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Molecular mechanisms of *Yersinia pseudotuberculosis* for adaptation and establishment of infection in host tissue

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Hall Betula, University hospital, Umeå, fredag den 23 april , kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Prof. Javier Pizarro-Cerda, Head, *Yersinia* Research Unit, Microbiology Department, Institut Pasteur, France

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Abstract

Bacterial pathogens can evade the host's immune defence to adapt and establish an infection within the host. Some even slip into a quiescent state to establish themselves without acutely harming the host. Phylogenetically unrelated bacteria can share similar strategies for the establishment of infection and for persistence. Our lab previously showed that *Yersinia pseudotuberculosis* underwent a dramatic reprogramming from a virulent phenotype expressing virulence genes, including T3SS and Yop effectors during early infection, to an adapted phenotype capable of persisting in tissue. The overall aim of my Ph.D. study was to dissect the mechanisms behind bacterial adaptation and maintenance of infection within host tissue using *Y. pseudotuberculosis* as a model pathogen. The ultimate goal is to identify key players of critical importance for the ability of the bacterium to maintain and establish infection in host tissue. In my studies, I mainly focused on bacterial biofilm and the role of the alternative sigma factor RpoN. Much of my studies involve RNA-Seq analyses, encouraging me to develop a convenient, time-efficient, and all-purpose RNA-Seq data analysis package especially designed for prokaryotic organisms. The package is available online as a free tool and can be used by any biologist with minimal computational knowledge. We systematically examined biofilm formation of *Y. pseudotuberculosis* under different stress conditions and found that biofilm development involved a series of adaptive responses against various stressors, including bile, pH, amino acid deprivation, and temperature and oxygen-level changes. Analyses of transcription profiles of bacteria forming biofilm in different conditions revealed a set of core genes that were similarly regulated in biofilm bacteria independently of induced environment. The transcriptional regulator RpoN, commonly known as sigma 54, was found to be important for biofilm formation, and a Δ*rpoN* mutant strain was severely attenuated in virulence. To understand the regulatory mechanisms involved, we investigated gene expressions in wild-type (WT) and the isogenic Δ*rpoN* mutant strain and also chromatin immunoprecipitation followed by sequencing. We have identified RpoN binding sites in the *Y. pseudotuberculosis* genome and revealed a complex regulation by RpoN involving both activation and repression effects. We also investigated the role of RpoN in regulation of the Type III secretion system (T3SS) and found that RpoN was required for a functional T3SS, which is essential for bacterial virulence properties in host tissue. Our work indicates that *Yersinia* modulates itself in multiple ways to create niches favourable to growth and survival in the host environment. We have identified some key regulators and genes that will be explored further for their potential as novel targets for the development of new antibiotics.

Keywords: ***Yersinia pseudotuberculosis*, RNA-Seq, Biofilm, RpoN, T3SS**

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