*Rag*γ*c*$^{-/-}$ mice injected with YS cells generated donor-derived myeloid cells, but this reconstitution was transient, and after 3 months donor-derived progeny were no longer observed. No lymphocytes were ever detected in these mice. Therefore, YS cells cannot generate lymphocytes, but can provide short-term myeloid reconstitution. By contrast, after injection of Sp-derived cells into *Rag*γ*c*$^{-/-}$ recipients, donor-derived myeloid cells, as well as B and T cells were generated. These myeloid and lymphoid cells were still present 8 months after injection, indicating that Sp-derived percursors can provide long-term reconstitution of recipient mice.

The authors conclude that the only cells capable of adult long-term haematopoiesis are from the Sp region. So, during mouse embryogenesis, HSCs are generated intra-embryonically and do not derive from the YS.

*Jenny Buckland*


**References and links**

**ORIGINAL RESEARCH PAPER** Cumano, A. *et al.* Intraembryonic, but not yolk sac hematopoietic precursors, isolated before circulation, provide long-term multilineage reconstitution. *Immunity* **15**, 477–485 (2001)


NATURAL KILLER CELLS

# Targeting tumour cells

**The 'missing-self' hypothesis, formulated by Klaus Kärre and colleagues in 1986, proposed that natural killer (NK) cells seek out and destroy cells that have lost expression of major histocompatibility complex (MHC) class I antigens. Two recent papers, published in *Nature* and in *Proceedings of the National Academy of Sciences*, now show that NK cells can reject tumour cells that express ligands for the activating NK receptor NKG2D, despite the expression of MHC class I molecules by the tumour cells.**

**The formulation of the missing-self hypothesis predicted the existence of receptors on NK cells that inhibit their activity and which recognize MHC class I molecules. Many of these receptors have now been identified. Recent work has also identified several activating NK receptors, including the lectin-like molecule NKG2D, whose engagement provides dominant activating signals to the NK cell. Previous work by Tom Spies' group showed that NK cells can kill NKG2D ligand-expressing cells *in vitro*. The mouse ligands for NKG2D are retinoic acid early inducible-1 (Rae-1) and H60, which are expressed by some tumour cells, but not by normal adult cells.**

**Both groups looked for direct evidence to support the idea that tumour cells ectopically expressing ligands for NKG2D could stimulate antitumour responses by NK cells. The Raulet group used a retroviral expression system to express Rae1β and H60 in three mouse tumour cell lines that express MHC class I molecules — EL4 thymoma cells, RMA T-cell lymphoma cells (which were used in the original Kärre study) and B16-BL6 melanoma cells. Transduced EL4 and B16-BL6 cells that were injected subcutaneously into recipient mice were rapidly and completely rejected. Tumour cells were rejected in wild-type mice depleted of CD8$^+$ T cells and in *Rag*$^{-/-}$ mice (which lack T and B cells), but grew in *Rag*$^{-/-}$ mice depleted of NK cells, indicating that conventional NK cells are responsible for the rejection. Rae1β- or H60-transduced RMA cells were also rejected in wild-type mice, but rejection required both CD8$^+$ T cells and NK cells.**

**The Lanier group also used the RMA cells to investigate NK cell responses. RMA cells stably transfected with Rae1γ or Rae1δ were injected intraperitoneally into recipient mice. Mice injected with mock-transfected cells developed tumours and died, whereas mice challenged with transfected cells rejected tumour cells in an NK-cell dependent manner.**

**So, NK cells can reject tumour cells expressing NKG2D ligands, despite MHC class I expression. But do mice primed with NKG2D ligand-expressing tumour cells develop an adaptive T-cell response against subsequent challenge by non-transduced parental tumour cells? This is where the results from the two groups differ. Raulet and colleagues found that NKG2D ligand-negative tumour cells were rejected by mice previously challenged with transduced tumour cells, and that this was a CD8$^+$ T-cell-dependent process. By contrast, Lanier and colleagues found that mice that had rejected Rae1γ-transfected RMA cells were unable to reject parental tumours on re-challenge.**

**These results show that NK cells can, and do, participate in rejection of MHC class-I bearing tumour cells and, although there are some discrepancies in the results, this approach might be effective for tumour vaccine development.**

***Elaine Bell***


**References and links**

**ORIGINAL RESEARCH PAPERS** Diefenbach, A., Jensen, E. R., Jamieson, A. M. & Raulet, D. H. Rae1 and H60 ligands of the NKG2D receptor stimulate tumour immunity. *Nature* **413**, 165–171 (2001) | Cerwenka, A., Baron, J. L. & Lanier L. L. Ectopic expression of retinoic acid early inducible-1 gene (*RAE-1*) permits natural killer cell-mediated rejection of a MHC class I-bearing tumor *in vivo*. *Proc. Natl Acad. Sci. USA* **98**, 11521–11526 (2001)

**WEB SITES**

**Lewis Lanier's lab:** http://cc.ucsf.edu/people/lanier_lewis.html

**David Raulet's lab:** http://mcb.berkeley.edu/labs/raulet/