More mature and more promiscuous

Epithelial cells in the thymus teach T cells what to ignore by presenting them with a comprehensive array of tissue-restricted self-antigens (TRAs) during development. According to Derbinski and colleagues on page 33, this promiscuous expression of TRAs—one of the mechanisms behind central T cell tolerance—increases as the epithelial cells mature.

Teaching T cells how to distinguish self-tissues from foreign invaders is essential for the prevention of autoimmune disease. This education process occurs in the thymus and depends on the presentation of a diverse array of self-antigens to developing thymocytes—a function of medullary thymic epithelial cells (mTECs). T cells that recognize these self-antigens are either deleted or become regulatory T cells.

Recent studies have shown that the transcriptional regulator Aire (autoimmune regulator), which is highly expressed in mTECs, drives the expression of many of these TRAs. But not all TRAs depend on Aire, and Aire expression is not limited to mTECs. Thus, the rules that govern the thymic expression of these tightly regulated genes remain largely mysterious.

Derbinski et al. now show that the expression of a majority of TRAs increases as the mTECs differentiate in the thymus, suggesting an intricate link between mTEC maturity and TRA expression. The level of Aire expression mirrored the increase in TRA expression, consistent with the established role of Aire in this process. The authors confirm, however, that Aire does not act alone, as many TRAs are up-regulated in mature mTECs from mice lacking the transcriptional regulator.

How do differentiating mTECs turn on these genes that are normally expressed only in peripheral tissue? The answer is not completely clear, but Derbinski and colleagues show that regulation occurs at many levels. Some TRAs were expressed by transcriptional read-through of genes that are clustered together in a contiguous chromosomal region. Others depended on de-repression of genes normally silenced by genetic imprinting. But exactly how mTEC differentiation triggers these changes in gene expression remains to be determined. JEM

Destructive T cells lured by lipids

T cells that are drawn to the airways by leukotrienes attack lung tissue and contribute to transplant rejection, according to Medoff and colleagues on page 97. Mice lacking the leukotriene receptor BLT1 were protected from lethal T cell attack. The authors thus suggest that drugs designed to block this receptor may have therapeutic potential in patients who develop a lethal complication of lung transplant called obliterative bronchiolitis.

Inflamed tissue, and their corresponding receptors on T cells. However, chemotactic lipid mediators such as leukotrienes and prostaglandins—known for attracting neutrophils and eosinophils—have recently been shown to contribute to T cell recruitment. Early lung invasion by T cells in response to an inhaled allergen was blunted in mice lacking the leukotriene B4 (LTB4) receptor BLT1. But this decrease did not persist, calling into question the significance of leukotriene-induced T cell migration in disease.

Medoff and colleagues now show that BLT1-deficient mice were less likely to develop T cell-mediated airway obstruction following allogeneic tracheal transplantation, demonstrating that leukotriene-induced T cell migration contributes to disease. This finding is consistent with previous studies showing that inhibition of BLT1 signaling was protective in other mouse models of allogeneic transplantation. However, the contribution of T cell trafficking was never evaluated in those models.

Elimination of BLT1 did not completely reverse T cell infiltration into the lung, suggesting that LTB4 does not act alone. The authors suggest that chemokines may also contribute to the T cell recruitment—a possibility they are currently investigating. JEM
Phased by Notch

On page 157, Sarmento and colleagues show how the developmental regulator protein Notch1 advances the cell cycle. Activation of Notch1 induced the production of a protein that chops up cell cycle inhibitors, leading to a shortened G1 phase and a faster transition into S phase (but not overall increase in proliferation).

The Notch family of transmembrane receptors regulates both cell fate decisions and the maintenance of adult stem cells, processes that require precise control of the cell cycle. Although Notch1 activation had previously been shown to alter the cell cycle in hematopoietic progenitor cells and to delay their commitment to the myeloid lineage, a direct link between Notch1 and cell cycle control pathways had not been established in these cells.

Sarmento et al. now find the link and show that constitutive Notch1 activation drives cell cycling by increasing the activity of cyclin-dependent kinase-2 (CDK2), a protein that promotes progression into the S phase of the cell cycle. CDK2 activation resulted from the degradation of the CDK inhibitor protein p27\(^{kip1}\), which was triggered by the Notch1-induced expression of a protein called SKP2—a component of a ubiquitin ligase complex that targets proteins for proteosomal degradation.

How Notch-induced changes in cell cycle kinetics influence differentiation programs is not completely clear. The authors suggest that a shortened G1 phase—during which cells are thought to be most responsive to fate-deciding differentiation signals—may minimize the window of differentiation opportunity and thus help maintain the progenitor cell pool. JEM

Stressed out and asthmatic

The ability to cope with stress may decrease susceptibility to asthma, according to Rangasamy and colleagues on page 47. The absence of the transcription factor Nrf2, which helps cells respond to oxidative stress, exacerbated allergic responses in mice, leading senior author Shyam Biswal to speculate that inducers of the Nrf2 pathway may have therapeutic potential for the treatment of human asthma.

Asthma is a complex disorder that involves the recruitment of inflammatory cells, including eosinophils, to the lungs. Once there, these cells release reactive oxygen species (ROS), which are thought to contribute to lung tissue damage.

Levels of ROS are normally counterbalanced by antioxidants, which are present at lower levels in the airways of asthma patients.

Here, Rangasamy and colleagues investigated the effect of oxidative stress on asthma in mice lacking Nrf2, which induces the expression of many antioxidant genes. They found that the lack of Nrf2 increased influx of cells into the airways, mucus production, airway hypersensitivity, and T helper 2 cytokine production—all characteristic symptoms of asthma—in response to challenge with an inhaled allergen.

Although the mechanisms involved remain largely unknown, the elevated cytokine levels likely resulted from increased activation of NF-κB, which is known to be activated by ROS. They now plan to look for alterations in the Nrf2 gene in asthma-prone humans, as they think defects in this gene might contribute to susceptibility to disease. JEM

Progenitor of all trades

Despite years of research, the identity of the bone marrow progenitor cells that seed the thymus, as well as the place where they ultimately commit to being T cells, have remained elusive. On page 21, Benz and Bleul identify the first multipotent progenitor cell in the adult thymus. The new data suggest that, for at least some progenitor cells, commitment to a T cell fate occurs after arrival in the thymus.

Populations of thymic precursor cells have been shown to generate multiple cell lineages, but it remains a matter of debate whether single precursor cells can give rise to all the possible thymic cell lineages—T cells, B cells, and dendritic cells (DCs).

Benz and Bleul now show that these cell types can indeed arise from a single precursor cell. By fusing EGFP with a marker of T cell development sites (CCR9), they pinpointed a small population of cells in the bone marrow that was able to populate the thymus.

Single-cell sorting of these precursor cells from the thymus revealed that a single cell could generate T cells, B cells and DCs, suggesting that these progenitor cells commit to a T cell fate in the thymus. Thymic cells with the same surface markers but lower levels of EGFP—presumably representing a slightly more mature population of cells (with decaying EGFP)—were no longer able to generate B cells, suggesting that the EGFP\(^{+}\) population marks the branching point of the T and B cell lineages. JEM