GENOME WATCH

Adaptation... that's what you need?

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This month's Genome Watch highlights how sequencing the genomes of multiple bacterial isolates from humans and animal infection models has revealed the presence of mutations that might represent adaptations for persistence in the host.

Pathogenic colonizers and their hosts are often engaged in a finely balanced confrontation, in which adaptation, perhaps through mutation, may be required for survival and persistence in their hosts. Studying such adaptations is important for the development of therapeutics, such as seasonal influenza vaccines, which are re-formulated each year on the basis of the evolution of the antigens that they target. Recently, whole-genome sequencing (WGS) studies have used different sample collections, including samples serially isolated from a single site that is present in multiple hosts and from multiple sites in a single host, to analyse the adaptive mutations that had emerged in the pathogen in relation to persistent colonization and the development of invasive disease.

Patients with chronic infections who have underlying diseases, such as cystic fibrosis, provide an interesting opportunity to identify potentially adaptive mutations that can then be experimentally validated to understand their biological relevance. Silva *et al.*[1] reported the emergence of extensive adaptive mutations in *Burkholderia multivorans* isolates that were sequentially sampled from a patient with cystic fibrosis over a period of 20 years. Analyses of the genomes of these isolates showed the evolution of the strains into multiple genetically distinct subpopulations that concurrently existed in their host but exhibited different mutation rates. Each of these subpopulations had independently acquired identical non-synonymous mutations, which indicates that positive selection for specific amino acid changes had occurred. These potential adaptive mutations could have phenotypic effects that are important for bacterial persistence, such as changes in antimicrobial resistance, the regulation of biofilm formation, changes in O-antigen presentation and increased intracellular cyclic-di-GMP metabolism.

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In a second study, using WGS and a novel mouse inhalation model for chronic infections caused by *Pseudomonas aeruginosa*, Fothergill *et al.*[2] searched for mutations in isolates that were sampled from the respiratory tract of mice over a minimum period of 28 days post-infection. After the initial intranasal inoculation, bacterial counts in the lungs steadily decreased to undetectable levels by day 14, whereas bacteria remained detectable at low levels in the nasopharynx. Interestingly, the bacterial count in the lungs increased again by 28 days post-infection, which suggests clonal expansion after adaptation. Analyses of the genomes of isolates that were collected at different time points after infection showed that adaptive mutations had occurred in *P. aeruginosa* isolates that persistently colonized the nasopharynx, thus enabling the strains with beneficial adaptations to expand and cause chronic infection in the lungs by 28 days post-inoculation. This work indicates that novel adaptations may occur during persistent colonization to drive and sustain chronic infection in individuals with cystic fibrosis.

In an earlier study, Young *et al.*[3] analysed 169 genomes from multiple patients and searched for adaptive mutations that promoted progression to disease during infection with *Staphylococcus aureus*. By comparing paired carriage and disease isolates, they identified up to eight mutations, with the majority of them resulting in truncated proteins. However, a similar recent study by Lees *et al.*[4] found no evidence of adaptation during progression in more than 800 cases of meningitis caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*. The absence of adaptive mutations in these cases implies that, although adaptive genetic changes may occur during transition from carriage to invasive disease in some pathogens, in others, such as *S. pneumoniae* and *N. meningitidis*, they may not be required for the transition between compartments in the host. Whether bacterial genetic predisposition has a role in the development of invasive disease still remains an open question.

Despite genomics studies that continue to reveal the complexity of genetic variations that occur in bacterial genomes during carriage and disease states, clear patterns of adaptation remain unknown. Broader sampling and deeper sequencing will provide better and more reliable analyses that could lead to not only a greater understanding of bacterial pathogenesis but also the discovery of novel therapeutic targets.

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Competing interests statement
The author declares no competing interests.