GENETICS

A little or a lot

PU.1 is a lineage-specific transcription factor that is essential for development of both myeloid and lymphoid cells, and is implicated in leukaemogenesis. There have been many reports of cancer-causing mutations in the coding regions of transcription factors, but now Frank Rosenbauer *et al.* describe the effects of disrupting a *cis*-regulatory element that controls PU.1 expression and tumour suppression.

In mice, PU.1 overexpression leads to erythroleukaemias, whereas loss of PU.1 blocks B-cell and myeloid development. So, different concentrations of PU.1 have important effects on different lineage fate decisions. This control is partially mediated by an upstream regulatory element (URE), a region distal to the gene that encodes PU.1 and is conserved across species.

Rosenbauer *et al.* investigated whether alterations in PU.1 expression levels might lead to cancer by disrupting this URE in mice. In the B cells of these mice, PU.1 expression was reduced, consistent with reports that URE normally acts as an enhancer of transcription in these cells. However, loss of PU.1 expression had different effects on different B-cell subsets. One population of B cells, known as 'B2' cells, disappeared, whereas another population, known as 'B1' cells, increased in number. Interestingly, these B1 cells have previously been shown to be the cell of origin in most cases of chronic lymphocytic leukaemia (CLL), and mice with deletions of the URE went on to develop a B1-lymphoproliferative syndrome with similarities to human CLL.

Disruption of this URE also affected T-cell development. PU.1 downregulation in early thymocytes is normally required for T-cell development. In mutant mice, however, these thymocytes expressed higher than normal levels of PU.1. So, unlike the B-cell precursors, the URE functions as a transcriptional repressor in thymocyte precursors. As a result, mice with URE disruptions also developed aggressive T-cell lymphomas.

The URE is therefore an important regulator of PU.1 concentrations, and its loss has different effects on PU.1 expression in different cell types. How might this occur? The URE contains a consensus binding site for TCF-family proteins — transcription repressor complexes that are converted into activators after binding to β-catenin. So, the URE would act as a repressor of PU.1 expression in the absence of WNT signalling, but increase PU.1 concentrations when WNT signalling is active. Disruption of the URE or any other point in this entire cascade could throw off PU.1 concentrations in B- or T-cell precursors and result in leukaemogenesis.

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References and links

ORIGINAL RESEARCH PAPER Rosenbauer, F. *et al.* Lymphoid cell growth and transformation suppressed by a key regulatory element of the gene encoding PU.1. *Nature Genet.* 27 Nov 2005 (doi: 10.1038/ng1679)