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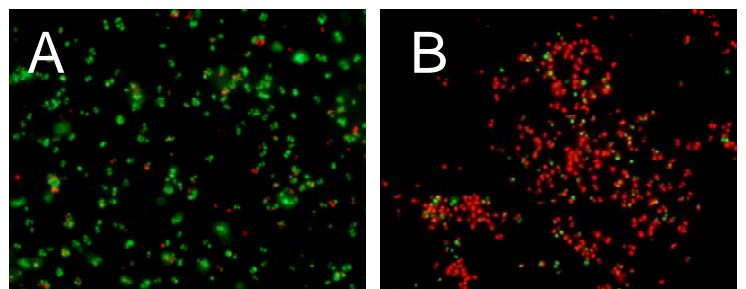
An essential signal transduction pathway controlling cell wall metabolism, virulence and biofilm formation in *Staphylococcus aureus*

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In order to survive, bacteria have developed a variety of highly sophisticated and sensitive signal transduction pathways with which they adapt their genetic expression to meet the challenges of their ever-changing surroundings. These mechanisms enable bacterial cells to communicate with their environment, their hosts and each other, allowing them to adopt specific responses, or develop specialized structures such as biofilms or spores to ensure survival, colonization of their ecological niches and dissemination. The so-called two-component systems (TCSs) are one of the most widespread and efficient strategies used for this purpose, where signal acquisition involves autophosphorylation of a sensor histidine kinase, and transduction takes place when the kinase phosphorylates its cognate response regulator protein, leading in turn to specific alteration of gene expression.

In their simplest form, TCSs elegantly combine sensing, transducing and transcription activation modules within two proteins, effectively coupling external signals to genetic adaptation. The high degree of conservation among TCS phosphotransfer domains, their ubiquitous nature and the fact that several are essential for cell viability has made them an attractive target for novel classes of antimicrobial compounds. The Walk/WalR (aka YycG/YycF) two-component system, originally identified in *Bacillus subtilis*, is very highly conserved and specific to low G+C Gram-positive bacteria, including several pathogens such as *Staphylococcus aureus*. While this system is essential for cell viability (see Figure below), both the nature of its regulon and its physiological role remain mostly uncharacterized. Using our results from studying this pathway in the model Gram-positive bacterium *Bacillus subtilis*, we have extended our analysis to the orthologous system in the major pathogen *Staphylococcus aureus*, unveiling a conserved function for this system in different bacteria and defining this signal transduction pathway as a master regulatory system for cell wall metabolism, which we have accordingly renamed Walk/WalR. The system controls cell wall biosynthesis and turnover as well as biofilm formation. Both these processes utilize a common metabolic intermediate, N-acetyl glucosamine, derived directly from the central carbon metabolism pathway. Our interest is now focused on the cellular function of the Walk/WalR TCS and the attractive target it constitutes for novel classes of antimicrobial compounds, as well as modeling the consequences of cell wall stress on this important pathogen, namely with respect to interactions with the host.

Fluorescence microscopy image of *S. aureus* cells containing (A) or lacking (B) the WalkR system. Fluorescent staining of cells with the LIVE/DEAD[®] BacLight[™] viability kit followed by fluorescence microscopy. SYTO 9-stained bacteria are alive and appear in green, while propidium iodide-stained bacteria are dead and appear in red.



From Work-Package 2.3 : Application to pathogens

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