

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Proinflammatory Components of *Francisella tularensis*

By

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The bacterium *Francisella tularensis* is the causative agent of tularemia and a potential agent of bioterrorism. Two strains of *F. tularensis* are commonly used for laboratory experiments, an attenuated live vaccine strain (LVS), which is pathogenic in mice but avirulent in humans, and the Schu S4 strain, which causes disease in both species. This dissertation work examines the inflammatory response of human and murine cells of innate immunity to attenuated and virulent strains of *F. tularensis*. When human monocyte-derived macrophages (huMDM) were stimulated with live or killed LVS, the cells secreted high levels of proinflammatory cytokines. In contrast, murine macrophages were unable to mount a robust inflammatory response. It was proposed that increased production of proinflammatory cytokines by the huMDM may help to draw other leukocytes into infected tissues, thereby controlling disease caused by the LVS. However, the Schu S4 strain elicited equivalent if not greater levels of cytokines when added to huMDM or human umbilical vein endothelial cells (HUVEC). These results indicate that attenuation of the LVS in the human host is not due to an enhanced inflammatory response.

Due to the ability of *F. tularensis* to elicit an inflammatory response, studies were undertaken to determine the bacterial components responsible for this effect. Typically, lipopolysaccharide (LPS) released from the Gram-negative outer membrane is a potent proinflammatory mediator. However, LPS from either the LVS or Schu S4 strain did not stimulate HUVEC and elicited a marginal response in huMDM. Fractionation of material released from the LVS revealed GroEL to be an inflammatory factor for huMDM. GroEL acted synergistically with *F. tularensis* LPS to further enhance production of cytokines by huMDM. Interestingly, GroEL from the Schu S4 strain had little activity towards these cells. Thus, there are multiple proinflammatory components released from the LVS, and these factors differ from those found in fully virulent strains, such as the Schu S4.

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