Review

CellPress

The gut microbiota in human energy homeostasis and obesity

Michael Rosenbaum[1], Rob Knight[2], and Rudolph L. Leibel[1]

[1] Columbia University, Department of Pediatrics, Division of Molecular Genetics, New York, NY 10032, USA
[2] Departments of Pediatrics and Computer Science and Engineering, University of California San Diego, La Jolla, CA 92093, USA

Numerous studies of rodents suggest that the gut microbiota populations are sensitive to genetic and environmental influences, and can produce or influence afferent signals that directly or indirectly impinge on energy homeostatic systems affecting both energy balance (weight gain or loss) and energy stores. Fecal transplants from obese and lean human, and from mouse donors to gnotobiotic mice, result in adoption of the donor somatotype by the formerly germ-free rodents. Thus, the microbiota is certainly implicated in the development of obesity, adiposity-related comorbidities, and the response to interventions designed to achieve sustained weight reduction in mice. More studies are needed to determine whether the microbiota plays a similarly potent role in human body-weight regulation and obesity.

Introduction

The human gut microbiota (see Glossary) consists of up to 100 trillion microbes that exist in largely symbiotic relationship with their human hosts, and carry at least 150 times more genes (the microbiome) than are present in the entire human genome [1,2]. There is significant cross-sectional variability in the microbiota between individuals and longitudinal variability within individuals. Both the abundance and the composition of the gut microbial population are influenced by diet, medication, weight, and overall metabolic state (energy balance, etc.,) of the host. In turn, and based largely on animal studies, the microbiota is capable of secreting or altering the production of molecules that affect both energy balance (weight gain or loss) and energy stores (fat mass) [3,4]. The microbiota may, in this context, be regarded as a responsive entero-endocrine organ composed of more cells and genes than the host. This manuscript reviews what has been done and what may be done to determine how translatable rodent data are to humans, and what the implications are for probiotic, prebiotic, and possibly targeted antibiotic approaches to the treatment or prevention of human obesity.

Composition of the microbiota

Although phylum-level and even family-level groupings of microbes are very broad, and can conceal variability at finer levels (including at the strain level) that is often important, some general trends emerge. The dominant phyla in the gut are Bacteroidetes (~20–25%), Firmicutes (~60–65%), Proteobacteria (~5–10%), and Actinobacteria (~3%), which together constitute over 97% of the gut microbe population (Table 1). The taxonomic variability in the human gut is much higher than the functional variability, as measured by a variety of methods, suggesting that many different configurations of the microbiota lead to essentially the same functional result [5,6].

Overview of rodent studies of obesity and the microbiota

In rodents, obesity is associated with an increase in the relative size of the Firmicutes versus Bacteroidetes populations in the gut [7], and a decrease in the diversity of the microbiota that is due to both weight and diet composition. The microbiota of diet-induced obese mice (DIO, induced by an *ad lib* high-fat diet, HFD), which are weight-reduced by a calorie-restricted HFD, is more diverse compared to DIO mice at maximal weight (similar diet, greater weight), and less diverse than control *ad libitum* fed mice on a chow diet (different diet, similar weight) [7]. There is much greater variability in human studies. Some studies report a similar increase in the ratio of Firmicutes/Bacteroides, as well as a decrease in the gut biodiversity in obese humans, but there are also numerous studies reporting contradictory findings in obese versus lean humans [8].

Studies of germ-free mice, or previously germ-free mice colonized with a defined microbial community ('gnotobiotic mice'), have provided substantial evidence that the diversity, as well as the presence and relative proportion, of different microbes in the gut play active roles in energy homeostasis. The overall importance of the microbiome is emphasized by the consequences of its absence and repletion. Germ-free mice are very inefficient at processing food, and gain weight when colonized with almost any gut microbes. Inoculation of germ-free mice with 'conventional' microbes results in weight gain to similar levels of fatness to the donor mice. Surprisingly, this weight gain occurs despite an approximately 30% increase in energy expenditure and 30% decline in energy intake, compared to the mice who remain germ-free [9]. As discussed below, weight gain, despite increased energy output and decreased intake, is consistent with a microbially mediated increase in energy harvest.

The amount of weight gained by gnotobiotic rodents differs substantially depending on which microbes are

Corresponding author: Rosenbaum, M. (mr475@cumc.columbia.edu).

1043-2760/
 http://dx.doi.org/10.1016/j.tem.2015.07.002

Glossary

Amylin: a hormone cosecreted with insulin from pancreatic β cells that slows gastric emptying, inhibits glucagon release, and promotes satiety.
Brain-derived neurotrophic factor (BDNF): a neurotrophic growth factor that supports the survival of existing neurons and favors the growth of new neurons and synapses in the central and peripheral nervous system.
Cocaine–amphetamine-related transcript (CART): an anorectic neuropeptide expressed in both the central and peripheral nervous systems as well as in multiple endocrine organs.
Ecological model: a framework for understanding the dynamic interrelations among various personal (individual) and environmental factors (ranging from family to cultural attitudes).
Gastric inhibitory peptide (GIP): an incretin secreted by the jejunum and ileum that stimulates insulin release, increases lipoprotein lipase activity in adipocytes, and slows the rate at which nutrient moves through the intestines by decreasing motility and acid secretion.
Genus: the second least inclusive taxonomic rank in the biological classification system of organisms (Domain, Kingdom, Phylum, Class, Order, Family, Genus, and Species).
Germ-free: raised in a sterile environment resulting in no microorganisms living in or on the animal.
Glucagon-like peptide-1 (GLP-1): an incretin secreted by the intestines that stimulates insulin secretion and sensitivity, promotes satiety, and inhibits secretion of glucagon.
Gnotobiotic: an animal in which only particular known strains of bacteria and other microorganisms are present, usually a formerly germ-free animals that has been intentionally colonized with a known microbial population. Technically, a germ-free animal is also gnotobiotic because its entire microbiome (which is none) is known.
Heritability: the fraction of the variability of a trait in a population that is attributable to genes.
Lipoprotein lipase (LPL): a water-soluble enzyme that hydrolyzes triglycerides and includes hepatic lipase, pancreatic lipase, and endothelial lipase.
Microbiome: the collection of genomes of microbes in a system.
Microbiota: the ecological community of commensal, symbiotic and pathogenic microorganisms that live in our body; in other words, the collection of organisms.
Neuropeptide Y (NPY): a neuropeptide produced in the hypothalamus and neurons of the sympathetic nervous system, and the most potent endogenous orexigen.
Peptide YY (PYY): an anorexigenic gut derived peptide secreted by the ileum and colon in response to feeding. PYY binds to NPY receptors, increases water absorption in the colon, and slows gastric emptying.
Phylum: the third most inclusive taxonomic rank in the biological classification system of organisms (Domain, Kingdom, Phylum, Class, Order, Family, Genus, and Species).
Prebiotic: selectively fermented nondigestible food ingredients or substances specifically supporting the growth and/or activity of health-promoting bacteria that colonize the gastrointestinal tract.
Probiotic: a live microorganism that when administered in adequate amounts confers a health benefit on the host.
Pro-opiomelanocortin (POMC): a precursor polypeptide that is cleaved to form adrenocorticotropic hormone (ACTH), the anorexiginic neuropeptide α-melanocyte stimulating hormone (α-MSH), and the endogenous opioids β-endorphin and [met]enkephalin.
Resting energy expenditure: the energy expended in cardiorespiratory work and in maintaining transmembrane ion gradients at rest. Generally it is about 50–60% of 24 h energy expenditure.
Species: the least-inclusive taxonomic rank in the biological classification system of organisms (Domain, Kingdom, Phylum, Class, Order, Family, Genus, and Species).
UniFrac distance (unique fraction metric): a measure of the phylogenetic distance between sets of taxa.

inoculated. Administration of microbes from leptin-deficient (Lep^{ob}) mice, that contain higher absolute and relative proportions of Firmicutes, similarly to other obese mice, results in greater weight and fat gain, lower energy expenditure, and increased energy harvest than does administration of microbiota from wild-type mice [10]. Similar donor adiposity-related effects are noted following inoculation of germ-free mice with the microbiota from monozygotic (MZ) and dizygotic (DZ) human twin pairs discordant for obesity. There was a progressively greater increase in both fat mass and fat-free mass in animals receiving microbes from the obese twins, despite no significant differences between groups in daily chow consumption [11].

The consequences of manipulation of the microbe population in rodents are also dependent on the environment in which they are studied. In the twin study described above [11], gnotobiotic mice developed the microbiota and somatotype of their human donors. Cohousing of lean (Ln^{ch}) and obese (Ob^{ch}) mice results in acquisition by Ob^{ch} mice of the microbiota of lean animals, but no corresponding acquisition of the obese microbiome or somatotype in Ln^{ch}. Ob^{ch} mice fed a low saturated fat, high fruit and vegetable diet demonstrated greater invasion of the Ln^{ch} microbiota. In addition, all mice on this diet with the lean microbiome (*Ln/Ln*, Ln^{ch}, and Ob^{ch}) gained less fat mass, compared to mice fed a high saturated fat, low fruit, and vegetable diet (*Ln/Ln* and Ln^{ch}), and to obese animals cohoused with a lean animal (Ob^{ch}) [11]. Similarly, studies of germ-free mice inoculated with microbiota from obesity-prone (OP, higher Firmicutes/Bacteroidetes ratio) versus obesity-resistant (OR) rats, show that there is greater weight gain in the OP-treated group, but only in the setting of a HFD [12].

In mice, there is some influence of host genotype (mouse strain) on the microbiome [13], but the effect of the mouse environment is greater. Ericsson *et al.* [14] compared the microbiota of six different strains of purchased mice (some strains duplicated) from three different laboratories and from 3.5 weeks of age to 24 weeks of age, during which time they were all housed and fed similarly and at a single site. The found roughly twice as many significant vendor effects within populations of Bacteroidetes, Firmicutes, and Proteobacteria compared to mouse strain effects. There was little change in these populations between 3.5 and 24 weeks of age, suggesting the importance of early gut colonization and strain × vendor interactions. Parks *et al.* [15] reported significant heritability of weight gain and of gut microbial composition and plasticity (potential for change) in response to a high-fat/high-sugar diet, However, neither the baseline enterotype nor the degree of plasticity (amount of change in response to diet) were independently predictive of weight gain in mice. In humans, the predominance of the environment in determining the composition of the gut microbiome is also evident [16].

Overview of the human gut microbiome

The pediatric microbiome

In so-called 'ecological models', child adiposity is influenced by home and school environments, parental eating behaviors, and food availability, in addition to adiposity of parents [17]. Similarly, the establishment of the gut microbial population in the neonate is a complex process that may involve interactions between the maternal and fetal genes and environment (as exemplified by studies discussed above of the interactions of the microbiome from genetically OP vs OR rats with diet type). These interactions may begin even before birth and progress through multiple stages under the influence of various internal factors, such as the early decline in the abundance of oxygen in the gut that influences the balance of aerobes and anaerobes, and external factors such as diet [18].