LYMPHOCYTE DEVELOPMENT

LRF and Notch go head to head

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LRF: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=51341

B and T cells develop in the bone marrow and thymus, respectively, from lymphoid progenitors, which arise from haematopoietic stem cells (HSCs) in the bone marrow. It is known that Notch signalling in the thymus drives the differentiation of T cells from lymphoid progenitors that have migrated there, but the precise molecular mechanisms governing the development of B cells in the bone marrow were undefined. Now, Maeda *et al.* show that the proto-oncogene *LRF* (leukaemia/lymphoma-related factor; also known as ZBTB7A and POKEMON) is a master regulator of B-cell and T-cell lineage commitment and functions by repressing Notch signalling in the bone marrow, allowing for the development of the B-cell lineage.

LRF is expressed by multiple haematopoietic lineages, especially germinal-centre B cells, and, recently, a homologue of LRF has been shown to be a master regulator of $CD4^+$ T-cell fate. So, the authors examined the role of LRF in lymphocyte development. Mice with a conditional deletion of *Lrf* in HSCs had reduced numbers of peripheral blood $B220^+$ B cells compared with control mice. In addition, the numbers of pro-B, pre-B and IgM^+ B cells were greatly reduced, whereas the numbers of pre-pro-B cells in the bone marrow were increased, indicating that in the absence of LRF B cells cannot progress to the pro-B-cell stage of development. Surprisingly, there was an accumulation of double-positive (DP) T cells in the bone marrow, making up nearly 30% of the mononuclear cells there. The development of these extrathymic

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T cells was independent of the thymus and was limited to the bone marrow, as these cells were not detected in the spleen or in Peyer's patches. So, in mice that lack LRF, HSCs or lymphoid progenitors give rise to DP T cells in the bone marrow.

Gene-expression analysis showed that in *Lrf*-conditional-knockout mice the expression of several factors involved in the early B-cell developmental programme was downregulated in the pre-pro-B cells. By contrast, the levels of mRNA encoding Notch1, Notch3 and Notch target genes were greatly elevated in these cells and they could differentiate into DP T cells, indicating that in the absence of LRF aberrant pre-pro-B cells develop that give rise to T-cell and not B-cell progenitors.

How does LRF favour the development of B cells in the bone marrow? Treatment of *Lrf*-conditional-knockout mice with a potent inhibitor of Notch signalling rescued aberrant lymphoid development, and normal numbers of pro-B cells and no DP T cells were observed in the bone marrow.

Taken together, the authors propose a model whereby, in HSCs and lymphoid progenitors, LRF suppresses low-level Notch signalling that is induced by bone-marrow stromal cells, which express moderate levels of Notch ligands. This suppresses the development of T-cell lineage progenitors, while allowing for the differentiation of B cells in response to other signals provided by stromal cells in the bone marrow. By contrast, in the thymus, where Notch ligands are highly expressed, Notch signalling would override the repressive role of LRF allowing for T-cell differentiation to occur.

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ORIGINAL RESEARCH PAPER Maeda, T. *et al.* Regulation of B versus T lymphoid lineage fate decision by the proto-oncogene LRF. *Science* **316**, 860–866 (2007)
FURTHER READING Maillard, I. & Pear, W. S. Keeping a tight leash on Notch. *Science* **316**, 840–842 (2007)