Abstract

The Gram-negative aerobic coccobacillus *Bordetella pertussis* is one of the few exclusively human pathogens and the main causative agent of the respiratory infectious disease called pertussis, or whooping cough. Despite global vaccination programs, pertussis remains an important public-health burden and still accounts for over 100,000 infant deaths and over a dozen of millions of whooping cough cases every year. Substantial effort is devoted to studies on the mechanisms of action of virulence factors of *B. pertussis*, but the biology of interactions of *B. pertussis* with its human host remains largely underexplored. Evolution, genetics and adaptation of *B. pertussis* to the complex environment of human nasopharynx and the mechanisms enabling *B. pertussis* to overcome host innate and adaptive mucosal immune defenses, remain poorly understood. In such situations, unbiased exploratory omics approaches represent valuable tools for uncovering of unknown aspects of host-pathogen interactions and open the path to detailed analysis of virulence-underlying processes by mechanistic studies.

In this thesis, I am presenting the results of three omics projects on *B. pertussis* biology that involved high-throughput proteomics. In the inital phosphoprotemics project, we analyzed the kinase signaling pathways hijacked in murine dendritic cells upon elevation of cytosolic cAMP levels by the cell-invasive adenylyl cyclase enzyme activity of the adenylate cyclase toxin (CyaA) of *B. pertussis.* In the second project, we identified and characterized Bkd1, a novel bacterial lysine deacetylase enzyme and characterized the acetylome of *B. pertussis.* By serendipity, we isolated a *B. pertussis* mutant exhibiting an intriguing pleiotropic phenotype that we characterized in depth in the third project, using a combination of proteomic and transcriptomic approaches. We showed that a point mutation, that deregulates expression of a ribosomal protein operon and increases production of the alpha subunit of RNA polymerase, provokes global *B. pertussis* genome expression deregulation and suppresses virulence factor production through reduced production of the key virulence regulating transcription factor BvgA~P. This work led to exploration of intracellular survival of *B. pertussis* inside primary human macrophage cells and revealed that downregulation of virulence factor production may represent an adaptation strategy of *B. pertussis* towards persistence within an intracellular niche.