Title of Ph.D. thesis: Molecular mechanisms of *Francisella tularensis* pathogenesis

Key words: *Francisella tularensis*, pattern recognition receptors, inhibition, TRAF6 and TRAF3 complexes

Annotation

Francisella tularensis is a highly infectious intracellular pathogen and the causative agent of the disease called tularemia. An important aspect of *Francisella tularensis* virulence represents the capacity to subvert the host immune response by inhibiting or disrupting of the innate immune cell functions. The initial stage of infection is characterized by the massive bacterial replication without apparent inflammatory response, which is crucial for the development of effective host defense against invading pathogen. The aim of this Ph.D. thesis was to describe the early pattern recognition receptors (PRR) signaling response to *Francisella tularensis* subsp. *holarctica* LVS (*F. tularensis* LVS) in primary bone marrow-derived macrophages. The obtained data show the capacity of *F. tularensis* LVS to simultaneously activate and suppress Toll-like receptors, RIG-I-like receptors, and cytosolic DNA sensors signaling pathways. *F. tularensis* LVS modulates these PRR pathways by the suppression of K63-linked polyubiquitination events and by the inhibition of the assembly of TRAF6 and TRAF3 signaling complexes. The use of the mutant strains with the impaired phagosomal escape (*ΔiglC*/LVS and *ΔdsbA*/LVS) showed that the suppressive effect of *F. tularensis* LVS was dependent on the functional type VI secretion system and/or on the presence of viable bacteria in the host cytoplasm. The results of this Ph.D. thesis demonstrate that the ability of *F. tularensis* LVS to escape into the cytoplasm and, concurrently, to inhibit multiple PRR signaling pathways accounts for the capability of the bacterium to proliferate in the host cell without triggering of the self-limiting innate immune response.