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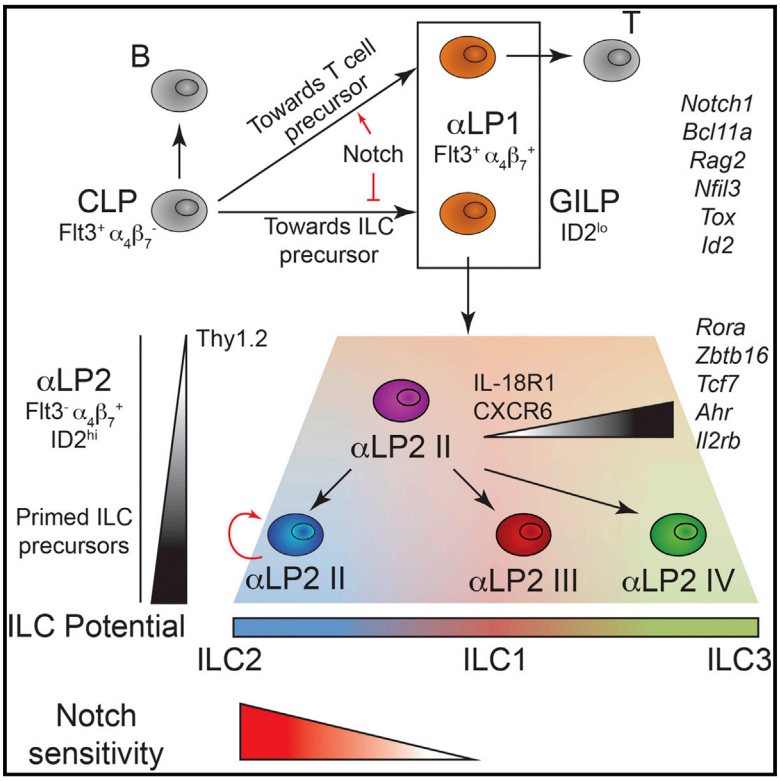
Single-Cell Gene Expression Analyses Reveal Heterogeneous Responsiveness of Fetal Innate Lymphoid Progenitors to Notch Signaling

Graphical Abstract



Highlights

- Global ILC progenitor and T precursors are found in the αLP1 compartment
- αLP2 compartment is heterogeneously composed of primed ILC precursors
- Notch signaling specifically acts on proliferation of an αLP2 ILC2 primed subset
- Constitutive NICD expression drives T cell development and restrains *Id2* expression

Authors

Sylvestre Chea, Sandrine Schmutz, Claire Berthault, ..., Hans-Reimer Rodewald, Ana Cumano, Rachel Golub

Correspondence

rachel.golub@pasteur.fr

In Brief

Molecular pathways and transcription factors involved in innate lymphoid cell (ILC) development are currently under intense investigation. Chea et al. now characterize different stages of ILC progenitors, from a global ILC progenitor (GILP) to committed ILC precursors, that are differentially sensitive to Notch signaling.

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Single-Cell Gene Expression Analyses Reveal Heterogeneous Responsiveness of Fetal Innate Lymphoid Progenitors to Notch Signaling

Sylvestre Chea,[1,2,3] Sandrine Schmutz,[1,4] Claire Berthault,[1,2,3] Thibaut Perchet,[1,2,3] Maxime Petit,[1,2,3] Odile Burlen-Defranoux,[1,2,3] Ananda W. Goldrath,[5] Hans-Reimer Rodewald,[6] Ana Cumano,[1,2,3] and Rachel Golub[1,2,3,*]
[1]Lymphopoiesis Unit, Immunology Department, Institut Pasteur, 75015 Paris, France
[2]University Paris Diderot, Sorbonne Paris Cité, Cellule Pasteur, 75013 Paris, France
[3]INSERM U1223, 75015 Paris, France
[4]Cytometry Platform, Institut Pasteur, 75015 Paris, France
[5]Molecular Biology Section, Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92093, USA
[6]Division of Cellular Immunology, German Cancer Research Center, 69120 Heidelberg, Germany
*Correspondence: rachel.golub@pasteur.fr
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SUMMARY

T and innate lymphoid cells (ILCs) share some aspects of their developmental programs. However, although Notch signaling is strictly required for T cell development, it is dispensable for fetal ILC development. Constitutive activation of Notch signaling, at the common lymphoid progenitor stage, drives T cell development and abrogates ILC development by preventing *Id2* expression. By combining single-cell transcriptomics and clonal culture strategies, we characterize two heterogeneous $\alpha_4\beta_7$-expressing lymphoid progenitor compartments. αLP1 (Flt3$^+$) still retains T cell potential and comprises the global ILC progenitor, while αLP2 (Flt3$^-$) consists of ILC precursors that are primed toward the different ILC lineages. Only a subset of αLP2 precursors is sensitive to Notch signaling required for their proliferation. Our study identifies, in a refined manner, the diversity of transitional stages of ILC development, their transcriptional signatures, and their differential dependence on Notch signaling.

INTRODUCTION

Innate lymphoid cells (ILCs) are a family of three groups (ILC1, ILC2, and ILC3) that rapidly respond to inflammatory signals by producing cytokines also involved in tissue homeostasis (Seillet et al., 2014). Group 1 is defined as distinct from conventional NK (cNK) cells and requires T-bet for its lineage specification (Bernink et al., 2013; Daussy et al., 2014; Fuchs et al., 2013; Klose et al., 2014). Group 2 expresses the transcription factors GATA3 and RORα (Hoyler et al., 2012; Klein Wolterink et al., 2013; Wong et al., 2012). Group 3 developmentally depends on the transcription factor RORγt and is composed of several distinct populations that emerge during ontogeny. During fetal life, only lymphoid tissue inducer (LTi) cells are present, and other ILC3 subsets appear after birth. LTi cells and their precursors are found in the fetal liver (FL) (Mebius et al., 2001). They are essential for the generation of secondary lymphoid tissues (Eberl et al., 2004) and express *Rorc*, which controls interleukin (IL)-17A and IL-22 production. LTi cells are CCR6$^+$c-Kit$^+$IL-7Ra^{hi} cells and are referred to as LTi_4 and LTi_0, depending on the expression of CD4 (Klose et al., 2013; Sawa et al., 2010). All ILCs initially derive from the common lymphoid progenitor (CLP) (Cherrier et al., 2012; Mebius et al., 2001; Possot et al., 2011; Wong et al., 2012; Yang et al., 2011b). A common feature to ILC commitment is the requirement for the transcriptional repressor regulator ID2 (Hoyler et al., 2012; Moro et al., 2010; Satoh-Takayama et al., 2010; Yokota et al., 1999), an inhibitor of E protein transcription factors. The current scheme of ILC development describes the global ILC (GILP) precursor as NFIL3$^+$TOX$^+$, which further becomes the ID2^{hi} common helper ILC precursor (CHILP) when cNK cell potential is lost (Constantinides et al., 2014; Klose et al., 2014; Seehus et al., 2015; Xu et al., 2015). After acquisition of *Zbtb16* expression, CHILP loses the capacity to differentiate into LTi cells, showing that LTi precursors stand at the bifurcation between GILP and CHILP (Constantinides et al., 2014).

The Notch pathway is conserved and involved in many biological processes (Hori et al., 2013). Activation of Notch receptors promotes their proteolysis, resulting in the release of the Notch intracellular domain (NICD), which enters the nucleus as a co-transcriptional factor with the DNA-binding protein RBP-Jκ (Recombination signal sequence-Binding Protein Jκ chain) (Hori et al., 2013). The activation of this canonical Notch signaling pathway is known to regulate the transcription of target genes (Iso et al., 2003). During hematopoiesis, the Notch pathway acts as a cell-fate switch between the lymphoid and myeloid lineages (Oh et al., 2013). Notch1 is essential for T cell development at the expense of B cell development (Han et al., 2002; Pui et al., 1999; Sambandam et al., 2005). Notch2 signaling is crucial to marginal zone B cells (Saito et al., 2003; Tanigaki et al., 2002) and to the development of CD11b$^+$ classical dendritic cells (cDCs) in spleen and intestine (Lewis et al., 2011; Satpathy et al., 2013).

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