T-CELL RESPONSES

Bacterial sensors synergize to seal T-cell fate

The recent discovery of a new T helper (T_H)-cell subset that produces interleukin-17 (termed the T_H17-cell subset) and that is involved in antimicrobial immunity and chronic inflammatory diseases has triggered a flurry of activity aimed at understanding when and how these cells are induced. In mice, transforming growth factor-β (TGFβ) and interleukin-6 (IL-6) are thought to drive T_H17-cell differentiation from naive T cells, whereas in humans, studies suggest that T_H17-cell production is driven by IL-1, IL-6 and/or IL-23. Now, van Beelen *et al.* show that stimulation of the intracellular bacterial sensor NOD2 (nucleotide-binding oligomerization domain protein 2) programmes dendritic cells (DCs) to promote IL-17 production by human memory T cells.

First, van Beelen *et al.* showed that human monocyte-derived DCs exposed to various bacterial strains but not viruses were able to induce high levels of IL-17 production in T-cell cultures. Then, by testing a range of known bacterial and viral ligands for Toll-like receptors (TLRs), they established that the most potent component eliciting the IL-17 response was the TLR2 ligand peptidoglycan (PGN), which is present in the cell walls of both Gram-negative and Gram-positive bacteria.

Given that, after internalization, PGN can be metabolized into muramyl dipeptide (MDP), which is a ligand for the intracellular pattern-recognition receptor NOD2, the authors next tested whether this pathway was involved in the observed IL-17 response. They showed that when DCs were stimulated with MDP in combination with various TLR ligands, their capacity to specifically promote IL-17 production by memory T cells was significantly enhanced. This was shown to occur through the induction of IL-23p19, IL-1α and IL-1β production by the DCs, as previously suggested.

A role for NOD2 in the synergistic effect of MDP was confirmed using monocyte-derived DCs from patients with Crohn's disease carrying a homozygous *NOD2* mutation that impairs ligand binding. Indeed, MDP was unable to enhance the IL-17-inducing capacity of TLR-primed DCs from these patients and failed to upregulate IL-23p19 and IL-1 expression.

Surprisingly, contrary to previous studies, the authors noted that the T_H17 cells induced by IL-1 and IL-23 did not arise from the differentiation of human naive T cells, but from the conversion of memory T cells.

So, NOD2 provides a key link between bacterial infection and the induction of a protective T_H17-cell response. How this pathway is involved in the pathogenesis of Crohn's disease needs further investigation, but the recent identification of the IL-23 receptor as a susceptibility gene in this disease is an interesting prospect.

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ORIGINAL RESEARCH PAPER van Beelen, A. J. *et al.* Stimulation of the intracellular bacterial sensor NOD2 programs dendritic cells to promote interleukin-17 production in human memory T cells. *Immunity* **27**, 660–669 (2007)
FURTHER READING Stetson, D. B. & Medzhitov, R. T helper 17 cells get the NOD. *Immunity* **27**, 546–548 (2007)