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INNATE IMMUNITY

DCs take one for the team

Intracellular pathogens are detected and phagocytosed by innate immune cells, including dendritic cells (DCs) and macrophages, and are then rapidly degraded in intracellular compartments to prevent further dissemination of the pathogen. However, some pathogens, such as *Legionella pneumophila*, can subvert these defence mechanisms and survive in intracellular vacuoles. So how do DCs overcome this and efficiently control bacterial infection? A study by Nogueira and colleagues now shows that DCs restrict the growth of *L. pneumophila* by rapidly dying through apoptosis.

Previous studies had shown that macrophages limit the replication of *L. pneumophila* through the induction of inflammasome-mediated cell death involving the pattern recognition receptor NAIP5 (NLR family, apoptosis inhibitory protein 5; which responds to bacterial flagellin in the cytoplasm) and caspase 1. However, DCs could undergo apoptosis and control bacterial growth in the absence of NAIP5 or caspase 1 following infection with *L. pneumophila*, with faster kinetics than those observed in macrophages. To examine this further, the authors investigated the effect of loss of caspase 3, a downstream mediator of apoptosis, in DCs from mice with defective NAIP5 signalling. Although caspase 3-deficient DCs showed similar responses to caspase 3-sufficient DCs from NAIP5 signalling-deficient mice 2 hours after infection, they showed significantly higher rates of infection and lower levels of apoptosis 10 hours after infection. This observation suggests that the caspase 3-dependent apoptotic pathway is important for inducing DC death, and therefore restricting pathogen replication early after infection.

Caspase 3 can be activated by the intrinsic (or mitochondrial) pathway of apoptosis, which involves the pro-apoptotic proteins BAK (BCL-2 antagonist/killer) and BAX (BCL-2-associated X protein). DCs deficient in BAK and BAX showed similar levels of apoptosis to wild-type DCs after infection, suggesting that the NAIP5-dependent pathway remains functional and compensates for the loss of BAK and BAX. However, the BAX- and BAK-deficient DCs showed significantly lower levels of apoptosis and supported increased bacterial replication when infected with a strain of *L. pneumophila* that has a mutation in the flagellin-encoding gene *flaA* (and consequently cannot trigger NAIP5 activation). Therefore, the NAIP5-dependent and intrinsic pathways are two independent pathways of apoptosis that can both restrict *L. pneumophila* replication. Interestingly, overproduction of B cell lymphoma 2 (BCL-2), which is a pro-survival protein that counteracts the effects of BAX and BAK, by DCs infected with the *flaA*-mutant strain of *L. pneumophila* limited apoptosis and therefore resulted in enhanced intracellular bacterial replication, confirming the importance of the intrinsic apoptotic pathway in this process.

The data indicate that both cell death pathways can prevent bacterial replication but that the intrinsic pathway of apoptosis operates much earlier during infection than the inflammasome-mediated pathway. The authors propose that the induction of apoptosis serves as an innate immune mechanism to prevent bacterial dissemination during DC migration to lymphoid organs.

Rachel David

ORIGINAL RESEARCH PAPER Nogueira, C. V. *et al.* Rapid pathogen-induced apoptosis: a mechanism used by dendritic cells to limit intracellular replication of *Legionella pneumophila*. *PLoS Pathog.* **5**, e1000478 (2009)

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