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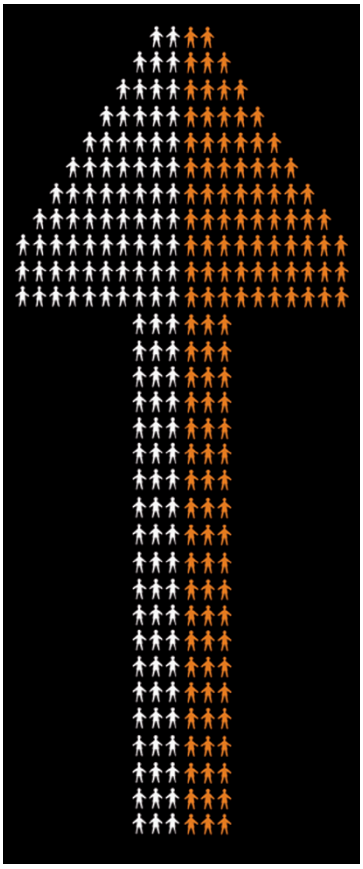
T CELLS

Notch and GATA3 join forces

Notch and GATA3 (GATA-binding protein 3) are well known as master regulators of intrathymic T-lineage fate determination and T helper 2 (T_H2)-cell differentiation, respectively, but never before have they been functionally linked. Now, two studies in *Immunity* report that Notch directly regulates *Gata3* expression, and together they ensure optimal T_H2-cell differentiation.

Besides its clear role in the thymus, Notch has been implicated in peripheral T-cell differentiation, but no consensus on this had been reached. Both Amsen *et al.* and Fang *et al.* therefore took a direct approach to investigate how Notch might be involved in T-cell differentiation. Signalling by Notch is initiated by ligand binding to its extracellular region, followed by proteolytic cleavage to release its intracellular domain (ICD). The ICD then translocates to the nucleus and forms a complex with the DNA-binding protein recombination-signal-binding protein-J (RBP-J; also known as CSL), to which Mastermind-like 1 (MAML1) and other co-activators are recruited, resulting in a transcriptional activator complex. Both groups observed that abrogation of Notch signalling in peripheral T cells, either by deleting *Notch1* and *Notch2*, by deleting *Rbpj* or by expressing a dominant-negative form of MAML1, prevented the production of the T_H2-cell-derived cytokine interleukin-4 (IL-4). Moreover, Amsen *et al.* confirmed previous studies showing that the robust T_H2-cell response normally induced by the injection of parasite antigens did not occur in mice with Notch-signalling-deficient peripheral T cells.



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Given that GATA3 is a key regulator of T_H2-cell differentiation, through its ability to drive epigenetic modification of the *Il4* locus, both groups examined whether Notch induces the T_H2-cell response by directly targeting *Gata3*. Indeed, compared with control cells, *Gata3* expression was upregulated in $CD4^+$ T cells expressing an activated allele of Notch ICD and was downregulated in T cells expressing dominant-negative MAML1 or lacking RBP-J. Importantly, Notch induced *Gata3* expression even in cells lacking STAT6 (signal transducer and activator of transcription 6), which is known to drive *Gata3* transcription induced by IL-4 receptor signalling. Further analysis revealed that, of the two promoters that are known to control *Gata3* gene expression, Notch preferentially targets the upstream one, through a conserved binding site for RBP-J.

To prove that the ability of Notch to induce IL-4 production and T_H2-cell responses requires GATA3, studies using T cells lacking GATA3 or expressing a dominant-negative form of GATA3 were performed. Forced expression of Notch ICD in these cells failed to increase IL-4 production under T_H2-cell polarizing conditions and instead led to a strong induction of the T_H1-cell cytokine interferon-γ, indicating that GATA3 is indeed crucial for Notch-mediated T_H2-cell responses. Fang *et al.* also showed that Notch and GATA3 synergize to promote IL-4 production and that their effect was independent of STAT6 and any further positive feedback from IL-4.

So, these studies confirm an important role for Notch in T_H2-cell differentiation, through direct regulation of *Gata3* expression.

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ORIGINAL RESEARCH PAPERS
Amsen, D. *et al.* Direct regulation of *Gata3* expression determines the T helper differentiation potential of Notch. *Immunity* **27**, 89–99 (2007) | Fang, T. C. *et al.* Notch directly regulates *Gata3* expression during T helper 2 cell differentiation. *Immunity* **27**, 100–110 (2007)
FURTHER READING Kubo, M. Notch: filling a hole in T helper 2 cell differentiation. *Immunity* **27**, 3–5 (2007)