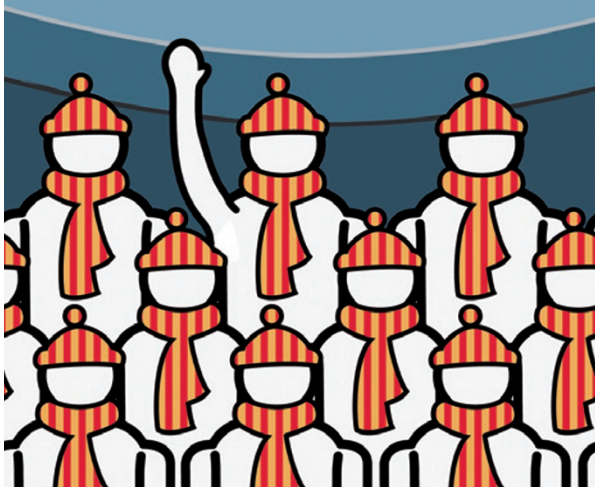
INNATE-LIKE LYMPHOCYTES

Will the real ILC1 please stand up?



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Innate lymphoid cells (ILCs) have important roles in immunity, as well as in tissue homeostasis and remodelling. ILCs can be grouped based on the resemblance of their cytokine-expression profile to that of T helper 1 (T_H1) cells (group 1 ILCs; includes natural killer (NK) cells), T_H2 cells (group 2 ILCs) and T_H17 and T_H22 cells (group 3 ILCs) (see further reading). However, not much is known of the transcription factors that control their specification or their functional plasticity. Three recent studies shed light on the role of the T_H1 cell-associated transcription factor T-bet in ILC specification and plasticity.

Group 3 ILCs have important functions at mucosal surfaces, produce interleukin-17A (IL-17A) and/or IL-22 and depend on the transcription factor retinoic acid receptor-related orphan receptor-γt (RORγt) for their development. Three subsets of group 3 ILCs have been described so far: those expressing the natural cytotoxicity receptor NKp46 (also known as NCR1) and termed NCR^+ ILC3s; NCR^- ILC3s; and lymphoid tissue inducer (LTi) cells.

Sciumè *et al.* showed that T-bet was highly expressed by NCR^+ IL-22-producing ILC3s in the mouse lamina propria. T-bet-deficient mice had low numbers of $NCR^+IL\text{-}22^+$ ILC3s, and their residual NCR^+ ILC3s had reduced RORγt expression and impaired IL-22 production (probably owing to a maturational block) compared with wild-type cells. This study suggests that T-bet has a crucial role in the generation of NCR^+ ILC3s.

Klose *et al.* also assessed the role of T-bet in mouse IL-22-producing $ROR\gamma t^+$ (group 3) ILCs and found that one-third of NCR^- ILC3s and almost all NCR^+ ILC3s in the small intestine express T-bet. $T\text{-}bet^+$ ILC3s did not express CC-chemokine receptor 6 (CCR6) and emerged postnatally under the control of the aryl hydrocarbon receptor (AHR). By contrast, most $T\text{-}bet^-$ ILC3s expressed CCR6, and these cells were the dominant population during fetal development. $T\text{-}bet^+CCR6^-$ ILC3s produced interferon-γ (IFNγ), whereas $T\text{-}bet^-CCR6^+$ ILC3s produced IL-17A and IL-17F, suggesting that IL-17-producing $CCR6^+IL\text{-}22^+$ ILC3s and IFNγ-producing $CCR6^-IL\text{-}22^+$ ILC3s may be separate lineages.

$CCR6^-$ ILC3s first upregulated T-bet expression and then expressed NKp46. NCR^+CCR6^- ILC3s were the only ILC3 population that was absent from T-bet-deficient mice, suggesting that T-bet is required for the development of NCR^+ ILC3s from $CCR6^-$ ILC3 progenitors. Further investigation showed that the microbiota and IL-23 had roles in the differentiation of IFNγ-producing $NCR^+T\text{-}bet^+$ ILC3s from their NCR^- ILC3 progenitors. Finally, $NCR^+T\text{-}bet^+$ ILC3s were found to be the main source of IFNγ in response to *Salmonella enterica* subsp. *enterica* serovar Typhimurium infection, and this cytokine induced mucus release by goblet cells. However, these cells also contributed to the enterocolitis induced by this infection.

In the third study, Bernink *et al.* identified a distinct population of group 1 ILCs in human tonsils, which they termed ILC1s. These cells lack expression of KIT and the human-specific NCR NKp44, express very low levels of RORγt and express high levels of T-bet and IFNγ. Furthermore, these cells are distinct from NK cells and are phenotypically and functionally stable. ILC1s could not be identified in the human fetal gut (which has yet to be colonized with commensals), but they were found at high numbers in the inflamed intestinal tissue of patients with Crohn's disease.

In addition, the authors identified a population of KIT^+NCR^- ILCs in human tonsil and fetal intestinal tissue that had features of immature ILCs. Stimulation of these cells with IL-2 and IL-12 promoted their differentiation into ILC1s. Furthermore, highly purified human fetal gut-derived NCR^+ ILC3s differentiated into ILC1s when cultured with IL-2 and IL-12, suggesting that ILCs are functionally plastic and can change their phenotype in response to their local cytokine environment.

So, T-bet has an intrinsic role in the development of IFNγ-producing ILCs, some of which are a developmentally distinct population (that is, ILC1s), whereas others can develop from ILC3s.

Olive Leavy

ORIGINAL RESEARCH PAPERS Sciumè, G. *et al.* Distinct requirements for T-bet in gut innate lymphoid cells. *J. Exp. Med.* **209**, 2331–2338 (2012) | Klose, C. S. N. *et al.* A T-bet gradient controls the fate and function of $CCR6^-ROR\gamma t^+$ innate lymphoid cells. *Nature* 16 Jan 2013 (doi:10.1038/nature11813) | Bernink, J. H. *et al.* Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nature Immunol.* 20 Jan 2013 (doi:10.1038/ni.2534)
FURTHER READING Spits, H. *et al.* Innate lymphoid cells — a proposal for uniform nomenclature. *Nature Rev. Immunol.* **13**, 145–149 (2013)

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