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***Francisella tularensis* suppresses the proinflammatory response of endothelial cells via the endothelial protein C receptor**D. C. Bublitz<sup>1</sup>, M. B. Furie<sup>1</sup>, J. L. Benach<sup>1</sup><sup>1</sup>Stony Brook University, Center for Infectious Diseases, Stony Brook, United States

**Aim:** To investigate the ability of *F. tularensis* to inhibit the proinflammatory response of human umbilical vein endothelial cells (HUVEC).

**Methods:** Using both the LVS and Schu S4 strains, HUVEC were exposed to living bacteria and material released from heat-killed *F. tularensis*. Pre-incubation times and multiplicities of infection of the living bacteria were varied. For other experiments, the living bacteria were separated from the HUVEC by Transwell inserts or exposed to the endothelial cells in the presence of a monoclonal antibody blocking the endothelial protein C receptor (EPCR). Conditioned media were assayed for the chemokine CCL2 by ELISA to assess proinflammatory activation of the HUVEC.

**Results:** Living *F. tularensis* LVS and Schu S4 did not stimulate secretion of the chemokine CCL2 by HUVEC, while material released from heat-killed bacteria did. Furthermore, the living bacteria suppressed secretion of CCL2 in response to heat-killed *F. tularensis*. This phenomenon was dose- and contact-dependent and occurred relatively rapidly. The living bacteria did not inhibit the activation of HUVEC by *E. coli* LPS, highlighting the relative specificity of this suppression. The EPCR confers anti-inflammatory properties when bound by activated protein C. When the EPCR was blocked, *F. tularensis* lost the ability to suppress activation of HUVEC.

**Conclusions:** The endothelium, when activated by various pathogens, secretes proinflammatory cytokines and recruits circulating leukocytes. These data demonstrate that *F. tularensis* actively inhibits proinflammatory activation of HUVEC. To our knowledge, this is the first report that a bacterial pathogen inhibits the host immune response via the EPCR. Endothelial cells are a critical component of the innate immune response, and suppression of their activation by *F. tularensis* is likely a mechanism that aids in bacterial dissemination and evasion of host defenses.