Investigation Of Contingent Mutations In The Rets-gacas Regulatory System In Clinical Pseudomonas Aeruginosa Isolates From Cystic Fibrosis Patients - DTU Orbit (08/11/2017)

Investigation Of Contingent Mutations In The Rets-gacas Regulatory System In Clinical *Pseudomonas Aeruginosa* Isolates From Cystic Fibrosis Patients

Introduction: *Pseudomonas aeruginosa* is a major pathogen infecting the airways of cystic fibrosis (CF) patients. From a collection of 474 full-genome sequenced *P. aeruginosa* isolates from 34 young CF patients, we have discovered parallel evolution in the RetS-GacAS regulatory system[2], a key factor in the reciprocal regulation of acute and chronic infection genes. Mutations in this system occur in a sequential manner, such that mutations in *retS* precede mutations in *gacS/gacA* . Methods: Using genomics, transcriptomics, and metabolomics (Biolog), we have investigated the effects of these mutations in seven clinical isolates from two patients with two distinct clone types of *P. aeruginosa*. Results: Mutations in the RetS-GacAS regulatory system have a major effect on the behavior of *P. aeruginosa*. Initially, mutations in *retS* cause a shift towards aggregation/biofilm formation, type VI secretion, and phenazine production. Later, mutations in *gacA/gacS* cause a reciprocal shift by increasing expression type III secretion and motility genes, while decreasing expression of the former. Addtionally, Biolog data show clone type specific shifts in carbon source utilization, where one clone type expands and the other decreases the metabolic repertoires. Conclusions: The sequential nature of the mutations in the RetS-GacAS regulatory system suggests that different behavioral patterns are needed at different times of infection, where the initial mutation in *retS* results in a defensive behavior, enabling establishment of infection. This is then offset by mutations in *gacA/gacS* leading to a more expansive phenotype by dissemination of the infection.

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