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INNATE IMMUNITY

Sensing bacterial messages

Many bacterial pathogens produce cyclic dinucleotides, such as cyclic diadenylate monophosphate (c-di-AMP), as secondary messengers to regulate bacterial metabolism, motility and virulence. A new study shows that endoplasmic reticulum membrane adaptor protein (ERAdP) senses c-di-AMP, triggering a pro-inflammatory immune response that is necessary to control infection with the bacterial pathogen *Listeria monocytogenes*.

Reporting in *Nature Immunology*, Xia *et al.* found that mice that lacked ERAdP in myeloid cells were highly susceptible to *L. monocytogenes* infection, showing increased bacterial loads and reduced serum levels of the pro-inflammatory cytokines tumour necrosis factor (TNF) and IL-6 compared with control mice. By contrast, susceptibility to viral infection and production of type I interferons were unaffected by the ERAdP deficiency. To determine whether sensing of bacterial nucleotides was involved in the pro-inflammatory cytokine response, the authors transfected bone marrow-derived macrophages (BMDMs) with *L. monocytogenes* DNA (LM-DNA), c-di-AMP or c-di-GMP and measured cytokine responses. Only c-di-AMP stimulation induced robust TNF and IL-6 production by BMDMs in an ERAdP-dependent manner. Moreover, the ERAdP-mediated cytokine production was independent of the cyclic GMP-AMP synthase (cGAS)–STING pathway, which senses cytosolic DNA and induces IFNβ production.

Precipitation assays confirmed that c-di-AMP interacted directly with ERAdP and experiments with various truncated recombinant proteins of ERAdP showed that its carboxy-terminal domain was crucial for binding c-di-AMP. Moreover, Xia *et al.* showed that ERAdP has a much higher affinity for c-di-AMP than STING. Accordingly, lack of STING did not affect *L. monocytogenes*-induced pro-inflammatory cytokine production *in vivo* or susceptibility to infection.

In terms of the mechanism, c-di-AMP was shown to induce dimerization of ERAdP, which enabled it to associate with and activate the kinase TAK1 (also known as MAP3K7). In turn, TAK1 activation led to the activation of nuclear factor-κB to induce pro-inflammatory cytokine production. The finding that BMDMs lacking TAK1 expression had a defective c-di-AMP-induced cytokine response confirmed the requirement for TAK1. Moreover, mice lacking both ERAdP and TAK1 showed even lower levels of serum pro-inflammatory cytokines and greater susceptibility to infection with *L. monocytogenes* than mice lacking only ERAdP.

So, this study identifies ERAdP as a direct sensor of the bacterial secondary messenger c-di-AMP that is crucial for protective immunity to bacterial infection.

Lucy Bird

> “c-di-AMP stimulation induced robust TNF and IL-6 production by BMDMs in an ERAdP-dependent manner”

ORIGINAL ARTICLE Xia, P. *et al.* The ER membrane adaptor ERAdP senses the bacterial second messenger c-di-AMP and initiates anti-bacterial immunity. *Nat. Immunol.* https://doi.org/10.1038/s41590-017-0014-x (2018)