

Persistent infection

by *Yersinia pseudotuberculosis*

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Abstract

Enteropathogenic *Yersinia* species can infect many mammalian organs such as the small intestine, cecum, Peyer's patches, liver, spleen, and lung and cause diseases that resemble a typhoid-like syndrome, as seen for other enteropathogens. We found that sublethal infection doses of *Y. pseudotuberculosis* gave rise to asymptomatic persistent infection in mice and identified the cecal lymphoid follicles as the primary site for colonization during persistence. Persistent *Y. pseudotuberculosis* is localized in the dome area, often in inflammatory lesions, as foci or as single cells, and also in neutrophil exudates in the cecal lumen. This new mouse model for bacterial persistence in cecum has potential as an investigative tool for deeper understanding of bacterial adaptation and host immune defense mechanisms during persistent infection. Here, we investigated the nature of the persistent infection established by *Y. pseudotuberculosis* in mouse cecal tissue using *in vivo* RNA-seq of bacteria during early and persistent stages of infection. Comparative analysis of the bacterial transcriptomes revealed that *Y. pseudotuberculosis* undergoes transcriptional reprogramming with drastic down-regulation of T3SS virulence genes during persistence in the cecum. At the persistent stage, the expression pattern in many respects resembles the pattern seen *in vitro* at 26°C. Genes that are up-regulated during persistence are genes involved in anaerobiosis, chemotaxis, and protection against oxidative and acidic stress, which indicates the influence of different environmental cues. We found that the Crp/CsrA/RovA regulatory cascades influence the pattern of bacterial gene expression during persistence. Furthermore, we show that ArcA, Fnr, FrdA, WrbA, RovA, and RfaH play critical roles in persistence. An extended investigation of the transcriptional regulator *rfaH* employing mouse infection studies, phenotypic characterizations, and RNA-seq transcriptomics analyses indicated that this gene product contributes to establishment of infection and confirmed that it regulates O-antigen biosynthesis genes in *Y. pseudotuberculosis*. The RNA-seq results also suggest that *rfaH* has a relatively global effect. Furthermore, we also found that the dynamics of the cecal tissue organization and microbial composition shows changes during different stages of the infection. Taken together, based on our findings, we speculate that this enteropathogen initiates infection by using its virulence factors in meeting the innate immune response in the cecal tissue. Later on, these factors lead to dysbiosis in the local microbiota and altered tissue organization. At later stages of the infection, the pathogen adapts to the environment in the cecum by reprogramming its transcriptome from a highly virulent mode to a more environmentally adaptable mode for survival and shedding. The *in vivo* transcriptomic analyses for essential genes during infections present strong candidates for novel targets for antimicrobials.

Keywords

Yersinia, persistent infection, T3SS, Flagella, *arcA*, *fnr*, *frdA*, *wrbA*, *rovA*, *rfaH*, microbiota, dysbiosis, RNA-seq, reprogramming, cecum, stress, neutrophils

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