Message from ROS

Previous work has indicated that reactive oxygen species (ROS) can function as signaling molecules at physiologically moderate concentrations. In *Nature*, Owusu-Ansah *et al.* show that ROS intrinsically control the differentiation of multipotent hematopoietic progenitors in drosophila. Disruption of genes involved in the generation or scavenging of ROS shows that higher ROS concentrations sensitize progenitors to differentiate into all three mature blood cell types in drosophila. In response to ROS-induced Jnk kinase signaling, activation of the transcription factor Foxo leads to generation of plasmatocytes and crystal cells, whereas repression of Polycomb activity induces lamellocyte differentiation. ROS expression is higher in mammalian common lymphoid progenitors, which are functionally similar to drosophila progenitors, than it is in hematopoietic stem cells, and higher ROS concentrations drive myeloid differentiation. This reflects a notable developmental conservation of the messenger role of ROS. ***IV***
***Nature*, 461, 537–541 (2009)**

One goes up, one comes down

In contrast to expression of the co-receptor CD8, which decreases during positive selection, it is unclear if CD4 expression changes during positive selection and how such changes might affect lineage choice. In *Immunity*, Sarafora *et al.* show that CD4 upregulation on thymocytes signaled by MHC class II is essential for error-free lineage choice. Upregulation of CD4 expression during the differentiation of $CD4^+CD8^+$ thymocytes is the result of increased *Cd4* transcription and is associated with lack of induction of the nuclear factor Runx3 but does not correlate with CD4 signal strength. In contrast to endogenous *Cd4*, CD4 transgenes under the control of various promoters fail to facilitate upregulation of CD4 surface expression and result in error-prone MHC class II–specific lineage choice, a situation exacerbated in T cell antigen receptor (TCR)-transgenic mice, in which thymocytes compete for a single selecting ligand. This observation refines the kinetic model of positive selection. *IV*
Immunity, **31**, 480–490 (2009)

Antimicrobial autophagy

Vitamin D3 and autophagy promote eradication of *Mycobacterium tuberculosis*, and vitamin D3 induces expression of the antimicrobial protein cathelicidin. In *Cell Host & Microbe*, Jo and colleagues link vitamin D3, cathelicidin and autophagy in a pathway leading to *M. tuberculosis* elimination. In line with data indicating that vitamin D3 induces autophagy in cancer cell lines, vitamin D3 triggers autophagy as well as fusion of autophagosomes and lysosomes in human monocytes. Cathelicidin facilitates these effects by activating the transcription factor C/EBPβ and the kinases Erk1, Erk2 and p38, which are needed for expression of the autophagy components beclin-1 and ATG5. Cathelicidin also localizes to autophagosomes. Cathelicidin-specific siRNA and autophagy inhibitors impair the ability of physiological concentrations of vitamin D3 to suppress the growth of *M. tuberculosis*. Precisely how cathelicidin orchestrates this complex set of vitamin D3 effector mechanisms remains unclear. ***CB***
***Cell Host & Microbe* 6, 231–243 (2009)**

Written by Christine Borowski, Laurie A. Dempsey & Ioana Visan

Modifying cytokine mRNA stability

The DNA polymerase β–like nucleotidyltransferase Zcchc11 interacts with adaptor proteins and influences Toll-like receptor–driven cytokine production. In *Nature Cell Biology*, Mizgerd and co-workers find that Zcchc11 also alters the stability of cytokine mRNA. Zcchc11-specific siRNA diminishes the stability and poly(A) tail length of mRNAs encoding some cytokines (including interleukin 6 (IL-6)) in human and mouse epithelial cell lines stimulated with tumor necrosis factor or *Escherichia coli*. Although Zcchc11 catalyzes the template-independent addition of UTP moieties to RNA, Zcchc11 does not directly uridylate the 3′ untranslated region of IL-6 mRNA. Instead, Zcchc11 seems to facilitate IL-6 expression at least in part by uridylating and thereby suppressing the activity of the miR-26 family of microRNAs, which binds to the IL-6 mRNA 3′ untranslated region and silences IL-6 expression. The mechanisms that control Zcchc11 activity and the full spectrum of miRNAs modified by Zcchc11 remain to be determined. *CB*
Nat. Cell. Biol. **11**, 1157–1163 (2009)

Wrestling with inflammation

Excessive inflammation can lead to tissue pathology and disease, especially in the brain. In *Molecular Cell*, Lee *et al.* show that the nuclear receptors LXRα and LXRβ inhibit the DNA-binding activity of the transcription factor STAT1 in interferon-γ-stimulated astrocytes. After ligand binding and nuclear translocation, these receptors are covalently modified by sumoylation by the SUMO E3 ligases PIAS1 and HDAC4. Sumoylation allows the formation of LXRα–PIAS1–phosphorylated STAT1 and LXRβ-HDAC4–phosphorylated STAT1 trimeric complexes and lowers the expression of STAT1 target genes. Activation of this LXR-SUMO–dependent pathway diminishes astrocyte expression of tumor necrosis factor and IL-6, whereas siRNA knockdown of HDAC4 or PIAS1 or inhibition of either LXRα or LXRβ blunts this inhibitory response. These results suggest brain inflammation can be dampened by sumoylation of LXRs, but further work is needed to determine if this process is triggered in more physiological scenarios and whether generation of endogenous LXR ligands occurs in response to inflammation. ***LAD***
***Mol. Cell* 35, 806–817 (2009)**

TCR tunes survival

Experiments in lymphopenic mice indicate that the survival of naive peripheral $CD8^+$ T cells requires common γ-chain cytokine signals as well as tonic signals induced by the interaction of TCRs with self peptide–MHC class I complexes. In the *Journal of Experimental Medicine*, Takada and Jameson revisit the requirement for TCR–self peptide–MHC class I interactions for the survival of naive $CD8^+$ T cells in experiments using lymphocyte-replete mice. The authors use bone marrow chimeras to avoid rejection of donor T cells by the small $CD8^+$ T cell populations present in $H\text{-}2K^b$–$H\text{-}2D^b$–deficient recipients. $H\text{-}2K^b$–$H\text{-}2D^b$–deficient $CD8^+$ donor cells survive longer in wild-type recipients than in $H\text{-}2K^b$–$H\text{-}2D^b$–deficient recipients. $CD8^+$ T cells in $H\text{-}2K^b$–$H\text{-}2D^b$–deficient recipients express less IL-7 receptor-α and CD5, but more CD8, and they are more sensitive to weak TCR agonists than are $CD8^+$ T cells in wild-type recipients. Thus, T cells deprived of self peptide–MHC class seem to 'tune up' co-receptor expression at the expense of pro-survival cytokine receptors. *LAD*
J. Exp. Med. (14 September 2009) doi:10.1084/jem.20082553