Activation of the diguanylate cyclase PleD by phosphorylation-mediated dimerization

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Diguanylate cyclases (DGCs) are key enzymes of second messenger signaling in bacteria. Their activity is responsible for the condensation of two GTP molecules into the signaling compound cyclic di-GMP. Despite their importance and abundance in bacteria, catalytic and regulatory mechanisms of this class of enzymes are poorly understood. In particular, it is not clear if oligomerization is required for catalysis and if it represents a level for activity control. To address this question we perform in vitro and in vivo analysis of the Caulobacter crescentus diguanylate cyclase PleD. PleD is a member of the response regulator family with two N-terminal receiver domains and a C-terminal diguanylate cyclase output domain. PleD is activated by phosphorylation but the structural changes inflicted upon activation of PleD are unknown. We show that PleD can be specifically activated by beryllium fluoride in vitro, resulting in dimerization and c-di-GMP synthesis. Cross-linking and fractionation experiments demonstrated that the DGC activity of PleD is contained entirely within the dimer fraction, confirming that the dimer represents the enzymatically active state of PleD. In contrast to the catalytic activity, allosteric feedback regulation of PleD is not affected by the activation status of the protein, indicating that activation by dimerization and product inhibition represent independent layers of DGC control. Finally, we present evidence that dimerization also serves to sequester activated PleD to the differentiating Caulobacter cell pole, implicating protein oligomerization in spatial control and providing a molecular explanation for the coupling of PleD activation and subcellular localization.

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