GENOME WATCH

You are where you live

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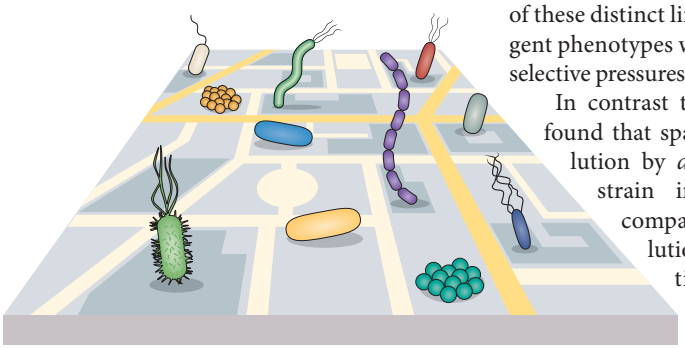
This month's Genome Watch discusses how whole-genome sequencing of bacteria from several body sites has provided insights into the spatial diversity of bacteria within patients.

When tracking bacterial disease outbreaks, whole-genome sequencing is usually carried out on a single isolate per host, based on the assumption that the isolate is representative of the infection. However, it is becoming increasingly clear that within-host diversity can be considerable, particularly in the context of chronic disease or superinfections. Longitudinal sampling has shown that this diversity can change over time, but we are now beginning to understand how it changes over space. Recently, several studies used whole-genome sequencing to investigate the diversity of bacterial isolates that were collected from several sites within an infected individual. This provided an opportunity to study and track how an infection spreads across the body using similar principles to those already being used to monitor global bacterial population diversity.

In the first study of its kind, Lieberman *et al.*[1] collected 2,693 post-mortem *Mycobacterium tuberculosis* isolates from several organ biopsies derived from patients co-infected with HIV. The authors found that diversification through *de novo* mutations had occurred, which led to the formation of several sub-lineages that inhabited different body sites. Phylogenetic comparisons of *M. tuberculosis* indicated that diversity within individual organs, such as the lungs, was similar to the diversity of samples that were isolated from different organs, which suggests that diversity does not depend on spatial proximity. This indicates that there are barriers that prevent direct pathogen migration between all sites, and suggests both inter-organ and intra-organ migration routes are equally similar. Despite this considerable diversity, the authors found that purifying selection was the prominent evolutionary force in this context, and, therefore, divergent lineages in different body sites are likely to have evolved through genetic drift.



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Interestingly, Jorth *et al.*[2] concluded that different evolutionary forces shape the diversification of *Pseudomonas aeruginosa* during respiratory infection. *P. aeruginosa* is a chronic inhabitant of the cystic fibrosis lung, which is extremely difficult to eradicate and thus infections often persist for years. Jorth *et al.*, sampled 12,000 isolates from the lungs of 10 patients with cystic fibrosis and found a large degree of diversity, with different lineages inhabiting different parts of the lungs. Isolates from the same region were found to have similar phenotypes, genotypes and express more similar protein profiles than those from different areas. In contrast to Lieberman *et al.*, they concluded that in addition to genetic drift, non-neutral selective forces also contributed to the evolution of these distinct lineages, and that the divergent phenotypes were the result of different selective pressures across the lungs.

In contrast to these two studies that found that spatial isolation drives evolution by *de novo* mutation, mixed strain infections that are not compartmentalized enable evolution through recombination. Cao *et al.*[3] showed that when co-infection of *Helicobacter pylori* occurs in the human gut, inter-strain recombination becomes possible when the bacteria occupy the same niche, which leads to an increased rate of evolution compared with *de novo* mutation. Two distinct lineages of *H. pylori* were found in the same single stomach biopsy, which the authors estimate had been co-evolving for 2–4 years. Moreover, the frequent recombination events that were observed demonstrate that they were able to occupy the same niche without one lineage outcompeting the other.

The genetic diversity of bacterial populations across the world has long been appreciated, but now we are beginning to delve into the biogeography of infections within individual patients. Such studies reveal that there are complex evolutionary dynamics at play, not only across continents but also within single organs in a single organism. This diversity also has important practical consequences for outbreak tracing and infection management, as these studies have shown that a single clinical sample may not always represent the diversity of the infection, and thus transmission links or antibiotic-resistance mutations may be missed. A better understanding of the diversity within patients may not only provide a more complete insight into *in vivo* evolution but also could have important clinical implications.

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1. Lieberman, T. D. *et al.* Genomic diversity in autopsy samples reveals within-host dissemination of HIV-associated *Mycobacterium tuberculosis*. *Nat. Med.* **22**, 1470–1474 (2016).
2. Jorth, P. *et al.* Regional isolation drives bacterial diversification within cystic fibrosis lungs. *Cell Host Microbe* **18**, 307–319 (2015).
3. Cao, Q. *et al.* Progressive genomic convergence of two *Helicobacter pylori* strains during mixed infection of a patient with chronic gastritis. *Gut* **64**, 554–561 (2015).

Competing interests statement
The authors declare no competing interests.