Allosteric control of cyclic di-GMP signaling

ID 153925
Author(s) Christen, Beat; Christen, Matthias; Paul, Ralf; Schmid, Franziska; Folcher, Marc; Jenoe, Paul; Meuwly, Markus; Jenal, Urs
Author(s) at UniBasel Jenö, Paul ; Jenal, Urs ;
Year 2006
Title Allosteric control of cyclic di-GMP signaling
Journal Journal of Biological Chemistry
Volume 281
Number 42
Pages / **Article-Number** 32015-24
Keywords Allosteric Site; Amino Acid Motifs; Amino Acid Sequence; Binding Sites; Cellulose/chemistry; Crystallography; X-Ray; Cyclic GMP/*chemistry; Escherichia coli/enzymology; Feedback; Biochemical; Molecular Sequence Data; Phosphoric Diester Hydrolases/chemistry; Phosphorus-Oxygen Lyases/chemistry; Salmonella enterica/enzymology; Signal Transduction
Cyclic di-guanosine monophosphate is a bacterial second messenger that has been implicated in biofilm formation, antibiotic resistance, and persistence of pathogenic bacteria in their animal host. Although the enzymes responsible for the regulation of cellular levels of c-di-GMP, diguanylate cyclases (DGC) and phosphodiesterases, have been identified recently, little information is available on the molecular mechanisms involved in controlling the activity of these key enzymes or on the specific interactions of c-di-GMP with effector proteins. By using a combination of genetic, biochemical, and modeling techniques we demonstrate that an allosteric binding site for c-di-GMP (I-site) is responsible for non-competitive product inhibition of DGCs. The I-site was mapped in both multi- and single domain DGC proteins and is fully contained within the GGDEF domain itself. In vivo selection experiments and kinetic analysis of the evolved I-site mutants led to the definition of an RXXD motif as the core c-di-GMP binding site. Based on these results and based on the observation that the I-site is conserved in a majority of known and potential DGC proteins, we propose that product inhibition of DGCs is of fundamental importance for c-di-GMP signaling and cellular homeostasis. The definition of the I-site binding pocket provides an entry point into unraveling the molecular mechanisms of ligand-protein interactions involved in c-di-GMP signaling and makes DGCs a valuable target for drug design to develop new strategies against biofilm-related diseases.
Publisher American Society for Biochemistry and Molecular Biology
ISSN/ISBN 0021-9258
edoc-URL http://edoc.unibas.ch/dok/A5258302
Full Text on edoc Available;
Digital Object Identifier DOI 10.1074/jbc.M603589200
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/16923812
ISI-Number WOS:000241235300087
Document type (ISI) Journal Article