Increased inflammation and impaired resistance to Chlamydophila pneumoniae infection in Dusp1(-/-) mice: critical role of IL-6.

Abstract:

The MAPK phosphatase DUSP1 is an essential negative regulator of TLR-triggered innate immune activation. Here, we have investigated the impact of DUSP1 on inflammatory and antimicrobial host responses to the intracellular pathogen Chlamydophila pneumoniae. Following nasal infection, DUSP1-deficient mice mounted an enhanced pulmonary cytokine (IL-1beta, IL-6) and chemokine response (CCL3, CCL4, CXCL1, CXCL2), leading to increased leukocyte infiltration. Of interest, the increased inflammatory response, in the absence of DUSP1, was associated with higher bacterial numbers in the lungs, although the expression of IFN-gamma and critical antichlamydial effector molecules, such as iNOS, was intact. Blockade of IL-6 trans-signaling by injection of a soluble gp130-Fc fusion protein corrected the overshooting chemokine production as well as the increased chlamydial load in Dusp1(-/-) mice. Furthermore, IL-6 enhanced the replication of C. pneumoniae in embryonic fibroblasts in vitro. These data show that DUSP1 is required to achieve a balanced response to chlamydial infection and identify IL-6 as critical for amplifying inflammation and benefiting chlamydial growth through direct effects on infected cells.

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