Universität Basel

Research Project

A novel role for cell autonomous immunity in inflammasome activation during Gram- negative bacterial infections

Third-party funded project

Project title A novel role for cell autonomous immunity in inflammasome activation during Gram- negative bacterial infections
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Recognizing the presence of invadingăpathogens is key to mounting an effective immune response1. Theămammalian innate immune system employs several classes of germline-encodedăpatternărecognition receptors (PRRs) to monitor the extracellular andăintracellular compartments of host cells for signs of infection. A subset ofăthese, the NOD-like receptors, detects the presence of pathogensăin theăcytoplasm and assembles so-called inflammasome complexes, which activate theămammalian cysteine protease caspase-1. Active caspase-1 is a key determinant ofăinflammation, since it promotesăthe secretion of pro-inflammaotory cytokinesălike interleukin (IL)-1b and IL-18, and induces an inflammatory cell deathăcalled “pyroptosis”1.

Recently, a novel non-canonicalăinflammasome pathway has been identified which leads to the activation ofăcaspase-112. We andăothers have shown that this pathway specifically responds toăintracellularăGram-negative bacteria but not to Gram-positive pathogens3,4. Consistently,ăcaspase-11 has been shown to promote lethality in a murine model of Lipopolysaccharaideă(LPS)-induced septicăshockă2. In line withăthese observations, it has been recently reported that cytoplasmic LPS is mostălikely the trigger of the non-canonical inflammasome5.

Interestingly,ăactivation of caspase-11 also requires preceding production ofătype-I-interferon, indicating an important role for one or severalăinterferon-induced genes in caspase-11 activationă3,4. Weăhave recently carried out a siRNA screen with the goal of defining factorsănecessary for caspase-11 activation. This led to the identification of a familyăof interferon-inducible GTPases that control aănumber of bacteriocidalămechanisms and restrict growth of pathogens in cells6. Basedăon these data, we propose a novel and original hypothesis in that the cytosolicădetection of bacteria by PRRsărequires preceding killing of bacteria byăinterferon-induced cell autonomous defense mechanisms, thus establishing aăsofar unrecognized link between these distinct arms of innate immunity.

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2471108, Meunier, Etienne; Dick, Mathias S.; Dreier, Roland F.; Schürmann, Nura; Kenzelmann Broz, Daniela; Warming, Søren; Roose-Girma, Merone; Bumann, Dirk; Kayagaki, Nobuhiko; Takeda, Kiyoshi; Yamamoto, Masahiro; Broz, Petr, Caspase-11 activation requires lysis of pathogen-containing vacuoles by IFN-induced GTPases, 0028-0836 ; 1476-4687, Nature, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

2834776, Meunier, Etienne; Broz, Petr, Interferon-induced guanylate-binding proteins promote cytosolic lipopolysaccharide detection by caspase-11, 1044-5498, DNA and cell biology, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

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