“Inflammasomes and Cytotoxic Lymphocytes Clear Bacterial From Different Intracellular Niches.”

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ABSTRACT

Vivien Ileana Maltez: Inflammasomes and cytotoxic lymphocytes clear bacteria from different intracellular niches
(Under the direction of Edward A. Miao)

Programmed cell death is a powerful anti-microbial defense. The innate immune system is our first line of defense against infection, and the induction of cell death can rapidly remove intracellular niches. Inflammasomes are cytosolic sensors that drive a lytic form of cell death termed proptosis. However, a lack of strong in vivo inflammasome phenotypes had led to the conclusion that inflammasomes merely slow the infection until the adaptive immune system is activated. The first part of my dissertation shows that inflammasomes can potently detect and clear ubiquitous environmental bacteria, revealing the strongest in vivo roles for inflammasome-mediated defense in the literature. Intriguingly, we found that inflammasomes alone could not defend the hepatocyte intracellular niche. Thus, the second part of my dissertation investigated how this niche could be cleared. Natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) are cytotoxic lymphocytes that can hunt down and execute host cells harboring intracellular pathogens. They use perforin to deliver granzyme B, which cleaves and activates the executioner caspases. Among these, caspase-3 is considered to be the most critical, while the physiologic importance of caspase-7 has remained nebulous. We show that caspase-7 is uniquely required for defense against two bacteria, Chromobacterium violaceum and Listeria monocytogenes, but not against two viruses, MCMV and LCMV. Our results suggest a paradigm in which caspase-7 is required for clearance of intracellular bacteria, but not viruses.