

***Salmonella typhimurium* adhesion as target for novel antimicrobials**

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New antimicrobials are imperative to fight against the growing problem of antibiotic resistance. Key criteria for new drug targets are their importance for bacterial infections and their absence in animals including man. Interesting targets include adhesins and two-component systems. Adhesins are essential for pathogenic bacteria to interact with human cells. Two-component systems play a critical role for bacterial pathogens to assign their location, to time virulence factor production and to defend against host cell response. The Cpx two-component system is activated by signals that typically emerge during infection such as elevated pH, increased osmolarity and surface contact. The membrane-integrated sensor kinase CpxA perceives the stimulus and the response regulator CpxR mediates the output response as a transcription factor of target genes. Cpx targets include important virulence factors of different pathogenic bacteria as well as proteins essential for the secretion, biogenesis and quality control of these virulence factors.

The complex interplay between biogenesis and quality control of a virulence factor by the Cpx pathway is best studied for the P pilus adhesin. The quality control system for P pili requires the third component of the Cpx pathway, the small periplasmic protein CpxP. Misfolded pilus subunits are degraded by the DegP protease only in the presence of CpxP. Moreover, CpxP is known as natural inhibitor of the Cpx pathway that prevents activation of the sensor kinase CpxA. We performed structural and functional studies to understand the dual functions of CpxP. Our results suggest CpxP as target for the rational design of a novel class of antimicrobials acting from the exterior of the bacterial cell.

For *Salmonella enterica* serovar Typhimurium (*S. typhimurium*) it was shown that attachment as well as invasion into epithelia cells is dependent on the CpxA sensor but not on the CpxR regulator. We confirmed these data and found in addition that *cpxA* deletion results in a twofold decreased attachment whereas *cpxP* deletion results in a more than twofold increased attachment and invasion efficiency. Furthermore, we analyzed the gene expression profiles for a *cpxA* and for a *cpxP* deletion strains. Interestingly, we found that the expression of five adhesins is reduced in the *cpxA* deletion strain but induced in the *cpxP* deletion strain indicating that these adhesins are involved in direct host cell contact.

In the graduate project, the impact of these Cpx dependent adhesins for *S. typhimurium* host cell contact should be characterized. Moreover, to investigate whether interaction between adhesin and CpxP is a suitable target for novel antimicrobials the implication of this direct protein-protein interaction for adhesion will be studied. The identification of the receptors and cell signalling pathway induced by the interaction of these adhesins with host cells are other tasks of this project.