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Cyclic di-GMP signaling in bacterial differentiation and antibiotic production

The multi-talented bacteria *Streptomyces* have been awarded the Nobel Prize twice (1952 and 2015) for their exceptional ability to produce diverse medically-useful natural products. The synthesis of these secondary metabolites is genetically and temporally tightly interlinked with the developmental life cycle of Streptomycetes. Facing the urgent need for new antibiotics it is of particular significance to understand the signals and pathways that control development in these bacteria. In our recent study, we have shown that the bacterial second messenger cyclic di-GMP (cdi-GMP), which is produced by GGDEF-type diguanylate cyclases and degraded by EAL or HDGYP-type phosphodiesterases, determines the timing of differentiation initiation in *S. venezuelae* by regulating the activity of the highly conserved developmental master regulator BldD. Our structural and biochemical analyses revealed that a tetrameric form of c-di-GMP activates BldD DNA-binding by driving a unique form of protein dimerization, leading to repression of the BldD regulon of sporulation genes during vegetative growth. Currently, we aim to understand which of the 10 putative c-di-GMP-metabolizing enzymes encoded by *S. venezuelae* contribute to c-di-GMP pools sensed by BldD and how the BldD-c-di-GMP complex is assembled. Our initial data indicate that a distinct set of GGDEF/EAL proteins influences the developmental program progression in *S. venezuelae* and that loading of BldD with tetrameric c-di-GMP is a two-step process. Altogether, our work will greatly improve our understanding of *Streptomyces* physiology and c-di-GMP signaling in multicellular differentiation and secondary metabolite production and can contribute to a better exploitation of genetic engineering in *Streptomyces* for the production of antibiotics.

Biography

Natalia Tschowri has studied Biology at the Freie Universität Berlin, where she also obtained her PhD under the supervision of Professor Dr. Regine Hengge with a thesis on blue light signaling in the control of biofilm formation in *Escherichia coli*. In September 2012 she has joined Professor Mark Buttner's Lab at the John Innes Centre in Norwich, UK as a Post Doctorate funded by the EMBO long-term fellowship and began to work on c-di-GMP signaling in *Streptomyces*. Back in Berlin in October 2013 she continued with her studies on the role of c-di-nucleotides in *Streptomyces* development and is presently an independent Group Leader at the Humboldt-Universitätzu Berlin.

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