

 T-CELL RESPONSES
Unlocking T_H17-cell differentiation

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Dan Littman and colleagues report in *Cell* that the differentiation of interleukin-17 (IL-17)-producing pro-inflammatory T helper (T_H) cells (known as T_H17 cells) is directed by the transcription factor and nuclear hormone receptor retinoic-acid-related orphan receptor- γ t (ROR γ t).

T_H17 cells are the most recently discovered subset of T_H cells, and they effect their role at the interface between the adaptive and the innate immune response. They regulate granulopoiesis and host defence against extracellular pathogens, and contribute markedly to the development of autoimmune disease. But what are the mechanisms that

regulate the differentiation of this effector-cell subset? Littman and colleagues looked to the orphan nuclear receptor ROR γ t to answer this question. ROR γ t is required for development of the lymph nodes, the Peyer's patches and other lymphoid tissues, and the expression of ROR γ t by CD4⁺CD8⁺ (double positive) T cells has been shown to extend their survival during clonal selection.

DNA-microarray analysis of CD4⁺ T cells revealed that culture with IL-23 (which favours differentiation into T_H17 cells) resulted in an increase in the amount of mRNA encoding ROR γ t. Because the authors had already found ROR γ t⁺ T cells in the intestinal lamina

propria of mice, they were prompted to ask whether these cells were of the T_H17-cell subset. A large proportion of lamina propria T cells were indeed found to produce IL-17, and ROR γ t was required for this expression. ROR γ t was also shown to be sufficient to induce the expression of IL-17 (and the related cytokine IL-17F) by naive CD4⁺ T cells that were stimulated with antigen, and it was required to induce IL-17 expression by these cells in response to IL-6 and transforming

growth factor- β (TGF β), cytokines that are known to induce IL-17 expression. Therefore, Littman and colleagues have shown that ROR γ t functions as a transcription factor downstream of IL-6 and TGF β and is required for the differentiation of T_H17 cells, both *in vitro* and in the lamina propria.

T_H17 cells have been shown to be pathogenic in several animal models of autoimmune disease, including experimental allergic encephalomyelitis (EAE). So the authors induced EAE in both wild-type mice and ROR γ t-deficient mice, and they examined the role of ROR γ t in the development of EAE. Mice that lacked endogenous ROR γ t were less susceptible to EAE, and the presence of ROR γ t was shown to be required for the *in vivo* differentiation of pathogenic T_H17 cells in the central nervous system during the EAE disease process.

Together, these results indicate that the transcription factor ROR γ t is a key immune regulator that directs the differentiation of T_H17 cells, which are pro-inflammatory. Manipulating the activity of ROR γ t might therefore be an attractive strategy for the treatment of various inflammatory diseases.

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ORIGINAL RESEARCH PAPER Ivanov, I. I. *et al.*
The orphan nuclear receptor ROR γ t directs the differentiation program of proinflammatory IL-17⁺ T helper cells. *Cell* **126**, 1121–1133 (2006)

