Molecular basis for Pseudomonas aeruginosa persistent infections in CF patients

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New research reveals Small Colony Variants (SCVs) of *P. aeruginosa* to be a hallmark of chronic infection in cystic fibrosis (CF) patients. Results, published March 12th in the open-access journal *PLoS Pathogens*, suggest that SCV-mediated persistence might be a good target for antimicrobial chemotherapy.

Cystic fibrosis is a widespread genetic disease that leads to progressive disability and early death. The principal cause of mortality and morbidity in CF patients is a progressive deterioration of the respiratory system caused by a chronic infection of the patients' lungs, mainly by the opportunistic bacterial pathogen Pseudomonas aeruginosa. CF lung infections can be treated with antibiotics, however full clearance is not possible due to the protective environment of the CF lung and the adaptation of infective species to a persistent lifestyle. This presents serious challenges for the long-term chemotherapy of CF patients.

Adaptive *P. aeruginosa* morphotypes include SCVs, slow-growing and strongly adherent variants that frequently arise in chronic lung infections. Because the appearance of SCVs correlates with poor lung function and antibiotic resistance, they have long been suspected of mediating the *P. aeruginosa* persistence phenotype in CF infections.

In this study, the researchers characterized a signaling system in *P. aeruginosa* called YfiBNR, mutations in which lead to the generation of SCV variants. Activation of YfiBNR resulted in increased levels of the signaling molecule c-di-GMP, which in turn triggered massive

production of exopolysaccharides and drastically reduced growth rates, two hallmarks of SCV behavior. YfiN-mediated SCVs were shown to be highly resistant to macrophage phagocytosis, suggesting a role for the SCV phenotype in immune system evasion. Consistent with this, activation of YfiN significantly increased the persistence of *P. aeruginosa* in long-term infections in a mouse model, establishing a firm causal link between SCV and persistence in chronic *P. aeruginosa* infections.

The authors conclude that 'c-di-GMP has long been a key suspect in chronic behavior of bacterial pathogens. The finding that the c-di-GMP-mediated SCV phenotype confers a persistent advantage in mice provides the first direct evidence in favor of such a model. This study thus opens up new avenues to specifically counteract persistent infections.'

More information: Malone JG, Jaeger T, Spangler C, Ritz D, Spang A, et al. (2010) YfiBNR Mediates Cyclic di-GMP Dependent Small Colony Variant Formation and Persistence in Pseudomonas aeruginosa. PLoS Pathog 6(3): e1000804. doi:10.1371/journal.ppat.1000804