Inflammasome activation during bacterial infections
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The inflammasome is a recently described immune signaling platform that assembles after recognition of danger signals and/or pathogens by a family of cytosolic receptors called NLRs (nucleotide binding domain and leucine rich repeats containing receptors). Inflammasome assembly leads to activation of caspase-1 resulting in pyroptosis, an inflammatory form of cell death. Inflammasome activation is critical for innate immune responses to numerous pathogens. However, mutations in inflammasome components have been linked to susceptibility to several auto-inflammatory diseases suggesting that aberrant activation of the inflammasome can lead to auto-inflammatory responses. Despite its critical role in both innate immune responses and autoimmune disorders, many questions about inflammasome biology remain unanswered. This research project aims to address some of these questions, using the facultative intracellular bacteria Francisella tularensis, the causative agent of tularemia, as a model system.

F. tularensis is a Gram-negative bacterial pathogen that is recognized by the inflammasome in the cytosol of infected macrophages and the inflammasome is crucial to fight Francisella infection. While the inflammasome adaptor ASC has been shown to be critical for caspase-1 activation during Francisella infection, we neither know the identity of the NLR nor its Francisella ligand within the inflammasome. I have recently shown that type I interferon (IFN), secreted by the macrophage after detection of cytosolic Francisella, is required for subsequent inflammasome activation. However the molecular basis for the type I IFN-mediated control of inflammasome activation is still unclear. Furthermore, recent work has shown that Francisella infection can signal for cell death in a type I IFN-dependent, ASC-dependent manner but independently of caspase-1. This cell death remains to be characterized. The objectives of my proposal are the following:

1. Characterization of the molecular mechanism of type I IFN-mediated control of inflammasome activation.
2. Identification of the host receptor and its Francisella ligand within the inflammasome.
3. Characterization of the type I IFN-dependent, ASC-dependent, caspase-1-independent cell death pathway.

This research will lead to novel insights into the physiological activation of the inflammasome during bacterial infection as well as into the pathological role of the inflammasome during auto-inflammatory diseases.