Detour to T_H1

When released from activated dendritic cells (DCs), interleukin 12 (IL-12) induces the production of interferon-γ (IFN-γ) and the initiation of T helper type 1 (T_H1) responses. In the *Journal of Experimental Medicine*, Nussenzweig and coworkers investigate the molecular basis of the T_H1 responses of IL-12–deficient mice. Neutralization of IL-12 squelches the $CD4^+$ T cell production of IFN-γ elicited *in vitro* by $CD8\alpha^+$ but not $CD8\alpha^-$ DCs. Toll-like receptor (TLR) stimulation induces expression of the Notch ligand DL4 on $CD8\alpha^-$ but not $CD8\alpha^+$ DCs. Blocking Notch-DL4 interactions or interrupting TLR signaling ablates the T_H1 differentiation induced *in vitro* by $CD8\alpha^-$ DCs and prevents the appearance of IFN-γ–producing $CD4^+$ T cells in IL-12–deficient but not wild-type mice. These findings emphasizing a 'division of labor' among DC subsets and delineating distinct yet redundant pathways leading to T_H1 responses might clarify existing controversial data on the function of Notch in T helper cell differentiation. ***CB***

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TAB connections

Signaling by transforming growth factor-β activates transcription factor NF-κB and inhibits caspase function via X-linked inhibitor of apoptosis (XIAP). In *Molecular Cell*, Lu *et al.* demonstrate molecular interactions of XIAP with the adaptor TAB1 leading to activation of TAK1 kinase and subsequently NF-κB. XIAP contains three conserved protein domains (BIR domains); two of these are associated with antiapoptotic activity, yet no function has been ascribed to BIR1 so far. Lu *et al.* now show that the BIR1 domain binds directly to TAB1. Mutants of either protein that disrupt this binding surface inhibit 'downstream' activation of NF-κB. To trigger this pathway, BIR1 must form homodimers and thereby draw the TAB1-associated kinase into proximity for activation. How transforming growth factor-β signals trigger the formation of BIR1 dimers remains to be determined. *LAD*

Mol. Cell **26**, 689–702 (2007)

Qualitative CD4 responses

Eliciting effective T cell responses to pathogens by vaccination remains a difficult challenge. In *Nature Medicine*, Seder and colleagues evaluate various vaccination strategies against *Leishmania major* in terms of the quality of $CD4^+$ T cell responses produced by each. They find that protection against challenge by leishmania is best achieved after subcutaneous vaccination with relatively low-dose adenovirus expressing the leishmania protein MML or with recombinant MML plus CpG, or live *L. major*. These three vaccination conditions elicit the highest frequency of $CD4^+$ T cells that also simultaneously express the effector cytokines IFN-γ, IL-2 and tumor necrosis factor. The number of $CD4^+$ T cells produced after vaccination multiplied by the mean fluorescence intensity of a given effector cytokine provides an immune correlate of protection called the 'integrated mean fluorescence intensity'. These findings should be useful for improving the design of vaccines aimed at producing protective T cell responses. ***DCB***

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

Delineating PDK1 functions

Thymocyte development requires phosphoinositide-dependent kinase 1 (PDK1), which phosphorylates multiple serine kinases in response to Notch signals. In the *EMBO Journal*, Cantrell and colleagues show that activation of PDK1 by the pre–T cell receptor and Notch upregulates the expression of amino acid and transferrin transporters, thereby modulating the growth properties of thymocytes. PDK1-deficient thymocytes fail to increase expression of nutrient transporters, but a PDK1 mutant that can phosphorylate protein kinase B but not other PDK1 substrates restores expression of these transporters and promotes the differentiation of double-negative thymocytes. Yet thymocytes expressing this PDK1 mutant fail to proliferate, suggesting that other 'downstream' kinases activated by PDK1 are necessary for thymocyte proliferation. Pharmacological inhibition of the PDK1 target kinase RSK blunts thymocyte proliferation in response to Notch, suggesting that this kinase is responsible. PDK1 therefore coordinates the activation of 'downstream' kinases during thymocyte development. *LAD*

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Antioxidative DCs

During infection, neutrophils and mononuclear phagocytes produce copious reactive oxygen species through NADPH oxidase activity. In the *Journal of Immunology*, Hellstrand and colleagues find that human myeloid DCs (mDCs) can protect natural killer cells and T cells from oxidative damage during inflammation and subsequent apoptosis. Incubation of natural killer cells and T cells with mononuclear phagocytes or with hydrogen peroxide results in lymphocyte apoptosis. However, if mDCs differentiated *in vitro* are added, the lymphocytes remain viable. There is no difference in the protection mediated by immature and mature mDCs. The authors find that lymphocyte protection requires catalase activity by mDCs; in addition, the mDCs have relatively high expression of oxidant-protective surface thiols such as glutamate, which are also upregulated on lymphocytes incubated with mDCs. These data explain how lymphocytes are protected from the oxidative damage associated with inflamed tissues. ***DCB***

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Gene-specific adaptation

After secondary encounter with the TLR4 ligand lipopolysaccharide (LPS), macrophages previously exposed to LPS show blunted induction of genes encoding proinflammatory mediators. In *Nature*, Medzhitov and colleagues demonstrate that this LPS 'tolerance' suppresses only a fraction of LPS-inducible genes. Primary LPS exposure results in the deposition of activating chromatin 'marks' on histones in genes that can and cannot be tolerized. However, mRNA and proteins produced after primary LPS stimulation mediate the selective removal of such 'marks' from the histones of genes that can be tolerized and promote the maintenance of such modifications on the histones of genes that cannot be tolerized. Genes that can be tolerized include many with the potential to inflict tissue damage, whereas genes that cannot, whose expression is actually amplified after secondary LPS exposure, include those essential for the maintenance of antimicrobial defenses. These findings emphasize a gene-specific mode of adaptation enforced by epigenetic modifications. The molecular 'code' responsible for the gene-specific targeting of chromatin-modifying enzymes remains to be identified. *CB*

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