T HELPER CELLS

Self-control by T_H1 cells

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IL-10

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Two studies published in *The Journal of Experimental Medicine* provide surprising evidence that T helper 1 (T_H1) cells are the main producers of the anti-inflammatory cytokine interleukin-10 (IL-10) during protozoan infection and chronic cutaneous leishmaniasis.

IL-10 is a key cytokine involved in limiting strong inflammatory (T_H1) responses to certain pathogens, thereby preventing immunopathology and mortality. But IL-10 can also suppress protective T_H1 responses, resulting in chronic infections. IL-10 can be produced by FOXP3⁺ T_{Reg} cells (forkhead box P3; CD4⁺CD25⁺ regulatory T cells), as well as a variety of other cell types, including T_H2 cells, B cells and antigen-presenting cells. But what is the specific cellular source of IL-10 during strong T_H1 responses?

The two papers used different models to address this question. Sacks and colleagues used a model of chronic cutaneous infection by *Leishmania major*, which is associated with an ongoing T_H1 response in the presence of increased IL-10 production. Sher and colleagues infected mice with the protozoan parasite

Toxoplasma gondii; host survival in these mice requires the production of both IL-10 and interferon- γ (IFN γ).

Sacks and colleagues found that IL-10 was produced by innate immune cells, T_{Reg} cells and CD4⁺CD25⁺FOXP3⁺ T cells in dermal lesions from mice infected with *L. major*. To further understand the cellular source of IL-10 in this model, the authors reconstituted recombination-activating-gene-1-deficient (*Rag*^{-/-}) or *Rag*^{-/-}*Il10*^{-/-} mice with cells from either *Il10*^{-/-} or wild-type mice, thereby restricting the source of IL-10 to either the T-cell or non-T-cell compartments. They found that although the main source of IL-10 in this chronic infection was innate immune cells, the production of IL-10 by antigen-specific T cells was necessary and sufficient to suppress protective immunity to *L. major*. Surprisingly, these CD4⁺ T cells were CD25⁺FOXP3⁺ and the majority of these cells also produced IFN γ .

In parallel with these findings, Sher and colleagues showed that the main cellular source of IL-10 during infection with *T. gondii* is IFN γ -producing CD4⁺CD25⁺FOXP3⁺ T cells.

Further characterization of these IL-10-producing T cells showed that they expressed the T_H1-associated transcription factor T-bet, indicating that these cells might arise from the same precursors as classical T_H1 cells. The authors also showed that the ability of these cells to produce IL-10 is not a stable phenotype and requires prior activation of the cell, whereas IFN γ production is not affected by the activation state of the cell.

So, both studies show that antigen-specific IFN γ -producing CD4⁺CD25⁺FOXP3⁺T-bet⁺ T_H1 cells are a crucial source of regulatory IL-10. The authors suggest that the production of IL-10 by T_H1 cells might be a feedback control mechanism to limit damage to the host caused by strong T_H1-polarizing conditions while maintaining an effector response.

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ORIGINAL RESEARCH PAPERS Anderson, C. F. et al. CD4⁺CD25⁺FOXP3⁺T_H1 cells are the source of IL-10-mediated immune suppression in chronic cutaneous leishmaniasis. *J. Exp. Med.* 5 February 2007 (doi:10.1084/jem.20061886) | Jankovic, D. et al. Conventional T-bet⁺FOXP3⁺T_H1 cells are the major source of host-protective regulatory IL-10 during intracellular protozoan infection. *J. Exp. Med.* 5 February 2007 (doi:10.1084/jem.20062175)