

# Making a commitment

T-bet, a member of the T-box family of transcription factors, has been implicated in the regulation of T-helper type 1 and 2 ( $T_H1$  and  $T_H2$ ) lineage commitment of  $CD4^+$  T cells. Two papers in *Science* by Laurie Glimcher and co-workers now show that mice lacking T-bet spontaneously develop an asthma-like phenotype and that T-bet is required for the control of interferon- $\gamma$  (IFN- $\gamma$ ) production in  $CD4^+$  T cells and natural killer (NK) cells but, unexpectedly, not in  $CD8^+$  T cells.

Human asthma is characterized by airway inflammation, airway hyper-responsiveness (AHR) and airway remodelling, and is associated with infiltration by  $T_H2$  cells. T-bet transactivates the gene that encodes IFN- $\gamma$  in  $T_H1$  cells and suppresses the development of  $T_H2$  cells. In the first paper, the group looked at the role of T-bet in asthma and observed that patients with allergic asthma had lower expression of T-bet in their lungs than non-asthmatics. To investigate the role of T-bet in asthma, T-bet-deficient mice were generated and examined for signs of asthma. *T-bet*<sup>-/-</sup> mice, in the absence of any immunogenic stimulation, spontaneously developed AHR and exhibited features of airway remodelling.

The second paper focused on the role of T-bet in the transcriptional control of IFN- $\gamma$  production. Previous studies showed that T-bet production correlates with IFN- $\gamma$  production in all cells examined but the mechanisms of control remain poorly understood. To investigate the role of endogenous T-bet in controlling IFN- $\gamma$  production in  $CD4^+$  T cells, cells were isolated from *T-bet*<sup>-/-</sup> mice and stimulated with anti-CD3 and anti-CD28 antibodies. IFN- $\gamma$  production was decreased in cells lacking T-bet, even in the presence of interleukin-12 (IL-12), which is a potent stimulator of IFN- $\gamma$  production. Next, they addressed the role of T-bet in  $T_H1$ - $T_H2$  polarization.  $CD4^+$  T cells were cultured under neutral or polarizing conditions and the phenotype of the effector T cells was examined by detecting cytokine production. When stimulated under  $T_H1$ -inducing conditions, *T-bet*<sup>-/-</sup> cells produced less IFN- $\gamma$  and more IL-4 and IL-5, indicating that they had instead developed a  $T_H2$  phenotype.



Further evidence of defective  $T_H1$  development in *T-bet*<sup>-/-</sup> mice came from experiments in which they were infected with *Leishmania major*, a protozoan that requires a  $T_H1$  response to resolve infection. C57BL/6 mice can control infection but BALB/c mice develop a  $T_H2$  response and are susceptible to infection. When T-bet was knocked out in the resistant C57BL/6 background, the mice became infected and failed to control the infection.

Is T-bet essential for IFN- $\gamma$  production in cells other than  $CD4^+$  T cells? NK cells produce IFN- $\gamma$  in response to stimulation with IL-12 and IL-18, but *T-bet*<sup>-/-</sup> NK cells produce less IFN- $\gamma$  than wild-type cells and their effector function is also impaired. In contrast to  $CD4^+$  and NK cells, *T-bet*<sup>-/-</sup>  $CD8^+$  T cells stimulated with cytokines produced similar amounts of IFN- $\gamma$  to wild-type  $CD8^+$  T cells. This result was surprising, because a previous study had shown that retroviral transduction of T-bet into type-2  $CD8^+$  T cells converted them into type-1 cells.

These results indicate that the *T-bet*<sup>-/-</sup> mouse is a new model for asthma, and confirm the crucial role of T-bet in  $T_H1$  lineage commitment. However, surprisingly, the transcriptional control of IFN- $\gamma$  production seems to be different in  $CD4^+$  and  $CD8^+$  T cells.

Elaine Bell

## References and links

**ORIGINAL RESEARCH PAPERS:** Finotto, S. *et al.* Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. *Science* **295**, 336–338 (2002) | Szabo, S. J. *et al.* Distinct effects of T-bet in  $T_H1$  lineage commitment and IFN- $\gamma$  production in  $CD4$  and  $CD8$  T cells. *Science* **295**, 338–342 (2002).

**FURTHER READING:** Rengarajan, J., Szabo, S. J. & Glimcher, L. H. Transcriptional regulation of  $T_H1$ / $T_H2$  polarization. *Immunol. Today* **21**, 479–483 (2000)

### WEB SITE

Laurie Glimcher's laboratory: <http://www.hsph.harvard.edu/facres/glmchr.html>

# IL-25 joins $T_H2$ team

T-helper type 2 ( $T_H2$ ) cell responses have a new star player. In the January issue of *Immunity*, Madeline Fort and co-workers report the discovery of a new cytokine — IL-25 — and show that it promotes  $T_H2$ -associated pathology.

IL-25 was identified in database searches for new molecules with homology to the proinflammatory cytokine IL-17. *Il25* mRNA is produced by polarized  $T_H2$  cells but not by naive T cells,  $T_H1$  cells or other cell types. To test the biological functions of IL-25, mice were treated with the purified protein. Unlike IL-17, IL-25 treatment leads to characteristic  $T_H2$  effects — increased serum IgG1 and IgE concentrations, increased eosinophil production, and inflammation of the lungs and gut.

So, does IL-25 mediate these effects by inducing the production of  $T_H2$ -type cytokines (IL-4, IL-5 and IL-13)? Quantitative PCR analysis of whole tissues confirmed that IL-25 treatment induces  $T_H2$ -type, but not  $T_H1$ -type, cytokine production. The roles of IL-4, IL-5 and IL-13 in mediating the effects of IL-25 were verified *in vivo*. However, identifying the responder cells was more difficult. *In vitro* assays of fractionated cell populations ruled out  $CD4^+$  T cells, B cells, monocytes, macrophages, eosinophils and NK cells. Instead, IL-5 and IL-13 production in response to IL-25 was attributed to a rare, lineage-negative cell that expresses high levels of MHC-class-II molecules. However, the source of IL-25-induced IL-4 was not identified.

This study indicates that IL-25 might be involved in promoting  $T_H2$  responses and could be a target for the treatment of allergy and asthma.

Jennifer Bell

## References and links

**ORIGINAL RESEARCH PAPER** Fort M.M. *et al.* IL-25 induces IL-4, IL-5, and IL-13 and  $T_H2$ -associated pathologies *in vivo*. *Immunity* **15**, 985–995 (2001).

### WEBSITE

Immunology department at DNAX: <http://www.dnaxresearch.com/department-immunology.html>

