CYTOKINES

IL-17-producing cells go it alone

Two recent reports in *Nature Immunology* identify interleukin-17 (IL-17)-producing cells as a unique T helper (T_H)-cell lineage with developmental requirements that are distinct from those of T_H1 and T_H2 cells.

IL-23-dependent, IL-17-producing $CD4^+$ T cells are associated with autoimmunity. However, it is not clear whether these cells differentiate along a pathway that is distinct from those pathways that give rise to T_H1 and T_H2 cells or whether they are derived from a T_H1-cell intermediate. Both groups set out to address this issue and found that, when naive $CD4^+$ T cells were stimulated *in vitro* through their T-cell receptor (TCR) in the presence of IL-23, few cells produced IL-17, but a substantial proportion produced interferon-γ (IFN-γ). However, if IFN-γ-specific antibody was also included in the culture then a large population of IL-17-producing cells emerged. A further increase in the proportion of IL-17-producing $CD4^+$ T cells was observed if IL-4-specific antibody was also added to the culture, indicating that IFN-γ and IL-4 independently inhibit the generation of IL-17-producing cells.

Harrington *et al.* further investigated the factors that are required for the development of IL-17-producing cells *in vitro*. They found that naive $CD4^+$ T cells isolated from mice that were deficient in signal transducer and activator of transcription 1 (STAT1), STAT4 or T-bet (factors that are required for differentiation into T_H1 cells) were not impaired in their ability to differentiate into IL-17-producing cells when stimulated through their TCR in the presence of IL-23. Similarly, the development of IL-17-producing cells was not impaired when the stimulated naive $CD4^+$ T cells were isolated from mice that were deficient in STAT6, which promotes differentiation into T_H2 cells.

Park *et al.* generated similar data *in vivo*: they found that the generation of IL-17-producing $CD4^+$ T cells following immunization with antigen and complete Freund's adjuvant (CFA) was not impaired in mice that were deficient in STAT4, STAT6 or T-bet. However, the generation of IL-17-producing $CD4^+$ T cells following immunization with antigen and CFA was impaired in mice that were deficient in CD80 and CD86 and in mice that were deficient in inducible T-cell co-stimulator (ICOS), indicating that CD28 and ICOS are required for the development of these cells.

These studies clearly define IL-17-producing $CD4^+$ T cells as a unique subset of T_H cells that develop along a pathway that is distinct from the T_H1- and T_H2-cell differentiation pathways. Given the clear pathogenic effects of IL-17-producing $CD4^+$ T cells in autoimmune disease, both groups suggest that upsetting the balance of IFN-γ and IL-4 could be a contributing factor to autoimmunity.

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References and links

ORIGINAL RESEARCH PAPERS Harrington, L. E. *et al.* Interleukin 17-producing $CD4^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nature Immunol.* **6**, 1123–1132 (2005) | Park, H. *et al.* A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nature Immunol.* **6**, 1133–1141 (2005)