Tug of war

Precisely how sphingosine 1-phosphate receptor type 1 ($S1P_1$) directs the exit of T cell from lymph nodes is not known. In *Immunity*, Cyster and colleagues demonstrate that $S1P_1$ promotes egress by counteracting retention signals. More *Ccr7*$^{+/-}$ T cells than wild-type T cells depart from lymph nodes, which indicates that the chemokine receptor CCR7 promotes T cell retention. Notably, T cells treated with pertussis toxin, and therefore relieved of chemokine-driven retention signals, show enhanced exit even when rendered unresponsive to $S1P_1$ by pharmacological or genetic means. CCR7 deficiency accelerates but $S1P_1$ deficiency inhibits T cell accumulation in cortical sinusoids in the lymph node T cell zone. Further work is needed to determine if these cortical sinusoids uniquely enable T cell egress and to understand how T cells integrate competing 'stay-versus-go' signals received through CCR7 and $S1P_1$. ***CB***

***Immunity* 28, 122–133 (2008)**

HIV-1 inhibits tetherins

Human immunodeficiency virus type 1 (HIV-1) produces six accessory proteins, most of which are needed to counter antivirus immune responses. In *Nature*, Bieniasz and colleagues determine that one function of HIV viral protein U (Vpu) is to prevent host cell–expressed 'tetherin' from inhibiting virus release. Using a directed strategy to find a functional target of Vpu, including microarray analysis of interferon-α-treated cells and evaluating only membrane-associated or secreted proteins, they have identified CD137, a membrane protein with no known function. Subsequent functional studies, including expression of CD137 in cells that do not normally express it, RNA interference of CD137 mRNA in cells that endogenously express it, and use of Vpu-deficient HIV-1 viruses, show that CD137 is necessary and sufficient for preventing the release of HIV-1 from cells unless Vpu is present. Inhibition of the release of mouse leukemia virus is also impaired when Vpu is present. These data identify CD137, or tetherin, as an essential target of Vpu activity that facilitates the release of HIV-1 particles from infected cells. *DCB*

Nature **451**, 425–430 (2008)

Dangerous connections

Evidence suggests that HIV-1 transmission is accelerated by the formation of virological synapses or filopodia between infected and uninfected cells. In *Nature Cell Biology*, Davis and coworkers add 'nanotubes' to the list of mechanisms capable of facilitating intercellular spread of HIV-1. Unlike membrane channels that link T cells after cell division, nanotubes do not permit unrestricted exchange of ions or proteins between T cells. Blockade of the interaction between host cell CD4 and the HIV-1 protein gp120 prevents spread of the HIV-1 Gag protein from infected to uninfected T cells connected by nanotubes, which suggests the existence of a receptor-dependent gating mechanism. Further work is needed to measure the effect of the formation of T cell nanotubes on the spread of HIV-1 *in vivo*. ***CB***

***Nat. Cell. Biol.* 10, 211–219 (2008)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Regulating adhesiveness

Inflammation activates endothelial cells to show proadhesive properties, including upregulation of the adhesion molecule VCAM-1. In the *Proceedings of the National Academy of Science*, Harris *et al.* report that VCAM-1 transcripts are *in vivo* targets of the microRNA miR-126. Resting endothelial cells express miR-126, which suppresses VCAM-1 expression by binding to its 3′ untranslated region. Modulation of miR-126 abundance by the use of antisense constructs or by overexpression of the precursor premiR-126 decreases or increases, respectively, TNF-dependent VCAM-1 expression. The half-life of the VCAM-1 transcripts is not altered by miR-126; instead, miR-126 negatively regulates VCAM-1 expression by blocking its translation. Likewise, recruitment of leukocytes to inflamed endothelial cell layers increases after dampening of miR-126 expression. How miR-126 itself is regulated by cytokine treatment is unknown. *LAD*

Proc. Natl. Acad. Sci. USA **105**, 1516–1521 (2008)

Extralymphoid T cell activation

Activation of lymphocytes by dendritic cells is thought to be a phenomenon that occurs mostly if not entirely in secondary lymphoid organs. In *Science*, Carbone and colleagues evaluate the extent to which $CD8^+$ T cell activation can occur in extralymphoid tissue, specifically in dorsal root ganglia (DRG) after herpes simplex virus (HSV) infection. With surgical removal of DRG from infected mice followed by transplantation of the tissue under the kidney capsules of recipient mice, activation of DRG-resident $CD8^+$ cells can be monitored after reactivation of latent HSV. Using a thymidine kinase–mutant HSV that fails to reactivate, and transfer of DRG into recipients deficient in the recombination-activating gene product, the authors show that DRG-resident $CD8^+$ cells proliferate in an antigen-specific way in response to reactivating virus and that DRG-resident $CD4^+$ T cells are required for this proliferation. The antigen-presenting cell is a monocyte-derived inflammatory dendritic cell that migrates to DRG during inflammation. These data show that extralymphoid tissue can be an effective site of lymphocyte activation. ***DCB***

***Science* 319, 198–202 (2008)**

Discriminating cytokines

The type II–polarizing cytokines interleukin 4 (IL-4) and IL-13 use common receptors yet can elicit different functional responses. In *Cell*, Garcia and colleagues examine ternary complexes of cytokines with their type I (γ_c–containing) receptors and type II (IL-13Rα–containing) receptors to determine the structural properties underlying ligand signaling specificity. For this, they have generated crystals of IL-4–IL-4Rα–γ_c, IL-4–IL-4Rα–IL-13Rα and IL-13–IL-4Rα–IL-13Rα. Both IL-4 and IL-13 nestle in a groove formed between the coreceptor subunits. Although IL-13Rα resembles γ_c, it ha an amino-terminal immunoglobulin-like extension that directly contacts the 'top' of the cytokine; hydrophobic interactions of this domain with IL-13 contribute substantially to the overall binding strength, but interactions with IL-4 do not. Each receptor-cytokine complex has distinct kinetic and thermodynamic assembly properties. IL-4 initially binds to IL-4Rα with high affinity and recruits either γ_c or IL-13Rα into the signaling-competent complex. Conversely, IL-13 binds IL-13Rα, followed by recruitment of IL-4Rα. Functionally, these interactions underlie the differences in cytokine signaling potencies and 'downstream' activation of STAT transcription factors. *LAD*

Cell **132**, 259–272 (2008)