THYMOCYTE DEVELOPMENT

Cytokines have the casting vote

Signals through the T cell receptor (TCR) are crucial for the positive selection of double-positive (DP) thymocytes and for the differentiation of CD4⁺ T cells. Far less is known about how CD8⁺ T cell lineage specification occurs; this study indicates that although TCR signalling sets the stage for the differentiation of CD8⁺ T cells, signalling by cytokines such as interleukin-7 (IL-7) is the deciding factor.

TCR-mediated positive selection converts cytokine-unresponsive DP thymocytes into cytokine-responsive intermediate thymocytes, the differentiation of which into CD4⁺ or CD8⁺ cells was thought to be determined by the duration of TCR signalling. The authors looked at the role of IL-7, the main cytokine to be expressed in the thymus, in this process using mice with a conditional deletion of signal transducer and activator of transcription 5a (*Stat5a*) and *Stat5b* in thymocytes from the DP stage onwards. These mice had normal numbers of CD4⁺ thymocytes but a 50% lower frequency of CD8⁺ thymocytes than wild-type mice. Mice deficient for both STAT5 and STAT6 had 85% fewer CD8⁺ thymocytes, which indicates that in the absence of STAT5, IL-7 might signal through

other STAT molecules. The authors conclude that STAT-mediated cytokine signalling is required for the generation of most, if not all, CD8⁺ thymocytes, which was supported by the total lack of CD8⁺ thymocytes in mice transgenic for the STAT signalling inhibitor suppressor of cytokine signalling 1 (*Socs1*).

In an *in vitro* model of positive selection, the Runt-family transcription factor *RUNX3* — which specifies the CD8⁺ T cell lineage — was expressed only after stimulation with IL-7 and required signalling through STAT5 and/or STAT6. Transgenic expression of *RUNX3* partially restored the generation of CD8⁺ thymocytes in *Socs1*-transgenic (cytokine-unresponsive) mice. These results indicate that *RUNX3* is expressed downstream of cytokine signalling and can induce a CD8⁺ thymocyte fate in the absence of cytokine signalling. However, transgenic expression of *RUNX3* did not fully restore CD8⁺ thymocyte numbers, which shows that cytokine signalling might have other important effects on these cells.

So, can cytokine signalling induce CD8⁺ thymocyte differentiation in the absence of TCR-mediated positive selection? Mice deficient for

the TCR-associated tyrosine kinase *ZAP70* were crossed with *Socs1*-knockout mice transgenic for the IL-7 receptor α -chain to produce mice in which thymocytes were arrested at a pre-selection DP stage, owing to a lack of TCR signalling, but were responsive to IL-7. *In vitro* culture of purified DP thymocytes from these mice with IL-7 or transgenic intrathymic expression of IL-7 *in vivo* resulted in *RUNX3* expression by thymocytes and the differentiation of CD8⁺ T cells expressing markers of functional competence.

These data support a model of CD8⁺ lineage specification that depends on cytokine signalling but for which TCR signalling is dispensable. The authors found that TCR signalling induces the expression of CC-chemokine receptor 7 (*CCR7*) by thymocytes, which promotes their migration from the cortex to the cytokine-rich medulla, where they receive the necessary cytokine stimulation for *RUNX3* expression and differentiation to CD8⁺ T cells.

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ORIGINAL RESEARCH PAPER Park, J.-H. et al. Signaling by intrathymic cytokines, not T cell antigen receptors, specifies CD8 lineage choice and promotes the differentiation of cytotoxic-lineage T cells. *Nature Immunol.* 31 Jan 2010 (doi:10.1038/nri.1840)