Lamprey diversification

Adaptive immunity mediated via the generation of antigen-specific receptors by genomic recombinatorial mechanisms is a property unique to jawed vertebrates. In *Science*, Alder *et al.* now show lampreys also generate a highly diverse antigen receptor repertoire by extensive somatic recombination. Lampreys, a jawless fish, shuffle multiple gene cassettes into the locus encoding their single expressed variable lymphocyte receptor (VLR). These cassettes, which flank the expressed *VLR* gene, encode leucine-rich repeat modules. Nucleotide sequence analysis of a large panel of expressed *VLR* genes indicates that positive selection acts on this locus to produce antigen-specific receptors after challenge. Specific VLRs can be selectively expressed, as demonstrated by an increase in activated lymphocytes and serum titers of antigen-specific VLRs after immunization of lampreys. Although the mechanism of rearrangement and exact number of cassettes used to 'template' *VLR* recombination remain unknown, the findings suggest lampreys can elicit adaptive immune responses. ***LAD***
***Science* 310, 1970–1973 (2005)**

Sensing calcium

Adult hematopoiesis occurs in the bone marrow. How hematopoietic stem cells (HSCs) recognize and engraft in this unique niche remains unclear. In *Nature*, Scadden and colleagues demonstrate that detection of extracellular calcium is key. HSCs express a calcium-sensing G protein receptor (CaR). Mice deficient in this protein have defective bone marrow environments (with few HSCs) and die as neonates. The HSC defect is cell autonomous, as CaR-deficient HSCs show a competitive disadvantage when cotransplanted with wild-type HSCs into irradiated mice. Although CaR-deficient HSCs are capable of generating multiple blood cell lineages, these cells fail to engraft in bone marrow endosteal niches, which are regions with high extracellular calcium concentrations. Similarly, CaR-deficient cells show defective adhesion to collagen I that is also expressed in this environment. These data demonstrate that CaR signals somehow mediate recognition of the bone marrow niche. *LAD*
Nature (28 December 2005) doi:10.1038/nature04247

Innate tumor signals

The activating receptor NKG2D is expressed by natural killer (NK) T cells, $\gamma\delta^+$ T cells, some $CD8^+$ T cells and all NK cells. The ligands for NKG2D include the family of Rae-1 proteins, which many tumors express, thus leading to NK cell–mediated antitumor activity. In the *Journal of Immunology*, Nausch and colleagues show that regulation of Rae-1ε occurs via the AP-1 transcription factor subunit JunB. Surface expression of Rae-1ε (but not Rae-1α, β, γ or δ) is greatly enhanced in *Junb*$^{-/-}$ cells; wild-type expression of Rae-1ε is restored after retrovirus transduction of the cells with JunB; Rae-1 expression is enhanced in an *in vivo* model of inflammation using mice lacking JunB in skin and lymphocytes; and *Junb*$^{-/-}$ mouse embryonic fibroblasts are targets of NK cell lysis. Thus, the specific loss of JunB may be important for the induction of ligands such as Rae-1ε that trigger the innate response mediated by natural killer cells. ***DCB***
***J. Immunol.* 176, 7–11 (2006)**

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

Helpful HLA-G

Certain maternal killer cell immunoglobulin-like receptor (KIR) and fetal HLA gene combinations that favor NK cell activation reduce susceptibility to preeclampsia, a pregnancy disorder characterized by insufficient blood flow to the developing fetus. In *PLoS Biology*, Long and colleagues identify soluble HLA-G, low plasma concentrations of which have been linked to increased frequency of preeclampsia, as a potential activator of uterine NK cells. Activation occurs via KIR2DL4-mediated endocytosis of soluble HLA-G. Unlike other NK cell receptors such as CD16 or CD244 that require crosslinking for activation, soluble antibodies and Fab fragments activate KIR2DL4. Although it has low expression on resting human NK cells, KIR2DL4 is rapidly internalized into endosomal compartments. KIR2DL4-mediated internalization of soluble HLA-G induces the secretion of proinflammatory and proangiogenic cytokines and chemokines from resting human NK cells. Such NK cell–derived proangiogenic cytokines might promote the vascular remodeling that is essential to ensure adequate fetal blood supply. *CB*
PLoS Biology (27 December 2005) doi:10.1371/journal.pbio.0040009

T_{reg} cells need LAT

The linker for activation of T cells (LAT) is a critical adaptor molecule that binds 'downstream' signaling molecules, including Grb2, Gads and PLC-γ1. Normal T cell development and signaling requires LAT. In the *Journal of Experimental Medicine*, Koonpaew and colleagues find that LAT is also essential for expression of the forkhead transcription factor FoxP3 and, thus, for the development of $CD4^+CD25^+$ regulatory T cells (T_{reg} cells). A published LAT^{Y136F} 'knock-in' mouse in which LAT does not bind PLC-γ1 is shown here to have autoimmune disease partly because of the lack of $FoxP3^+$ T_{reg} cells in the periphery. Adoptive transfer of wild-type T_{reg} cells into the LAT^{Y136F} mice alleviates the autoimmune disease, and the transferred T_{reg} cells control endogenous $CD4^+$ T cell expansion by expressing granzymes A and B and transforming growth factor-β. Thus, the LAT–PLC-γ1 interaction is critical for $FoxP3^+$ T_{reg} cell function. ***DCB***
***J. Exp. Med.* (27 December 2005) 10.1084/jem.20050903**

Stopping the silence

Human histone deacetylases (HDACs), some of which (HDAC1–HDAC3 and HDAC8) are ubiquitously expressed, maintain 'transcriptional silence' by removing acetyl groups from histone lysine residues. Yet, even in the presence of HDACs, many proinflammatory stimuli induce rapid gene transcription mediated by transcription factor NF-κB. In *EMBO Reports*, Van Dyke and colleagues demonstrate inhibitor of NF-κB kinase 2 (IKK2)–mediated HDAC protein depletion as one mechanism that might contribute to the rapid gene expression triggered by tumor necrosis factor (TNF), interleukin 1β and lipopolysaccharide. In breast carcinoma cells, TNF-induced depletion of nuclear HDAC1 protein is sensitive to inhibitors of proteasome and IKK activity, and nuclear HDAC1 depletion occurs in wild-type but not IKK-deficient mouse embryonic fibroblasts. TNF treatment results in an absence of HDAC1 and an increase in histone H3 acetylation at the promoter of *Cdkn1a*. Whether HDAC depletion contributes to proinflammatory gene expression *in vivo* and if depletion occurs in response to IKK-independent proinflammatory signaling pathways remain to be determined. *CB*
EMBO Reports (23 December 2005) doi:10.1038/sj.embor.7400613