HUMAN MICROBIOME

A gut feeling for disease

The largest metagenomic survey so far of human gut microbial genes sets the scene for comparing gut microbiome profiles to differentiate between healthy and diseased states.

Three studies showcase the growing interest in using genetics and genomics to understand how the huge numbers of bacteria that live in human guts influence our biology. The largest metagenomic survey so far of human gut microbial genes sets the scene for comparing gut microbiome profiles to differentiate between healthy and diseased states. Two other studies use mouse genetics to examine the relationship between the gut microbiome and the immune system, providing insights into metabolic diseases and susceptibility to infection.

The MetaHIT Consortium used high-throughput short-read sequencing to analyse the gut microbiomes of 124 Europeans. They identified approximately 3.3 million non-redundant genes, most of which were bacterial, had not been found in smaller studies and had novel or poorly characterized functions. From the numbers of genes, it was deduced that around 1,000 bacterial species were harboured by the cohort. At least 160 species were present in each individual, showing that the set of 1,000 was largely shared. Some 57 of the previously sequenced species were present in >90% of the

individuals surveyed, supporting this conclusion. Nevertheless, the gene profile for normal individuals differed markedly from that of patients with inflammatory bowel disease, highlighting the potential to use metagenomic studies to understand the relationship between gut bacteria and disease.

Changes in the gut microbiome have already been implicated in obesity. Vijay-Kumar and colleagues extend these findings to show how changes in gut bacteria due to altered immune signalling might contribute to metabolic syndrome. They showed that mice that are genetically deficient for Toll-like receptor 5 (TLR5) — a component of the innate immune system that is expressed in the gut — develop key features of metabolic syndrome. Sequencing of bacterial 16s ribosomal RNA genes revealed that the gut microbiome is altered in TLR5-deficient mice, and transplanting the gut bacteria from these mice to wild-type, germ-free animals conferred several features of the TLR5-deficient phenotype. The authors conclude that abnormal immune system functioning alters the normal composition of the gut microbiome, resulting in low-grade

inflammation and development of metabolic syndrome.

A third study shows that the interaction between the immune system and gut bacteria works both ways. Clarke and colleagues found that a peptidoglycan produced by gut bacteria primes the innate immune system to fend off pathogenic bacteria. Using genetic knockouts, the authors showed that the NOD1 receptor protein is required for this priming and that *NOD1*-knockout mice have increased susceptibility to pneumococcal sepsis.

The concept of links between gut microbes and human disease is not new. However, these studies collectively suggest specific mechanisms that underlie this relationship and demonstrate tools that promise to provide further insights.

Louisa Flintoft

ORIGINAL RESEARCH PAPERS Qin, J. et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65 | Vijay-Kumar, M. et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 4 Mar 2010 (doi:10.1126/science.1179721) | Clarke, T.B. et al. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nature Med.* **16**, 228–231 (2010)