EnAbling TCR signaling

The functions of the nonreceptor tyrosine kinases c-Abl and Arg are unclear, but involvement in the immune system is suggested by the phenotype of c-Abl-deficient mice, which have immune-related defects. In *Current Biology*, Zipfel *et al.* now show that both kinases are critical for T cell receptor (TCR) signaling. Activation of Abl kinases after TCR stimulation is dependent on Lck but not Zap70. Phosphorylation of Zap70 at Y319 and Zap70's subsequent phosphorylation of the adaptor LAT required Abl kinase activity. Deficiency of both kinases impaired binding of phospholipase Cγ to LAT, interleukin 2 production and T cell proliferation. These data therefore show Abl kinases are involved in regulating key molecules in the TCR signaling pathway. *JDKW*
Curr. Biol. **14**, 1222–1231 (2004)

Regulating latency

Some bacteria and parasites persist in their hosts after apparent control of the disease and may reactivate in suitable conditions. The mechanism of this break in latency is unclear. In the *Journal of Experimental Medicine*, Mendez *et al.* observe that mice chronically infected with *Leishmania major* reactivate the disease at the primary site of infection when challenged with parasites at a distal secondary site. The reactivation correlates with an increase in $CD4^+CD25^+$ T (T_R) cells. Transfer of T_R cells alone from infected mice is sufficient to reactivate the disease in chronically infected mice. In contrast, depletion of $CD25^+$ cells prevents reactivation. Thus, a balance between effector and T_R cells determines effective control of the disease. *PTL*
J. Exp. Med. **200**, 201–210 (2004)

Making DC subsets

The transcriptional events controlling dendritic cell (DC) differentiation and function are not well defined. In *Immunity*, Szatmari *et al.* found the lipid-activated transcription factor peroxisome proliferator activated receptor-γ (PPAR-γ) promotes the development of a specific DC subtype. PPAR-γ is upregulated early during DC differentiation and enhances the endocytic activity of immature DCs. Agonists of PPAR-γ downregulate group 1 CD1 molecules but, interestingly, induce upregulation of CD1d, a group II CD1 molecule linked to natural killer T (NKT) cell activation. PPAR-γ activation consistently enhanced NKT cell proliferation induced by αGalCer-pulsed DCs. Thus, the transcription factor PPAR-γ promotes the development of a DC subset with an enhanced ability to induce NKT cell population expansion. *JDKW*
Immunity **21**, 95–106 (2004)

Chemotaxing to different PI3Ks

Lymphocytes transit throughout the body and in lymphoid tissues by following chemokine gradients. Ligands bind to chemokine receptors and trigger the activation of phosphoinositide-3 kinase (PI3K), and high local concentrations of phosphatidylinositol-3,4,5-triphosphate are then generated at the leading edge of migrating cells. In the *Journal of Immunology*, Reif *et al.* find that T cells and B cells rely on different PI3K isoforms to respond to chemokine signals, despite expressing both forms. Loss of PI3K p110γ led to inefficient T cell migration, but did not affect B cell responses to chemokines. Conversely, B cell migration and homing to secondary lymphoid tissues was reduced when PI3K p100δ expression was abolished, especially in response to the chemokine CXCL13. Such differential usage of PI3Ks might fine-tune chemotactic responses to multiple chemokine signals. *LAD*
J. Immunol. **173**, 2236–2240 (2004)

Written by Laurie A. Dempsey, Peter T. Lee and Jamie D.K. Wilson.

Driving the transcytosis highway

Polarized epithelial cells convey polymeric immunoglobulin A (pIgA) through the cell from basolateral surfaces and release it into the lumen as secretory IgA. Transport begins with binding of pIgA to the polymeric immunoglobulin receptor (pIgR), but how pIgR traffic navigates in the cell is not clear. In *Nature Cell Biology*, Mostov and colleagues show that pIgR binds to the retromer, a multiprotein complex that directs intracellular vesicle sorting and delivers pIgR and its cargo to the apical surface. Transcytosis requires only a subset of the retromer proteins: Vps35, Vps26 and Vps29. Vps35 binds to the C terminus of pIgR. Altering expression of Vps35 in cells led to coordinated changes in Vps26 and Vps29 expression and in pIgR-IgA transport efficiency. Hence, the retromer guides intracellular transport of IgA. *LAD*
Nat. Cell Biol. **6**, 763–769 (2004)

Beneficial attraction

Idiopathic pulmonary fibrosis is usually a fatal lung disease characterized by continual fibrosis progression after tissue injury. Because the chemokine receptor CXCR3 is important in mediating the pathogenesis of several diseases, Jiang *et al.* investigated its involvement in tissue injury and repair. They report in the *Journal of Clinical Investigations* that it has a nonredundant function in limiting tissue fibroproliferation: CXCR3-deficient mice are more susceptible to bleomycin-induced injuries, showing progressive fibrosis. Recruitment of $CD8^+$ T cells and NK cells during injury is reduced in CXCR3-deficient mice. This reduction results in decreased interferon-γ (IFN-γ) expression in the lungs, which is important in limiting tissue fibrosis. Thus, exogenous IFN-γ reverses the fibrotic phenotype, whereas neutralizing IFN-γ enhances lung injury due to fibrosis. Transfer of wild-type cells restores IFN-γ production and reverses the fibrosis in CXCR3-deficient mice. *PTL*
J. Clin. Invest. **114**, 291–299 (2004)

More than just a bug sensor

Because commensal bacteria in the gut express the same molecular patterns as pathogenic bacteria that trigger Toll-like receptors (TLRs), the gut epithelium is thought to provide the barrier that prevents unnecessary triggering of these receptors. However, Rakoff-Nahoum *et al.* report in *Cell* that triggering of TLRs occurs and is necessary for maintaining homeostasis of the intestine. Mice that are deficient in MyD88, an essential TLR adaptor molecule, are particularly vulnerable to injuries of the gut mucosa. Normal signaling through TLRs induces the production of tissue protective factors such as interleukin 6, tumor necrosis factor and heat-shock proteins. Mice depleted of commensal bacteria are susceptible to mucosal injuries, whereas protection can be restored with TLR ligands. This finding demonstrates an unexpected function for TLRs in tissue homeostasis. *PTL*
***Cell* 118, 229–241 (2004)**