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# Host-pathogen interactions during *Campylobacter* and *Yersinia* infections

**Nayyer Taheri**

## Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för  
avläggande av filosofie/medicine doktorsexamen framläggs till offentligt  
försvar i Hörsal D Unod T9, in the NUS area,  
fredagen den 15 februari, kl. 09:00.  
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Docent, Dr. Elena Vikström,  
Inst. för klinisk och experimentell medicin, Linköpings universitet,  
Linköping, Sweden.

Department of Molecular Biology

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Umeå University  
Department of Molecular Biology  
SE-90187, Umeå

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**Author**

Nayer Taheri

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**Abstract**

The innate immune system is known for protecting the host against invading pathogens, for instance enteropathogens infecting the gastrointestinal tract. The production of e.g. antimicrobial peptides, cytokines, and chemokines by innate immune cells and intestinal epithelial cells contribute to bacterial clearance. Given the significance of this system in overall defense, pathogens affect and/or manipulate immune cells and responses in favor of their own survival. This thesis focuses on how the Gram-negative enteropathogenic bacteria *Yersinia pseudotuberculosis* and *Campylobacter jejuni* affect the host, either directly *via* type 3 secretion system (T3SS) effector proteins or *via* outer membrane vesicles (OMVs), and how host factors potentially affect their virulence.

*Yersinia pseudotuberculosis* uses its T3SS to translocate virulence factors that disable various immune responses and subvert phagocytosis. Neutrophils are main target cells during *Yersinia* infection. They release granules that contain proteins with antimicrobial properties to the cell's exterior upon activation through a process called degranulation. We found that extracellular *Y. pseudotuberculosis* could prevent neutrophil degranulation upon cell contact. Prevention of degranulation was shown to be mediated *via* co-operative actions of the two anti-phagocytic *Yersinia* outer proteins YopH and YopE. Bacterial contact with neutrophils resulted in a transient inhibition of degranulation and further prevented degranulation upon subsequent contact with avirulent *Y. pseudotuberculosis* (lacking YopE and YopH) as well as *Escherichia coli*. Thus, *Y. pseudotuberculosis* impairs several neutrophil defense mechanisms to remain in the extracellular environment and to increase its survival during infection.

*Campylobacter jejuni* lacks a T3SS and appears to use OMVs and flagella as its main secretion apparatus. During passage through the intestine *C. jejuni* is exposed to bile, an important physiological component and part of the natural barrier of the intestine, and ability to resist bile is advantageous for *C. jejuni* survival. We investigated how *C. jejuni* OMV production and protein content is affected by bile. The main invasion and colonization of *C. jejuni* occurs in the lower part of the intestine where the concentration of bile is low compared with the proximal intestine. The OMV proteomic profiles were radically altered when bacteria were grown in low concentration of bile corresponding to cecal concentrations. Twenty-five percent of the detected proteins of OMVs showed an altered abundance in the presence of low concentration of bile. In contrast, the overall proteome of the bacteria was unaffected. Moreover, OMVs from bile-exposed bacteria could enhance adhesion as well as invasion of bacteria into intestinal epithelial cells, suggesting a role of OMVs to the virulence of *C. jejuni* in the gut. The body temperature differs between the asymptomatic avian carriers of *C. jejuni* and humans, which develop symptomatic disease. We investigated whether the bacterial growth temperature affects the OMV proteome and found that 59 proteins were differentially expressed at 37°C. Among the higher abundant proteins, significantly more proteins were predicted to be related to virulence. Thus, temperature has an impact on the property of the OMVs, and this might affect the outcome of infection by *C. jejuni* in different hosts.

*C. jejuni* OMV interactions with innate immune cells were studied by analyses of OMV-mediated inflammasome activation. OMVs were found to induce ASC- and caspase-1-dependent inflammasome activation in murine and human macrophages and dendritic cells as well as in human neutrophils. While *C. jejuni* infection induced a low level of inflammasome-dependent cell death, OMV-induced inflammasome activation did not result in cell death. Thus, OMVs disseminate into tissue without bacteria can be a vehicle for virulence factors without inducing inflammatory cell death.

**Keywords**

*Campylobacter jejuni*, *Yersinia pseudotuberculosis*, OMV, bile, temperature, proteomic, inflammasome, IL-1 $\beta$ , degranulation, neutrophils, T3SS, Yops

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