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INFLAMMASOME

To die or not to die

Inflammasome activation by pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) leads to dendritic cell (DC) activation and interleukin-1β (IL-1β) release, but also causes cell death through pyroptosis. Kagan and colleagues now describe a second inflammasome-mediated DC activation state in response to simultaneous exposure to PAMPs and damage-associated molecular patterns (DAMPs) that promotes DC survival as well as IL-1β release.

One such DAMP is the oxidized phospholipid oxPAPC (derived from 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine), which is found at high concentrations in damaged tissues. In line with other DAMPs such as ATP that only induce cytokine release from cells previously exposed to PAMPs, oxPAPC induced IL-1β release from LPS-primed DCs. Using knockout mice, the authors showed that oxPAPC-induced IL-1β release depends on the inflammasome components ASC, caspase 1, caspase 11 and NLRP3. Furthermore, oxPAPC induced the formation of ASC- and caspase 1-containing 'specks' (representing individual inflammasomes) in LPS-pretreated DCs in a caspase 11-dependent manner. Thus, non-canonical inflammasome assembly mediated by caspase 11 occurs in response to oxPAPC.

> "oxPAPC and LPS induce caspase 11-mediated IL-1β release by different mechanisms"

Multiple other TLR ligands could prime DCs to respond to oxPAPC, which shows that oxPAPC does not simply function as an LPS carrier to caspase 11. Both LPS and oxPAPC captured endogenous caspase 11 from DC lysates, but they were shown to bind to distinct domains. The caspase 11 catalytic domain bound oxPAPC, whereas the CARD (caspase activation and recruitment domain) of caspase 11 bound LPS. Also, the catalytic activity of caspase 11 was required for LPS-induced, but not oxPAPC-induced, IL-1β release. The results suggest that oxPAPC and LPS induce caspase 11-mediated IL-1β release by different mechanisms; indeed, oxPAPC, but not LPS, can also bind caspase 1.

The downstream effects of non-canonical inflammasome activation in response to LPS and oxPAPC were also different. Whereas LPS induced caspase 11-dependent pyroptosis, the ability of oxPAPC to induce similar levels of IL-1β release without causing DC death resulted in a state of DC 'hyperactivation' that was more effective at stimulating adaptive immunity than traditionally activated DCs. The authors showed enhanced T cell activation in response to vaccination with a model antigen when LPS and oxPAPC were used as an adjuvant compared with LPS alone.

The distinct modes and outcomes of activation of caspase 11 by PAMPs and DAMPs might have different physiological functions, which suggests previously unrecognized flexibility in the ways in which the innate immune system responds to infection. LPS alone induces pyroptosis of infected cells to expose intracellular pathogens to killing by innate immune cells. In the case of uncontrolled, high levels of infection, the presence of both LPS and tissue damage (oxPAPC) promotes DC survival to induce an adaptive immune response.

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ORIGINAL ARTICLE Zanoni, I. *et al.* An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells. *Science* **352**, 1232–1236 (2016)
FURTHER READING Man, S. M. & Kanneganti, T.-D. Converging roles of caspases in inflammasome activation, cell death and innate immunity. *Nat. Rev. Immunol.* **16**, 7–21 (2016)