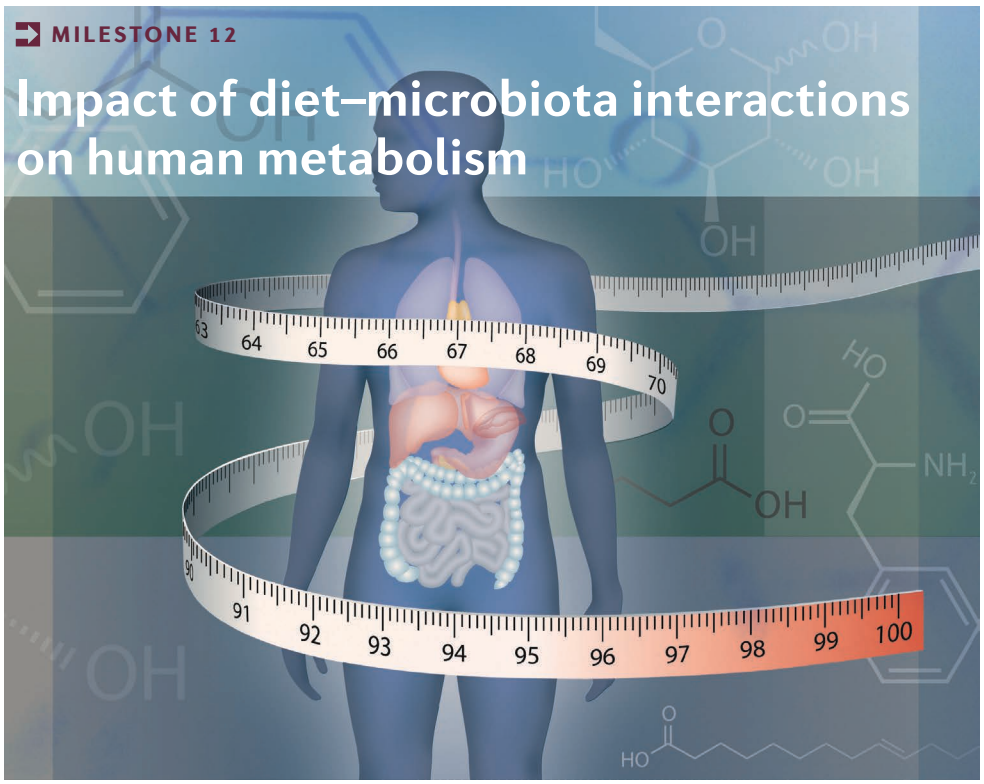
MILESTONE 12

Impact of diet–microbiota interactions on human metabolism



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While studies had made it clear that our gut microbiota could metabolize dietary components (MILESTONE 10), it was yet to be confirmed whether these diet–microbiota interactions had implications for human health.

Jeffrey Gordon's group jump started research into the links between the gut microbiota and obesity with a series of mouse studies. In 2004, this group found that germ-free mice had reduced body fat compared to conventional mice, even though they consumed less food. A year later it was shown that a mouse model of obesity had an altered ratio of the two main phyla present in the gut; the Bacteroidetes and the Firmicutes. A functional analysis of these microbiomes revealed that an obesity-associated microbiota had an increased capacity for energy harvest, and this phenotype could be transferred through faecal microbiota transplant (MILESTONE 11).

Members of the Gordon lab continued this line of research, but this time in humans. In 2006, Ley et al. found that obese individuals had a reduction in the relative abundance of Bacteroidetes compared to lean individuals, and that this could be reversed using diet. This triggered numerous studies of the microbiota in the context of obesity and malnutrition. While many were in agreement and identified an obesity-associated microbiota, others identified no trend, the opposite trend or found that diet was in fact the main driver, rather than the obese state. Given the conflicting results, three reanalysis papers were published, using publicly available datasets, in an attempt to uncover conserved microbiota signatures of obesity. The overarching results were that phylum-level signatures were not generalizable, especially at the population level, however Shannon diversity and evenness, the number of operational taxonomic units, and obesity status did have significant associations, albeit relatively weak.

However, diet was found to consistently alter the gut microbiota. For example, the high-fibre diets that are typically consumed by rural communities were associated with increased microbial diversity, an enrichment of *Prevotella* species, higher concentrations of health-promoting short-chain fatty acids and a reduction in metabolic disease.

> “These studies highlight the crucial impact that diet can have on the gut microbiota and host metabolism”

Studies on a range of other metabolic diseases in relation to the microbiota and diet, such as type 2 diabetes and cardiovascular disease, also emerged. A clear link between the ability of the gut microbiota to metabolise dietary phosphatidylcholine into trimethylamine-*N*-oxide and the development of cardiovascular disease was confirmed in a series of papers by Stanley Hazen and colleagues.

Given the substantial impact of diet on the microbiota, numerous research groups have attempted to harness this power in order to modulate the gut microbiota to alleviate metabolic disease. In 2015, Zeevi et al. used gut microbiota data, together with blood parameters and metadata, to develop a machine-learning algorithm that could predict an individual's glycemic response to a particular meal, resulting in a personalized diet that could lower post-meal glucose. A more general dietary intervention was recently used for the treatment of type 2 diabetes mellitus. In 2018, Zhao et al. used a high-fibre diet to promote colonization by short-chain fatty acid producers and to improve haemoglobin A1c levels, which was used as a readout of type 2 diabetes status.

These studies highlight the crucial impact that diet can have on the gut microbiota and host metabolism, the resulting implications for human health, and how we can use our knowledge of these interactions to develop nutrition-based treatments.

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