γδ T CELLS

Innate source of IL-17

Interleukin-17 (IL-17) has been the subject of a great deal of recent research, mainly as the cytokine that characterizes the $CD4^+$ T helper cell subset known as T_H17 cells. Now, two studies published in *Immunity* show that γδ T cells are also an important source of IL-17, which is produced by these cells without ligation of their T cell receptor (TCR) and contributes to a first line of defence against pathogens and to the early stages of autoimmune inflammation.

Characterization of IL-17-producing γδ T cells by both groups revealed similarities of these cells to T_H17 cells. These include the expression of CC-chemokine receptor 6 (CCR6), IL-23 receptor, retinoic acid receptor-related orphan receptor-γt (RORγt) and aryl hydrocarbon receptor, as well as the production of IL-17 and IL-22. However, in contrast to T_H17 cells, γδ T cells did not require TCR ligation to induce IL-17 production in the presence of IL-1 and IL-23, cytokines that can be produced by dendritic cells (DCs) following triggering of Toll-like receptor 2 (TLR2), NOD-like receptors or dectin 1. Indeed, Martin *et al.* showed that the IL-17-producing γδ T cell subset rapidly expanded following injection of mice with heat-killed *Mycobacterium tuberculosis* or *Candida albicans* hyphae (which activate TLR2 and dectin 1, respectively).

Evidence for a direct role of IL-17-producing γδ T cells in the defence against pathogens was provided by Martin *et al.*, who showed that $CCR6^+$ IL-17-producing γδ T cells, but not other γδ T cell subsets or T_H17 cells, express TLR1, TLR2 and dectin 1 and proliferate *in vitro* following stimulation with ligands for these innate immune receptors but not with the TLR4 ligand lipopolysaccharide — an effect that was further enhanced in the presence of IL-23. Moreover, transfer of wild-type γδ T cells into TLR2-deficient mice followed by intraperitoneal injection of the TLR1 and TLR2 ligand $Pam_3CysSerLys_4$ led to the recruitment of IL-17-expressing γδ T cells and neutrophils, suggesting that γδ T cells can sense certain pathogens and initiate an appropriate immune response.

Sutton *et al.* described an important role for IL-17-producing γδ T cells in the early stages of experimental autoimmune encephalomyelitis (EAE). Large numbers of these cells infiltrated the brain 7 days after induction of EAE, and peak levels were reached at day 10–14. The IL-17-producing γδ T cells were found to be required for the subsequent infiltration by autoantigen-specific $CD4^+$ T cells during the development of EAE; accordingly, EAE was less severe in γδ T cell-deficient mice. IL-17 produced by γδ T cells following exposure to IL-1 and IL-23 establishes an amplification loop by acting directly on T_H17 cells to promote their IL-17 production and indirectly on DCs to promote their IL-23 production, which in turn supports the production of further T_H17 and γδ T cells. So, γδ T cells provide an innate source of IL-17 in response to pathogenic signals to amplify immune responses in certain infectious or inflammatory disease settings.

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ORIGINAL RESEARCH PAPERS Martin, B., Hirota, K., Cua, D. J., Stockinger, B. & Veldhoen, M. Interleukin-17-producing γδ T cells selectively expand in response to pathogen products and environmental signals. *Immunity* **31**, 321–330 (2009) | Sutton, C. E. *et al.* Interleukin-1 and IL-23 induce innate IL-17 production from γδ T cells, amplifying Th17 responses and autoimmunity. *Immunity* **31**, 331–341 (2009)

FURTHER READING Kapsenberg, K. L. γδ T cell receptors without a job. *Immunity* **31**, 181–183 (2009) | Hayday, A. C. γδ T cells and the lymphoid stress-surveillance response. *Immunity* **31**, 184–196 (2009)