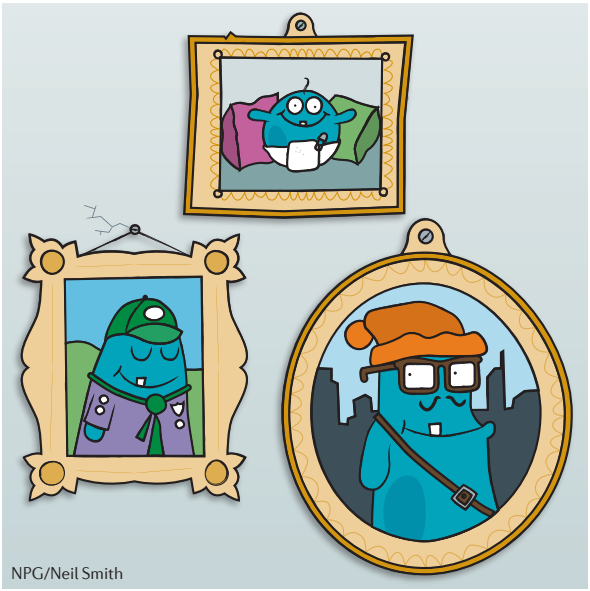
Nature Reviews Immunology | AOP, published online 14 February 2014; doi:10.1038/nri3629

INNATE LYMPHOID CELLS

On the origin of ILCs



NPG/Neil Smith

> The elusive ILC precursor

Innate lymphoid cells (ILCs) serve as an early source of effector cytokines that are typically associated with T helper (T_H) cell subsets. Indeed, they have been subdivided into three main groups according to their production of T_H1, T_H2 or T_H17 cell-associated cytokines. However, ILC lineage relationships are not clear and an important question has remained unanswered — which progenitor cells do ILCs arise from? Now, Constantinides *et al*. have identified the elusive ILC precursor in mice. This precursor cell is characterized by a high expression level of the transcription factor promyelocytic leukaemia zinc finger (PLZF), and is present in both the fetal liver and the adult bone marrow.

PLZF (encoded by *Zbtb16*) promotes the acquisition of innate effector functions in natural killer T (NKT) cells, a distinct population of innate-like lymphocytes. To study PLZF expression patterns throughout the immune system, the authors generated reporter mice that enabled the detection of cells that currently express, or have previously expressed, *Zbtb16*. Using these mice, the authors confirmed that NKT cells express PLZF, and that this is most prominent during their early development. Common lymphoid progenitors (CLPs), T cells or B cells did not express PLZF, and they did not seem to express PLZF during their development from haematopoietic stem cells (HSCs). Although mature ILCs do not express PLZF, fate-mapping suggested that ILC1s, ILC2s and ILC3s do express PLZF at some stage during their development from HSCs. However, natural killer (NK) cells and lymphoid tissue-inducer (LTi) cells (currently classified as group 1 and group 3 ILCs, respectively) do not appear to express PLZF at any stage of their development.

This suggested that ILCs may develop from a PLZF-expressing precursor, and the authors identified a rare subset of $PLZF^{hi}$ cells in the fetal liver and bone marrow. These cells did not express markers associated with immune cell lineages (they were LIN^-), but were IL-7Rα^+KIT$^+\alpha4\beta7$ integrin^{hi} — a phenotype that has previously been associated with CLP-derived cells that give rise to LTi cells. Notably, the $PLZF^{hi}$ cells expressed other transcription factors associated with ILC development, including GATA3 and RORγt, and they also expressed high levels of TOX, which is necessary for NK cell and LTi cell development. To study developmental potentials, the authors transferred $PLZF^{hi}$ cells and CLPs into immunodeficient mice. They found that $PLZF^{hi}$ cells gave rise to all ILC lineages, except for LTi cells. Also, although both $PLZF^{hi}$ cells and CLPs generated NK cells, CLPs primarily gave rise to 'classical' NK cells ($DX5^+CD49a^-NK1.1^+$), whereas $PLZF^{hi}$ cells generated a distinct $DX5^-CD49a^+NK1.1^+$ subset. Unlike CLPs, $PLZF^{hi}$ cells did not show B cell or T cell developmental potential.

Notably, purified $PLZF^{hi}$ cells also gave rise to ILCs in *in vitro* culture studies, and these experiments suggested that commitment to individual ILC lineages occurs rapidly during the $PLZF^{hi}$ stage of ILC development. Interestingly, fetal liver-derived $PLZF^{hi}$ cells showed increased ILC3 potential in these studies, compared with their bone marrow-derived counterparts. Finally, the authors showed that PLZF is required for the development of ILC1s and ILC2s, but not for that of ILC3s, despite expression of this transcription factor during ILC3 development.

In summary, the $PLZF^{hi}$ cell seems to represent a precursor that is committed to the development of ILC subsets, with the exception of classical NK cells and LTi cells. This study shows that ILC1s, ILC2s and ILC3s are closely related to, but developmentally distinct from, classical NK and LTi cells.

Yvonne Bordon

ORIGINAL RESEARCH PAPER
Constantinides, M. G. *et al.* A committed precursor to innate lymphoid cells. *Nature* http://dx.doi.org/10.1038/nature13047 (2014)
FURTHER READING Spits, H. *et al.* Innate lymphoid cells — a proposal for uniform nomenclature. *Nature Rev. Immunol.* **13**, 145–149 (2013)