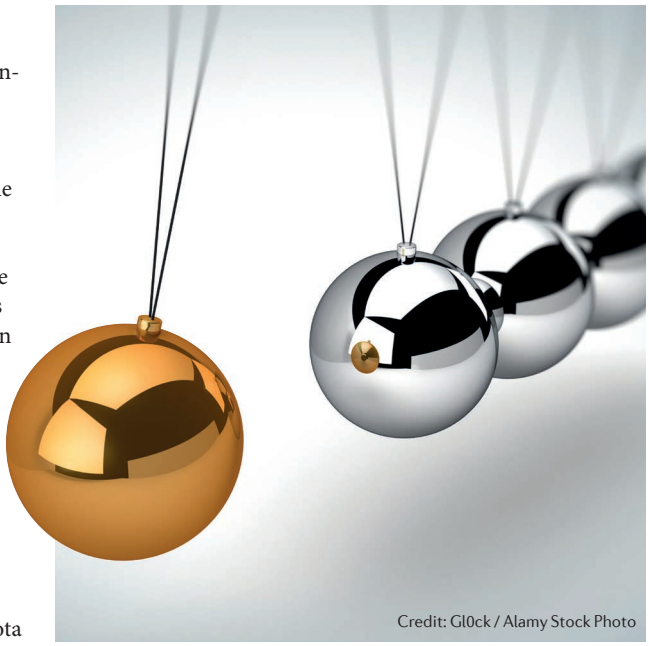
MILESTONE 11

Transfer of host phenotypes through microbiota transplantation

Chronic inflammatory conditions, such as obesity, diabetes, heart disease, autoimmune disorders and cancer, have long been associated with a Westernized diet. Environmental factors also play a role, with the gut microbiota taking centre stage in the past two decades. Indeed, high-fat diets (HFDs) regulate microbial communities in drastic fashion. The microbiota is now acknowledged as having direct, even causative roles in mediating connections between the environment, food intake and chronic disease.

Early studies using germ-free mice showed that body fat content and insulin resistance are transferable from obese to lean mice through exposure to faecal material. In a pioneering paper, researchers found that the microbiota of obese mice are more efficient at extracting energy from the host diet compared to the microbiota of lean ones and that increased adiposity is transferable. When the microbiota from the cecum of obese mice, which had a higher Firmicutes/Bacteroidetes ratio than lean donors, were transplanted into germ-free recipients, there was a greater increase in body fat than in recipients of microbiota from lean mice. Notably, the structure of the established colonizing community in the recipient was highly similar to that of the original donor, suggesting that the composition of the donor microbiota is critical for development of the obese phenotype.

Subsequent studies using gnobiotic mice (with a defined microbiota) showed that a single endotoxin-producing *Enterobacter* species isolated from an obese human's gut was sufficient to induce obesity, insulin-resistant phenotypes and systemic inflammation in mice fed a HFD. The results, derived from the first gnobiotic mouse obesity model, also represent the first demonstration of a causative role of the microbiota in human obesity.



Credit: Gl0ck / Alamy Stock Photo

These findings have raised the possibility of developing therapies based on modulating the microbiota. One such proof-of-principle study found that small intestinal infusion of the gut microbiota from a lean donor restored insulin sensitivity and increased the microbial diversity (with concomitant short-chain fatty acid metabolism) in obese human subjects with untreated metabolic syndrome. This study also described a role for butyrate from gut microbial metabolism in improving insulin sensitivity, a first step in defining specific species and mechanisms used by gut microorganisms to modulate host physiology. Extending these findings beyond adiposity and insulin resistance, host phenotypes were also found to be transferable in mice by co-housing or through vertical transmission. For instance, a colitis phenotype (resembling human ulcerative colitis) can be induced by genetic mutation or can be transferred, vertically to wildtype progeny or horizontally to wildtype cage-mates, through co-housing — a process that is blocked with antibiotics.

> “These findings have raised the possibility of developing therapies based on modulating the microbiota”

More recently, the intestinal microbiota has been shown to modulate neurological and psychiatric diseases, as well as cancer, adding to those phenotypes that can be transferred by faecal material or mother-to-child transmission. Intestinal tumours can be induced in mice harbouring an oncogenic mutation in *Kras* with a HFD, independent of obesity, and this effect can be transferred to healthy adult, normal-diet, *Kras* mutant mice via the dysbiotic gut microbial community found in the faecal material of HFD mice. Inflammation-induced colorectal cancer is transferrable to co-housed mice, an effect that is blocked by antibiotic treatment of donor mice. The impact of gut microorganisms on promoting obesity and liver cancer induced by a Westernized diet is trans-generational — it can be seen in the progeny as well as the grandchildren of mother mice consuming the diet, even though the mothers themselves are unaffected by these conditions. Finally, the intestinal microbiota influences brain development and function in mice. For instance, distinct anxiety levels of different mouse strains are linked to distinct microbiota compositions and the phenotypes are transferrable via faecal matter.

There is a large body of anecdotal and direct evidence suggesting that the microbiota has a role in the health of many human functional systems. Being able to transmit phenotypes via whole microbiota, individual microorganisms or, eventually, through individual microorganism-derived metabolites, should prove revolutionary for treatment of disease and maintenance of a healthy human condition.

Mirella Bucci, *Nature Chemical Biology*

ORIGINAL ARTICLE Turnbaugh, P.J. et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **444**, 1027–1031 (2006).
FURTHER READING Bäckhed, F. et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101** 15718–15723 (2004) | Garrett, W.S. et al. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell* **131**, 33–45 (2007) | Vrieze, A. et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **143**, 913–916 (2012) | Fei, N. et al. An opportunistic pathogen from the gut of an obese human causes obesity in germfree mice. *ISME J.* **7**, 880–884 (2013) | Schulz, M.D. et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* **514**, 508–512 (2014) | Poutahidis, T. et al. Dietary microbes modulate transgenerational cancer risk. *Cancer Res.* **75**, 1197–1204 (2015) | Collins, S. M. et al. The adoptive transfer of behavioural phenotype via the intestinal microbiota: experimental evidence and clinical implications. *Curr. Opin. Microbiol.* **16**, 240–245 (2013) | Hu, B. et al. Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proc. Natl Acad. Sci. USA* **110**, 9862–9867 (2013).