TOLERANCE

There's something in the Aire

How is tolerance to organ-specific antigens maintained? It was assumed originally that tolerance depends mainly on immunological 'ignorance' or peripheral regulatory mechanisms. However, evidence that organ-specific antigens are expressed by rare thymic medullary epithelial cells has indicated that central-tolerance mechanisms might be important also.

Humans with autoimmune polyendocrinopathy syndrome type 1 — which results from mutations in the autoimmune regulator (*AIRE*) gene — develop a range of organ-specific autoimmune diseases. Chris Goodnow and colleagues are the first to show that self-tolerance might be defective in these patients owing to a failure of negative selection in the thymus. As AIRE seems to be a transcriptional regulator and is expressed mainly by rare thymic stromal cells, this protein is likely to be important for the thymic expression of otherwise organ-specific antigens and their role in central tolerance.

In T-cell receptor (TCR)-transgenic 3A9-insHEL mice, which produce T cells with specificity for hen egg lysozyme (HEL) and express HEL under control of the rat insulin promoter, the TCR-transgenic T cells are deleted in the thymus as a result of thymic antigen expression. To analyse the effects of Aire on this process, the TCR-transgenic mice were crossed with *Aire*-mutant mice. No difference was observed in the positive selection of TCR-transgenic T cells between $Aire^{+/+}$ and $Aire^{-/-}$ mice that lacked expression of insHEL. In $Aire^{+/+}$ 3A9-insHEL mice, few $CD4^+$ T cells were present, indicating efficient negative selection, and those T cells that remained were anergic. However, in $Aire^{-/-}$ 3A9-insHEL mice, normal numbers of mature $CD4^+$ T cells were produced, indicating a failure of thymic deletion.

Reconstitution experiments were used to determine the lineage requirements for expression of Aire. $Aire^{-/-}$ T cells were deleted normally in the thymi of $Aire^{+/+}$ mice, whereas $Aire^{+/+}$

LYMPHOCYTE DEVELOPMENT

Mint- flavoured B cells

Notch-family proteins are highly conserved receptors that regulate binary cell-fate decisions. Their roles in embryogenesis — from flies to mammals — have been well described and their involvement in lymphopoiesis is beginning to be appreciated. In *Drosophila*, the Notch signalling pathways are controlled by the nuclear negative-regulator Hairless, but no Hairless homologue has been found in vertebrates. Now, Kuroda and colleagues report in *Immunity* the identification of a new nuclear inhibitor of Notch signalling, which is the first described mammalian functional equivalent of Hairless.

The DNA-binding protein RBP-J, also known as CSL or CBF1, is a crucial mediator of Notch signalling. In the absence of a Notch signal, RBP-J represses target-gene transcription by associating with a co-repressor complex. Following interaction with Notch ligands, the intracellular domain of Notch is cleaved and moves to the nucleus, where it displaces the co-repressors from RBP-J allowing it to recruit transcriptional activators. However, both RBP-J and its interacting proteins are ubiquitously expressed, so the basis of the tissue-specific effects of Notch–RBP-J signals is unknown.

Using the yeast two-hybrid system to identify RBP-J-binding proteins, the authors picked out MSX2-interacting nuclear target (Mint), which was previously reported to be a transcriptional repressor. Mint strongly inhibited RBP-J-mediated transcriptional activation induced by Notch1, 2, 3 and 4, and, unlike RBP-J, Mint has a restricted expression pattern, indicating that it might be involved in tissue-specific Notch regulation.

Disruption of the *Mint* gene proved to be lethal during embryogenesis, so the role of Mint *in vivo* was investigated by transferring cells from the fetal liver (the site of fetal haematopoiesis) into lymphocyte-deficient $Rag2^{-/-}$ mice. These mice had a normal ratio of T and B cells — so Mint is not important in the T- versus B-cell lineage choice. However, in the spleen, there were greater numbers of marginal-zone B cells compared with follicular B cells. These results indicate that Mint regulates the decision of precursor B cells to differentiate into marginal-zone or follicular B cells, a checkpoint that had previously been shown by this group to involve Notch–RBP-J signalling.

So Mint, as a repressor of RBP-J, is the first mammalian functional homologue of Hairless. More work is required to fully resolve the molecular and cellular events involved at this decision point. But, tantalizingly, it was observed that Notch2-expressing cells line up along the outer edge of the marginal zone. The authors propose that these could be transitional B cells waiting to have their fate determined by interactions with Notch-ligand-bearing cells, such as dendritic cells.

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References and links

ORIGINAL RESEARCH PAPER Kuroda, K. *et al.* Regulation of marginal zone B cell development by MINT, a suppressor of Notch/RBP-J signalling pathway. *Immunity* **18**, 301–312 (2003)

FURTHER READING Allman, D. *et al.* An invitation to T and more: Notch signalling in lymphopoiesis. *Cell* **109**, S1–S11 (2002)

WEB SITE

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