IMMUNE EVASION

The disarming effects of anthrax

Bacterial pathogens use many strategies to avoid being detected by the host's immune system. New work published in *Nature* indicates that *Bacillus anthracis*, the causative agent of anthrax, targets dendritic cells (DCs) and the adaptive immune response as an immune-evasion strategy.

B. anthracis has two main virulence factors: the capsule, which protects the bacteria from phagocytosis, and the anthrax toxin. Anthrax toxin has three components: two A subunits — oedema factor (EF) and lethal factor (LF) — and a single B subunit known as protective antigen (PA). The combination of PA plus LF forms a complex known as lethal toxin (LT), which kills mice when injected intravenously.

The effects of LT on DCs were first analysed *in vitro*. Agrawal *et al*. found that, after exposure to LT, the ability of DCs to secrete pro-inflammatory cytokines and upregulate the expression of co-stimulatory molecules in response to antigen challenge was markedly reduced. Viability studies showed that, in contrast to the effects on macrophages, the suppressive effects of LT on DCs are not a result of cell death. Further *in vitro* experiments indicated that DCs treated with LT were unable to prime naive T cells efficiently.

To assess whether anthrax LT also impaired the function of DCs *in vivo*, researchers used a transgenic mouse model that allowed the fate of antigen-specific $CD4^+$ T cells to be tracked. LT-treated DCs failed to prime antigen-specific $CD4^+$ T cells *in vivo*, and the results indicated that the T cells were activated initially but failed to differentiate into memory cells. In BALB/c mice injected with LT then challenged with antigen, the antigen-specific T- and B-cell responses were reduced, confirming that the effects of LT on DCs result in an impaired adaptive immune response *in vivo*.

Finally, the authors probed the mechanism of action of LT. By looking at the effects of LT on the phosphorylation of downstream effectors in the mitogen-activated protein kinase (MAPK) pathway and analysing the effects of a mutated version of the LF protein, they showed that LT disrupts the MAPK intracellular signalling pathway in DCs by cleaving mitogen or extracellular signal regulated kinase kinases (MEKs). Previous work had shown that this is also the mechanism LT uses to disrupt the function of macrophages.

DCs are often referred to as the sentinels of the human immune system, patrolling the body on the look out for invading microorganisms. Impressively, *B. anthracis* has now been shown to be capable of disarming even these most efficient antigen-presenting cells.

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Nature Reviews Microbiology

References and links

ORIGINAL RESEARCH PAPER Agrawal, A. *et al.* Impairment of dendritic cells and adaptive immunity by anthrax lethal toxin. *Nature* **424**, 329–334 (2003)

FURTHER READING Mourez, M. *et al.* 2001: a year of major advances in anthrax toxin research. *Trends Microbiol.* **10**, 287–293 (2002)

WEB SITE
Bali Pulendran's lab: http://www.emory.edu/WHSC/YERKES/VRC/scientists/pulendran.html