SUMMARY

Nearly a third of the world’s population is infected with *Mycobacterium tuberculosis*, the causative agent of human tuberculosis (TB). The organism evades the host’s immune response by manipulating host cell signalling pathways. To design novel therapeutics and to rationalize vaccination strategies against mycobacterial diseases, it is of foremost importance to understand the mechanisms by which mycobacteria subvert the protective immune response. Two parts of this dissertation focus on how two effectors from *M. tuberculosis* regulate the innate immune response.

Early secreted antigenic target protein 6 (ESAT-6) is a member of a unique family of secreted proteins of *Mycobacterium tuberculosis* (M.tb.). We have investigated the role of miRNAs in ESAT-6 treated murine RAW264.7 cells and bone marrow-derived macrophages (BMDMs), focusing on miR-155, the most highly upregulated miRNA. We observed that miR-155 upregulation by ESAT-6 is directly linked to the attenuation of expression of BTB and CNC homology 1 (Bach1) and SH2-containing inositol 5-phosphatase (SHIP1). Bach1 is a transcriptional repressor of haem oxygenase-1 (HO-1), whereas SHIP1 inhibits the activation of the serine/threonine kinase AKT. We hypothesize that ESAT-6-induced miR-155 induction leads to repression of Bach1, which augments the expression of HO-1, a documented activator of the *M. tuberculosis* dormancy regulon. SHIP1 repression facilitates AKT activation, which is required for *M. tuberculosis* survival. Thus, our results offer new insights into the role of ESAT-6 in modulating miRNA expression in treated macrophages.

Mannose-capped lipoarabinomannans (Man-LAMs) are members of the repertoire of *M. tuberculosis* modulins which the bacillus uses to subvert the host innate immune response. Mycobacterial Man-LAMs modulate the immune response by dampening IL-12 production in macrophages and dendritic cells and attenuating apoptotic signalling. Here we use an unbiased approach to understand how ManLAM regulates macrophage cell signalling. We demonstrate that the ability of ManLAM to attenuate host cell apoptosis rests in part on its ability to induce expression of the anti-apoptotic Bcl2 family member A1 in macrophages. Knock down experiments confirmed that the apoptosis-attenuating effect of ManLAM depends partly on A1.

The third part of this dissertation focuses on *Helicobacter pylori*, a Gram-negative microaerophilic bacterium that is able to establish a life-long chronic infection in the stomach of more than half of
the human population. The infection is most of the times asymptomatic but, in some cases, *H. pylori* causes gastroduodenal pathologies, including stomach and duodenal ulcers, adenocarcinomas and stomach lymphomas. *H. pylori* is characterized by high genetic variability, not only in gene sequence but also in gene content. HP0175 is a peptidyl prolyl *cis, trans*-Isomerase that induces apoptosis of gastric epithelial cells through TLR4. Autophagy is an intracellular catabolic process which is required to maintain cellular homeostasis. Pathogen-elicited host cell autophagy may favour containment of infection or may help in bacterial survival. Pathogens have developed the ability to modulate host autophagy. Here we show that HP0175 executes autophagy in gastric epithelial cells. Autophagy is dependent on the unfolded protein response (UPR) which activates the expression of PKR-like ER kinase (*PERK*). This is accompanied by phosphorylation of eIF2α and transcriptional activation of *ATF4* and *CHOP*. Knockdown of UPR-related genes inhibits the conversion of LC3I to LC3-II, a marker of autophagy. The autophagy-inducing ability of *H. pylori* is compromised when cells are infected with an isogenic *hp0175* mutant. Autophagy precedes apoptosis. Silencing of *BECLIN 1* augments apoptosis. Increased apoptosis of gastric epithelial cells is known to be linked to *H. pylori*-mediated gastric inflammation and carcinogenesis. This study provides evidence of how HP0175, endowed with moonlighting functions, links UPR-dependent autophagy and apoptosis during *H. pylori* infection.