Coordinated actions

Sphingosine-1-phosphate (S1P) mediates intracellular calcium release in mast cells after the activation of FcεRI receptor. In the *Journal of Experimental Medicine*, Jolly *et al.* show that mast cells can also secrete S1P after being activated. Mast cells have two receptors, $S1P_1$ and $S1P_2$, that initiate chemokine secretion, remodeling of actin skeleton and chemotaxis. Signaling through $S1P_1$ is important for migration toward antigens, whereas $S1P_2$ functions in degranulation. Signaling through $S1P_2$ impairs migration. Because $S1P_1$ is exquisitely sensitive to S1P, and $S1P_2$ is upregulated after antigen cross-linking, it is likely that in physiological conditions, mast cells migrate toward antigen, stop and then degranulate. *PTL*

J. Exp. Med. **199**, 959–970 (2004)

Noncompetitive inhibition

CTLA-4 functions as an inducible inhibitory receptor to dampen T cell responses. CTLA-4 binds with higher affinity to the same B7 molecules as the costimulatory receptor CD28. Thus, increased surface expression of CTLA-4 might be expected to dominate CD28 responses *in vivo*. In *International Immunology*, Yi *et al.* show that cytoplasmic tyrosine residue 201 (Y201) mediates CTLA-4 inhibitory activities. Y201 affects CTLA-4 surface expression and internalization. CTLA-4-deficient mice reconstituted with CTLA-4 mutated to Y201V display increased surface CTLA-4, but still develop lymphoproliferative diseases. Thus CTLA-4 Y201 has additional signaling functions in inhibiting T cell responses. *LAD*

Int. Immunol. **16**, 539–547 (2004)

Adapting mouse liver

In vivo models to study the human immune system are available that make use of immunocompromised mice, but these are limited by their lack of functional immune responses. As reported in *Science*, Manz and colleagues transplanted CD34$^+$ human cord blood into the livers of newborn *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which then developed dendritic cells, B cell and T cells with a diverse repertoire. How human T cells were selected by a mouse thymus is unclear at present, but the mature T cells could distinguish between self and allogeneic major histocompatibility complex. Structured primary and secondary lymphoid organs were formed and functional immune responses against tetanus toxoid and Epstein-Barr virus could be induced. This _in vivo_ model should therefore prove useful for analysis of the human immune system. *JDKW*

***Science* 304, 104–107 (2004)**

Silencing kinetics

Genes associated with antigen receptor diversification can be irreversibly silenced in developing lymphocytes after positive selection. However, the sequence of events that leads to such silencing has remained unclear. In *Nature Genetics*, Su *et al.* show that irreversible silencing of the *Dntt* locus, which encodes mouse terminal transferase, follows a specific temporal order. Histone H3 modifications begin in the promoter region and spread bidirectionally, accompanied by repositioning of the locus pericentromerically in the nucleus. Protein synthesis is not required for deacetylation of H3 lysine 9 (H3-K9) or nuclear repositioning, both early events, but it is required for subsequent H3-K4 demethylation and H3-K9 methylation. Proliferation is not required for these modifications, which supports the idea of the existence of a histone demethylase activity associated with silencing. *LAD*

Nat. Genet. **36**, 502–506 (2004).

Research notes written by Laurie A. Dempsey, Peter T. Lee and Jamie D.K. Wilson.

New interferon-inducible secretoglobin

Interferon-γ (IFN-γ) induces expression of uteroglobin, a member of the secretoglobin (SCGB) superfamily that has anti-inflammatory and immunoregulatory properties. In the *Journal of Immunology*, Choi *et al.* characterize a previously unknown SCGB superfamily gene called IFN-γ-inducible SCGB (IIS). As its name implies, IFN-γ augmented IIS expression in lymphoblastoid cells. Polymorphisms were detected in human genomic DNA samples but the importance of this remains unclear. IIS mRNA was expressed in many tissues, including resting and activated lymphoblasts. Specifically, IIS mRNA was increased notably in activated CD8$^+$ T cells and CD19$^+$ B cells, but not in activated CD4$^+$ T cells. Functional inhibition of IIS using antisense oligonucleotides inhibited chemotactic migration and invasion. Therefore, IIS, like uteroglobin, probably has an immunological function. *JDKW*

J. Immunol. **172**, 4245–4252 (2004)

Regulating virus escape

CD8$^+$ T cells are essential for resolution of acute Friends virus (FV) infection but are ineffective during chronic infection. In *Immunity*, Dittmer *et al.* investigate the cause of T cell dysfunction during persistent FV infection. FV-specific CD8$^+$ T cells expressed activation markers and proliferated, but did not produce IFN-γ or impair viral loads when transferred into chronically infected mice. Cotransfer experiments in which acutely infected mice received FV-specific CD8$^+$ T cells with CD4$^+$ T cells from chronically infected mice diminished the CD8$^+$ T cell response. Treatment of persistently infected mice with antibody to GITR to diminish the suppressive functions of regulatory T cells increased IFN-γ production by CD8$^+$ T cells and reduced viral load. Thus, FV takes advantage of regulatory T cells to escape CD8$^+$ T cells. *JDKW*

Immunity **20**, 293–303 (2004)

Caught in translation

Viral vectors are important tools for the introduction of specific genes into cells. However, commonly used vectors are not ideal carriers for multiple genes because of limitations such as the inability to express equal amounts of multiple proteins and limited cloning capacity because of large promoters. In *Nature Biotechnology*, Szymczak *et al.* overcome these hurdles by using small viral 'self-cleaving' 2A peptides to link and translate multiple genes through a ribosomal skip mechanism. With the use of two such retroviruses, all six chains of the T cell receptor–CD3 complex were efficiently introduced into CD3-deficient mice, resulting in the rescue of T cell development and function. Effective production of multiple proteins from a single vector holds considerable potential for research and therapy. *PTL*

Nat. Biotechnol. **22**, 589–594 (2004)