Innate T-bet

Although of unknown etiology, the autoimmune disease scleroderma results in excessive production of T helper type 2 (T_H2) cytokines. In the *Proceedings of the National Academy of Sciences USA*, Glimcher and coworkers document a protective role for T-bet, a transcription factor that promotes T_H1 immune responses, in scleroderma sensitivity. T-bet–deficient mice are more susceptible to scleroderma induced by bleomycin, a Toll-like receptor 2 agonist; and this increased susceptibility depends on the presence of interleukin 13. However, despite the well established role of T-bet in T cells, T cell–specific overexpression of a transgene encoding T-bet does not enhance scleroderma sensitivity. These data suggest that T-bet works within innate immune cells to suppress scleroderma susceptibility by indirectly or directly controlling interleukin 13 activity. Identification of the signals regulating T-bet activity and scleroderma sensitivity remains for future investigation. ***CB***

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Blimp speed

The transcription factor Blimp-1 is required for plasma cell function in follicular B cells (commonly called B-2 cells) but whether Blimp-1 upregulation plays a similar regulatory role in B-1 or marginal zone B cells is unclear. In the *Journal of Immunology*, Fairfax *et al.* show that B-1 cells express low but detectable amounts of Blimp-1 but do not spontaneously synthesize antibodies. Rather, antibody secretion follows Blimp-1 upregulation upon B-1 cell stimulation. Blimp-1 expression is upregulated more rapidly in B-1 cells than in other B cell subsets. The faster kinetics reflect differences in the abundance of other transcription factors expressed in B-1 cells, including Pax5, Bcl6 and IRF4, as compared with B-2 cells. These data imply that B-1 cells are under similar regulatory constraints for antibody production, but are 'poised' to respond faster to external stimulation. *LAD*

J. Immunol. **178**, 4104–4111 (2007)

Lineage diversion

The transcription factor cKrox is essential for thymocyte commitment to the $CD4^+$ T cell lineage and, when overexpressed, can divert thymocytes expressing major histocompatibility complex (MHC) class I–restricted T cell receptors into the $CD4^+$ T cell lineage. In the *Journal of Experimental Medicine*, Bosselut and colleagues show that ectopic expression of cKrox also alters mature $CD8^+$ T cell lineage identity. $CD8^+$ splenocytes infected with a cKrox-expressing retrovirus contain fewer transcripts encoding perforin, granzyme B and interferon-γ, at least in part owing to cKrox-mediated reduction in expression of the transcription factor Eomes, which activates various $CD8^+$ T cell lineage genes. Overexpression of cKrox also suppresses *Cd8* transcription, but does not trigger CD4 expression. These findings indicate that some features of T cell lineage commitment are 'flexible' whereas others appear to be 'fixed', perhaps by epigenetic modifications introduced during differentiation. ***CB***

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Research notes written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey

Leukemic loss of PAX5

Pax5 enforces the B cell lineage expression program. In *Nature*, Downing and colleagues identify several genetic mutations that contribute to the generation of B-progenitor acute lymphoblastic leukemias (B-ALL) in children. A high frequency of mutations occurs in the *PAX5* locus in these children. Many of these mutations involve loss-of-function gene deletions (especially of exons encoding DNA-binding or transcriptional regulatory domains), reduced expression or the generation of hypomorphic PAX5 alleles, all of which can lead to reduced PAX5 function during B cell development. Expression of the mutant PAX5 proteins in reporter assays confirms this notion of decreased functional activity. The genetic signature from B-ALL cells is consistent with a regulatory network controlled by PAX5 that is perturbed upon leukemic transformation. Alterations in PAX5 dosage or function thus can contribute to development of B-ALL. *LAD*

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Foxp3 actively represses

Expression of forkhead transcription factor FoxP3, characteristic of regulatory T cells (T_{reg} cells), induces and represses many genes required for T_{reg} cell differentiation. In *Proceedings of the National Academy of Sciences USA*, Greene and colleagues find that FoxP3 is acetylated and interacts with the histone acetyltransferase TIP60 and two histone deacetylases, HDAC7 and HDAC9. The proline-rich N-terminal region of FoxP3 is critical for its transcriptional repression activity and for interaction with TIP60, which, like FoxP3, is expressed in human T_{reg} cells; they also find that HDAC7 associates with TIP60 in human T_{reg} cells. 'Knockdown' of endogenous TIP60 prevents FoxP3-mediated transcriptional repression, and the FoxP3-TIP60-HDAC7 complex is required to repress interleukin 2 production in Jurkat T cells. T cell receptor stimulation abrogates FoxP3 interaction with HDAC9, which can be restored by treatment with the HDAC inhibitor trichostatin A. The data suggest dynamic formation of FoxP3-TIP60-HDAC7 and/or FoxP3-HDAC9 complexes regulates transcription in T_{reg} cells. ***DCB***

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Maintaining precursors

Pluripotent blood cell progenitors in *Drosophila melanogaster* proliferate and mature into differentiated immune cells called hematocytes in the lymph gland. In *Nature*, Banerjee and colleagues demonstrate that the posterior signaling center (PSC) of the lymph gland, a region of cells expressing the protein Serrate, a ligand of the transcription factor Notch, is specified early in embryogenesis by the homeotic protein Antennapedia (Antp). PSC cells also express the signaling molecule Hedgehog (Hh), which is required for maintaining undifferentiated hematopoietic cells in the medullary region of the lymph gland. Blocking Hh signaling in the lymph gland or preventing PSC formation by mutating Antp leads to loss of undifferentiated medullary hematopoietic cells, which more rapidly differentiate into mature cells. The data highlight the complex interplay of essential developmental factors that, in the lymph gland, maintain undifferentiated hematopoietic cells so that other differentiation or immune-based signals can stimulate them. *DCB*

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