T-CELL MEMORY

If your name's not down, you're not coming in

According to a recent report in *Science*, CD8αα could be the long-sought marker of effector T cells that are destined to enter the memory pool. Only a small fraction of the effector T-cell population that expands during a primary response survives as long-lived memory T cells after antigen has been cleared, but until now, the mechanism of this selection process has been unclear.

Madakamutil *et al.* used tetramers of the non-classical MHC class I molecule thymic leukaemia antigen (TL) — which is a unique ligand for CD8αα — to show that mature CD8αβ$^+$ T cells upregulate the cell-surface expression of CD8αα after stimulation through CD3. CD8αα upregulation was also seen after stimulation of OT-1 T-cell receptor (TCR)-transgenic splenocytes with their cognate antigen (ovalbumin, OVA). This effect was greatest when OT-1 splenocytes were stimulated with OVA presented by TL-expressing antigen-presenting cells, indicating that interaction between CD8αα and TL is necessary to maintain CD8αα expression. TL is expressed by activated dendritic cells and monocytes, indicating that such an interaction could occur physiologically.

Expression of CD8αα correlated with high levels of expression of the anti-apoptotic proteins Bcl-2 and Bcl-X_L and with increased T-cell survival *in vitro*. These results were confirmed *in vivo* after infection of mice with lymphocytic choriomeningitis virus (LCMV); CD8αα was upregulated on a subset of LCMV-specific CD8αβ$^+$ T cells after infection, and these T cells expressed high levels of Bcl-X_L and survived long term (for up to 60 days after infection).

As CD8αα is only upregulated on a subset of effector T cells and promotes long-term survival, it might be a marker of memory T-cell precursors. To test this, they transferred TCR-transgenic P14 T cells (specific for an LCMV peptide) to naive recipients, then re-isolated the P14 T cells 8 days after LCMV

LYMPHOCYTE SIGNALLING

Lay your bets: 2–1 on NK and NKT cells

The lymphoid-restricted T-box transcription factor T-bet is known to have a key role in the generation of T helper 1-cell immune responses. Now, an in depth analysis of T-bet-deficient mice, published in *Immunity*, indicates that this transcription factor also regulates the late stages of development of natural killer (NK) cells and of NKT cells that express the semi-invariant Vα14 T-cell receptor (TCR) — Vα14*i* NKT cells.

C57BL/6 mice express the NK-cell receptors NK1.1 and Ly49d. Therefore, to assess the role of T-bet in NK-cell development and function, T-bet-deficient mice were backcrossed onto the C57BL/6 background. Flow cytometric analysis indicated that T-bet-deficient mice had reduced numbers of NK cells in the spleen, liver and peripheral blood, and that the remaining cells had an immature phenotype — as determined by reduced expression of CD43, CD11b and DX5, and increased expression of c-Kit — but expressed a normal repertoire of activating and inhibitory NK-cell receptors. Similarly, using α-galactosyl ceramide-loaded CD1d tetramers to identify Vα14*i* NKT cells, T-bet-deficient mice were shown to have almost no Vα14*i* NKT cells in the liver, spleen and thymus. By contrast, Vα14*i* NKT-cell maturation intermediates in the thymus, previously defined as tetramer-positive cells expressing CD44 but not NK1.1 or Ly49 receptors, were detected in T-bet-deficient mice, indicating that, as for NK cells, Vα14*i* NKT-cell terminal maturation is blocked in the absence of T-bet.

By using wild-type or T-bet-deficient bone marrow to reconstitute wild-type and T-bet-deficient mice, the authors showed that the defect in NK-cell and Vα14*i* NKT-cell development was intrinsic to T-bet-deficient bone marrow. Furthermore, when a mixture of wild-type and T-bet-deficient bone marrow was used to reconstitute a T-bet-sufficient host, the NK cells and Vα14*i* NKT cells were largely derived from the wild-type bone marrow, indicating a stem-cell-intrinsic role for T-bet in the development of the NK-cell and Vα14*i* NKT-cell lymphoid compartments. Consistent with a cell-intrinsic role in terminal maturation, overexpression of T-bet in T-bet-deficient haematopoietic stem cells increased the number and maturation status of NK cells in the spleen.

To further determine the role of T-bet in NK-cell and Vα14*i* NKT-cell maturation, the authors analysed the effector functions of T-bet-deficient cells. Interleukin-12 (IL-12) and IL-18 stimulation of NK cells results in a rapid burst of interferon-γ (IFN-γ) secretion that was not impaired in T-bet-deficient NK cells. However, T-bet was required to maintain IFN-γ production during prolonged NK-cell stimulation. By contrast, T-bet-deficient Vα14*i* NKT cells were unable to produce IFN-γ when stimulated *in vivo* with α-galactosyl ceramide. The authors suggest that this distinct dependence on T-bet for regulating IFN-γ production could result from redundancy between T-box transcription factors, as NK cells but not Vα14*i* NKT cells express the T-box-family member eomesodermin.

This study identifies a novel role for T-bet as a regulator of the terminal differentiation of NK cells and Vα14*i* NKT cells. However, further studies are required to determine whether the molecular role of this transcription factor is the same in these two cell types.

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References and links

ORIGINAL RESEARCH PAPER Townsend, M. J. *et al.* T-bet regulates the terminal maturation and homeostasis of NK and Vα14*i* NKT cells. *Immunity* **20**, 477–494 (2004)