Progress and Challenges in Developing Metabolic Footprints from Diet in Human Gut Microbial Cometabolism

Linda C Duffy, Daniel J Raiten, Van S Hubbard, and Pamela Starke-Reed

Abstract

Homo sapiens harbor trillions of microbes, whose microbial metagenome (collective genome of a microbial community) is estimated to be at least 100-fold that of human cells, which comprise 23,000 genes. This article highlights some of the current progress and open questions in nutrition-related areas of microbiome research. It also underscores the metabolic capabilities of microbial fermentation on nutritional substrates that require further mechanistic understanding and systems biology approaches of studying functional interactions between diet composition, gut microbiota, and host metabolism. Questions surrounding bacterial fermentation and degradation of dietary constituents (particularly by Firmicutes and Bacteroidetes) and deciphering how microbial encoding of enzymes and derived metabolites affect recovery of dietary energy by the host are more complex than previously thought. Moreover, it is essential to understand to what extent the intestinal microbiota is subject to dietary control and to integrate these data with functional metabolic signatures and biomarkers. Many lines of research have demonstrated the significant role of the gut microbiota in human physiology and disease. Probiotic and prebiotic products are proliferating in the market in response to consumer demand, and the science and technology around these products are progressing rapidly. With high-throughput molecular technologies driving the science, studying the bidirectional interactions of host-microbial cometabolism, epithelial cell maturation, shaping of innate immune development, normal vs. dysfunctional nutrient absorption and processing, and the complex signaling pathways involved is now possible. Substantiating the safety and mechanisms of action of probiotic/prebiotic formulations is critical. Beneficial modulation of the human microbiota by using these nutritional and biotherapeutic strategies holds considerable promise as next-generation drugs, vaccinomics, and metabolic agents and in novel food discovery. J Nutr 2015;145:1123S–30S.

Keywords: diet, metagenomics, microbial-host co-metabolism, microbiome, probiotics/prebiotics

Introduction

Metagenomic sequencing represents a powerful advance for analyzing the profound effect that the microbial genome...
products of microbial metabolism are released under similar conditions of reduced dietary intake and may coevolve expanded metabolic capabilities that our mammalian genomes lack. Cells of Bifidobacterium spp. cells able to use glycan substrates as an energy source is assumed to be selective for these substrates. Moreover, because none of the oligosaccharide-derived glycans can be metabolized by infant digestive enzymes, the evolutionary value of their production is assumed to be selective for these substrates by Bifidobacteria spp. Cells able to use glycan substrates as an energy source is assumed to have host energy advantage during periods of reduced dietary intake and may coevolve expanded metabolic capabilities that our mammalian genomes lack. Understanding the intricate role of microbial ecology and the variability of microbial gene sets in individual phenotypes that comprise the microbiome within a complex metagenome (aggregate DNA of host and microbiota) has implications for preventing disease susceptibilities and diagnosis of human pathologies.

An important question is to determine whether diet-derived products of microbial metabolism are released under similar conditions in the presence of carbohydrate, fat, and protein food substrates. By understanding bacterial biotransformation via chemical and enzymatic pathways that modulate colonic and systemic inflammation, obesity, and host gut metabolism, the role of macronutrients that drive microbial metabolism, metabolite production, and food matrix byproducts will begin to be more clearly elucidated.

After a meeting in Paris in 2005, the International Human Microbiome Consortium was officially launched in 2008 and continues to generate shared metagenomic-scale data resources for understanding our microbial genomes, their encoded metabolic functions, and interaction with the host ecosystem. The Human Microbiome Project (HMP) sponsored by the NIH has been a member of the international consortium since its inception. An overarching goal of the current ongoing HMP efforts is to create metabolic signatures that further refine our understanding of major implications of coevolution and metabolism of the microbiome for promoting human health and disease prevention. The HMP based at the NIH complements other large-scale sequence-based projects such as the European Union’s Metagenomics of the Human Intestinal Tract (MetaHIT) project. Both projects are focused on examination of the gut microbiome for a wide range of health statuses and physiologic characteristics.

Complementing the international consortium efforts, the first genome sequence of a lactic acid bacterium, Lactococcus lactis subsp. lactis, was completed in 2001. The U.S. Department of Energy Joint Genome Institute and the Lactic Acid Bacteria Genome Consortium continue to examine polysaccharide-glycoside hydrolyses encoded in microbial genomes for a broad repertoire of commensal microorganisms and their enzymatic ability to convert between different energy sources. Despite the relatively small size of their genomes, a number of biologic systems controlling the internal environment and energy metabolism may be responsible for lactic acid bacteria (LAB) (e.g., Lactobacilli, Bifidobacteria spp.) survival. Function-based “omics” approaches are needed to further examine microbial utilization and degradation of diet-derived polysaccharides, including transport functions and regulatory interactions in commensal LAB organisms. Collectively, these resources serve as invaluable comparative model systems for guiding future investigations and are essential framework components for advancing human microbiome research. Diet-induced obesity and related chronic diseases are the single largest cause of morbidity and mortality, affecting >50% of the adult population in Western countries. Our contemporary lifestyle is associated with an epidemic of metabolic abnormalities, most prominently characterized by excessive body fat accumulation, high BMI, and high fasting plasma glucose. Hildebrandt et al. (5), for example, showed in a diet-induced murine model that periods of reduced dietary intake and may coevolve expanded metabolic capabilities that our mammalian genomes lack (10). The HMP based at the NIH complements other large-scale sequence-based projects such as the European Union’s Metagenomics of the Human Intestinal Tract (MetaHIT) project. Both projects are focused on examination of the gut microbiome for a wide range of health statuses and physiologic characteristics.

Complementing the international consortium efforts, the first genome sequence of a lactic acid bacterium, Lactococcus lactis subsp. lactis, was completed in 2001 (14). The U.S. Department of Energy Joint Genome Institute and the Lactic Acid Bacteria Genome Consortium continue to examine polysaccharide-glycoside hydrolyses encoded in microbial genomes for a broad repertoire of commensal microorganisms and their enzymatic ability to convert between different energy sources (14, 15). Despite the relatively small size of their genomes, a number of biologic systems controlling the internal environment and energy metabolism may be responsible for lactic acid bacteria (LAB) (e.g., Lactobacilli, Bifidobacteria spp.) survival. Function-based “omics” approaches are needed to further examine microbial utilization and degradation of diet-derived polysaccharides, including transport functions and regulatory interactions in commensal LAB organisms. Collectively, these resources serve as invaluable comparative model systems for guiding future investigations and are essential framework components for advancing human microbiome research (16).

Diet, Microbial Diversity, and Host Metabolism

From phenotypic analysis (metabolomics) and compositional (metagenomic) assessments, diet is a fundamental driver of gut microbial diversity and stability that arise between 2 and 4 y of age (17). Changes in diet and energy expenditure related to energy-dense foods are implicated as causing a major shift in bacterial numbers, SCFA production, satiety signaling, and the increased prevalence of obesity in Western populations (18). The increasing rates of obesity in Western populations are attributed to the evidence that ancestral human populations relied on diets containing more indigestible plant material than do modern high-energy, low-fiber, and high-fat foods (19). Frost et al. (20) found a relation between hormonal appetite pathways and complex metabolites of protein-derived fermentation that plays a greater role in appetite suppression or stimulation than with resistant starch and other dietary fibers. Pig model systems that have similar gastrointestinal tracts and diets to humans and germ-free mice humanized with human intestinal microbes provide comparative approaches for examining microbiota interactions with specific diets (8). Alternatively, in a rodent model, Devkota et al. (21) provided further evidence that dietary fats alter conditions for gut microbial assemblage, which can perturb immune homeostasis. The results implicate immune sensing of microbial metabolites that may be regulating host homeostatic set points in communicating with the microbiota. Table 1 presents some of the essential properties of the gut microbiome. Metabolomics, defined as the measurement of multivariate metabolic responses to physiologic stimuli or genetic modification, is a high-throughput molecular approach to understanding metabolic regulation of an organism and its microbial origins. From phenotypic analysis (metabolomics) and compositional (metagenomic) assessments, diet is a fundamental driver of gut microbial diversity and stability that arise between 2 and 4 y of age (17). Changes in diet and energy expenditure related to energy-dense foods are implicated as causing a major shift in bacterial numbers, SCFA production, satiety signaling, and the increased prevalence of obesity in Western populations (18). The increasing rates of obesity in Western populations are attributed to the evidence that ancestral human populations relied on diets containing more indigestible plant material than do modern high-energy, low-fiber, and high-fat foods (19). Frost et al. (20) found a relation between hormonal appetite pathways and complex metabolites of protein-derived fermentation that plays a greater role in appetite suppression or stimulation than with resistant starch and other dietary fibers. Pig model systems that have similar gastrointestinal tracts and diets to humans and germ-free mice humanized with human intestinal microbes provide comparative approaches for examining microbiota interactions with specific diets (8). Alternatively, in a rodent model, Devkota et al. (21) provided further evidence that dietary fats alter conditions for gut microbial assemblage, which can perturb immune homeostasis. The results implicate immune sensing of microbial metabolites that may be regulating host homeostatic set points in communicating with the microbiota. Table 1 presents some of the essential properties of the gut microbiome. Metabolomics, defined as the measurement of multivariate metabolic responses to physiologic stimuli or genetic modification, is a high-throughput molecular approach to understanding metabolic regulation of an organism and its microbial origins.
adiposity or, alternatively, could represent a host-mediated adap-
argued that integrating biologic knowledge in transgenomic,
microbial functional and metabolic interactions, Holmes et al. (28)
entero-endocrine and epithelial cells. In studying a broad array of
signaling mechanisms involving innate immune responses and
microbes contribute to host energy balance by using interactive
plasma LPS concentration has gained attention as a plausible
and weight gain via transport of LPS out of the gut. Reducing
should be targeted in early life and across the life span.
chronic diseases such as obesity, diabetes, and other metabolic
diseases. Energy-harvesting studies by Puertollano et al. (31)
showed that the normal gut microbiome converts indigestible
plant polysaccharides by scavenging hydrogen during fermen-
tation and methane production into SCFAs (acetate, propionate,
and butyrate). In addition to being energy sources, SCFAs control colonic gene expression and metabolic regulation by G-protein–coupled receptors (32). Further studies are needed
that examine whether different SCFA signaling receptors [e.g.,
through G-protein-coupled receptor (GPR43)] are similarly
involved in host energy balance and whether selected microbial
communities interact differently with these molecules.

Prebiotics/Probiotics and Energy
Metabolism

The gut microbiota is considered a modifiable target for
preventing gut metabolic diseases. Microbial products directly
affect intestinal function, liver, brain, and adipose tissue, which
consequently may affect diet-induced obesity and other meta-

cal conditions. Nondigestible food ingredients, including plant cell wall
polysaccharides (cellulose, xylan, and pectin) that stimulate
specific microbes to improve metabolic regulation, are increas-
ingly being introduced into the Western diet, many of which are
claimed to have prebiotic properties (33). A prebiotic is a
“nonviable food component that confers a health benefit on the
host associated with modulation of the microbiota” (34). Prebiotics such as galacto-oligosaccharides, together with inu-
lins and their fructo-oligosaccharide derivatives, were shown
to modify the species composition of the colonic microbiota
(35). Changes in carbohydrate intake of a prebiotic inulin, for
example, were shown to increase concentrations of Faecalibac-
terium prausnitzii and Bifidobacterium spp. in humans and
correlated with reduced adiposity (36).

Probiotics are defined as “live microorganisms which when
administered in adequate amounts confer a benefit on the host”
(37). Probiotics have been available as foods and dietary supple-
ments for decades. Lactobacillus and Bifidobacterium strains used
in foods were initially marketed in yogurts and kefir products, and
their use has skyrocketed in consumer products in recent years.
Potentially, probiotic-grade strains may affect metabolism of
dietary components in the small intestine (partial hydrolysis of
lactose in fermented foods; lipid and oxalate metabolism) and
metabolism of indigestible carbohydrates, p-cresol excretion, and
colic protein and ammonia metabolism in the large intestine.
The benefits of probiotic consumption are still inconclusive,
although the role of probiotics in maintaining health is broadly
attributed to the combined effect on competitive exclusion of
pathogens, epithelial barrier integrity, and immune regulation (38).

Firm conclusions regarding probiotic metabolic effects on
modifications of dietary protein or xenobioc metabolism, gut
mucosa, and liver metabolic activities remain priorities for
future research. Immunosenescence and effects of aging on the
microbiota are less studied areas of research, with reduction in
bifidobacterial counts presumed to be mediated by diet changes,
including institution or community living. Perez et al. (39) found
that probiotic manipulation of the gut microbiota may poten-
tially improve adaptive immune responses and reduce inflam-
matory secretions, thus compensating for age-related effects.
Systematic reviews, meta-analyses, and conference proceedings
on the regulatory science of prebiotic/probiotic foods and health
supplements are available in the literature and beyond the scope
of this article (40–43).

Microbial Fermentation of Polysaccharides
to SCFAs

The gut microbiota manipulates the provision of calories to the
host by hydrolysis of indigestible plant polysaccharides. Com-
plex carbohydrates, such as dietary fiber, are metabolized by the
colon microbiota to oligosaccharides and monosaccharides
and then fermented to SCFAs, which function both as an energy
source and as a signaling molecule (29). Dietary fiber (e.g.,
cellulose, pectin) abundance and type are directly related to the
species composition of the microbiota and their metabolic
interactions. As a fuel source for intestinal epithelial cells and
gut epithelial function, SCFAs are suppressed with antibiotic
perturbation, are not confined to the intestinal tract, and can
disseminate systemically and be detected in the blood (30).

Carbohydrate fermentation in the colon resulting in produc-
tion of SCFAs provides an intriguing pathway for studying
chronic diseases such as obesity, diabetes, and other metabolic

table metabolism

<table>
<thead>
<tr>
<th>TABLE 1  Complexity of host microbial cometabolism</th>
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<tr>
<td>● The human microbiota comprises &gt;100 trillion microbial cells; our adult bodies harbor 10 times more microbial cells than human cells</td>
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<tr>
<td>● The human gut microbiome is estimated to contain ∼3.3 million nonredundant genes, compared with the human genome, which consists of 23,000 genes (1)</td>
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<tr>
<td>● Microbes make up 90% and human cells ∼10% of cells in the human body</td>
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<tr>
<td>● The human gut microbiome is mostly acquired shortly after birth from the maternal and living environment (diet, genotype, environmental interactions)</td>
</tr>
<tr>
<td>● The metabolic role of the gut microbiota is essential for carrying out functional biochemical processes of human physiology, including the following:</td>
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<tr>
<td>- salvage of energy</td>
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<td>- generation of absorbable compounds</td>
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<tr>
<td>- production of SCFAs, vitamins, and essential nutrients</td>
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<td>- xenobiotic metabolism</td>
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<td>- metabolite production</td>
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In principle, point-source interventions, including prebiotics/probiotics, are not likely to provide sufficient leverage to shift the entire microbiota system. The use of prebiotic/probiotic systems biology models are desirable targeted approaches, however, for understanding bacterial homeostasis. It may be especially worthwhile to establish a food safety index system of probiotic-grade LAB organisms for assessing obesogenic and related diet-induced metabolic risk conditions based on functional interaction models in simulated in vitro and in vivo biologic systems (44, 45). As the molecular basis of human-microbe interactions is unraveled, selection criteria for probiotics for different clinical indications are gaining increasing attention on the basis of their metabolic, anti-inflammatory, immunomodulatory, and antimicrobial effects (42, 46). Strain-specific analyses remain the standard for current physician recommendations for probiotic use. However, conclusive evidence is lacking to definitively guide the clinical use of prebiotic and probiotic interventions.

Current consumption patterns obligate the need for substantiating the safety and functional value of prebiotic and probiotic products sold as food and dietary supplements, given the increasing number of institutions recommending routine use. Some U.S. policy makers argue that a probiotic regulatory framework should be established where consideration is given for a strain to be regulated simultaneously at different risk levels for different applications (45). In the meantime, practitioner guidelines for consumer health are still unclear. Hence, practitioners must weigh the available evidence, and manufacturers share the responsibility of providing guidance about the type and extent of safety assessments that have been conducted on its products (46).

**Maternal Factors and Developing the Gut Microbiome**

Microbial ecology niche colonization profoundly affects immune maturation and disease susceptibility during infancy (47). Table 2 lists key mechanisms by which initial microbiota colonization patterns in neonates are beneficially influenced by maternal factors (48, 49).

As stated earlier, dietary glycans from human breast milk are vitally important in shaping the structure and functional performance of the neonatal intestinal microbiota. Humans lack the various glycolytic enzymes that degrade complex oligosaccharide bonds, whereas selected commensal microbes possess the glycosylhydrolases and transport proteins to break down the glycans humans cannot digest (10, 50). The human milk-oriented microbiota plays a critical role in gut barrier protection during infant growth and development, a period when selective substrates of oligosaccharides allow bifidobacteria to colonize the niche at high abundances (51). Interactions between dietary nutrients and low-molecular-weight molecules of indigenous microbiota during infancy may be key determinants that affect gene expression pathways in the host metagenome via epigenetic processes (i.e., individual genotype and environment) and biochemical mechanisms (52, 53). Understanding how the biochemical and immunologic features of human milk and infant microbiota coevolve during the neonatal period when a mother is healthy, obese, or malnourished is an intriguing question.

With metabolomic and other functional “omics” technologies available, a full spectrum of microbe-relevant metabolites (e.g., secreted antimicrobials), metabolic signatures, and specific functional benefits of selected commensal probiotic-grade organisms to infant health will be uncovered. Bacteriocins are an abundant and diverse class of ribosomal antimicrobial peptides derived from the gut microbiota (54). These compounds are produced by all known lineages of intestinal bacteria and archaea, which suggests they play an important coevolutionary role in host resilience and niche adaptation. Bacteriocins are among a group of antimicrobial compounds that also may enhance the ability of commensal strains, particularly Bifidobacterium and Lactobacillus spp. to compete against potentially pathogenic microbes. Although their exact ecological function in niche communities is unknown, metagenomic analyses suggest that bacteriocins may contribute to commensal and probiotic strain selectivity as 1) colonizing peptides facilitating competitive exclusion of pathogens, 2) killing peptides directly eliminating pathogens, or 3) signaling peptides for other bacteria or the immune system (55).

The indigenous microbiota is also essential for the early development and homeostasis of the host immune system. Maslowski et al. (56) found that nutrient- and microbe-derived SCFAs may stimulate potent immunomodulatory effects by acting on G-coupled receptors. *Bacteroides fragilis* was recently used to describe how key microbial players develop into a network and induce a beneficial immune response (e.g., via capsular polysaccharide A) (57). Moreover, the intestinal microbiota plays a vital role in developmental gut barrier structure and function, signaling the innate immune system through pattern recognition receptors [e.g., Toll-like receptors (TLRs)] that bind to specific microbial macromolecules [i.e., LPS, peptidoglycans] and that ultimately lead to release of protective peptides, cytokines, and phagocytes (58).

**Metabolic Footprints of Gut-Microbial Cometabolism in Global Health**

Dietary differences in vegetable and animal protein intake modulate the gut microbiota via metabolic activities that include processing of glycans and isoprenoids, production of vitamins (vitamins A and K and biotin), amino acid synthesis, SCFA effects on cholesterol and glucose metabolism, and bile acid biotransformation (59). In extreme under- and overnutrition states, microbial metabolic activities are of long-term health significance. Nutrition systems biology coupled with “omics”-based technologies holds an essential key to further probing host-gut microbiome interactions that can inform global public health and the practice of 21st century health care (60–62).

The Biomarkers of Nutrition for Development (BOND) program sponsored by the NIH Eunice Kennedy Shriver National Institute of Child Health and Development, in collaboration with global partnerships representing the food and nutrition enterprise, is designed to support development of

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**TABLE 2** Maternal contributions to the development of a healthy infant microbiome

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tr>
<td>Maternal diet/nutritional status</td>
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<tr>
<td>In utero exposure to maternal microbiota</td>
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<tr>
<td>Vaginal delivery</td>
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<tr>
<td>Gestational age</td>
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<td>Breastfeeding</td>
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<tr>
<td>- surface contact</td>
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<tr>
<td>- prebiotic and probiotic potential of human milk</td>
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methodologies and biomarkers needed to improve nutrient measurement systems (63). Additional global efforts also identified the need for robust biomarkers to assess the vicious cycles of undernutrition, infectious disease (diarrheal diseases), and physical and neurological development as a global priority (64). Inflammation- and diet-related chronic diseases give rise to microbial perturbation and are emerging as a major target of biomarker surveillance efforts (65). Large-scale sampling methods for population health research to integrate gene-environment predisposition with diet-gut microbiome interactions are a way to generate more informed public health planning (66) and will provide the basis for studies to evaluate the safety and effectiveness of alternative diet-based interventions (67).

The gut microbiota contributes to the risk and pathogenesis of global rates of undernutrition through nutrient metabolism, infection, and disturbances in immune function (68). Complicating this set of conditions, environmental factors cannot be separated in the real world because a number of chemical agents contaminate food chains. Consequently, for much of the world, inadequate dietary and microbial methylation patterns can alter one-carbon metabolism, resulting in hypomethylation and elevated plasma homocysteine concentrations, with increased risk of hepatotoxicity effects. Microecological imbalances caused by impairment of important epigenomic pathways can also lead to the onset of chronic metabolic disturbances (33, 69). Kwashiorkor, a severe acute malnutrition, is exacerbated by environmental insults. Smith et al. (70) observed that the combination of the Malawian diet and kwashiorkor microbiome produced marked weight loss in recipient mice and perturbations in amino acid and carbohydrate metabolism.

**Metabolic Consequences from Modern Diets and Obesity**

Obesity is essentially the imbalance between energy intake and energy expenditure, and it is now estimated that ~65% of Americans are overweight (71). The obesogenic state has an increased capacity to harvest energy from the diet and alters gut microbial ecology and metabolic disturbances from fat deposits and gut immune system inflammatory responses, which have strong influences on energy sensing and energy balance in humans. Turnbaugh et al. (72) showed that colonization of germ-free mice with an obese microbiota results in a significantly greater increase in total body fat than does colonization with a lean microbiota.

Ley et al. (73) earlier found that host diet and phylogeny both influence bacterial diversity. Fat in large deposits, for example, evolved in birds and mammals, giving a species-selective advantage in managing wide fluctuations in energy supply and expenditure. When energy consumption overrides energy expenditure, the only tissue capable of expanding to store large amounts of excess nutrients is adipose tissue. This adipocentric view of obesity derives from the hypothesis that chronic health disorders of obesity are secondary to adipose tissue capacity to store leptin (74). Another view describes the innate immune system as a prewired set of cellular and humoral components and that obesity in childhood is associated with the activation of the innate immune system. Increases in inflammatory biomarkers such as C-reactive protein and neutrophilia are seen in obese children as young as 3 y of age, which supports the notion that obesity-induced inflammation may be initiated early in development (75).

Inflammatory effects of obesity are generated by an intricate cascading of immune signaling events that increase the proliferation of macrophages in adipose tissue. There remain many questions in unraveling the precise function of adipose tissue macrophages in different fat depots and pathologic contexts (76). The inflammatory response in obesity is also generated in response to nutrient excess and metabolic dysregulation (77). Collectively, these compounds include proteins, carbohydrates, lipoproteins, nucleic acid species, and pathogen- and microbe-associated molecular patterns. Mammals have also coevolved a set of pattern recognition receptors designed to sense and trigger a response to various antigens they encounter and that play a key role in immune homeostasis. A critical set of the membrane-bound pattern recognition receptors are the set of 10 TLRs in humans (78). TLR2 is essential for epithelial barrier function and in regulating inflammation. How these immunologic receptors form critical links between metabolism and inflammation is unclear.

In summary, the cascade effect evidenced in macrophages recruited to fat depots releases additional proinflammatory molecules. Although this biologic programming works to combat pathogens, it cumulatively causes damage to normal tissue. Hence, by understanding how the gut microbiome may influence calorie balance through the regulation of calorie dissipation (heat generation), the side effects of fat-provoked inflammation, including weight gain, may be better controlled. Along another fascinating line of inquiry, Blum et al. (79) recently reported that the *Drosophila* system may represent an alternative mutualism strategy termed “quotidian replenishment,” defined as the need to obtain daily replenishment from the ecosystem environment to obtain a consistent microbial community in a biologic system, as earlier proposed by Storelli et al. (80). Further study may reveal general principles of why frequent dietary ingestion from an external reservoir might be of mutual host-microbial benefit, promoted by symbiotic microbial farming, and underscores the rationale for probiotics that target host-microbial cometabolism and their consumption in a safe and precise manner.

**Conclusions**

Much has been learned about the factors influencing the ontogeny, maintenance, and function of the human gut microbiome. Much remains to be done. Table 3 contains a brief, not exhaustive, list of research priorities to move this important public health agenda forward.

Large database efforts such as the MetaHIT and the NIH HMP continue to play major roles in the International Human Microbiome Consortium and have contributed vastly to our understanding of the complex ecosystem of the gut microbiome that starts at birth, assembling within the human host, and of its role in perturbations and disease across the human life span. Despite the gaps and challenges, the human microbiome holds great potential for accelerating the translational pipeline, equipped with “-omics” precision tools that now allow us to sculpt microbiome interventions with diet, prebiotics, probiotics, and targeted antibiotics to prevent and treat disease. Although many questions remain unanswered, what we do know about key functions of the gut microbiota is primarily related to digestion, with energy production playing a primary role in the digestion of complex polysaccharides and fibers that are otherwise indigestible for humans. A key end product of gut digestion and fermentation is production of SCFAs, which cells need for energy. An additional role is microbial synthesis of chemicals and nutrients, including production of anti-inflammatory...
compounds, particularly bacteriocins, antibiotic products, and vitamins.

The rapidly expanding product line of probiotics in the marketplace has not been conclusively proven as safe or effective for any specific health claims here in the United States. Targeted models of how single (and combination) bacterial organisms affect homeostasis and can influence human tissue (e.g., bile stress response) will serve as building blocks of the evolving nutrigenomic landscape. Germ-free mice and especially pig models colonized by humanized microbiota could help in identifying biomarkers to characterize the impact of diet and probiotic/prebiotic intake and provide proof-of-principle, host-microbial cometabolism models needed to assess restorative ecology and functional impacts on health.

Programs such as BOND and the Biomarker Initiative sponsored by the Foundation for the NIH are moving to provide food technology and medical communities with robust biomarkers as valid and reliable measurements. One of the ultimate goals of the NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development National Children's Study and BOND initiatives is profiling metabolites in comprehensive time-series studies to define their relation with diet in healthy individuals at various stages of life (e.g., in women before, during, and after pregnancy and in their children during the first 5 y after birth) (81). Moreover, the realization of the long-term vision of the international consortium and existing microbiome framework of the NIH HMP, MetaHIT, and expanding global networks depends on the long-range commitment of stakeholders in academia, government, philanthropy, and industry to bring the resources available via technology-driven platforms into fuller partnership with better planning and industry to bring the resources available via technology.


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