METABOLISM IN 2013

The gut microbiota manages host metabolism

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In 2013, studies in rodents and humans have reaffirmed the essential role of the gut microbiota in host metabolism. More importantly, several converging results have increased our knowledge regarding the taxa and functions of the gut microbiota that contribute to the management of energy homeostasis, glucose metabolism and metabolic inflammation.

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Over the past decade, it has become clear that the inhabitants of our gut, the gut microbiota, must be considered as a novel partner that is involved in the numerous interactions between our own organs.[1] A few years ago, an exciting advance in the field was demonstrated: transplanting the gut microbiota from obese animals replicated the phenotype in gnotobiotic mice (that is, animals reared free of germs or only in the presence of known or specified microorganisms), proving a causal link between gut microbes and host metabolism.[2] Using different approaches, key studies from 2013 have identified convergent issues regarding the metabolic functions of the gut microbiota and have pinpointed a restricted number of taxa involved in these functions.

The most effective strategy developed for the treatment of obesity and type 2 diabetes mellitus (T2DM), is the gastric bypass, a procedure characterized by rapid and sustained weight loss. Changes in the abundance of specific gut microbes have been reported in individuals who have undergone a gastric bypass.[3] However, a causal link between changes in the gut microbiota induced by gastric bypass surgery and the host phenotype (that is, weight loss, improved glycaemic control and insulin sensitivity) was not demonstrated.

In 2013, this problem was partly resolved by Liou and colleagues,[4] who found that transferring the gut microbiota of mice that underwent a gastric bypass into germ-free mice that did not undergo surgery decreased body weight and fat mass compared with animals receiving the gut microbiota from sham-surgery donors. In addition, gastric bypass surgery resulted in an increase in the relative abundance of *Alistipes*, Gammaproteobacteria, *Akkermansia* and Archaea.[4] A similar shift in the gut microbiota composition had previously been identified in humans with obesity who underwent a gastric bypass; in particular, Gammaproteobacteria, *Akkermansia* and Archaea were enriched after surgery.[3] Whether other bacterial groups affected by the gastric bypass influence metabolism warrants further investigation.

Another discovery by Liou *et al.* was a change in the levels of short-chain fatty acids (SCFAs): acetate levels were decreased and propionate levels were increased, whereas butyrate concentration was unaffected, both in mice that underwent a gastric bypass and in germ-free animals colonized with the gut microbiota from mice that had undergone a gastric bypass, compared with animals colonized with microbes from control donors. These data suggest that specific taxa and/or metabolic functions are shaped by the surgery and play a part in host metabolism.

Translating these animal studies to humans is extremely difficult because of the relative contributions of early-life development of the gut microbiota, genetic background, dietary habits, and eventually interpersonal differences in the gut microbiota structure. In 2013, Ridaura *et al.* overcame some of these obstacles by using an outstanding strategy.[5] By transferring the gut microbiota from female human twins discordant for obesity into adult germ-free mice, they determined that the phenotype of obesity was transmissible. In other words, mice receiving the faecal microbiota from the obese twin displayed a greater fat mass than mice receiving the lean twin's gut microbes. Co-housing obese and lean animals prevented increased adiposity. The researchers identified several members of the Bacteroidetes phylum within the microbiota of lean mice that successfully 'invaded' the microbiota of obese mice;[5] however, whether these species were responsible for the lean-like state remains to be proven.

Functional analysis revealed that the microbial gene repertoire, the microbiome, from mice colonized with the lean twins' microbiota was enriched with genes involved in the digestion of plant-derived polysaccharides and the fermentation of SCFAs, such as butyrate and propionate. Accordingly, propionate and butyrate levels were increased in the caecal content of mice colonized with the transplanted microbiota from lean twins.[5] By contrast, the microbiome from obese twins had 305 enzymes that were differentially expressed.[5] Collectively, these data highlight the need to examine the relationships between gut microbes and physiological parameters, not only at the taxonomic level but also at the level of the metabolic functions and metabolites resulting from these complex interactions.

Partially addressing this need, two studies in 2013 of different cohorts of individuals demonstrated that the richness of gut microbial genes, and microbial composition, correlates with susceptibility to weight loss upon dietary restriction[6] and with metabolic markers (for example, body weight, fat mass, inflammation, glucose and lipid metabolism).[7] Using multiple sequencing technologies, the researchers detected a bimodal distribution of microbial genes.[7] They stratified the population as 'low gene count' (LGC) and 'high gene count' (HGC), according to the number of genes in the gut microbiome, which gives an indication of the different microbial communities

Key advances

- Alterations in the gut microbiota resulting from gastric bypass have a major role in host metabolism[4]
- Functional and metabolic activities of the gut microbiota regulate metabolism[5–7]
- Increased intestinal SCFA production and the presence of *Akkermansia* are associated with reduced obesity, insulin resistance, inflammation and an improved gut-barrier function[4,5,7,9]

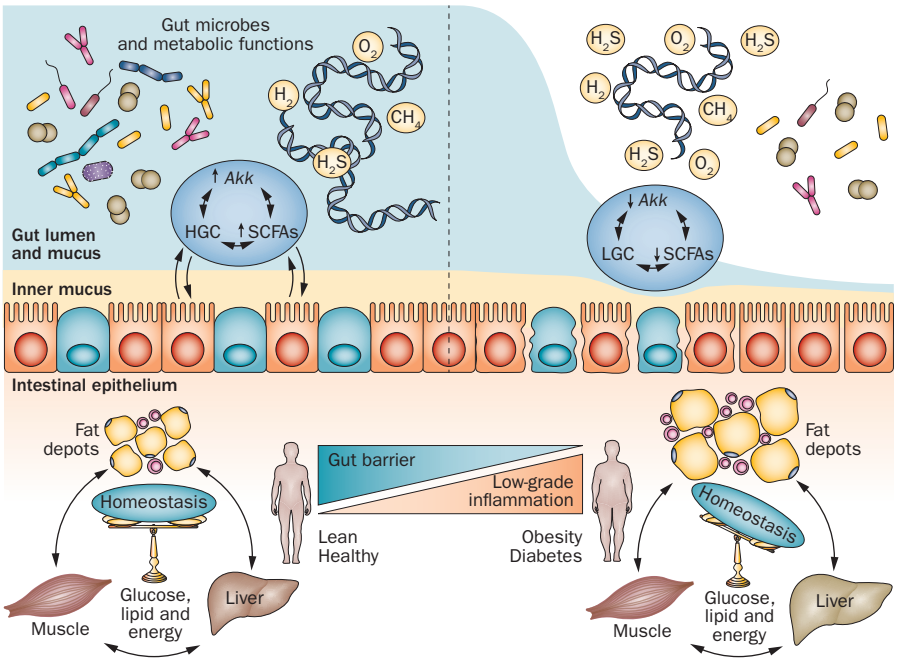

Figure 1 | Changes in gut microbiota composition and metabolism. The gut microbiota of healthy individuals is characterized by an abundance of specific genes (that is, HGC) or specific bacteria (for example, *Akkermansia*) or metabolites, such as SCFAs, that interfere with the host gut-barrier function and metabolism. Obesity and type 2 diabetes mellitus are characterized by a lower abundance of specific bacteria, SCFAs and LGC, thereby leading to gut-barrier dysfunction, low-grade inflammation and altered glucose, lipid and energy homeostasis. Abbreviations: *Akk*, *Akkermansia*; HGC, high gene count; LGC, low gene count; SCFA, short-chain fatty acids.

present as well as their different metabolic functions. Individuals with an LGC (23% of the population) were characterized by more marked weight gain over time, adiposity, insulin resistance and inflammation than HGC individuals.[7] Moreover, microbial gene richness was modified in part by dietary intervention.[6] Very interestingly, dietary restriction was less efficient in LGC than in HGC individuals.[6] These findings suggest that the efficacy of dietary intervention can be predicted through stratification by microbial gene richness.

The abundance of several taxa was significantly associated with bacterial gene richness and phenotype.[7] For example, HGC individuals exhibited an enrichment of genes associated with a higher production of specific metabolites, such as SCFAs, and a higher hydrogen production potential than LGC individuals. Conversely, a shift towards sulphate reduction was suggested in those with an LGC. These results were associated with specific phylogenetic or functional signals, suggesting a shift between specific bacterial species (for example, *Faecalibacterium prausnitzii* and *Akkermansia muciniphila)* or metabolic functions (for example, production of butyrate, mucus, CH_4 and H_2). These factors might be associated with a protective role of the gut barrier against bacteria, such as *Ruminococcus torques* and *Campylobacter*, and processes involved in alterations in the gut barrier (for example, increased H_2S and mucus degradation; Figure 1). Finally, the signatures of unknown species that were associated with HGC or LGC were also identified.[7]

Although based on a model proposed following a different genetic signal, these data are in perfect accordance with previous results obtained in rodents.[8,9] These studies had suggested a role for the gut microbiota and specific metabolites in gut-barrier function and in the development of inflammation in obesity and T2DM.

One of the common denominators of the studies presented here is the observation that some bacterial metabolites, such as the levels of SCFAs, and/or some genera of bacteria (for example, *Akkermansia*) have a key role in regulating various disease states (Figure 1). Along these lines, my group has demonstrated that *A. muciniphila* was decreased in obese and type 2 diabetic mice, and that administration of *A. muciniphila* partially protects mice against diet-induced obesity, insulin resistance, metabolic inflammation and gut-barrier dysfunction.[9] Prebiotics (that is, oligofructose) are a useful tool to increase the intestinal abundance of this microbe.[8,9] Of note, *Akkermansia* is a propionate producer, and SCFAs have been shown to link gut microbiota with host metabolism.[10] Hence, although the link might not be obvious, the findings of these studies are clearly intertwined.

Overall, these reports suggest that key common mechanisms underlie both the success of gastric bypass surgery and the discordant gut microbiota observed in individuals with obesity and T2DM (that is, with respect to gene richness and capacity to induce an obese phenotype) and that key metabolites, such as SCFAs, are involved. The next challenge will be to determine whether specific bacterial groups or their microbial activities can be harnessed for future therapeutic strategies in humans.

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Competing interests
The author declares no competing interests.

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