Helicobacter pylori: Molecular insights into regulation of adhesion properties

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**Abstract**

*Helicobacter pylori* infects the human stomach and triggers an inflammatory response that damages the gastric tissue. This host-pathogen interplay has dire consequences as up to 20% of infected individuals develop peptic ulcer disease or gastric cancer. Given that half of the world’s population is infected, the number of afflicted humans is staggering and also tells that *H. pylori* is extremely efficient in spreading and maintaining infection. To enable persistent infection many factors play a role, but one important feature of *H. pylori* is its impressive ability to adhere to the slimy gastric mucus layer and the underlying epithelial cells. This occurs mainly via the BabA and SabA proteins that bind ABO/Le^- and sLe^x/sLe^-antigens. I have in my thesis studied how these two proteins are utilized and regulated.

*H. pylori* transcription is in part controlled by two-component systems (TCSs) that use a sensor protein and a DNA-binding response regulator. We have studied how these systems control sabA and to some extent babA and indeed found a better map of how sabA and babA is regulated at the transcriptional level. We also found that variations in a polynucleotide T-tract located in the sabA promoter could fine-tune SabA expression/ sLe^-binding. Thus we have exposed how strict regulation by TCSs combined with stochastic processes together shapes attachment in the bacterial population.

As the buffering mucus layer is constantly exfoliated, placing *H. pylori* in bactericidal acid, we hypothesized that low pH should abrogate adhesion. SabA expression was indeed repressed in low pH, however BabA expression remained unaffected. The BabA/ Le^-binding was instead directly reversibly hampered by low pH and the degree of pH sensitivity was strain dependent and encoded in the BabA sequence. We believe that the pH dependent loss of binding is one key factor *H. pylori* utilizes to maintain persistent infection.

BabA is divided in generalists that bind ABO antigens and specialists that only bind blood group (bg) O. We co-crystallized BabA bound to these receptors and established the structural basis for generalist vs. specialist discrimination. We furthermore found a disulfide-clasped loop (CL2) in the center of the binding domain crucial for binding. Breaking CL2 with N-Acetylcysteine (NAC) disrupted binding and *H. pylori* infection mice experiments revealed inflammatory reduction upon NAC-treatment.

In sum, I have in my thesis dissected how *H. pylori* controls its adhesive abilities and how intrinsic properties in binding can be exploited for therapeutic purposes.

**Keywords**

*Helicobacter pylori*, SabA, BabA