

Sublethal Ciprofloxacin Treatment Leads to Rapid Development of High-Level Ciprofloxacin Resistance during Long-Term Experimental Evolution of *Pseudomonas aeruginosa* - DTU Orbit (09/11/2017)

Sublethal Ciprofloxacin Treatment Leads to Rapid Development of High-Level Ciprofloxacin Resistance during Long-Term Experimental Evolution of *Pseudomonas aeruginosa*

The dynamics of occurrence and the genetic basis of ciprofloxacin resistance were studied in a long-term evolution experiment (940 generations) in wild-type, reference strain (PAO1) and hypermutable (PAO Δ mutS and PAOMY-Mgm) *P. aeruginosa* populations continuously exposed to sub-MICs (1/4) of ciprofloxacin. A rapid occurrence of ciprofloxacin-resistant mutants (MIC of ≥ 12 $\mu\text{g/ml}$, representing 100 times the MIC of the original population) were observed in all ciprofloxacin-exposed lineages of PAO Δ mutS and PAOMY-Mgm populations after 100 and 170 generations, respectively, and in one of the PAO1 lineages after 240 generations. The genetic basis of resistance was mutations in *gyrA* (C248T and G259T) and *gyrB* (C1397A). Cross-resistance to beta-lactam antibiotics was observed in the bacterial populations that evolved during exposure to sublethal concentrations of ciprofloxacin. Our study shows that mutants with high-level ciprofloxacin resistance are selected in *P. aeruginosa* bacterial populations exposed to sub-MICs of ciprofloxacin. This can have implications for the long-term persistence of resistant bacteria and spread of antibiotic resistance by exposure of commensal bacterial flora to low antibiotic concentrations.

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