NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

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Hosted by Manish (Graduate Student)



Cytosolic anti-bacterial immunity: sensing and execution

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Inflammatory caspases including caspase-1, 4, 5 and 11 are critical for cytosolic immune defenses against bacterial infections. Caspase-1 is activated by canonical inflammasomes mediated by a scaffold protein responsible for sensing the infection. We identify the NAIP family of NLR proteins as inflammasome receptors for bacterial flagellin and the needle/rod subunits of bacterial type III secretion system (T3SS), which activates caspase-1 through an adaptor NLR protein NLRC4. We discover that Pyrin, encoded by the familial Mediterranean fever disease gene MEFV, forms an canonical inflammasome complex in response to bacterial modifications/inactivation of host Rho GTPases, including glucosylation by Clostridium difficile cytotoxin TcdB, ADP-ribosylation by C. botulinum C3 toxin and deamidation by B. cenocepacia. We also demonstrate that caspase-4/5 in human and caspase-11 in mice are receptors for cytosolic LPS and activated by direct LPS binding to their CARD domains, playing a critical role in anti-bacterial defense and septic shock. Common to inflammatory caspases activation is pyroptosis, a programmed necrotic cell death. Using genome-wide CRISPR/Cas9 screens we identify GSDMD as a pyroptosis substrate for all inflammatory caspases. GSDMD-deficient cells resist pyroptosis induction by both canonical inflammasome agonists and cytosolic LPS. IL-1 release is also inhibited in the absence of GSDMD. The caspases specifically cleave GSDMD, releasing the intramolecular inhibition on the N-terminal Gasdermin-N domain that harbors intrinsic pyroptosis-inducing activity. GSDMD belongs to a large Gasdermin family; other family members are not cleaved by inflammatory caspases but share the autoinhibition and pyroptosis-inducing activity. These findings offer significant insights into inflammatory caspases-mediated immunity/diseases, and also suggest a new paradigm for understanding pyroptosis and programmed necrosis.

Artwork by Ann Nee, DBS, NUS