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**Type A *F. tularensis* induces caspase-3-dependent macrophage death in infected tissues**

J. R. Wickstrum<sup>1</sup>, S. M. Bokhari<sup>1</sup>, J. L. Fischer<sup>1</sup>, D. M. Pinson<sup>2</sup>, H. W. Yeh<sup>3</sup>, R. T. Horvat<sup>2</sup>,  
M. J. Parmely<sup>1</sup>

<sup>1</sup>University of Kansas Medical Center, Microbiology, Kansas City, United States, <sup>2</sup>University of Kansas Medical Center, Pathology and Laboratory Medicine, Kansas City, United States, <sup>3</sup>University of Kansas Medical Center, Biostatistics, Kansas City, United States

**Aims:** Although *Francisella tularensis* subsp. *tularensis* is known to cause extensive tissue necrosis, the mechanism of in situ cell death is not known.

**Methods:** Using a mouse respiratory challenge model of tularemia, we have defined the pathological responses that occur in infected tissues during the first 4 days after infection with the type A *F. tularensis* strain KU49.

**Results:** Three days post-infection, well organized inflammatory infiltrates developed in the spleen and liver that resembled those found in mice infected with the Live Vaccine Strain of *F. tularensis* subsp. *holarctica*. However, by day 4 of infection with KU49, numerous cells with double strand DNA breaks appeared throughout these inflammatory foci. Dying cells within KU49-infected tissues expressed activated caspase-3, but very little activated caspase-1. Moreover, infected caspase-1-deficient mice showed the same pathological changes as infected wild type mice, including extensive cell death and foci of necrosis in the liver and spleen. KU49-infected caspase-3-deficient mice showed diminished pathology and much less death among their splenic F4/80-positive cells. These infected mutant mice also retained the ability to express splenic tumor necrosis factor- $\alpha$  and inducible NO synthase, responses that were completely lost in infected wild type mice. Ly-6G-positive cells in the spleen and lungs were not spared death in caspase-3-deficient infected mice, indicating that death of myeloid cells occurs by a caspase-3-independent mechanism. With the destruction of hepatic granulomas on day 4 of infection with KU49, *Francisella* antigens were found disseminated throughout the liver, rather than confined to the granulomas. In infected caspase-3-deficient mice, this effect was significantly decreased, indicating that caspase-3-dependent cell death results in a decreased ability to limit dissemination of the infection.

**Conclusions:** These findings suggest that Type A *F. tularensis* benefits from caspase-3-dependent macrophage apoptosis, which dampens potentially important innate immune responses to the pathogen and permits its dissemination throughout infected organs.

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