Absent in melanoma 2 is required for innate immune recognition of Francisella tularensis

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Macrophages respond to cytosolic nucleic acids by activating cysteine protease caspase-1 within a complex called the inflammasome. Subsequent cleavage and secretion of proinflammatory cytokines IL-1beta and IL-18 are critical for innate immunity. Here, we show that macrophages from mice lacking absent in melanoma 2 (AIM2) cannot sense cytosolic double-stranded DNA and fail to trigger inflammasome assembly. Caspase-1 activation in response to intracellular pathogen Francisella tularensis also required AIM2. Immunofluorescence microscopy of macrophages infected with F. tularensis revealed striking colocalization of bacterial DNA with endogenous AIM2 and inflammasome adaptor ASC. By contrast, type I IFN (IFN-alpha and -beta) secretion in response to F. tularensis did not require AIM2. IFN-I did, however, boost AIM2-dependent caspase-1 activation by increasing AIM2 protein levels. Thus, inflammasome activation was reduced in infected macrophages lacking either the IFN-I receptor or stimulator of interferon genes (STING). Finally, AIM2-deficient mice displayed increased susceptibility to F. tularensis infection compared with wild-type mice. Their increased bacterial burden in vivo confirmed that AIM2 is essential for an effective innate immune response.

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