Poster Presentation

MS036.P03

Structural biology of c-di-GMP mediated signaling

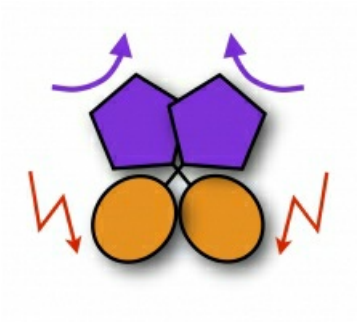
Tlilman Schirmer[1]
[1]*Biozentrum, University Of Basel, Basel, Switzerland*
E-mail: tilman.schirmer@unibas.ch

In addition to the well-known cyclic nucleotides, cAMP and cGMP, bacteria utilize cyclic di-guanosine monophosphate (c-di-GMP) to control various cellular processes. Hereby, the cellular level of the messenger is set by the antagonistic activities of diguanylate cyclases and specific phosphodiesterases. In a given organism, there are usually multiple variants of the two enzymes, which are tightly regulated by a variety of external and internal cues due to the presence of specialized sensory or regulatory domains. Fundamental cellular processes, such as bacterial life style, biofilm formation, and cell cycle control are thus getting controlled in a coordinated fashion by downstream c-di-GMP receptors in response to the input signals.

Crystal structures in combination with biochemical and biophysical analyses reveal that both GGDEF diguanylate cyclase [1] and EAL phosphodiesterase domains [2] are active only as homotypic dimers. In the full-length enzymes, attainment of the competent quarternary structure depends on the signaling state of the accessory domains (e.g. Rec, PAS, GAF), that typically dimerize or change their dimeric structure upon signal perception. Histidine kinases and transcription factors use very similar regulatory domains to control output function in a dimeric context. It can be inferred that the modular arrangement of catalytic and regulatory dimers, both forming homotypic interactions, facilitates their recombination during evolution.

As an example for c-di-GMP mediated allosteric control of a downstream effector, the effect of c-di-GMP binding to the bifunctional histidine kinase CckA from C. crescentus will be presented. It was found that c-di-GMP promotes the phosphatase activity of the enzyme via stabilization of the phosphatase competent constellation due to non-covalent domain cross-linking [3]. In silico analyses predict that c-di-GMP control is widespread among bacterial histidine kinases, arguing that it can replace or modulate canonical transmembrane signaling.

[1] Schirmer,T. (2016) J. Mol. Biol., 428, 3683–3701.
[2] Sundriyal,A., Massa,C., Samoray,D., Zehender,F., Sharpe,T., Jenal,U. & Schirmer,T. (2014) J. Biol. Chem., 289, 6978–6990.
[3] Dubey,B.N, Lori,C., Ozaki,S., Fucile,G., Plaza-Menacho,I., Jenal,U. & Schirmer,T. (2016) Science Advances, 2, e1600823–e1600823.



Keywords: second messenger, signal transduction, enzyme regulation