T-CELL DEVELOPMENT

Getting the balance right

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URLs

Tcrb http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=21577
Ptcra http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=19208

What determines the balance between effector and regulatory T-cell development in the thymus? The prevailing view is that agonist selection through the T-cell receptor (TCR) on T-cell progenitors is the determining factor in the development of these cells. However, Hayday and colleagues now show that *trans*-conditioning of double-negative (DN; CD4⁺CD8⁻) thymocytes by double-positive (DP; CD4⁺CD8⁺) thymocytes significantly contributes to the differential competence of these early thymic progenitors to develop into T cells with an effector or regulatory phenotype.

During T-cell development, DN thymocytes can give rise to two cell populations: $\gamma\delta$ T cells and DP thymocytes. Previous work by this group has shown that, in addition to being the progenitors for single-positive CD4⁺ or CD8⁺ $\alpha\beta$ T cells, DP thymocytes also 'condition' the differentiation of DN thymocytes in *trans*. The data also indicated that $\gamma\delta$ T cells that were not conditioned in *trans* by DP thymocytes might develop along an alternative pathway.

To further understand

this pathway, the authors examined $\gamma\delta$ T-cell development in TCR- β -chain-deficient (*Tcrb*^{-/-}) mice, which have very few DP thymocytes. $\gamma\delta$ T cells from *Tcrb*^{-/-} mice expressed low levels of pro-inflammatory and cytolytic molecules. Furthermore, culture of effector CD4⁺ T cells with activated splenic $\gamma\delta$ T cells from *Tcrb*^{-/-} mice, but not wild-type mice, suppressed CD4⁺ T-cell expansion *in vitro*, indicating that these $\gamma\delta$ T cells might have regulatory potential.

Forkhead box P3 (FOXP3) is a crucial transcription factor in CD4⁺CD25^{hi} regulatory T cells, but its expression by $\gamma\delta$ T cells has not been reported. In this study a small proportion of $\gamma\delta$ T cells from the spleen or thymus of *Tcrb*^{-/-} mice, but not wild-type mice, expressed FOXP3. In addition, a fraction of $\gamma\delta$ T cells from pre-TCR- α -chain-deficient (*Ptcra*^{-/-}) mice expressed FOXP3, highlighting that the differentiation of $\gamma\delta$ T cells is switched towards an aggregate regulatory phenotype in mice with reduced numbers of DP thymocytes.

Although the pre-TCR α -chain is absent in *Ptcra*^{-/-} mice, some $\alpha\beta$ CD4⁺ T cells still develop in these mice. Interestingly, this pool has a higher percentage of CD25^{hi}FOXP3⁺ T cells (25–30%) than in wild-type mice (2.5–4.5%), indicating that, in the small population of CD4⁺ effector T cells that matures in mice with reduced numbers of DP thymocytes, the ratio of regulatory to effector T cells is increased.

So how do these studies relate to normal thymocyte differentiation? In wild-type mice, two subpopulations of cells in the DN2 stage of development were identified and referred to as DN2 small (DN2S) and DN2 large (DN2L) cells. The DN2S cells, a product of reduced *trans*-conditioning, resembled *Ptcra*^{-/-} DN2 cells, and CD4⁺ T cells derived from these cells expressed higher levels of a panel of regulatory-T-cell-associated genes, including FOXP3, compared with those derived from the DN2L population.

So, in wild-type mice, *trans*-conditioning promotes the expansion of DN2L cells that become conventional DP cells, which mature as single positive effector cells or die by negative selection. By contrast, a small population of cells that receive less *trans*-conditioning (DN2S cells) gain the competence to differentiate into CD25^{hi}FOXP3⁺ regulatory T cells if they encounter cognate self antigen.

Therefore, *trans*-conditioning by DP cells directly affects the ability of thymocytes to develop into effector or regulatory T cells. This study might provide insight into the mechanisms of regulatory T-cell enhancement in certain conditions in which DP cells are depleted, such as pregnancy.

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ORIGINAL RESEARCH PAPER Pennington, D. J. et al. Early events in the thymus affect the balance of effector and regulatory T cells. *Nature* **444**, 1073–1077 (2006)