increased butyrate production and decreased propionate production (Weaver et al. 1997), suggesting that dietary indigestible carbohydrates may indeed select against *Bacteroides* spp. This could be partly due to the effects of fermentation on pH. Lactate produced by bifidobacteria reduces the colonic pH, which inhibits the growth of *Bacteroides* species, thus giving an advantage to the acid-tolerant butyrate producers. A few studies have shown a negative association between the fecal abundances of bifidobacteria and *Bacteroides* (Korpela et al. 2016, Zhernakova et al. 2016).

There is currently no clear understanding of how *Akkermansia* responds to changes in diet composition in humans (reviewed in Zhou 2017). Although *Akkermansia* grows on pure mucus and is not dependent on dietary substrates, its abundance has been found to respond positively to both oligosaccharide intake (Halmos et al. 2015) and a fiber-depleted diet (David et al. 2014).

As the fermentation continues, the amount of carbohydrates declines toward the distal colon. This decline depends on the amount of fermentable carbohydrates in the diet and on the transit time: Fast transit and a high abundance of dietary fiber results in more carbohydrates reaching the distal colon. In a typical low-fiber Western diet, gut transit is slow, the amount of carbohydrates reaching the colon is small, and the carbohydrates are thus increasingly depleted. The overall fermentation and organic acid production slow down along the length of the colon, and the pH increases, allowing the acid-sensitive *Bacteroides* and Proteobacteria to increase in abundance (Duncan et al. 2009, Walker et al. 2005). Indeed, vegans and vegetarians, with higher carbohydrate intake and lower fecal pH, have low fecal abundance of *Bacteroides* and Proteobacteria (Zimmer et al. 2012).

Protein

There appears to be a major trade-off between saccharolytic and proteolytic fermentation in the human colon, which is reflected in the taxonomic and functional profiles and is dependent on diet (**Figure 1**). Colonic bacteria favor carbohydrate fermentation over protein fermentation, and consequently protein fermentation occurs mostly in the distal colon (Macfarlane et al. 1992), where the fermentable carbohydrates are depleted and the pH is close to neutral. Both carbohydrate availability and low pH reduce protein fermentation in vitro (Smith & Macfarlane 1996). The activity of protein fermentation in the colon depends on diet more strongly than the production of SCFAs does (Salonen et al. 2014), indicating that dietary modulation can be an effective way to affect protein fermentation. Plant-based diets reduce bacterial protein fermentation products in feces (David et al. 2014, Ling & Hanninen 1992) and blood (Wu et al. 2016). A recent mouse study demonstrated that the amount of carbohydrates and protein in the diet has a decisive impact on the gut microbiota composition by selecting which bacteria are able to thrive: Low-protein diets select for microbiota able to utilize endogenous nitrogen obtained from host-derived substrates, such as mucus (Holmes et al. 2017).

Several bacterial species, including bacilli, streptococci, *Propionibacterium*, *Clostridium*, and *Bacteroides*, are able to degrade proteins (Macfarlane et al. 1986); however, all but *Bacteroides* form a minor component of the human colonic microbiota. *Bacteroides* can reach relative abundances of more than 50% and dominates the community, especially in the close to neutral pH of the distal colon (Walker et al. 2005), and thus likely contributes significantly to protein degradation in humans. Indeed, *Bacteroides* has been identified as the predominant proteolytic taxon in human fecal samples (Macfarlane et al. 1986). In vitro, a high-protein fermentation medium increases the abundance and the richness of *Bacteroides* (Aguirre et al. 2016), whereas a low peptide concentration

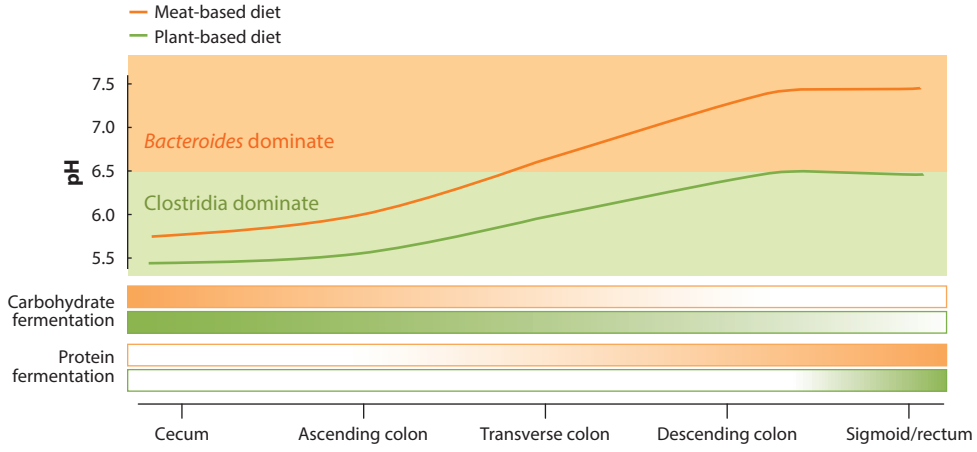

Figure 1

A hypothetical schematic of the colonic pH, dominant organisms, and fermentation patterns in meat-based and plant-based diets. A plant-based, high-fiber diet results in an abundant supply of carbohydrates to the colon, where active fermentation produces organic acids and reduces the pH below the optimum for *Bacteroides*, allowing the acid-tolerant clostridia to dominate the community (*shaded green area*). Protein fermentation is restricted. A low-fiber, meat-based diet results in the depletion of carbohydrates, resulting in reduced carbohydrate fermentation toward the distal colon and increased pH, allowing *Bacteroides* to reach dominance (*shaded orange area*). Protein fermentation is stimulated by the increase in pH and the depletion of carbohydrates.

in the culture medium reduces the production of propionate but not that of butyrate (Walker et al. 2005), supporting the idea that *Bacteroides* species benefit from dietary protein. The abundance of *Bacteroides* has been shown to correlate positively with habitual meat consumption (Wu et al. 2011, Zimmer et al. 2012). The abundances of *Bacteroides*, and the related *Alistipes* and *Parabacteroides*, increase during meat-based and decrease during plant-based dietary interventions (David et al. 2014, O'Keefe et al. 2015). Furthermore, European and North American populations consuming meat-based diets invariably have higher abundances of *Bacteroides* and lower microbial diversity than South Americans, Africans, and Asians consuming traditional plant-based diets (De Filippo et al. 2010, Gomez et al. 2016, Lin et al. 2013, Obregon-Tito et al. 2015, Ou et al. 2013, Schnorr et al. 2014). Overall, the results indicate that *Bacteroides*, together with *Alistipes* and *Parabacteroides*, may be the primary proteolytic taxon in the human colon.

Few studies have investigated the association between plant protein intake and the gut microbiota. Zhernakova et al. (2016), characterizing the microbiota of more than 1,000 Europeans, showed a positive association between several bifidobacterium species and plant protein intake. This suggests that plant and animal protein, possibly via the differences in the overall nutrient composition of high-protein plants versus meat, may have different effects on the gut microbiota.

Fat

Dietary fat is normally absorbed in the small intestine, and only small amounts reach the colon. Fat is not a primary energy source for colonic microbiota, and in mice it has a minor impact on the microbiota compared to the effects of carbohydrates and protein (Holmes et al. 2017). Nevertheless, the effects of even modest microbiota changes on the host may be significant. A fat-supplementation study in humans showed an increase in the Gram-negative Enterobacteriaceae, *Parabacteroides*, and *Prevotella*, as well as in a member of Erysipelotrichia, in response to

monounsaturated fat, but not to polyunsaturated fat, indicating that different fatty acids may have varying effects on the gut microbiota (Pu et al. 2016). Polyunsaturated fatty acids (PUFAs) have antimicrobial effects (De Weirdt et al. 2017). Gut bacteria metabolize dietary PUFAs, producing conjugated and saturated fatty acids (De Weirdt et al. 2017). Such PUFA metabolism is identified in several butyrate producers, including members of Lachnospiraceae (De Weirdt et al. 2017), and, indeed, Lachnospiraceae increased in response to PUFA supplementation in a dietary intervention (Pu et al. 2016). Furthermore, the microbiota of individuals with high n-3 PUFA intake have a reduced propensity for protein fermentation (Yang & Rose 2014), suggesting that specific fatty acids may influence the microbial metabolism of other dietary components.

Rodent studies support the beneficial effect of n-3 PUFAs, showing that they prevent the antibiotic-induced increase in inflammatory Proteobacteria and the decrease in bifidobacteria, resulting in improved gut barrier function and inhibition of endotoxemia (Kaliannan et al. 2016). Intriguingly, n-6 PUFAs have the opposite, inflammatory effect (Kaliannan et al. 2015). The effects are not direct but are mediated via intestinal alkaline phosphatase, which is upregulated by n-3 PUFAs and downregulated by n-6 PUFAs in host tissues (Kaliannan et al. 2015).

Dietary fat can influence the microbiota indirectly via the stimulation of bile secretion by the host (Devkota et al. 2012, Islam et al. 2011). Bile acids are toxic to many bacteria, and bile production is considered an important mechanism by which the host reduces the bacterial load in the small intestine. Most of the bile acids are absorbed in the small intestine, but a small fraction passes on to the colon and can influence the colonic microbiota (Islam et al. 2011). The amount of bile acids present in the colon is dependent on dietary fat: High-fat diets increase the amount of bile secreted and consequently the amount of bile acids present in the colon (Cummings et al. 1978). How the amount and composition of bile depend on diet and affect the gut microbiota in humans is currently not clear. A further complication arises from the fact that the microbiota metabolize the host-produced primary bile acids, altering the bile acid pool and making it difficult to distinguish cause and effect.

Sugars and Sweeteners

Sugar intake likely mostly affects the small intestinal community, as little dietary sugar normally reaches the colon, although amounts exceeding the digestive capacity of the small intestine lead to rapid sugar fermentation in the colon, often producing uncomfortable gastrointestinal symptoms (Fedewa & Rao 2014). Simple sugars can be present in large amounts in the small intestine. Owing to the pulsatile nature of substrate supply and the fast transit, the microbiota of the small intestine consist of fast-growing bacteria efficiently utilizing simple sugars and amino acids (Zoetendal et al. 2012). Indeed, the bacterial taxa positively associated with sugar intake appear to be small intestine inhabitants, such as *Prevotella*, *Streptococcus*, and Veillonellaceae (Wu et al. 2011, Zhernakova et al. 2016). Furthermore, the *Prevotella* enterotype is positively associated with sugar intake (Wu et al. 2011), consists of bacteria of the small intestine (Arumugam et al. 2011), and reflects fast gut transit (Falony et al. 2016), presumably resulting in the high abundance of upper intestinal tract organism being detected in feces. Interestingly, most *Prevotella* species are oral inhabitants, whose abundance is associated with periodontal disease (Wang et al. 2013). It has been suggested that sugar intake could have similar inflammatory effects in the mouth and in the intestine (Spreadbury 2012).

Fructose, in particular, has been shown to influence the gut microbiota in mice, with potentially detrimental effects on host health (Bergheim et al. 2008). In various species, including mice, monkeys, and humans, excessive fructose consumption induces endotoxemia and systemic inflammation (Bergheim et al. 2008, Jin et al. 2014, Kavanagh et al. 2013). The effect is caused by a

weakened gut barrier, leading to the leakage of LPS into the circulatory system, and can be prevented by continuous antibiotic treatment targeting the Gram-negative LPS-producing bacteria (Bergheim et al. 2008). Whether fructose directly increases the abundance of the Gram-negative Proteobacteria in humans is currently not clear.

The microbiota can contribute beneficially to sugar degradation: Supplementation with bifidobacteria has been shown to improve symptoms of lactose intolerance (Jiang et al. 1996). A recent study showed that genetically lactase-deficient individuals tend to have higher abundances of bifidobacteria than individuals with the genetic capacity to degrade lactose, but no difference was observed in dairy product consumption between the groups (Bonder et al. 2016). Furthermore, the abundance of bifidobacteria was positively associated with dairy product consumption only in the lactase-deficient group. A possible explanation is that bifidobacteria benefit from the presence of lactose and may render genetically lactose-intolerant individuals able to tolerate lactose in their diet. This is supported by the fact that bifidobacteria are absent or reduced in populations that do not consume milk (Obregon-Tito et al. 2015, Schnorr et al. 2014) and are at reduced abundances in vegetarians and vegans (Zimmer et al. 2012).

Artificial sweeteners that are unabsorbed in the small intestine represent a source of fermentable substrates for the colonic microbiota. The consumption of artificial sweeteners is thought to interfere with normal glucose homeostasis, and animal studies suggest that this may be mediated by changes in the gut microbiota (Suez et al. 2014). However, the negative effects of artificial sweeteners are not evident in all studies (Bergheim et al. 2008), and beneficial, prebiotic effects on the microbiota are possible as well (Daly et al. 2014). Further research in humans is needed to identify the species that respond to different types of sugars and artificial sweeteners.

Habitual Diet as the Driver of Inter-Individual Microbiota Differences

Overall, consistent patterns of microbiota configuration and habitual diet are beginning to emerge. Although *Prevotella* presumably has an important fiber degradation role in non-Westernized populations (De Filippo et al. 2010, Gomez et al. 2016, Lin et al. 2013, Obregon-Tito et al. 2015, Ou et al. 2013, Schnorr et al. 2014), it appears that *Prevotella* spp. in Western populations prefer simple sugars, and, in fact, the abundance of *Prevotella* correlates negatively with fiber intake (Wu et al. 2011). Indeed, Westernization is associated with the replacement of *Prevotella* with members of Clostridia as the main fiber degraders, as observed in a study comparing an African hunter-gatherer population to a neighboring agricultural population (Gomez et al. 2016).

Bacteroides as an abundant gut inhabitant appears to be a modern adaptation to the Western diet and may be an indicator of a fiber-starved ecosystem. Although *Bacteroides* species are famous for the large repertoire of carbohydrate-degradation enzymes (El Kaoutari et al. 2013), the genus *Bacteroides* as a whole does not seem to benefit from increased carbohydrate intake in humans. Notably, the substrate flexibility of *Bacteroides* spp. also encompasses various animal-derived glycans, including those produced by the host, such as mucins (El Kaoutari et al. 2013), which are the main fermentation substrates when dietary fiber is not available. This substrate flexibility likely enables *Bacteroides* spp. to thrive on low-fiber diets when the fiber specialists are unable to grow.

The accumulating data suggest that, among Western populations, *Bacteroides* is associated with meat-based diets, Ruminococcaceae and Lachnospiraceae are associated with diets rich in complex plant polysaccharides, and *Prevotella* is associated with diets high in sugar but low in fat and protein. Notably, the association between diet and the major bacterial taxa is reversed in mice compared to humans: *Bacteroides* are generally associated with plant-based polysaccharide-rich diets, whereas clostridia and other Firmicutes seem to benefit from Western-type diets in mice (Holmes et al. 2017). This demonstrates the need for caution when interpreting rodent studies.

MICROBIOTA MEDIATE DIET-INDUCED CHANGES IN HOST METABOLISM

Benefits of Fiber Fermentation

During most of our evolution, the human species has subsisted on largely plant-based diets supplemented with varying amounts of lean meat and fish (Jew et al. 2009). It is estimated that the Paleolithic diet contained approximately 100 g fiber per day, 4 times more than the currently recommended 25 g, and 6 times more than the average intake of 15 g in Western populations (Jew et al. 2009). Most of the carbohydrates in modern diets come from flour-based foods consisting of digestible starch. However, uncooked starch occurs naturally in tightly packed dehydrated granules and is encased within the indigestible plant cell wall; thus, it is resistant to digestion (Fuentes-Zaragoza et al. 2010). Many starchy foods consumed raw or unground, rather than being digested and absorbed in the small intestine, contribute a significant amount of carbohydrates to the colonic bacteria. Thus, in modern diets, microbially fermented carbohydrates have been replaced by digestible sugar and starch. It has been suggested that the difference in carbohydrate quality may have a decisive effect, via the gut microbiota, on host metabolic health (Spreadbury 2012). Dietary fibers have a multitude of beneficial effects on the host, mostly due to their stimulation of fermentative activity and production of SCFAs by the gut microbiota (**Figure 2**). Diets

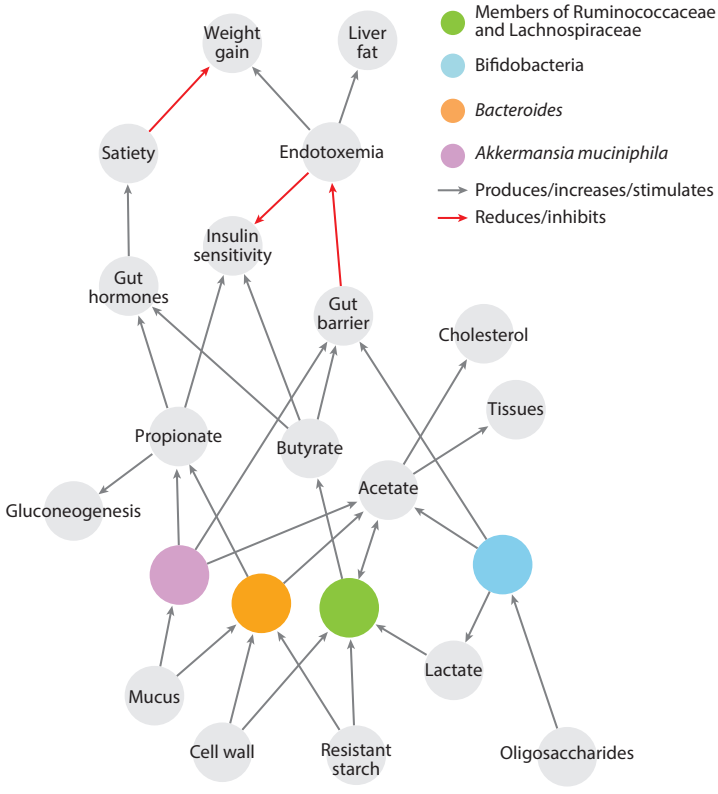

Figure 2

A simplified representation of how microbiota mediate the beneficial effects of diets high in fiber and moderate in protein. Depicted are four important groups of bacteria, the main substrates that they degrade, main fermentation products, and their effects on the host metabolic health.

high in fiber reduce the risk of colorectal cancer and improve metabolic health (Aune et al. 2011, Threapleton et al. 2013).

Fiber-degrading bacteria stimulate the gut barrier, which is important for metabolic health. Butyrate, bifidobacteria, and *Akkermansia* are known to induce tight junction proteins and mucus secretion in the gut epithelium, stimulating the maintenance of the gut barrier and inhibiting the leakage of inflammatory bacterial components into the circulatory system. Endotoxemia, the leakage of LPS from the intestine into the circulatory system, has been shown to drive weight gain, insulin resistance, and fat accumulation in the liver in mice and humans (Cani et al. 2007a, Mehta et al. 2010, Zelber-Sagi et al. 2007). This is mediated via inflammation triggered by the activation of the CD14/TLR4 receptor (Cani et al. 2007a). In humans, serum endotoxin levels are higher in diabetics and predictive of diabetes incidence in nondiabetics (Pussinen et al. 2011). Improvement of the gut barrier reduces diet-induced endotoxemia and inhibits diet-induced insulin resistance and adiposity in mice (Plovier et al. 2017), and it is associated with healthy metabolic markers in humans (Dao et al. 2016). Reducing the leakage of LPS by improving the gut barrier via supplementation with fiber (Pendyala et al. 2012), bifidobacteria (Cani et al. 2007b), or *Akkermansia* (Everard et al. 2013) can effectively promote metabolic health. Conversely, vancomycin treatment, which reduces the abundance of SCFA-producing species and increases the abundance of LPS-producing species in the gut, negatively affects insulin sensitivity (Vrieze et al. 2014). The depletion of bifidobacteria in early life is associated with increased weight gain in later childhood (Korpela et al. 2017), indicating that bifidobacteria, promoted by oligosaccharides in breast milk, are particularly important for healthy metabolic programming in infancy.

In addition to improving the gut barrier, SCFAs have systemic effects on host metabolism via SCFA receptors in the liver, adipose tissue, and skeletal muscle and by stimulating the production of gut hormones (reviewed in Canfora et al. 2015). A single dose (60 g) of fiber improves the glucose and insulin responses to the following meal (Robertson et al. 2003). This effect is most likely due to the production of SCFAs because supplementation with propionate has been shown to reduce postprandial glucose and insulin responses (Liljeberg et al. 1995) and improve insulin sensitivity (Venter et al. 1990). In addition, SCFAs, either supplemented directly or produced by the gut microbiota from supplemented prebiotics, induce satiety via gut hormone PYY and GLP-1 stimulation (Cani et al. 2009, Chambers et al. 2015, Liljeberg et al. 1995), and consequently can reduce weight gain in the long-term (Chambers et al. 2015). According to a dose-escalation study, more than 35 g of oligofructose per day are required to observe changes in gut hormone levels (Pedersen et al. 2013), indicating that the recommended amount of 25 g of fiber per day may be insufficient for full metabolic benefits. It can be argued that starving our microbes by eating too little fiber may result in aberrant appetite regulation and hyperphagia, a situation characteristic of obesity.

Effects of Protein and Fat

Meat-based diets contain both saturated fat and animal protein, which likely influence the gut microbiota and host health synergistically. Protein fermentation results in the production of diverse end products: SCFAs, branched-chain fatty acids (BCFAs), ammonia, amines, and phenolic and indolic compounds (Macfarlane et al. 1992).

Butyrate can be produced from the amino acids glutamate and lysine by *Fusobacterium* and *Megasphaera*, but unlike the pyruvate-to-butyrate pathway employed by clostridia, this pathway involves the production of ammonia, which may be harmful (Anand et al. 2016). Bacteria use ammonia for amino acid synthesis, and ammonia utilization is increased if peptide availability is low (Walker et al. 2005), indicating that low-protein diets may increase ammonia utilization in the gut.

The fermentation of sulfur-containing amino acids results in the production of hydrogen sulfide (Devkota et al. 2012). In addition, the heme in red meat induces the production of nitroso compounds (Kuhnle et al. 2007). Many of the protein fermentation products, especially hydrogen sulfide and nitroso compounds, are toxic to intestinal cells and are implicated in the etiology of colorectal cancer (Hughes et al. 2000). Indeed, cancer usually occurs in the distal parts of the intestine, where protein fermentation takes place, and can be attributed to dietary factors such as excessive meat intake and low fiber intake (Aune et al. 2011, Larsson & Wolk 2006). However, it appears that non-meat-derived proteins may not increase the risk of colorectal cancer (Kato et al. 1997, Windey et al. 2012). It is possible the culprit is not protein fermentation per se, but that protein fermentation products act in synergy to induce carcinogenesis in the presence of N-nitroso compounds, hydrogen sulfide, and bile acids, promoted by meat and saturated fat intake. In addition, saturated fat consumption compromises the gut barrier, increasing the translocation of LPS from the gut and inducing systemic inflammation (Erridge et al. 2007, Pendyala et al. 2012).

Fat intake stimulates bile release, and dietary protein can affect the composition of bile (Hardison 1978). Diet modifies the bile acid pool and the microbiota composition, and, thereby, the microbial metabolism of bile acids. Bile acids are conjugated to glycine or, less commonly in humans, taurine. In humans, the abundance of taurine-conjugated bile acids is dependent on the availability of dietary taurine, which is present in meat and shellfish (Hardison 1978). Glycine- and taurine-conjugated bile acids have decisively different effects on the gut microbiota and the host in mice (Devkota et al. 2012). Taurine is a sulfur-containing amino acid and favors the expansion of sulfite-reducing bacteria, resulting in the production of highly toxic hydrogen sulfide (Devkota et al. 2012). The proportion of taurine-conjugated bile acids thus represents a key determinant of how the microbial metabolism of bile acids affects the host.

Importantly, bile acids act as hormones, regulating all aspects of metabolism by activating the receptors FXR and TGR5, which affect bile production as well as diverse metabolic functions including insulin sensitivity, lipid metabolism, and energy expenditure (reviewed in Wahlström et al. 2016). Bacteria deconjugate and dehydroxylate the host-secreted primary bile acids, altering their affinity to the receptors and thus their impact on host metabolism. However, the interactions between diet, bile acids, and microbiota are complex and poorly characterized in humans. In mice, bile-salt hydrolase activity of the microbiota has been shown to reduce host weight gain, insulin resistance, and blood cholesterol by altering FXR and TGR5 signaling (Joyce et al. 2014, Watanabe et al. 2006). Mice and humans have different bile acid pools, so direct comparison is not possible, but it is likely that bacterial modification of bile acids has significant metabolic consequences in humans as well. An example is the secondary bile acid ursodeoxycholic acid (UDCA), which increases shortly after gastric bypass surgery, and this is suggested to mediate the rapid amelioration of diabetes in these patients (Albaugh et al. 2015). UDCA is a strong agonist of TGR5, which increases energy expenditure and insulin sensitivity (Wahlström et al. 2016). In children, antibiotic use causes a reduction in bacterial bile-salt hydrolases (Korpela et al. 2016), thus reducing the ability of the microbiota to metabolize bile acids, demonstrating that antibiotic use can have important metabolic effects on the host via changes in the gut microbiota.

The metabolism of health-promoting dietary substances by the gut microbiota can induce detrimental effects on the host. L-Carnitine, present mainly in meat, and choline/phosphatidylcholine (lecithin), present in meat, eggs, soybeans, and fish, have several important biological activities and are associated with beneficial effects on metabolic and cardiovascular health (DiNicolantonio et al. 2013, Zeisel & da Costa 2009). However, the gut microbiota metabolize these into trimethylamine (TMA), which is converted into trimethylamine oxide (TMAO) in the liver by the enzyme FMO3 (Koeth et al. 2013, Wang et al. 2011). TMAO is associated with cardiovascular disease

(Koeth et al. 2013, Wang et al. 2011). Furthermore, the conversion of choline into TMA results in reduced choline bioavailability to the host, increasing the risk of choline deficiency (Romano et al. 2015). FMO3 is stimulated by FXA, which in turn is activated by primary bile acids but inhibited by the secondary bile acid UDCA (Wahlström et al. 2016). Thus, the production of TMAO is dependent on interactions between diet and microbiota in a complex manner. The whole spectrum of bacterial species involved in this process is currently not known. The microbiota of vegetarians and vegans have a significantly reduced capacity to produce TMA, suggesting that the important TMA-producing species are ones that are promoted by meat-based diets (Koeth et al. 2013). Romano et al. (2015) identified eight human gut colonizers as producing TMA from choline but not from L-carnitine. These strains were members of the Firmicutes families Tissierella (one strain), Lachnospiraceae (one strain), and Clostridiaceae (two strains) and of Proteobacteria (five strains). None of the Bacteroidetes or Actinobacteria strains produced TMA (Romano et al. 2015).

Protein versus Carbohydrates

Low-carbohydrate–high-protein diets appear to have detrimental effects on the gut microbiota, with potentially negative long-term health consequences for the host. A long-term study in obese individuals comparing a low-carbohydrate–high-protein diet and a recommended diet that stressed increased fiber and reduced sugar intake, showed initially a faster weight loss in the low-carb diet but more stable sustained weight loss in the recommended diet (Mellberg et al. 2014). After the two-year intervention, there was no difference in body mass index (BMI) reduction between the groups, despite significantly higher energy consumption in the recommendation diet group. Microbiota composition was not analyzed, but shorter studies have shown unfavorable microbiota changes in response to high-protein diets (David et al. 2014, Duncan et al. 2007, O'Keefe et al. 2015, Russell et al. 2011). Animal-based low-carbohydrate diets are associated with increased mortality, whereas plant-based reduced-carbohydrate diets, characterized by high intake of whole grains and low intake of sugar, appear healthy (Fung et al. 2010). If consumed chronically, even moderate intake of animal, but not plant, protein is associated with reduced life span (Levine et al. 2014, Solon-Biet et al. 2014), which may be partly explained by the effects of diet on the gut microbiota (Holmes et al. 2017).

As humans regulate food intake to meet their protein requirement, a diet deficient in protein leads to overeating (Simpson & Raubenheimer 2005). However, it should be noted that the gut microbiota regulate food intake to meet their carbohydrate requirement, and a diet deficient in fiber leads to overeating as well. A healthy diet must therefore meet the protein requirement of the host and the carbohydrate requirement of the gut microbiota. For sustained metabolic improvement, modifying the quality of dietary carbohydrates may be more effective than replacing them with excess protein and fat. Indeed, successful weight loss can be achieved by ad libitum diets designed to promote a healthy microbiota by supplying a rich variety of fermentable carbohydrates and plant proteins (Xiao et al. 2014).

MICROBIOTA MODULATION FOR IMPROVED METABOLIC HEALTH: CHALLENGES AND OPPORTUNITIES

The powerful effect of the gut microbiota on host metabolism is demonstrated by the long history and extensive use of antibiotic growth promoters in animal production, the object of which is to alter the gut microbiota to achieve improved conversion of feed to host biomass (Dibner & Richards 2005). The growth-promoting effect of antibiotics has been verified in mice, in which early-life antibiotic exposure increases the susceptibility to later-life diet-induced adiposity via transient

changes in the gut microbiota (Cox et al. 2014). There are reasons to believe that antibiotics act as growth promoters in humans as well, especially in early life. Antibiotics are recommended in the treatment of severe malnutrition because of their efficacy in promoting growth (Trehan et al. 2013). Several studies have shown a positive association between early-life antibiotic use and BMI in later childhood (Saari et al. 2015, Trasande et al. 2013). Antibiotic use in humans is associated with increased abundance of propionate-producing and LPS-producing bacteria and decreased abundance of the gut-barrier-promoting butyrate producers and bifidobacteria (Vrieze et al. 2014, Falony et al. 2016, Korpela et al. 2016). The same patterns are observed in individuals on high-fat and meat-based diets, suggesting that diet and antibiotic use may induce weight gain and metabolic dysfunction via the same microbiota-mediated mechanisms.

Modulation of the gut microbiota clearly offers opportunities, but dietary interventions often yield varying results. This is not unexpected, as the microbiota composition determines how the dietary components are utilized. All humans have very similar enzymatic capacities for the degradation of dietary compounds, but individuals differ widely in their microbial enzymatic repertoire (Qin et al. 2010). A great part of our individuality is in the gut microbiota, and the individual differences in microbiota composition and gene content may explain individuality in response to dietary change. There is individual variation in the ability of the microbiota to degrade different dietary components (Walker et al. 2011, Yang & Rose 2014), leading to potential differences in the response to dietary substrates.

The responses of individual microbial taxa to dietary interventions depend on their baseline abundance (Bouhnik et al. 2004, Korpela et al. 2014). It is therefore essential to consider the baseline abundance of each taxon when assessing their response to an intervention. Furthermore, the overall gut microbiota composition is extremely stable in adults, and the general configuration does not usually change in response to short-term dietary interventions (Wu et al. 2011). An individual's microbiota is adapted to the habitual diet, and initially the dominant bacteria likely attempt to cope with the dietary changes, maintaining their dominance and possibly even inhibiting other taxa from responding and becoming more competitive. The availability of dietary nitrogen determines which bacteria win the competition for dietary carbohydrates (Holmes et al. 2017): Low-protein diets select for bacteria that can utilize mucus-derived nitrogen. Thus, differences in habitual protein intake may influence how the microbiota respond to fiber supplementation. This was shown in vitro, where fecal samples from individuals on meat-based diets showed a *Bacteroides*-dominated response to the added fiber, whereas samples from individuals on plant-based diets showed a butyrogenic response (Yang & Rose 2014).

There are examples showing that individuals with a high abundance of *Bacteroides* spp. and/or low microbiota diversity at baseline fail to respond positively to dietary interventions (Cotillard et al. 2013, Kovatcheva-Datchary et al. 2015, Louis et al. 2016). One possible explanation is that *Bacteroides*, by adapting flexibly to different dietary components, are able to resist change during short-term dietary interventions. Conversely, individuals with a high abundance of *Akkermansia* at baseline have been shown to respond positively to weight-loss diets (Dao et al. 2016, Louis et al. 2016). This indicates that in some individuals, with a permissive microbiota, a beneficial response can be elicited rapidly, whereas others may need long-term dietary manipulation to alter the ecological balance in the gut. Indeed, the full effects of a dietary intervention may require microbiota adaptation, a process that may take up to a year (Freeland et al. 2010).

It is possible to use the information on individual microbiota differences to predict an individual's response to a dietary intervention (Korpela et al. 2014). This approach has tremendous practical potential, as demonstrated by Zeevi et al. (2015) by building an individual-based predictive model of blood glucose responses to different food items and using this to construct individual dietary recommendations to diabetics, successfully maintaining healthy blood glucose levels. Rather

than treating individuals as random variation around the population mean, information on the individual microbiota can be utilized to make tailored treatment decisions.

CONCLUSION

On the basis of the above considerations, it can be deduced that much of the beneficial effects of healthy diets are mediated by the microbiota. Conversely, it should be recognized that any diet failing to promote favorable microbiota is unlikely to produce optimal health outcomes for the host. The gut microbiota are a central metabolic regulator, affecting all aspects of host energy homeostasis from eating and processing of dietary components to storage and use of energy. The effects of dietary components on host metabolic health largely depend on how the microbiota respond to and process them, which is dependent on the microbiota composition. The microbiota composition ultimately depends on the type and availability of fermentation substrates provided by the habitual diet. It appears that plant-based and animal-based diets have fundamentally different effects on the ecology of the gut microbiota and their metabolic products. Fiber supplementation, as well as probiotics and postbiotics (microbial products such as SCFAs or bile acids), offers untapped opportunities with respect to weight management. However, inadvertently altering the microbiota and its metabolism may carry risks as well. Antibiotics especially should be acknowledged as powerful microbiota modulators with effects on metabolic health.

SUMMARY POINTS

1. There is a trade-off between protein-driven and carbohydrate-driven fermentation in the gut that depends on diet.
2. Meat-based diets select for *Bacteroides* and protein fermentation; plant-based diets select for butyrate producers and carbohydrate fermentation.
3. The human host and the gut microbiota have adapted to high-fiber diets, and diets deficient in fiber may promote obesity and metabolic dysfunction.
4. A healthy diet must meet the protein requirement of the host and the carbohydrate requirement of the gut microbiota.
5. The response of the microbiota and the host to short-term dietary interventions depends on the baseline microbiota composition.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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