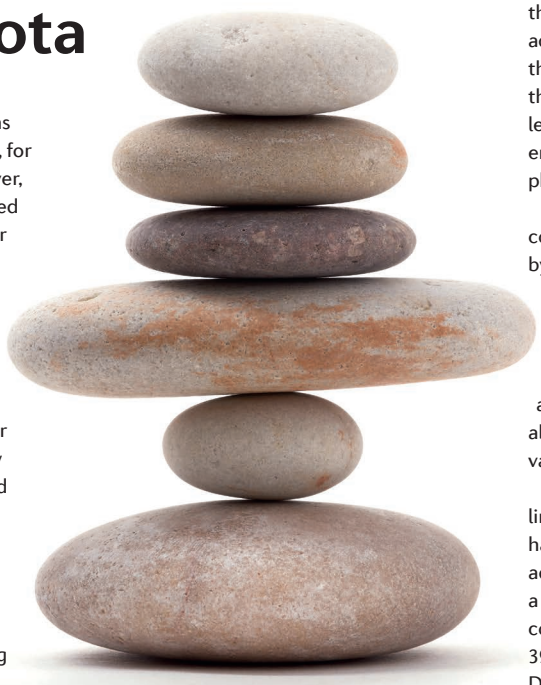
MILESTONE 7

Stability and individuality of adult microbiota



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A plethora of studies conducted over the past few decades have revealed strong associations between a disrupted microbiota and diseases, for example, inflammatory bowel disease. However, the key to understanding the role of a disrupted microbiota in human diseases is first to answer the question: what is a 'normal' microbiota? This question still frustrates many microbiologists, even with the advent of high-throughput sequencing and 'omics techniques. Prior to the availability of these technologies, however, several studies were instrumental in answering similar questions to help define 'normal', such as how much microbial variation is there between and within adults, and is the microbiota stable?

In 1998, when conventional microbiological techniques involving plate count analyses had reached an impasse in what they could reveal about human microbial diversity, molecular approaches were instead beginning to be implemented. A study by Willem de Vos and colleagues used polymerase chain reaction amplification of regions of the 16S ribosomal (r)RNA gene, which is often used to infer the genetic relationships between organisms, and then temperature gradient gel electrophoresis (TGGE) to visualize the diversity of the amplified gene. Comparisons of the banding profiles generated by TGGE from 16 adult faecal samples indicated that each individual has their own unique microbial community. Furthermore, by monitoring two individuals over time, the researchers showed that the TGGE profiles were stable over a period of at least six months.

Similar molecular approaches were applied to different sites of the human body, with the goal of improving our understanding of adult human microbial diversity. In 2005, one study moved beyond using faecal microbiota as a surrogate for the entire gut microbiota and sampled multiple colonic mucosal sites from three healthy individuals. Through an analysis of 13,335 16S rRNA gene sequences, this work confirmed marked microbial variation between individuals and showed that the adult gut mucosal microbiota was dominated by Bacteroidetes and Firmicutes, whereas Actinobacteria, Proteobacteria and Verrucomicrobia were relatively minor constituents.

Another study went one step further, in 2009, and examined bacterial diversity of 27 body sites from at least seven individuals and at four different time points. High interpersonal variability was found across all body sites but individuals experienced minimal temporal diversity. Other studies dedicated to skin and vaginal microbiomes were also key to our understanding of an individualised microbiota. It was found that comparable skin sites had similar bacterial communities, but that the complexity and temporal stability of the communities were site-dependent, whereas other studies found that the vaginal microbiome differs among individuals and, markedly, change over a short time. Together, these studies revealed that the human microbiota is highly variable both within and between individuals.

One of the goals of many studies characterising the diversity and stability of the human microbiota was to establish whether there was a core microbiota — are there bacterial species that we all share? In 2010, the international MetaHIT (Metagenomes of the Human Intestinal Tract) project published a gene catalogue derived from 576.6 gigabases of metagenomic sequences from the faecal samples of 124 individuals. These genes were found to be largely shared by individuals of the cohort, and 18 species were detected in all individuals. However, a key study that examined the faecal microbiomes of six adult twin pairs and their mothers suggested that there was an identifiable core microbiome at the gene level rather than the microbial species level. In this study, individuals shared >93% of the enzyme-level functional groups, but no bacterial phylotypes were present at >0.5% in all samples.

Many of these concepts were subsequently confirmed in large-population studies published by the Human Microbiome Project (HMP) Consortium. Analysis of samples collected from 242 healthy adults from up to 18 body sites showed that each habitat is characterized by a small number of highly abundant signature taxa, but that the relative abundance of taxa and genes in each habitat varies between individuals.

One drawback to the HMP dataset is the limited temporal scope. Instead, other studies have shed further light on the stability of the adult microbiota. For example, in one study, a human microbiota time series was obtained covering two individuals at four body sites over 396 time-points (daily for up to 15 months). Despite finding stable differences between body sites and individuals, this high-resolution temporal analysis did show pronounced variability in an individual's microbiota across months, weeks and days. In another study, an analysis of the faecal microbiota of 37 individuals found that ~60% of bacterial strains remained stable for up to five years.

Overall, samples obtained from the same individual are more similar to one another than those from different individuals, suggesting each person has a microbiota that is distinct and stable. Much is still unknown regarding how stable the microbiota is to perturbations, such as those arising from antibiotics, diet and the immune system. However, further studies in-line with those discussed here will no doubt enhance our view of human microbiota dynamics to ultimately understand what is 'normal'.

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