Zooming into the structure of the microbiome

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This month's Genome Watch highlights how genome sequencing can be used to understand the strain-level diversity, evolution and spatial structure of the human microbiome, and to inform therapeutic strategies.

Genome sequencing of microorganisms that have been sampled from different sites in and on the human body is revealing the complexity of the communities that constitute our microbiome and the impact they can have on human health and disease. Until recently, studies of the spatial structure of the human microbiome have largely focused on taxonomic characterization at the species level or higher, and at broad spatial scales such as between organs or gross anatomical sites such as the skin, the gut and the respiratory tract. However, variation in the microbiome may also be promoted by smaller-scale anatomical structures and involve diversity within as well as among microbial species.

Several recent studies have used metagenomic and/or whole-genome sequencing (WGS) combined with fine-scaled sampling to characterize the spatial structure of important components of the human microbiome. For instance, two recent studies have investigated how the anatomy of the skin promotes the within-species diversity of two keystone members of the skin microbiome: *Cutibacterium acnes* and *Staphylococcus epidermidis*. Conwill et al.[1] investigated variation within *C. acnes*, which prefers to grow within skin pores, across two spatial scales: between regions of the skin (for example, nose, shoulder, chin and back) and between individual pores[1]. The authors found that individuals carry multiple lineages of *C. acnes*, and that this diversity is maintained within individuals not by specialization to different regions of the skin, but by neutral forces that promote variation between individual pores. The authors suggest that this may be due to infrequent between-pore migration or priority effects that lead to an advantage for early colonizers. The authors suggest that similar crypt-like anatomical structures could promote population bottlenecks and intraspecies diversity in other microbiomes, although the impact of these sorts of small-scale anatomical features is likely to vary across bacterial species.

In contrast to *C. acnes*, Zhou et al.[2] showed that diversity within *S. epidermidis* results from the specialization of different founder lineages to particular regions of the skin, combined with variable migration rates between regions and genetic exchange, which they found also seems to suppress virulence[2]. In addition to exploring specificity to particular regions of the skin, this study considered the impact of the composition of the wider skin microbiome in these regions. Importantly, as *S. epidermidis* is both an opportunistic pathogen and a reservoir of genes for other pathogens, the authors found evidence of the maintenance of lineages with different resistance profiles, and the dissemination of resistance genes across lineages within a host. These two studies highlight the

different mechanisms by which spatial structure can lead to the maintenance of strain-level diversity and different scales of spatial structure within the microbiome.

Similar patterns of spatial segregation and specialization to particular regions of an organ have been found within important bacterial pathogens that infect the lung, such as *Pseudomonas aeruginosa*[3]. Spatial structures of the lung have been found to promote polyclonal infections. This has important implications for the treatment of these infections when these lineages differ in their susceptibility to antibiotics.

Understanding the appropriate spatial and taxonomic scales in the study of the microbiome are essential in guiding sampling strategies. A recent study that used multispectral fluorescence imaging to investigate the spatial organization of the tongue microbiome found evidence of structure that is only captured at the micrometre scale[4]. And although WGS provides the maximum possible taxonomic resolution, preliminary data (not peer reviewed) suggest that high-resolution metagenomic approaches can also enable the detailed characterization of within-species diversity[5].

Spatial structure driven by the anatomy of the human body can promote genetic diversity and limit competition both within and among microbial species. It is therefore central to understanding the drivers of diversity in microbial populations and predicting their capacity to evolve and adapt to selective challenges. It is likely to be important in designing microbiome-based therapeutics, for instance in revealing which factors influence the success of an introduced microbial population relative to an extant one, and in treating infections, particularly in the case of polyclonal infections with variable susceptibilities to antibiotic treatments.

References

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