Rapid bacterial evolution in cystic fibrosis lung infections

Researchers at the University of York and the University of Liverpool are collaborating on Wellcome Trust funded research which uses genome sequencing to understand how rapid evolution of bacterial pathogens in lung infections of cystic fibrosis patients affects their prognosis and the varied response of these infections to antibiotic treatments.

Cystic fibrosis (CF) affects around 100,000 people worldwide. Individuals with CF carry a genetic mutation leading to the production of thicker mucus, which traps bacteria in the small airways of the lungs resulting in lifelong lung infections. These infections are very hard to treat, being resistant to most antibiotics, and cause unpredictable flare-ups of symptoms where CF sufferers experience serious breathing difficulties and require hospital care.

This project, led by Michael Brockhurst at the University of York and Steve Paterson and Craig Winstanley at the University of Liverpool, investigates whether it is the rapid evolution of bacterial populations within the CF lung that is causing the failure of antibiotic treatments and the flare-ups of symptoms in CF patients. To do this, the evolution of bacterial populations infecting the lungs of 10 CF patients will be tracked in real-time over the course of 3-years by sequencing the entire genomes of 1000s of bacterial colonies sampled from their lungs.

This builds on earlier work by the team, published in 2011 by the American Journal of Respiratory and Critical Care Medicine. They demonstrated that populations of the bacterial pathogen *Pseudomonas aeruginosa* infecting CF lungs harbour huge amounts of diversity, including variation in antibiotic resistance and secretion of toxins. This diversity must have evolved within each lung because each patient had originally been infected by a single type of the bacterium. What's more, the composition of these diverse populations was not stable but rather changed dramatically over the course of several weeks within individual patients, suggesting very fast on-going evolutionary change. By zooming-in on the detail, this new outlook calls into question current diagnostic procedures, which pick only a single bacterial colony for tests used to select antibiotic treatments.

The key next step, to be addressed in the Wellcome Trust funded research, is to discover the specific genetic changes in the bacteria underlying this vast diversity. Specifically, the researchers will ask whether evolution is repeatable among multiple patients, or whether each infection follows its own unique evolutionary pathway. Gaining such an unprecedentedly detailed view of the evolution of bacterial populations in CF infections raises exciting possibilities:

- If certain evolutionary pathways are repeatable and occur predictably in most infections, these might suggest a weak point in the bacteria that could be a target for new types of interventions or drugs.
- If evolutionary responses to antibiotic treatments are predictable this might suggest different combinations of drugs that could be used to prevent the evolution of antibiotic resistance in bacteria.
- If particular genetic changes or shifts in the composition of the bacterial population are predictably associated with the flare-ups of patients’ symptoms, this could suggest new targets for drugs that reduce virulence.
A colony of *Pseudomonas aeruginosa*, the primary pathogen of cystic fibrosis lung infections.
An eBurst diagram showing the diversity of *Pseudomonas aeruginosa* colonies isolated from cystic fibrosis patients that were initially infected with a single genotype (represented in blue). We screened 1720 colonies for 15 clinically important traits and identified 398 unique types; each blob is a unique type and the size of the blob denotes the frequency with which that type occurred.