

P2-35

A novel role for *Francisella tularensis* antioxidant enzymes in modulating human macrophage signaling and activationA. Melillo¹, J. A. Melendez¹, C. S. Bakshi¹¹Albany Medical College, Center for Immunology and Microbial Disease, Albany, United States

Francisella tularensis strains demonstrate differential regulation of host immune responses and sensitivity to redox cycling drugs.

Aims: In this study, we test the hypothesis that *F. tularensis* antioxidants play a key role in regulating host immune signaling events.

Methods: In our experimental model we examined the effects of infection with *F. tularensis* Live Vaccine Strain (LVS), a mutant lacking the catalase gene (LVS Δ katG), as well as, the highly virulent SchuS4, on macrophage activation and function. Following infection of primary human monocytic derived macrophages (hMDM), we examined intracellular growth, cytokine production, NF κ B activation and phosphoinositide-3-kinase (PI3K) signaling pathway by ELISA and immunoblotting. PI3K activates Akt, a key component of the macrophage signaling network, which drives inflammatory cytokine gene expression.

Results: Infection of inactivated hMDM with LVS suppresses cytokine production, while infection of IFN γ -activated hMDM elicits a significant increase in cytokine production. SchuS4 infection severely inhibits proinflammatory cytokines secretion from both inactivated and IFN γ -activated hMDM when compared to LVS. Interestingly, infection with LVS Δ katG fails to suppress macrophage cytokine production. In addition, NF κ B activation is suppressed following infection with SchuS4, but not with LVS. SchuS4 infection also suppressed AKT phosphorylation which correlates with increased expression of its antagonist the dual lipid protein phosphatase PTEN. Oxidation of PTEN can lead to its inactivation and a subsequent increase in Akt signaling. SchuS4 infection prevented H₂O₂-dependent PTEN oxidation, while LVS infection only partially blocked PTEN oxidation and infection with LVS Δ katG was unable to block oxidation.

Conclusions: Together, these findings suggest a novel mechanism, by which, *F. tularensis* antioxidants restrict macrophage signaling by preserving phosphatase activity and tempering kinase signaling.