Multi-talented PKC

PKCθ is required for the activation of mature T cells and for interleukin 2 (IL-2) production through AP-1 and NF-κB stimulation. During T cell activation, PKCθ is selectively recruited to the immunological synapse (IS), a process mediated by a phospholipase C (PLC)- and diacylglycerol (DAG)-independent pathway. In the *Journal of Experimental Medicine*, Baier and colleagues generated PKCθ-deficient mice to further analyze the physiological function of this kinase. Consistent with previous findings, proliferation and IL-2 production by PKCθ-deficient T cells was abrogated. Unexpectedly, PKCθ was found to be essential for antigen-receptor-induced calcium signaling and subsequent NFATp and NFATc transactivation. Because PLCγ1initiates calcium mobilization, these data indicate that PKCθ is also essential upstream of PLCγ1 in TCR-induced NFAT activation. *JDKW*

J. Exp. Med. **197**, 1525–1535 (2003)

Critical NOS

Cystic fibrosis (CF) patients are highly susceptible to virus infections. In *Immunity*, Zheng *et al.* investigate why CF airway epithelial cells are less effective at eliminating parainfluenza virus infection. Increased proinflammatory cytokine (IL-6 and IL-8) production, which aggravates the severity of virus infections, was associated with increased virus replication in CF cells. These cells also showed defective induction of 2′,5′-oligoadenylate synthetase and nitric oxide synthase 2 (NOS2), components of the innate immune response. Conversely, NOS2 overexpression protected CF cells from virus infection. NOS2 deficiency was due to impaired STAT1 activation. Thus, NOS2 is sufficient for antiviral host defense of human airway epithelial cells and its absence explains the susceptibility of CF patients to respiratory virus infections. *JDKW*

Immunity **18**, 619–630 (2003)

Good death, bad death?

Influenza A virus infection can induce apoptosis both *in vitro* and *in vivo*, but whether this is beneficial for virus replication or for the host immune response remains controversial. In *The EMBO Journal*, Ludwig and colleagues inactivated caspase 3, a central player in the apoptotic signaling machinery, using inhibitors or RNA interference. Caspase 3 inactivation strongly impaired efficient influenza virus propagation. Conversely, overexpression of procaspase 3 boosted virus production in caspase 3–sufficient cell lines and restored replication in caspase 3–deficient cells that normally replicate influenza virus poorly. In caspase 'knockdown' cells, export of virus ribonucleoprotein complexes from the nucleus to the cytoplasm was blocked, preventing virus assembly. Thus, influenza-induced apoptosis seems essential for efficient virus replication. *JDKW*

EMBO J. **22**, 2717–2728 (2003)

Surveyor of bugs

Although MHC class I–restricted $CD8^+$T cells are important in defense against mycobacterial infection, they function inefficiently because mycobacteria have developed evasion mechanisms that disrupt peptide presentation pathways in host cells. In *The Journal of Immunology*, Kawashima *et al.* show that MHC-independent $CD8^+$ T cells dominate the response against live *Mycobacterium bovis* bacillus Calmette-Guérin (BCG). The specificity of the $CD8^+$ T cells' restriction element was shown by the ability of antibodies to CD1a, CD1b and CD1c, but not MHC, to block the $CD8^+$ T cell response to BCG. These $CD8^+$ T cells preferentially respond to live rather than dead BCG. Thus, CD1-restricted $CD8^+$ T cells that recognize lipids presented by a distinct pathway may be important in monitoring live mycobacterial infection. *PL*

J. Immunol. **170**, 5345–5348 (2003)

Notch again

Notch genes are expressed during most stages of B cell development. Although Notch1-deficient mice show normal B cell lymphopoiesis, RBP-J conditional knockout mice have defects in marginal zone B (MZB) cell development. In *Immunity*, Saito *et al.* generated Notch2 conditional knockout mice to determine if this receptor is responsible for MZB cell differentiation. Mature B cells preferentially expressed *Notch2* and mice with *Notch2*$^{-/-}$ B cells virtually lacked MZB cells and their presumed precursors, $CD1d^{hi}$ T2 B cells. Development of other B cell lineages was normal. Expression of *Deltex1*, a signal modulator and downstream target of Notch, mirrored *Notch2* expression in mature B cells, indicating that Notch2 tightly regulates *Deltex1* expression. These data therefore indicate that Notch2 controls MZB cell development by interacting with RBP-J and Deltex1. *JDKW*

Immunity **18**, 675–685 (2003)

MIF receptor

Macrophage migration inhibitory factor (MIF) is a T cell–derived protein that promotes macrophage activation and is associated with inflammation and autoimmunity. Despite its broad-ranging action, the receptor for MIF is unknown. In *The Journal of Experimental Medicine*, Leng *et al.* identifies CD74, the surface form of MHC class II–associated invariant chain, as the cell surface MIF-binding protein. MIF stimulates the phosphorylation of Erk1and Erk2 in wild-type but not in CD74-deficient macrophages. Blocking of CD74 prevents MIF-induced proliferation of the human Raji B cell line and primary murine fibroblasts. Although a previous report showed that MIF may be internalized and bind directly to transcription factors, the current data indicate that CD74 may be an additional pathway for MIF-mediated function. *PL*

J. Exp. Med. **11**, 1467–1476 (2003)

SH3–SLP-76 connection

Efficient response of an immune cell requires the controlled association of several signaling molecules through adaptors that contain the Src homology 2 (SH2) or SH3 domains. To gain a better understanding of SH3 domain interactions, Harkiolaki *et al.* in the *EMBO Journal* solved the crystal structure of a complex between the C-terminal SH3 of a signaling protein, Mona, and an important T cell adaptor, SLP-76. The structure shows an unusual binding configuration of the SLP-76 peptide, which forms a clamp around the barrel-like SH3 domain. Additional electrostatic and hydrophobic interactions with the SH3 epitopes result in high-affinity binding. In addition, the structure allowed the prediction and testing of an ion-dependent dimerization process in solution, which seems to be Zn^{2+}-mediated, thus further enhancing our understanding of the mechanism of action of signaling molecules. *PL*

EMBO J. **22**, 2571–2582 (2003)