

Role of the gut microbiome in metabolic health: are bacteria in part to blame for human obesity?

journal date: 22/04/2009

Burning more energy than one takes in is usually considered to be an effective weight management approach. A growing amount of evidence suggests, however, that the obesity epidemic cannot solely be explained by changes in everyday physical activity, nutritional habits, or the human genome. The "zoo" of bacteria in the distal gut may play an even more crucial role in maintaining body weight balance.

Excitingly, studies in mice have identified a link between distal gut microbiota and the energy that the mice harvest and store from food.¹⁻⁴ Conventionally raised mice—those harboring microbiota since birth—had 42% more total body fat than comparable mice raised in the absence of micro-organisms. This was the case despite the fact that the conventional mice consumed 29% less chow than the germ-free mice. When the distal intestine microbiota from the conventional mice was colonized to the germ-free mice, the previously lean germ-free mice increased their body fat by about 60% in 2 weeks.

Additional studies have shown that obese mice have a 50% higher representation of the gut Firmicutes bacteria and a proportionally lower representation of the Bacteroidetes bacteria than matched lean mice. Firmicutes have been shown to possess a higher capacity for breaking down complex carbohydrates than Bacteroidetes. Thus, these findings suggest that an increased capacity to harvest energy and to promote fat deposition is transmissible, at least in mice.

What about humans?

In a 1-year study of 12 obese individuals randomly assigned to either a fat-restricted or a carbohydrate-restricted low energy diet, the gut microbiota of each volunteer was examined at baseline, 12 weeks, 26 weeks, and 52 weeks. Baseline assessments showed obese individuals had a higher proportion of Firmicutes and a lower proportion of Bacteroidetes than lean persons. As subjects lost weight, the proportional representation of the Firmicutes decreased and the relative amount of Bacteroidetes increased. In other words, weight loss was associated with gut flora more resembling that of a lean person.^{5,6} Besides the ability of the gut Firmicutes to increase the capacity for harvesting residual energy from the diet in the distal intestines, a complementary mechanism has been proposed; namely, the ability of certain intestinal microbiota to induce an increase in plasma levels of lipopolysaccharides that in the host organism trigger low-grade inflammation, hyperinsulinemia, insulin resistance, and visceral obesity.⁷ In addition, certain probiotics can affect the production of bile acids, which in turn affect how much fat people absorb.

Still it remains a major challenge to achieve detailed and representative profiling of the obesity-associated gut microbiota, since it appears that the majority of members of the human intestinal microflora are difficult to culture and therefore almost never studied. Therefore, several metagenome and microbiome high-throughput sequencing projects have recently been launched, including the National Institutes of Health-sponsored

Human Microbiome Project and the European Union–sponsored MetaHiT consortium, to identify the genomes of the microflora in noncultured human feces samples.⁸ This will be an enormous task since the human gut microflora is composed of 10¹³-10¹⁴ microorganisms whose collective genome ("microbiome") contains at least 100 times as many genes as our own genome.

For the motivation of the ongoing microbiome research in this exciting field, it may be appropriate to consider the gut microbiota as a "microbial organ" localized within the host organism. The perspective is that probiotics, antibiotics, various forms of microbiota replacements, specific prebiotic dietary fibers, or bacteria-produced metabolites/nutrients may be identified and developed as efficacious adjunct means of treating and preventing obesity and related metabolic disorders.

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