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INNATE LYMPHOID CELLS

Human ILCs face redundancy

Innate lymphoid cells (ILCs) have been assigned important roles in maintaining tissue homeostasis on the basis of *in vitro* studies and experimental challenges in mice. However, the lack of mouse models enabling selective targeting of ILC subsets has made it hard to assess the contribution of these cells to 'natural' immune responses *in vivo*. A new study of patients with long-term deficiency of ILCs who have no apparent clinical phenotype suggests that human ILCs may be redundant for immune protection in the presence of adaptive immunity.

Alain Fischer, Eric Vivier and colleagues studied a small cohort of patients with severe combined immunodeficiency (SCID) caused by mutation of the common cytokine receptor γ-chain (*IL2RG*) or Janus kinase 3 (*JAK3*). IL-2Rγc and JAK3 mediate signalling downstream of interleukin-7 (IL-7) and IL-15, which are required for T cell and natural killer (NK) cell development, respectively. ILC1, ILC2 and ILC3 subsets are also dependent on IL-7, and indeed no circulating ILCs could be detected in the peripheral blood of three JAK3-deficient patients who were analysed before treatment.

The standard treatment for the life-threatening T cell deficiency of SCID is allogeneic haematopoietic stem cell transplantation (HSCT). 18 patients with IL-2Rγc deficiency ($n = 12$) or JAK3 deficiency ($n = 6$) who had undergone HSCT (without myeloablation) many years previously were analysed for immune cell reconstitution. All patients showed T cell reconstitution of donor origin, but NK cells, ILC2s and ILC3s could not be detected in peripheral blood. A small number of ILC1s were present in the blood of a few patients but as this subset has not been well defined these might not correspond to *bona fide* ILC1s. Similarly, no ILCs could be found in skin and gut biopsies from these patients. Thus, the lack of circulating and tissue-resident ILCs in IL-2Rγc- and JAK3-deficient patients with SCID persists after non-myeloablative HSCT.

These patients had no increase in the size of non-conventional T cell subsets, such as γδ T cells and invariant NKT cells, that could compensate for the absence of ILCs. Nevertheless, there were no apparent clinical effects of ILC deficiency over very long periods of follow-up (7–39 years since HSCT) in terms of susceptibility to infection, growth or quality of life. Two female JAK3-deficient patients went on to have healthy pregnancies, which also questions the role of ILCs in reproduction.

The results suggest that ILCs are redundant in humans with a functional adaptive immune system "at least in the context of modern medicine and hygiene". However, the authors note that their cohort was too small to assess a potential role of ILCs in tumour immunosurveillance and that longer-term study, beyond 40 years after HSCT, will be required to determine whether the contribution of ILCs changes with age.

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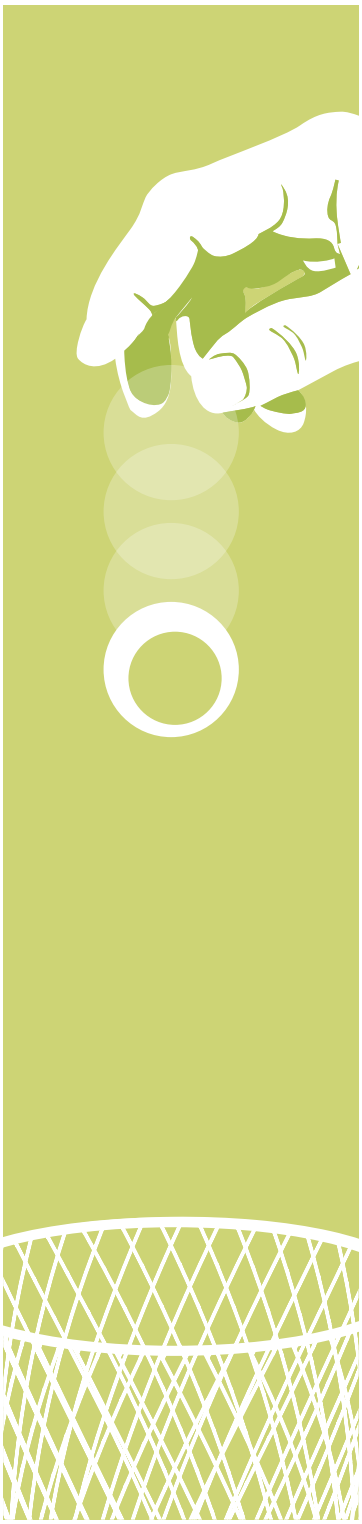
ORIGINAL ARTICLE Vély, F. *et al.* Evidence of innate lymphoid cell redundancy in humans. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3553 (2016)



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