Strong signal readout

The transcriptional pathways that control the development of γδ T cells remain poorly characterized. In the *EMBO Journal*, Park *et al.* show that the zinc-finger transcription factor Th-POK is induced by T cell antigen receptor (TCR) signaling and promotes the maturation of γδ T cells in the thymus. Mice that lack functional Th-POK have fewer mature γδ thymocytes and, conversely, mice that constitutively express Th-POK during T cell development have many more. The DRE element, which controls the induction of Th-POK in CD4$^+$ T cells, is sufficient to mediate Th-POK transcriptional control in γδ thymocytes. In addition, Th-POK expression is induced in γδ thymocyte subsets (NK1.1$^+$) that recognize ligands with relatively high affinity. This resembles Th-POK induction in αβ thymocytes, in which major histocompatibility complex class II–restricted TCRs transmit stronger signals than do major histocompatibility complex class I–restricted TCRs, and suggests that Th-POK induction is mediated by strong TCR stimuli. *IV*

***EMBO J.* (15 June 2010) doi:10.1038/emboj.2010.113**

Understanding prime-boost

The next generation of vaccines will rely in part on the ability to elicit effective CD8$^+$ T cell memory. However, the immunological parameters required for this remain poorly understood. In the *European Journal of Immunology*, Badovinac and colleagues address these issues through the use of a highly defined prime-boost regimen to determine the effect of primary CD8$^+$ T cell memory on the secondary response. By varying the quality (presence of adjuvant) or quantity of the initial immunization, they control the size and phenotype of the primary memory pool. Remarkably, this has no effect on the subsequent secondary (boost) response, except when the amount of antigen is extremely low in the initial priming. This has important implications for vaccination and suggests that as long as priming is above a certain threshold of stimulation, the boosting phase is the critical parameter for determining efficacy. *ZF*

Eur. J. Immunol. (21 April 2010) doi:10.1002/eji.201040310

Crohn's disease and infection

Much evidence links viral infections to the etiology of particular autoimmune diseases. However, the precise interaction of these external factors with genetic susceptibilities is unclear. In *Cell*, Virgin and colleagues carefully delineate the relationship between Crohn's disease and norovirus, a common enteric pathogen. Mice with targeted disruption of the autophagy gene *Atg16L1*, a known human allele linked to susceptibility to Crohn's disease, show abnormalities of intestinal Paneth cells after norovirus infection. The virus–plus–susceptibility gene interaction alters the transcriptional signature of Paneth cells and makes mice more vulnerable to toxin-induced Crohn's disease. Autoimmune pathology is dependent on both proinflammatory cytokines and the presence of commensal bacteria. This study clarifies how a perfect storm of an environmental 'hit' in the form of specific viral infection and a particular genetic susceptibility can culminate in the manifestation of autoimmune disease. *ZF*

***Cell* (25 June 2010) doi:10.1016/j.cell.2010.05.009**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

One naive cell, multiple fates

How effector or memory T cells differentiate from naive T cell clones remains a subject of intense debate. Alternative models predict that fate decisions are taken before the first division or during the first asymmetric division or are determined by cumulative effects during subsequent division cycles. In the *Journal of Experimental Medicine*, Schumacher and colleagues use thymocytes labeled with unique genetic tags ('bar codes') for large-scale fate mapping of naive T cells at the single-cell level. Their study finds that effector and memory T cells are progeny of the same naive T cell in both systemic and local infection and that this is independent of the anatomical site in which they reside. This applies to T cell responses of different functional avidities and to memory defined as long-term persistence or capacity for secondary expansion. Thus, one naive cell adopts multiple fates. *IV*

J. Exp. Med. **207**, 1235–1246 (2010)

Keeper of T cell identity

It has remained unclear how Notch1 regulates the specification and commitment of the T cell lineage because very few Notch targets are known. In *Science*, L. Li *et al.*, Ikawa *et al.* and P. Li *et al.* identify the transcription factor Bcl-11b as a critical regulator of the transition from double-negative 2a (DN2a) to DN2b, which marks the loss of myeloid and dendritic cell potential and commitment to the T cell lineage. Although Bcl-11b-deficient DN2 cells express genes associated with T cell differentiation, such as *Gata3* and *Tcf7*, they fail to downregulate stem cell–like genes and have higher expression of genes associated with natural killer cells, such as *NKp46*, *Id2* and *E4bp4*. *In vitro* and *in vivo* deletion of Bcl-11b at various stages of T cell development can reprogram T cells into natural killer–like cells. Bcl-11b is shown to be a direct target of Notch signaling, and its expression is controlled by interleukin 7 signaling. *IV*

***Science* 329, 85–89, 89–93 & 93–96 (2010).**

In an emergency, call STAT3

The number of circulating neutrophils is tightly regulated. Infection can trigger the enhanced production and release of neutrophils from the bone marrow by a process called 'emergency granulopoiesis'. Similar mobilization is induced clinically by administration of the cytokine granulocyte colony-stimulating factor (G-CSF). In *Blood*, Zhang *et al.* delineate the conflicting roles assigned to the transcription factor STAT3 in emergency granulopoiesis. STAT3 acts downstream of the G-CSF receptor; however, mice with STAT3-deficient bone marrow show neutrophilia, which suggests that STAT3 acts as a negative inhibitor of neutrophil generation, at least in the steady state, by activating transcription of the signaling inhibitor SOCS3. Thus, how STAT3 signaling can increase neutrophil production remains unknown. STAT3 also controls expression of the transcription factor C/EBPβ. In the steady state, pluripotent Lin$^-$Sca-1$^+$c-kit$^+$ bone marrow progenitors and immature granulocytes express more C/EBPα, a transcription factor related to C/EBPβ that acts to repress cell-cycle genes such as *Myc*. Infection or treatment with G-CSF alters the ratio of C/EBPβ to C/EBFα in a STAT3-dependent way. STAT3 also binds to *Myc* regulatory elements and facilitates C/EBPβ-mediated displacement of the binding of C/EBPα to *Myc*, thereby enhancing c-Myc expression. This circuitry allows for a burst of bone marrow proliferation in response to systemic alarms, to allow more neutrophils. *LAD*

Blood (25 June 2010) doi:10.1182/blood-2009-12-259630