Runx3 reactivates *Cd8*

$CD4^+CD8^+$ double-positive (DP) thymocytes undergo positive selection, which triggers transient downregulation of CD8 expression, before becoming either $CD4^+$ or $CD8^+$ single-positive (SP) cells. Yet the molecular details of *Cd8* re-expression have remained unknown. In *Immunity*, Sato *et al.* identify the transcription factor Runx3 as a key participant in the activation of *Cd8* expression in the intermediate $CD4^+CD8^{lo}$ positively selected population. Runx3 proteins specifically bind to *Cd8* regulatory elements, and binding correlates with gene activation and commitment to $CD8^+$ SP cells. Dominant negative Runx3 expression blocks $CD8^+$ SP development. Runx proteins therefore enforce $CD8^+$ fate decisions by silencing *Cd4* (as shown before) and by upregulating *Cd8*. *LAD*
Immunity **22**, 317–328 (2005)

Dissecting NF-κB activation

T cell receptor (TCR)–induced activation of the transcription factor NF-κB requires recruitment of the PKC-θ–IKK and Bcl-10–CARD11–MALT signaling complexes to lipid rafts. In *Science*, Ghosh and colleagues elucidate how these events are controlled. RNA interference–mediated 'knockdown' of the kinase PDK-1 reduces phosphorylation and recruitment of PKC-θ to lipid rafts. This defect substantially diminishes recruitment of the IKK complex to the rafts. PDK-1 'knockdown cells' are also deficient in the recruitment of CARD11, which hampers the movement of Bcl-10–MALT1 to rafts when stimulated through the TCR. Thus, PDK-1 seems to have an essential nucleating function linking the TCR to two signaling cassettes, PKC-θ–IKK and Bcl-10–CARD11–MALT, thereby promoting activation of NF-κB. *JDKW*
Science **308**, 114–118 (2005)

Making much of IRF-7

Induction of type I interferon (IFN-α/β) in response to virus infection can be mediated by a systemic MyD88-independent or Toll-like receptor (TLR)–MyD88–dependent pathway. In *Nature*, Taniguchi and colleagues investigate the importance of the transcription factor IRF-7 in the induction of IFN-α/β by these two pathways. Virus-mediated MyD88-independent IFN-α/β induction is considerably impaired in IRF7-deficient fibroblasts. This pathway is important for innate antiviral defense, as IRF-7-deficient mice are more susceptible to virus infections than are MyD88-deficient mice. IRF7-deficient plasmacytoid dendritic cells (pDCs) also show defective IFN-α/β induction by the TLR9-MyD88-dependent pathway, which is essential for the induction of $CD8^+$T cell responses. These data therefore show that IRF-7 is a 'master regulator' of IFN-α/β-dependent innate and adaptive immune responses. *JDKW*
Nature (23 March 2005) doi:10.1038/nature03507

Stressing Ikaros

Ikaros transcription factors are essential in developing lymphocytes. Alternative splicing generates various Ikaros isoforms that can either repress or activate gene expression by recruiting chromatin-remodeling complexes. In the *Journal of Clinical Investigation*, Ezzat *et al.* show that Ikaros is expressed in pituitary cells, where it regulates expression of the immunomodulatory hormone adrenocorticotrophic hormone. Loss of Ikaros function leads to defects in pituitary corticomelanotroph survival and reduced serum corticosterone concentrations. Bone marrow transfer does not rescue these defects. Thus, Ikaros further intertwines the homeostatic relationship between the nervous and immune systems. *LAD*
J. Clin. Invest. **115**, 1021–1029 (2005)

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

Foxp3 for the rest of us

Foxp3 seems to be essential for the development of regulatory T cells. However, it may also be important in the function of other cells, as shown by the manifestation of severe autoimmune disease by Foxp3-deficient mice. In the *Proceedings of the National Academy of Sciences USA*, Bettelli *et al.* show that Foxp3 suppresses the secretion of cytokines by activated $CD4^+$ T cells. Foxp3 physically associates with and thus acts as a specific transcriptional corepressor of the transcription factors NFAT and NF-κB. Stimulation of Foxp3-deficient cells leads to a notable increase in NF-AT and NF-κB activities compared with that of wild-type cells, whereas overexpression of Foxp3 in autoreactive T cells limits their effector functions substantially. Thus, Foxp3 is important in regulating normal T cell function. *PTL*
Proc. Natl. Acad. Sci. USA **102**, 5138–5143 (2005)

Cautionary tales for siRNA

A convenient method for reducing gene expression is the use of small interfering RNA (siRNA). These small duplex RNAs typically fail to activate cellular sensors that elicit antiviral responses. In *Nature Medicine*, Hornung *et al.* report that specific siRNAs elicit immunostimulatory activity when transfected into pDCs. A specific nonamer induces type I IFN expression by pDCs (but not by other myeloid cells) *in vitro* and also *in vivo* when administered to mice. IFN-α expression is independent of TLR3 and TLR9 but is not induced in TLR7-deficient cells or mice. Hence, pDCs have a TLR7-dependent sensor that recognizes short RNAs that might signal danger. Further work is needed to clarify how this sensor operates. *LAD*
Nat. Med. **11**, 263–270 (2005)

Deceiving TIR

The TLR family of molecules are important sensors of pathogens. This information is conveyed into the cell via molecules containing Toll–interleukin 1 receptor (TIR) domain. In the *Journal of Experimental Medicine*, Stack *et al.* find that a vaccinia virus protein, A46R, also contains the TIR domain and disrupts TLR signaling by interacting with cellular TIR domain–containing molecules. Ectopic expression of A46R prevents interleukin 1–induced activation of the kinases Jnk and Erk as well as NF-κB. A46R interacts with the TLR adaptor protein MyD88, resulting in the disruption of responses to a range of TLR ligands. A46R also interacts with other TIR molecules such as TLR4, Mal, TRAM and TRIF, hence affecting both the MyD88-dependent and MyD88-indpendent pathways. Thus, vaccinia virus may use A46R to evade innate immunity. *PTL*
J. Exp. Med. **201**, 1007–1018 (2005)