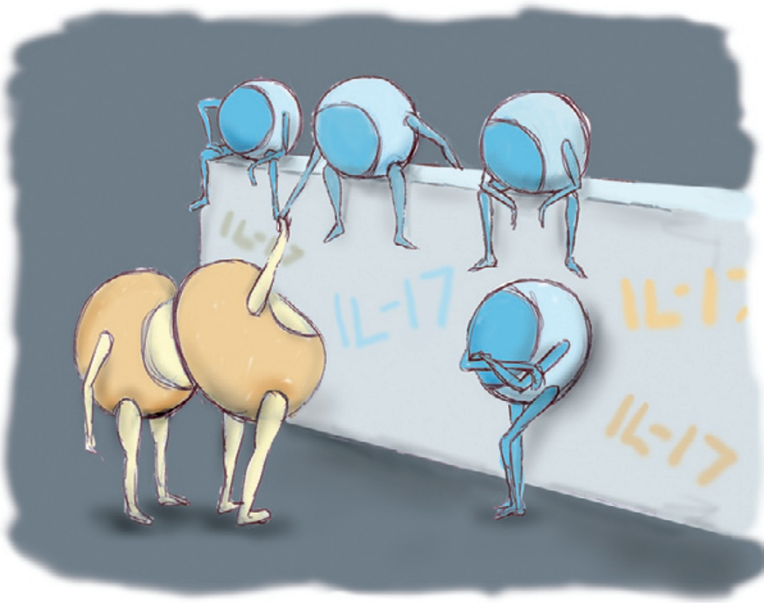
NKT CELLS

NKT cells join the IL-17 gang

Natural killer T (NKT) cells are a unique T-cell subset defined by the co-expression of NK-cell markers and a T-cell receptor (TCR), and are characterized by their ability to rapidly produce immunomodulatory cytokines following TCR ligation. Now, Caspi and colleagues report that one of these cytokines is interleukin-17 (IL-17), which has recently received much attention as the signature cytokine of T helper 17 (T_H17) cells.

Mouse T_H17 cells have been reported to require IL-6 and transforming growth factor-β (TGFβ) for lineage commitment and IL-23 for maintenance. So, Caspi and colleagues were surprised to find that IL-6-deficient splenocytes were as efficient as their wild-type counterparts at producing IL-17 24 hours after stimulation with CD3-specific antibody and IL-23. Further analysis revealed that the source of this IL-17 was in fact NKT cells (defined as $DX5^+TCR\beta^+$). Stimulation of purified NKT cells with the NKT-cell ligand α-galactosylceramide and purified $CD11c^+$ antigen-presenting cells confirmed NKT cells as early producers of IL-17. The ability to produce IL-17 did not belong to any particular NKT-cell subset, but seemed to be associated with those that lacked expression of the NK-cell marker NK1.1.



In T_H17 cells, IL-6 is thought to be important for upregulating the expression of the IL-23 receptor (IL-23R) and the T_H17-cell-lineage-specific transcription factor RORγt (retinoic-acid-receptor-related orphan receptor-γt). Consistent with their ability to produce IL-17 rapidly and independently of IL-6, NKT cells, unlike naive T cells, were found to express IL-23R and RORγt constitutively. Memory T cells also showed constitutive expression of IL-23R and RORγt and had a similar ability to rapidly produce IL-17 after TCR ligation.

Further analysis of the requirements for IL-17 production by NKT cells revealed that either TCR ligation or IL-23 alone were sufficient to induce IL-17 production, and that exposure to both signals had a synergistic effect.

Finally, the authors extended these observations to NKT cells *in vivo*, showing that injection of mice with α-galactosylceramide induced a rapid, transient expression of *Il17* mRNA in the spleen that peaked at 6 hours after injection.

So, although this study highlights a new source of IL-17, the significance of this innate pathway awaits further investigation.

Lucy Bird

ORIGINAL RESEARCH PAPER Rachitskaya, A. V. *et al.* NKT cells constitutively express IL-23 receptor and RORγt and rapidly produce IL-17 upon receptor ligation in an IL-6-independent fashion. *J. Immunol.* **180**, 5167–5171 (2008)