Ito cells as APCs

Naive CD8$^+$ T cells can be primed in the liver, but the capacity of various intrahepatic cell types to stimulate T cells is not well understood. In *Immunity*, Kaufmann and colleagues show that hepatic Ito cells can activate many T cell populations. Endogenous antigens presented by Ito cells trigger, in a CD1d- and interleukin 15 (IL-15)–dependent way, homeostatic proliferation of natural killer T cells *in vitro* and *in vivo*. Ito cells also process and present endogenous or bacteria-derived proteins to major histocompatibility complex (MHC) class I– or MHC class II–restricted conventional αβ T cells, resulting in their proliferation, cytokine production and/or cytotoxicity. Intravenous injection of Ito cells loaded with a bacterial antigen induces antigen-specific CD8$^+$ T cell proliferation and protection against subsequent bacterial infection. Whether Ito cells are essential for the homeostasis of liver natural killer T cells and immune defense *in vivo* remains to be determined. ***CB***

***Immunity* 26, 117–129 (2007)**

Dual inhibition

T cell receptor (TCR) signaling activates the calcium-sensitive phosphatase calcineurin, whose activity is required for IL-2 expression and other 'downstream' activation events. In *Nature*, Pan *et al.* identify carabin as a calcineurin inhibitor whose expression is itself induced by TCR signaling. Carabin blocks activation of the transcription factor NFAT by inhibiting dephosphorylation of NFAT by calcineurin. Carabin also inhibits Ras-mediated signaling. Carabin binds to both calcineurin and Ras, albeit through different domains. Carabin has intrinsic GTPase activity that increases the abundance of inactive Ras-GDP. Notably, TCR-induced expression of carabin is blocked by cyclosporin A, suggesting that its expression requires calcineurin and thus that carabin fits the criteria of a true feedback inhibitor. *LAD*

Nature **445**, 433–436 (2007)

'Innate' TSLP effectors

When released from epithelial cells, the cytokine thymic stromal lymphopoietin (TSLP) exacerbates atopic and allergic disease by stimulating dendritic cells to promote T helper type 2 cell differentiation. In the *Journal of Experimental Medicine*, Delespesse and colleagues show that mast cells expressing the TSLP receptor and stimulated with the proinflammatory cytokines IL-1, tumor necrosis factor and TSLP release T helper type 2 cytokines as well, which helps explain why overexpression of TSLP induces allergy even in T cell–deficient mice. The amount of TSLP in skin lesions from patients with atopic dermatitis or in supernatants of human airway epithelial cells exposed to proinflammatory stimuli is sufficient to elicit mast cell activation. The data suggest that TSLP-activated mast cells may be responsible for mediating pathology in cases of immunoglobulin E–independent 'intrinsic' asthma and thus that TSLP may influence the effector activity of other non–T cells. ***CB***

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LAG-ging T cells

Control of T cell proliferation is normally strictly regulated by several mechanisms, including cell-extrinsic factors, such as antigen and growth factor concentration, and cell-intrinsic factors, such as expression of inhibitory molecules like CTLA-4 and LAG-3. In the *EMBO Journal*, Li *et al.* find that cleavage of LAG-3 by metalloproteinases such as ADAM10 and ADAM17 leads to increased T cell proliferation. LAG-3 is highly expressed in activated T cells and natural killer cells and has higher affinity for MHC class II molecules than does CD4. Treatment of wild-type T cells with a metalloproteinase inhibitor increases antigen-induced T cell proliferation; similarly, LAG-3-deficient cells proliferate more. Soluble, cleaved LAG-3 itself does not inhibit T cell proliferation; however, ectopic expression of an uncleavable mutant LAG-3 substantially suppresses T cell proliferation, as does blocking ADAM10 expression by RNA interference. These data indicate that the use of metalloproteinase inhibitors may prevent inflammation by directly countering T cell proliferation. *DCB*

EMBO J. **26**, 494–504 (2007)

CD25 prevents memory

Regulatory T cells (T_{reg} cells) express CD4 and CD25 and require both IL-2 and cell-intrinsic expression of the transcription factor Foxp3 for full development and maintenance of function. In the *Journal of Immunology*, Sharma *et al.* demonstrate that mice deficient in IL-2 and IL-2 receptor-α (IL-2Rα; CD25) or scurfy mice (lacking Foxp3), all of which lack T_{reg} cells, have distinct CD8$^+$ T cell phenotypes. Mice lacking IL-2Rα have many more CD44$^+$CD62L^{hi}CD69^{lo}Ly6C^{hi} central memory-like cells ('mCD8$^+$ cells') in addition to higher serum IL-2 concentrations. Purified mCD8$^+$ cells proliferate more than do wild-type cells *in vitro* in response to recombinant IL-2, consistent with relatively high expression of the low-affinity IL-2R on mCD8$^+$ cells. Adoptive transfer of wild-type T_{reg} cells into IL-2Rα-deficient mice prevents mCD8$^+$ cell development. The data suggest that expression of IL-2Rα provides a required 'sink' for excessive IL-2 that can stimulate mCD8$^+$ cell proliferation. ***DCB***

***J. Immunol.* 178, 1251–1255 (2007)**

Counting stem cells

Inbred mouse strains have heritable differences in the population sizes (total numbers) of bone marrow hematopoietic stem cells (HSCs). In *Nature Genetics*, Van Zant and colleagues identify a gene, *Lxn,* that regulates the population size of HSCs in mice. *Lxn* encodes latexin, which was previously identified as a metalloendopeptidase inhibitor. *Lxn* is expressed more abundantly in HSCs of C57BL/6 mice than in HSCs of DBA/2 mice, which correlates with larger numbers of stem cells in DBA/2 mice. Lentiviral transfection of *Lxn* into bone marrow cells from mice with low expression of *Lxn* causes a reduction in the number of stem cells that develop after transfer of the transduced bone marrow into syngenic recipients. The data suggest that latexin functions as a cell-autonomous negative regulator of HSC numbers. How latexin regulates HSC numbers remains to be determined. *LAD*

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