The Journal of Immunology

ABSTRACT | MAY 01 2024

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J Immunol (2024) 212 (1_Supplement): 0182_4505.
https://doi.org/10.4049/jimmunol.212.supp.0182.4505

182-4505

A non-canonical role for caspase-1 in controlling antimicrobial resistance of intracellular Salmonella

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Caspase-1 is a key effector molecule involved in inflammasome activation and has a well-established role in restricting the growth of pathogens by triggering a form of cell death called pyroptosis. Here we reveal a non-canonical, cell death-independent role for caspase-1 in controlling the transcriptional state and drug resistance of an intracellular pathogen. Using Pathogen-sequencing, a method for sensitive transcriptional profiling of minuscule numbers of intracellular bacteria from infected macrophages, we show that host caspase-1 decreases the resistance of intracellular *Salmonella* to endogenous cationic antimicrobial peptides, and to a cationic polypeptide antibiotic used as a last-line drug in Gram-negative bacterial infections. These effects of caspase-1 were independent of its enzymatic activity but dependent on its ability to repress the activation of a two-component signal transduction system in intracellular bacteria. These effects were also independent of caspase-11. Our data suggest an activity and inflammasome-independent role for caspase-1 later in infection in restricting intracellular *Salmonella* which evade initial inflammasome-dependent restriction by caspase-1. Our findings thus take host caspase-1 beyond the well-studied inflammasomes and tie it to signal transduction and drug resistance of an intracellular pathogen with possible implications for host-directed therapy to combat antimicrobial resistance.

SESSION: Inflammation, Immune Signaling, and Immunomodulation (AM)

FUNDING: NIH and ISB