Title: Structural basis for the activation of the pathogenesis-inducing PqsE-RhlR protein complex from Pseudomonas aeruginosa

Abstract: Pseudomonas aeruginosa is an opportunistic pathogen that causes disease in immunocompromised individuals and individuals with underlying pulmonary disorders. P. aeruginosa virulence is controlled by quorum sensing (QS), a bacterial cell-cell communication mechanism that underpins transitions between individual and group behaviors. In P. aeruginosa, the PqsE enzyme and the QS receptor RhlR directly interact to control the expression of genes involved in virulence. Here, we show that three surface-exposed arginine residues on PqsE comprise the site required for interaction with RhlR. We show that a noninteracting PqsE variant [PqsE(NI)] possesses catalytic activity, but is incapable of promoting virulence phenotypes, indicating that interaction with RhlR, and not catalysis, drives these PqsE-dependent behaviors. Biochemical characterization of the PqsE-RhlR interaction coupled with RNA-seq analyses demonstrates that the PqsE-RhlR complex increases the affinity of RhlR for DNA, enabling enhanced expression of genes encoding key virulence factors. These findings provide the mechanism for PqsE-dependent regulation of RhlR and identify a unique regulatory feature of P. aeruginosa QS and its connection to virulence.