Summary of the Thesis
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„CagA-induced signalling cascades during *Helicobacter pylori* infection“

Helicbacter pylori is a predominantly extracellular pathogen and the major etiological agent in the development of chronic gastritis, duodenal ulcer and gastric carcinoma in humans. The pathogenesis of *H. pylori* is dependent on a type IV secretion system (T4SS) encoded by the *cag* pathogenicity island and its only known effector protein CagA. The goal of this project was to characterize the CagA-dependent signalling cascades leading to actin cytoskeletal rearrangements and IL-8 secretion. Using the AGS gastric epithelial cell model system and molecular biological, biochemical as well as cell biological methods we obtained novel insights into CagA-induced signalling.

A brief summary of the major findings is present below:

I. With this work we identified and dissected a novel CagA-induced pathway leading to proinflammatory responses. Independent of its phosphorylation CagA can activate the Ras>Raf>Mek>Erk pathway resulting in NF-κB activation. CagA is able to induce IL-8 secretion in a time- and strain-dependent manner. We could identify high and low IL-8 inducing *H. pylori* strains depending on the CagA protein. Furthermore, we could show by exchanging specific *cagA* genes that high IL-8-inducing strains could be converted into low inducing strains and *vice versa*.

II. With this work we could show that Abl kinase is activated and a novel crucial mediator of *H. pylori*-induced signalling. The *H. pylori*-induced actin cytoskeletal rearrangements were inhibited by using specific Abl kinase inhibitors and knockdown of Abl kinases by siRNA. Furthermore, we could show that Abl kinase is rapidly and continuously activated upon autophosphorylation at Y-412. Our results demonstrate that the known phosphorylation-sites Y-899, Y-918 and Y-972 within the EPIYA repeats of CagA serve as substrate for both Abl and Src kinases.

III. We could identify the adapter protein CrkII as a critical component of the CagA-induced signalling. CrkII is a substrate of Abl kinase and phosphorylated at Y-221 by *H. pylori* activated Abl. Phosphorylated CagA forms a physical complex with Abl and phosphorylated CrkII *in vivo*. In addition we could show that the expression of a phosphotyrosine deficient CrkII blocks the *H. pylori*-induced actin cytoskeletal rearrangements. Furthermore, we could show that ADP-ribosylation and inactivation of Crk by ExoT blocks phosphorylation of Crk at Y-221, which is important for the CagA-induced signalling.

IV. We investigated the role of small Rho-GTPases members RhoA, Rac1, Cdc42 and H-Ras during infection with *H. pylori* by using specific bacterial toxins, DN constructs and specific siRNA. We identified Rac1 and H-Ras, but not RhoA or Cdc42, as crucial components of the CagA-induced signalling leading to actin cytoskeletal rearrangements.