Allosteric activation of exopolysaccharide synthesis through cyclic di-GMP-stimulated protein-protein interaction

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In many bacterial pathogens, the second messenger c-di-GMP stimulates the production of an exopolysaccharide (EPS) matrix to shield bacteria from assaults of the immune system. How c-di-GMP induces EPS biogenesis is largely unknown. Here, we show that c-di-GMP allosterically activates the synthesis of poly-β-1,6-N-acetylglucosamine (poly-GlcNAc), a major extracellular matrix component of Escherichia coli biofilms. C-di-GMP binds directly to both PgaC and PgaD, the two inner membrane components of the poly-GlcNAc synthesis machinery to stimulate their glycosyltransferase activity. We demonstrate that the PgaCD machinery is a novel type c-di-GMP receptor, where ligand binding to two proteins stabilizes their interaction and promotes enzyme activity. This is the first example of a c-di-GMP-mediated process that relies on protein-protein interaction. At low c-di-GMP concentrations, PgaD fails to interact with PgaC and is rapidly degraded. Thus, when cells experience a c-di-GMP trough, PgaD turnover facilitates the irreversible inactivation of the Pga machinery, thereby temporarily uncoupling it from c-di-GMP signalling. These data uncover a mechanism of c-di-GMP-mediated EPS control and provide a frame for c-di-GMP signalling specificity in pathogenic bacteria.
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