HIV-1 enters via endosomes

Because the envelope glycoprotein of human immunodeficiency virus type 1 (HIV-1) promotes fusion with target cells at a neutral pH, it is assumed that HIV-1 fusion occurs at the cell surface. However, in *Cell*, Melikyan and co-workers provide evidence that HIV-1 fusion actually occurs in endosomes. Ongoing HIV-1 fusion is more rapidly inhibited by a shift to low temperature than by the addition of a membrane-impermeant fusion inhibitor, which suggests that fusion occurs slowly and in an intracellular location. In support of this idea, there is a time delay between the dispersion of viral lipids into the plasma membrane and subsequent expulsion of viral contents into the cell cytoplasm. Content release occurs coincident with or just after an increase in viral velocity—a sign of uptake into the cell—and several inhibitors of dynamin block viral fusion and infection. Thus, whereas HIV-1 undergoes hemifusion with the plasma membrane, complete fusion occurs later, after viral uptake. *CB*

***Cell* 137, 433–444 (2009)**

Mast cell inflammasome

Urticarial rash in patients with cyropyrin-associated periodic syndrome (CAPS) that have mutations in the gene encoding the Nod-like receptor family NLRP3 constitutively produces interleukin-1β (IL-1β). In the *Journal of Experimental Medicine*, Nakamura *et al.* identify the cells in the skin that are responsible for causing the urticarial rash associated with CAPS. They find that the skin of CAPS patients contains resident mast cells that constitutively produce mature IL-1β. Secretion of IL-1β by mouse mast cells is critically dependent on the NLRP3 inflammasome. Expression of mouse NLRP3 mutants in a mast cell line results in constitutive production of IL-1β *in vitro*, and transfer into mouse skin leads to neutrophil-rich inflammation and vascular leakage *in vivo*. It remains unclear why CAPS-associated NLRP3 mutants can constitutively produce IL-1β in mast cells in the absence of the microbial stimuli that are a known requirement for inflammasome activation. *JDKW*

J. Exp. Med. (13 April 2009) doi:10.1084/jem.20082179

HIV-1-specific NK cell responses

The function of natural killer (NK) cells in maternal-infant HIV-1 transmission has not been investigated. In the *Journal of Immunology*, Tiemessen *et al.* analyze a cohort of HIV-1-infected mothers and their infants to investigate immune correlates of protection against HIV-1. Unexpectedly, they find that $CD3^-$ HIV-1-specific responses to envelope and regulatory peptides is strongly associated with a lack of maternal-infant HIV-1 transmission. They show that these $CD3^-$ cells are NK cells using a range of criteria, including expression of NKp46, an NK cell receptor present on all NK cells. These HIV-specific NK responses require the presence of human plasma, which explains why previous studies using isolated mononuclear cells failed to detect such immune correlates in HIV-1 infection. How NK cells recognize HIV-1-specific peptides is yet to be elucidated. *JDKW*

***J. Immunol.* 182, 5914–5918 (2009)**

Written by Christine Borowski, Laurie A. Dempsey & Jamie D.K. Wilson

Border security

The endothelial and parenchymal basement membranes that underlie central nervous system blood vessels contribute to the restriction of leukocyte entry across the blood-brain barrier. In *Nature Medicine*, Sorokin and colleagues report that laminin α5 blocks laminin α4–integrin $\alpha_6\beta_1$ signaling interactions and thereby decreases the extravasation of T cells into brain tissues in a mouse model of experimental autoimmune encephalomyelitis. Mice that lack laminin α4 but express laminin α5, both components of post-venule capillary basement membranes, have less-severe experimental autoimmune encephalomyelitis despite mounting normal immune responses in other peripheral tissues. Previous work has reported T cell extravasation at laminin α4–rich sites in the brain but little or no transmigration in regions where laminin α4 and laminin α5 colocalize. Data from *in vitro* assays suggest that laminin α5 actively blocks integrin $\alpha_6\beta_1$–mediated transmigration of T cells across laminin α4 matrices in a dose-dependent way. The mechanistic details that underlie this functional difference between laminin α4 and laminin α5 remain unknown. *LAD*

Nat. Med. (26 April 2009) doi:10.1038/nm.1957

Regulation by Itk

The Tec family tyrosine kinase Itk mediates signaling 'downstream' of the T cell antigen receptor and is necessary for αβ thymocyte development and the ability of naive αβ T cells to express type 2 cytokines. In the *Proceedings of the National Academy of Science*, Felices *et al.* show that Itk negatively regulates γδ T cell development and function. Itk-deficient mice have more γδ T cells in their thymus, spleen, liver and mesenteric lymph nodes but no difference in intestinal intraepithelial γδ T cell numbers relative to those in wild-type mice. Much of this increase is due to more $V_\gamma1.1^+V_\delta6.3^+$ $CD4^+$ or $NK1.1^+$ 'unconventional' γδ T cells. Unlike Itk-deficient αβ T cells, γδ T cell lacking Itk express the transcription factors GATA-3 and PLZF. Likewise, these Itk-deficient γδ T cells have high expression of IL-4 mRNA and rapidly secrete IL-4 and IL-13 after T cell antigen receptor stimulation. These findings help to explain the previously confounding phenotype of Itk-deficient mice, which have higher titers of immunoglobulin E and heightened allergic reactions. *LAD*

***Proc. Natl. Acad. Sci. USA* (1 May 2009) doi:10.1073/pnas.0808459106**

Turning on Pax5

The transcription factor Pax5 is responsible for activating and suppressing B lineage and non–B lineage genes, respectively. In *Immunity*, Busslinger and colleagues identify promoter and enhancer elements that direct B cell lineage–specific expression of Pax5. A bacterial artificial chromosome transgene lacking intron 5 of the *Pax5* locus shows minimal expression in developing and mature B cells. B cell–specific hypersensitivity sites exist in intron 5 and in the promoter of *Pax5*. Together, these hypersensitivity regions of the promoter and intron 5 enhancer are sufficient to recapitulate Pax5 expression in the B cell lineage. EBF1 binds to one hypersensitivity site in the promoter, and hypersensitivity sites in the promoter but not in intron 5 bear repressive chromatin marks in $Ebf1^{-/-}$ progenitors. PU.1, IRF4 and IRF8 bind one hypersensitivity site in intron 5 in pro–B cells and mature B cells, and NF-κB binds this site exclusively in mature B cells. Thus, B cell–specific Pax5 expression is orchestrated by stepwise activation of two distinct *cis*-regulatory elements. *CB*

Immunity **30**, 508-520 (2009)