Defining the genetic basis of intracellular signaling regulating the expression of virulence factors by *Pseudomonas aeruginosa*

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Introduction

Pseudomonas aeruginosa is an opportunistic human pathogen that is responsible for a range of infections in individuals with a variety of predisposing immune-compromising conditions. It is also the major pathogen of individuals with cystic fibrosis, where it is the key contributor to the destructive lung disease (5). The ability of pathogenic bacteria such as *P. aeruginosa* to colonize the host is largely attributed to elaborated signal transduction pathways of environmental stimuli and the conversion of the signals into a cellular response (2, 4).

bis-(3',5')-cyclic-di-guanidine monophosphate (c-di-GMP) is a bacterial signaling molecule that functions as a second messenger in the signal transduction of environmental stimuli (6, 9). c-di-GMP regulates a number of complex cellular processes, and in particular processes that affect pathogenesis such as biofilm formation (7, 8, 10, 11, 13), motility (15, 17) and the expression of virulence factors(17).

The conversion of the c-di-GMP mediated signal into a cellular response depends on effector proteins that bind c-di-GMP (6, 9, 17). There is only limited set of known effector proteins, as c-di-GMP binding is carried out by domains that exhibit relatively high diversity from each other (1, 6, 11, 14, 16). Moreover, although there are studies that show that c-di-GMP directly affects gene expression, little is known of gene expression regulators that are directly responsive to c-di-GMP (7, 16). The mechanism of how c-di-GMP affects regulators of gene expression is not clear as well.

Hypothesis

c-di-GMP is a co-factor of transcriptional or translational regulators in *Pseudomonas aeruginosa*.

Proposed research activity

First, to identify novel c-di-GMP receptors and effectors proteins that function as regulators of gene expression in *P. aeruginosa*. In addition, to study the mechanism of how c-di-GMP modulates the activity of these regulators through biochemical, biophysical and structural studies.

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