Review

MOLECULAR METABOLISM

A healthy gastrointestinal microbiome is dependent on dietary diversity

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ABSTRACT

Background: Like all healthy ecosystems, richness of microbiota species characterizes the GI microbiome in healthy individuals. Conversely, a loss in species diversity is a common finding in several disease states. This biome is flooded with energy in the form of undigested and partially digested foods, and in some cases drugs and dietary supplements. Each microbiotic species in the biome transforms that energy into new molecules, which may signal messages to physiological systems of the host.

Scope of review: Dietary choices select substrates for species, providing a competitive advantage over other GI microbiota. The more diverse the diet, the more diverse the microbiome and the more adaptable it will be to perturbations. Unfortunately, dietary diversity has been lost during the past 50 years and dietary choices that exclude food products from animals or plants will narrow the GI microbiome further.

Major conclusion: Additional research into expanding gut microbial richness by dietary diversity is likely to expand concepts in healthy nutrition, stimulate discovery of new diagnostics, and open up novel therapeutic possibilities.

Keywords Microbiome; Microbiota; Gastrointestinal; Dietary diversity; Agrobiodiversity; Microbiota richness

Twenty-five years ago, Epstein et al. described treating a group of 25 children between the ages of 6–12 years of age who were 45% overweight in conjunction with one of their parents who was also overweight. The treatment period lasted for 8 months and consisted of diet instruction, behavioral management training, exercise and contingency contracting in which money was deposited and $5 returned at visits if weight had been lost. The parents and children both lost weight during the treatment period, but ten years after the treatment the children were still maintaining a 7.5% reduction in their percent overweight below baseline. In contrast, the parent that was treated at the same time with the child increased their percent overweight from baseline by 9.1% [1]. The reason for the ability of pre-pubertal subjects to maintain weight loss but not their parents who were treated with them in the same program remains a medical mystery.

That study was performed before there was an appreciation of the interactions between the gastrointestinal (GI) microbiome and physiological systems regulating metabolism. At the end of 2007, the US National Institutes of Health (NIH) launched the Human Microbiome Project (HMP) and, in early 2008, the European Commission and China initiated the Metagenomics project of the Human Intestinal Tract (MetaHIT). These large efforts apply advanced sequencing and bioinformatic tools to characterize the microbes living in and on our bodies. Each community of microbiota is studied as an ecosystem, utilizing the science and language of ecology [2]. Biodiversity is a critical aspect of ecosystem function and has been the intense focus of the HMP and MetaHIT projects [3,4]. Like all healthy ecosystems, some level of species richness characterizes the GI microbiome in healthy individuals [5]. Additions or losses of species with similar roles tend to only have small effects on microbiome function. However, domination by few species or lack of species diversity may impact function significantly.

The pre-adolescent children that were capable of maintaining weight loss may have a much greater level of species richness than their parent. Indeed, biodiversity of the GI microbiome of healthy pre-adolescent children aged 6–12 years of age is much greater than that of healthy adults living in the same city [6]. A greater the biodiversity renders a greater resilience of the ecosystem to recover from or adjust to perturbations. Conversely, a loss in species richness in the GI microbiome is a common finding in several disease states.

During the past 50 years, prevalence of obesity [7], type 2 diabetes [8], and inflammatory bowel diseases [9] sharply increased. A shared discovery for each of these pathologies is a reduction of the GI microbiome biodiversity [10,11,12; respectively]. This biome is flooded with energy in the form of undigested and partially digested foods, and in some cases drugs and dietary supplements. Each microbiotic species in the biome transforms that energy into new molecules, which

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Abbreviations: FXR, farnesoid X receptor; FODMAP, fermentable oligo-, di-, monosaccharides and polyols; FDA, Food and Drug Administration; GI, gastrointestinal; GIMM, GI microbiome modulator; GLP-I, glucagon-like peptide-1; GLUT, glucose transporter; HMP, Human Microbiome Project; MCFA, medium chain fatty acids; MetaHIT, Metagenomics project of the Human Intestinal Tract; NIH, National Institutes of Health; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; SCFA, short chain fatty acid; SGLTs, sodium–glucose cotransporter; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; VSG, vertical sleeve gastrectomy

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may signal messages about energy intake and the state of digestion to physiological systems of the host. Thus, by our dietary choices, we are selecting substrates for some species and providing a competitive advantage over other GI microbiota. The more diverse the diet, the more diverse the microbiome and the more adaptable it will be to perturbations. Pre-adolescent children may have a more diverse GI microbiome than their parents because the diet is transitioning from the simple infant liquid diet to the foods of an adult, testing and selecting new foods along the way. By adulthood, habitual diets have been established based on lifestyle, palate and unwillingness to explore new foods. Adults, therefore, adopt a personalized GI microbiome [13,14] making comparisons of GI microbiotal communities difficult unless one contrasts populations from different cultures [15]. Regardless, richness of the GI microbiome is well correlated with health [5].

Unfortunately, dietary diversity has been lost during the past 50 years because of economic pressures for greater food production to support a growing world population. This decreased agrobiodiversity, or the decline in rearing varied edible plant varieties and animal breeds, is occurring at an incredible rate. According to the Food and Agricultural Organization of the United Nations [16], 75 percent of plant genetic diversity has been lost, as farmers worldwide have left their multiple local varieties for genetically uniform, high-yielding varieties. Of the 250,000 to 300,000 known edible plant species, humans use only 150 to 200. Six livestock breeds are lost each month in favor of high production practices. Today, 75 percent of the world's food is generated from only 12 plants and five animal species.

Agricultural practices of using antibiotics as growth promoters for poultry, swine and cattle further narrow the GI microbiome. The FDA approves use of antibiotics for growth of livestock because such low levels in the carcass do not produce significant blood levels in humans after ingestion. However, the GI microbiome is exposed to the antibiotics, which was not appreciated when the drugs were approved as growth promoters. Indeed, such exposure may produce substantial taxonomic and functional changes in the GI microbiome [17]. Crop agricultural practices rely on use of pesticides to protect the plants from damaging influences such as weeds, fungi, and insects. Like use of antibiotics as growth promoters, residual pesticide in food crops may be sufficient to modulate the GI microbiome when consumed. This practice could also handicap the plant's own defense system by eliminating the need for the plant to produce phytoalexins [18]. Phytoalexins may provide key micronutrients that expand the GI microbiome when ingested [19]. Thus, economic pressures force agricultural practices that have limited the richness of the GI microbiome over the past century.

Diet will facilitate taxonomic shifts in as little as 3 days after dietary modification [20,21]. Dietary choices that exclude products from animals or from plants will eliminate crucial microbiota by purging the principal nutrients needed to supply the necessary energy for survival in their habitat. Although temporarily excluding an essential nutrient will only briefly reduce diversity, such losses of microbiota cannot be reversed after prolonged elimination of nutrients such as fermentable fiber [22]. It follows that fad diets also reduce microbiota richness if the dietary plan strategizes to eliminate one or more dietary macronutrients such as carbohydrates. Although, the first line of treatment for diabetes includes reduction of sugar and starch intake, those carbohydrates could be replaced by indigestible carbohydrates like oligosaccharides which the microbiota could still metabolize. Diets that advocate intermittent fasting may inadvertently establish occasional harvesting of the intestinal mucosal barrier by microbiota species that are capable of foraging on mucin glycans for fuel [23,24]. Even the use of dietary emulsifiers, which are commonly used in the manufacture of prepared foods, reduce microbial richness, and may contribute to colitis and metabolic syndrome [25].

Because energy of micro- and macro-nutrients can be converted by inhabitants of the GI microbiome into novel molecules that interact with the host, the greater the repertoire of signals, the more likely is the ability to maintain homeostasis when dietary intake is perturbed. This is illustrated well by Wang et al. [26,27]. Phosphatidylcholine, rich in foods such as shellfish, eggs, milk, red meat and poultry, are converted by intestinal microbes to trimethylamine (TMA), which is efficiently absorbed by the host and oxidized to the atherosclerotic associated trimethylamine-N-oxide (TMAO) [26]. However, including dietary foods common to Mediterranean diets such as balsamic vinegar, red wine, cold-pressed extra virgin olive oil or grapeseed oil contains an inhibitor of TMA production [27].

After excessive consumption of sugars and starches, the facilitated transporters (GLUTs) and the active transporter gene family (SGLTs) responsible for sugar absorption in the upper gut become saturated [28], and as a result, carbohydrates are presented to the lower gut where they are converted to short chain fatty acids (SCFAs), which are produced in mole quantities by GI microbiota [29]. These SCFA's serve as secretagogues for release of PYY and GLP-I [30], which in turn, act to reduce further food intake, slow gastric emptying and GI transit, and increase insulin secretion. These actions limit further food ingestion and allow ingested glucose to enter cells for storage. In addition, SCFAs compete with medium chain fatty acids (MCFA) for binding the enzyme ghrelin O-acyltransferase and thereby block activation of ghrelin by MCFA [31,32]. Active ghrelin stimulates appetite [33]. Fermentable oligo-, di-, monosaccharides and polyols (sugar alcohols) (FODMAPs) may trigger GI symptoms in patients with irritable bowel syndrome or inflammatory bowel disease. Therefore, a low FODMAP diet is often prescribed as part of the therapy for these patients. While it may help with postprandial symptoms, such a diet may have long lasting consequences by eliminating the signaling described with possible long-term shifts in the GI microbiome [22].

Stable, diverse and healthy GI microbial ecosystems are an important component to consider when using diet to perturb physiological systems in animal models of disease, and it is an aspect often overlooked. A common model to study obesity and insulin resistance is one in which the diet is switched from a basic chow diet to a "Western" or "high fat" diet with a predominance of fat and sugar. Conclusions are typically based on the shift to the calorie dense diet. However, chow diets are classically more diverse. They contain macronutrients from many sources such as whole wheat, dehulled soybean meal, ground corn, animal fat and condensed whey (for example, Purina 5015 Mouse Diet). A common diet used to induce obesity in a mouse is much less diverse such as Research Diets D12492 that contains casein as the source of protein, cornstarch and sucrose as the carbohydrate, and lard as the fat source. The loss of dietary biodiversity may be an important component for the development of obesity that is associated with a narrowing of GI microbiome diversity [34].

Assuming study diets are similar, based only on macronutrient constituents, may hinder comparison of studies with diets made from components of differing diversity within the macronutrient composition. As stated above, SCFA production by microbiota could inhibit activation of ghrelin. Thus, diets rich in plant polysaccharides could blunt ghrelin actions [35] while a more diverse diet may be less inhibitory. Zhao and colleagues [36] demonstrated that ghrelin plays an important role as a counter regulatory hormone to prevent hypoglycemia during calorie restriction, an action observed in wild type mice

but not in mice incapable of activating ghrelin. Yi and colleagues [37] were unable to validate those findings using 4 different mouse mutants with loss of ghrelin function. The 2 groups used different diets, although seemingly similar when based on macronutrient content. The diet used by Zhao et al. (Teklad diet 7002) contained 18% calories from fat, 33% calories from protein and 49% calories from carbohydrates. Yi et al. used the Teklad LM-485 diet containing 17% calories from fat, 25% calories from protein and 58% calories from carbohydrates. But a closer look at the diversity of dietary components reveals that the LM-485 diet is a vegetarian diet comprised primarily of ground corn, dehulled soybean meal, ground oats, wheat middlings, dehydrated alfalfa meal, soybean oil and corn gluten meal. The 7002 diet is more diverse containing animal products and less fermentable carbohydrate (ground corn, porcine meat and bone meal, dehulled soybean meal, wheat middlings, ground wheat, ground oats, dehydrated alfalfa meal, brewers dried yeast, cane molasses, porcine fat, dried whey and casein). Thus, it is possible that LM-485 diet drives a microbial community supporting higher levels of SCFAs than does the 7002 diet and wild type mice consuming LM-485 would have lower levels of circulating ghrelin than wild type mice consuming 7002.

Clues to solve another medical mystery are derived from secondary bile acids that are a result of GI microbiota processing. Bariatric procedures such as Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are associated with considerable improvements in co-morbidities of obesity rapidly after the procedure and prior to significant weight loss. Outcomes from RYGB [38] and VSG [39] appear to be related to bile acid signaling through the farnesoid X receptor (FXR) — to regulate physiological systems and also to increase gut permeability by reducing the mucosal barrier. It is now clear that bile acid diversity is dependent on the gut microbial diversity [40,41]. Expanding dietary fat diversity (for example, saturated-, monosaturated and polyunsaturated fatty acids) can shift microbiome diversity [42] and thus regulate the bile acid diversity.

Additional research into expanding gut microbial richness by dietary diversity is likely to expand concepts in healthy nutrition, stimulate discovery of new diagnostics, and open up novel therapeutic possibilities. In the future, an adult seeking treatment for obesity may be surveyed about dietary preferences and present a stool specimen. Weight loss therapy may begin with a specific dietary plan to widen that person's GI microbiome richness as a prelude to obesity treatments to maintain a weight loss over a long period, as is the case for preadolescent children with obesity and obesity surgery. Indeed, short-term personalized dietary interventions based on a personalized GI microbiome, can improve postprandial glucose regulation in prediabetics and T2D [14]. Already a GI microbiome modulator (GIMM) has been developed and tested to treat prediabetes [43], which opens new avenues for drug discovery.

CONFLICT OF INTEREST

MLH is an employee of MicroBiome Therapeutics. FLG is on the Clinical Advisory Board and holds stock options in Microbiome Therapeutics.

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