Forcing HSC development

In several vertebrate species, the production of hematopoietic stem cells (HSCs) in the aorta-gonads-mesonephros region of embryos starts just after initiation of the heartbeat and blood circulation. In *Cell* and *Nature*, teams led by Daley and Zon show that biomechanical force associated with blood flow induces, via nitric oxide (NO), differentiation of HSCs in mice and zebrafish. Shear stress of a magnitude similar to that in the aorta-gonads-mesonephros region of mouse embryos induces expression of Runx1 and c-Myb—transcription factors needed for HSC function—in mouse embryonic hematopoietic precursors. Inhibitors of blood flow suppress HSC development in zebrafish. NO is essential for shear stress–induced formation of HSCs, and injection of an NO donor 'rescues' defective HSC development in mutant zebrafish lacking a heartbeat. NO synthase enzymes promote HSC development in a cell-autonomous way. Whether NO-mediated alterations in Notch and/or Wnt signaling influence HSC differentiation remains to be seen. ***CB***

***Nature* (13 May 2009) doi:10.1038/nature08073 & *Cell* 137, 736–748 (2009)**

Targeting TRIM25

The NS1 protein of influenza virus blocks host interferon production. In *Cell Host & Microbe*, García-Sastre and colleagues show that NS1 binds to the ubiquitin ligase TRIM25, preventing its oligomerization and ability to ubiquitinylate the caspase-recruitment domain of the viral sensor RIG-I. Cells infected with wild-type influenza virus do not assemble competent RIG-I signaling complexes and fail to activate the transcription factor IRF3, which explains their defective interferon expression. Overexpression of TRIM25 overcomes this defect. NS1 interacts with the coiled-coil domain of TRIM25, which is distinct from its SPRY and E3 ligase domains required for RIG-I interaction. Substitution of amino acids Glu96 and Glu97 of NS1 prevents the binding of TRIM25 and likewise abolishes the viral anti-interferon response. Mice challenged with similar viral doses survive infection with E96AE97A virus but die after infection with wild-type virus. The findings elucidate how influenza virus has adapted to avoid innate immune responses. *LAD*

Cell Host Microbe **5**, 439–449 (2009)

IL-21 provides a helping hand

Robust antiviral $CD8^+$ T cell responses require help from $CD4^+$ T cells throughout chronic infection. In *Science*, two groups led by Brooks and Zajac show that interleukin 21 (IL-21) mediates such help during chronic viral infection. Deficiency in IL-21 or its receptor (IL-21R) results in lower frequency and effector function of antiviral $CD8^+$ T cells during chronic infection with lymphocytic choriomeningitis virus (LCMV). Bone marrow chimeras made with $Il21r^{+/+}$ and $Il21r^{-/-}$ donor cells show that IL-21 acts directly to promote and sustain the $CD8^+$ T cell response during chronic LCMV infection. It is unclear at present whether IL-21 is an essential component of $CD4^+$ T cell help in other chronic viral infections. ***JDKW***

***Science* (7 May 2009) doi:10.1126/science.1174182 & doi:10.1126/science.1175194**

Written by Christine Borowski, Laurie A. Dempsey & Jamie D.K. Wilson

Fatty acids lead to memory

The molecular pathways that underlie memory development remain unclear. In *Nature*, Pearce *et al.* show that fatty acid metabolism triggered by the AMP-activated kinase (AMPK) pathway is crucial for $CD8^+$ T cell memory. Mice lacking expression of the adaptor protein TRAF6 in $CD8^+$ T cells do not develop memory cells, despite mounting a normal robust primary effector cell response. During the contraction phase, TRAF6-deficient $CD8^+$ T cells fail to upregulate enzymes involved in mitochondrial fatty acid oxidation, a necessary switch from glycolytic metabolism after IL-2 withdrawal. Metformin, which increases AMPK activation, leads to increases in memory $CD8^+$ T cell numbers in both wild-type and TRAF6-deficient mutants after primary infection. These memory $CD8^+$ T cells are functional, as metformin-treated mice can readily reject tumors after rechallenge. What remains unclear, however, is how TRAF6 leads to activation of AMPK and how 'upstream' signals trigger this pathway. *LAD*

Nature (3 June 2009) doi:10.1038/nature08097

Benefits for host and virus

$P58^{IPK}$, a cellular inhibitor of the kinase PKR, is thought to benefit influenza virus by maintaining a high rate of viral mRNA translation. In *PLoS Pathogens*, Goodman *et al.* unexpectedly show that $P58^{IPK}$ deficiency is detrimental to the host during influenza infection. $P58^{IPK}$-deficient mice infected with influenza virus show greater lung pathology. Gene-expression analysis shows that loss of $P58^{IPK}$ results in higher expression of genes encoding inflammatory, immune-response and apoptosis-related molecules during early influenza infection. Consistent with that, virus-infected $P58^{IPK}$-deficient mice also have more proinflammatory cytokines IL-6 and interferon-β at the protein level. $P58^{IPK}$-deficient mice infected with a reconstructed 1918 pandemic influenza virus also show an amplified inflammatory response. These data suggest that $P58^{IPK}$ represents a new class of molecule that not only benefits the virus but also is needed to limit the host innate immune response. ***JDKW***

***PLoS Pathog.* (22 May 2009) doi:10.1371/journal.ppat.1000438**

One is better than two

Small subsets (1–8%) of human and mouse peripheral T cells express two surface T cell antigen receptors (TCRs), each with a distinct TCRα chain. In the *Journal of Immunology*, Morris and Allen show that these 'dual-TCR' cells contribute disproportionately to alloreactive T cell responses in mice. T cell populations that proliferate in allogeneic mixed-lymphocyte reactions (and thus can be classified as alloreactive) have a higher percentage of cells expressing two TCRs than do undivided T cell populations. Splenocytes from mice unable to express two distinct TCRα chains in a single cell have a much lower frequency of alloreactive T cells. Peripheral T cell populations from mice that receive allogeneic bone marrow cells and splenocytes, and that suffer from graft-versus-host disease, have a higher proportion of dual-TCR cells than do those from recipients of syngeneic cells. The extent to which dual-TCR cells contribute to graft-versus-host disease in humans remains unclear. *CB*

J. Immunol. **82**, 6639–6643 (2009)