Responding to injured membranes

Certain cellular insults trigger calcium-dependent lysosomal exocytosis, whereby lysosomes fuse with the plasma membrane to release their internal contents. Membrane-bound synaptotagmins (Syts) are key in the transduction of this calcium signal. In *Science*, Roy *et al.* show that SytVII on lysosomes senses membrane damage inflicted by intracellular pathogenic bacteria such as salmonella. Calcium was required to trigger phagolysosomal fusion, as was an intact bacterial secretion system, which induces membrane pores and calcium influx. Lysosome fusion with bacteria-laden phagosomes was blocked in SytVII-deficient cells. Hence, the SytVII system is an innate intracellular defense against intracellular pathogens. *LAD*

Science **304**, 1515–1518 (2004)

Pull to activate

Transforming growth factor-β (TGF-β) is a pleiotropic cytokine that is synthesized as a complex with latency-associated peptide (LAP) and latent TGF-β-binding protein (LTBP). This latent complex needs to be activated by triggers such as integrin $\alpha_v\beta_6$ before signaling through its receptor. In the *Journal of Cell Biology*, Annes *et al.* show that activation by $\alpha_v\beta_6$ requires LTBP to anchor to the extracellular matrix (ECM). The action of LTBP is isoform specific, in which a unique 'hinge domain' in LTBP-1 targets the ECM. The authors hypothesized that this anchoring of the latent complex to the ECM promotes focal adhesion and allows $\alpha_v\beta_6$ to pull against the LAP, resulting in the release and activation of TGF-β. This process serves to regulate the activity of TGF-β. ***PTL***

***J. Cell Biol.* 165, 723–734 (2004)**

Defining fly recognition

Gram-negative bacteria in drosophila stimulate antimicrobial peptide production via the IMD pathway. The components of Gram-negative bacteria that are recognized by the receptor PGRP-LC to activate the IMD pathway remain controversial. In *Immunity*, Silverman and colleagues show that monomeric and polymeric Gram-negative peptidoglycan, but not purified lipopolysaccharide, could stimulate the IMD pathway. PGRP-LC recognition required the stem peptide residue diaminopimelic acid, found in peptidoglycan from Gram-negative bacteria. RNAi 'knockdown' of PGRP-LC splice variants showed that although polymeric Gram-negative peptidoglycan is recognized by PGRP-LCx, monomeric peptidoglycan recognition requires both PGRP-LCx and PGRP-LCa. This suggests that PGRP-LCx and PGRP-LCa may function as a heterodimer for monomeric peptidoglycan recognition. Whether a mammalian equivalent of drosophila PGRP-LC exists is unclear. *JDKW*

Immunity **20**, 637–649 (2004)

Looking for *Francisella tularensis*

Francisella tularensis is the causal agent of tularemia, a highly virulent and often fatal zoonotic disease that has come under recent scrutiny because of its potential as a bioterrorism agent. Yet little is known about the infectious cycle that *F. tularensis* uses *in vivo*. In *Infection and Immunity*, Clemens *et al.* find *F. tularensis* in human macrophages at various times after infection. *F. tularensis* alters host phagosomal maturation by resisting acidification and lysosomal fusion by undefined mechanisms. Infected phagosomes accumulate densely staining cytoplasmic coats before vacuole fragmentation and bacterial release into the cytoplasm. These findings suggest potential vaccines should target major histocompatibility complex class I presentation pathways. *LAD*

Infect. Immun. **72**, 3204–3217 (2004)

Inflammasome cues

Macrophages release interleukin 1β (IL-1β) and IL-18 in response to inflammation and intracellular pathogens. Both cytokines are synthesized as inactive precursors that must be cleaved by caspase-1 to liberate bioactive molecules. In *Nature*, Dixit and colleagues show the inflammasome adaptors ASC and Ipaf have different functions linking caspase-1 activation to inflammatory stimuli. Lipopolysaccharide (LPS)-activated macrophages from ASC-deficient mice cannot activate caspase-1 and thus cannot release IL-1β or IL-18. ASC-deficient mice also survived lethal doses of LPS. In contrast, Ipaf-deficient macrophages could activate caspase-1 and secrete IL-1β in response to LPS. However, Ipaf was required for caspase-1 activation in response to intracellular salmonella infection. Future work should sort out the functions of these inflammosome adaptors in natural infection models. *LAD*

Nature (9 June 2004) doi:10.1038/nature02664

More antiretroviral factors

Many human cells carry an innate resistance to HIV-1, mediated by APOBEC3G. This member of the cytodine deaminase family is packaged into HIV-1 virions and inhibits the infectivity of the virus. HIV-1 produces the Vif protein, which can bind to APOBEC3G in the cytoplasm, thereby sequestering it and allowing productive virion generation. Cullen and colleagues in the *EMBO Journal* and Peterlin and colleagues in the *Journal of Virology* now describe another member of the APOBEC3 family, APOBEC3F, that has antiretroviral activity. HIV-1, however, successfully uses Vif to intercept and inhibit APOBEC3F, just as it restrains APOBEC3G. Thus, HIV-1 Vif has evolved to bind and inactivate multiple host targets. *JDKW*

J. Virol. **78**, 6073–6076 (2004) & *EMBO J.* (20 May 2004) doi: 10.1038/sj.emboj.7600246

The suppressive group

The function of CD1d-restricted natural killer T (NKT) cells has been enigmatic because of their seemingly conflicting abilities to enhance some immune responses yet suppress autoimmunity. In particular, how NKT cells regulate autoimmunity remains unclear. In the *Journal of Immunology*, Ho *et al.* separate human NKT cells into $CD4^+CD8^-$, $CD4^-CD8^+$ and $CD4^-CD8^-$ subsets and show that the $CD4^-CD8^+$ subset suppresses proliferation of antigen-activated T cells. These NKT cells do not act directly on the T cells but instead seem to limit antigen-specific T cell proliferation by killing CD1d-expressing antigen-presenting cells. $CD4^-CD8^+$ NKT cells show delayed proliferation after activation, suggesting that this subpopulation of cells may act to limit immune responses. *PTL*

J. Immunol. **172**, 7350–7358 (2004)

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