T-CELL DEVELOPMENT

Committing to the CD4 lineage

The molecular mechanisms that regulate one of the key decisions in T-cell development — the CD4/CD8 lineage choice — have been difficult to identify. Now, in a study published in *Nature*, the transcription factor T-helper-inducing POZ/Krüppel-like factor (Th-POK; also known as cKROX and ZFP76) is characterized as the central regulator of this decision.

Positive selection of a thymocyte occurs if its T-cell receptor (TCR) interacts with a self-peptide–MHC complex. The CD4/CD8 lineage choice occurs concomitantly with this, and it correlates with TCR engagement of self-peptide–MHC class II or class I, respectively. Previous studies of mice with a spontaneous recessive mutation, the helper deficient (HD) mutation, identified a locus that is required for CD4 lineage commitment, because in these mice, MHC-class-II-restricted thymocytes are redirected to the CD8 lineage. So, He *et al.* set out to characterize the molecular defects in HD mice. Initial studies showed that the redirection of MHC-class-II-restricted thymocytes to the CD8 lineage was not the result of either a defect in CD4 expression or inappropriate upregulation of CD8 expression. Similarly, no defects in signalling downstream of the TCR were detected, indicating that the HD mutation affects only T-cell lineage commitment.

Genetic mapping and a bacterial-artificial-chromosome complementation approach were used to identify *Th-pok* as the candidate HD gene. Consistent with this, in HD mice, cDNA encoding Th-POK was shown to have a single nucleotide substitution that resulted in an amino-acid substitution at a position predicted to mediate DNA binding.

In the thymus of wild-type mice, mRNA encoding Th-POK was specifically expressed by CD4 single positive (SP) thymocytes and by MHC-class-II-restricted $CD4^+CD8^{low}$ thymocytes. Overexpression of wild-type Th-POK by bone-marrow cells from HD mice led to the TCR-dependent generation of $CD4^+$ SP thymocytes and an absence of $CD8^+$ SP thymocytes. Further evidence of a crucial role for Th-POK in lineage commitment was provided by the observation that the $CD8^+$ SP thymocyte population found in transgenic mice expressing an MHC-class-I-restricted TCR was absent if the T cells of these mice were engineered to express Th-POK. Instead, these mice had $CD4^+$ SP thymocytes that expressed *Gata3* mRNA (a marker of CD4 lineage commitment) but not perforin mRNA (a marker of CD8 lineage commitment).

This study shows that Th-POK is a crucial regulator of T-cell lineage commitment: during positive selection its expression leads to CD4 lineage commitment, and only in its absence can a cell become committed to the CD8 lineage. Future studies to identify the factors controlled by Th-POK will provide insight into the molecular pathways that determine the CD4/CD8 lineage choice.

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References and links

ORIGINAL RESEARCH PAPER He, X. *et al.* The zinc finger transcription factor *Th-POK* regulates CD4 versus CD8 T-cell lineage commitment. *Nature* **433**, 826–833 (2005)