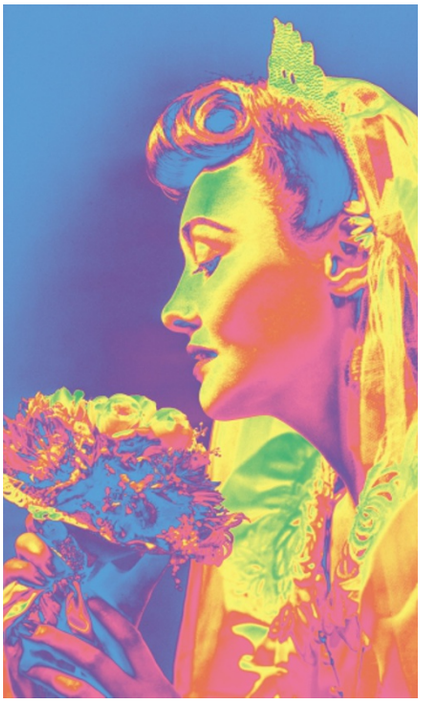
IMMUNE REGULATION

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-γ (IFN-γ) 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-γ 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*$^{-/-}$ 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-γ production. Previous studies showed that T-bet production correlates with IFN-γ production in all cells examined but the mechanisms of control remain poorly understood. To investigate the role of endogenous T-bet in controlling IFN-γ production in $CD4^+$ T cells, cells were isolated from *T-bet*$^{-/-}$ mice and stimulated with anti-CD3 and anti-CD28 antibodies. IFN-γ production was decreased in cells lacking T-bet, even in the presence of interleukin-12 (IL-12), which is a potent stimulator of IFN-γ 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*$^{-/-}$ cells produced less IFN-γ 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*$^{-/-}$ 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-γ production in cells other than $CD4^+$ T cells? NK cells produce IFN-γ in response to stimulation with IL-12 and IL-18, but *T-bet*$^{-/-}$ NK cells produce less IFN-γ than wild-type cells and their effector function is also impaired. In contrast to $CD4^+$ and NK cells, *T-bet*$^{-/-}$ $CD8^+$ T cells stimulated with cytokines produced similar amounts of IFN-γ 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*$^{-/-}$ 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-γ 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-γ 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

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IMMUNE REGULATION

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