Drug-Driven Phenotypic Convergence Supports Rational Treatment Strategies of Chronic Infections

Chronic *Pseudomonas aeruginosa* infections evade antibiotic therapy and are associated with mortality in cystic fibrosis (CF) patients. We find that *in vitro* resistance evolution of *P. aeruginosa* toward clinically relevant antibiotics leads to phenotypic convergence toward distinct states. These states are associated with collateral sensitivity toward several antibiotic classes and encoded by mutations in antibiotic resistance genes, including transcriptional regulator *nfxB*. Longitudinal analysis of isolates from CF patients reveals similar and defined phenotypic states, which are associated with extinction of specific sub-lineages in patients. In-depth investigation of chronic *P. aeruginosa* populations in a CF patient during antibiotic therapy revealed dramatic genotypic and phenotypic convergence. Notably, fluoroquinolone-resistant subpopulations harboring *nfxB* mutations were eradicated by antibiotic therapy as predicted by our *in vitro* data. This study supports the hypothesis that antibiotic treatment of chronic infections can be optimized by targeting phenotypic states associated with specific mutations to improve treatment success in chronic infections.