Structural investigations on c-di-AMP production and regulation in *Staphylococcus aureus*

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Staphylococcus aureus is a Gram-positive opportunistic bacterial pathogen that can cause infections ranging from osteomyelitis to pulmonary diseases and sometimes endocarditis. Antibiotic-resistant strains, such as Methicillin-resistant S. *aureus* (MRSA) strains, have emerged making this organism nowadays one of the leading causes of antibiotic-resistant infections in hospitals worldwide [1]. Due to the difficulties in effectively treating *S. aureus* infections with current antibiotics, novel bacterial targets for therapeutic interventions are being explored.

The cyclic dinucleotide c-di-AMP has emerged as a novel essential signalling molecule in *S. aureus* and a number of other Gram-positive bacterial pathogens. It contributes to the regulation of a variety of cellular processes including osmotic and cell wall homeostasis [2]. A decrease in cellular c-di-AMP levels has been shown to render *S. aureus* more susceptible to beta-lactam antibiotics [3]. As part of this work, we investigated the regulation of c-di-AMP production in *S. aureus.* More specifically, we investigated the interaction between the staphylococcal c-di-AMP producing enzyme DacA and the phosphoglucosamine mutase enzyme GlmM, another essential enzyme required for the production of a peptidoglycan intermediate [4]. We show that interaction of GlmM with DacA halts or reduces c-di-AMP production both *in vitro* and *in vivo*, highlighting that GlmM is a negative regulator of DacA activity. To further characterize the interaction between DacA and GlmM, we solved the crystal structures of the individual DacA and GlmM enzymes and we are currently optimizing the crystallization conditions for the purified DacA/GlmM complex. A structural characterization of this complex will help us to shed light on the interdependency of these two essential *S. aureus* enzymes and might pave the way for novel therapeutic applications.

References

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