

Persistent thymic output

Maintenance of CD8⁺ T cell responses during chronic infection is thought to be antigen dependent, whereas maintenance of memory CD8⁺ T cells after acute infection is not. In the *Journal of Experimental Medicine*, Lukacher and colleagues find that during chronic infection, naive CD8⁺ T cells are continuously recruited from the thymus and are primed by persisting antigen. Such newly primed CD8⁺ T cells, which can be generated long after the resolution of acute infection, have differences in cell surface markers and are defective in homeostatic proliferation compared with CD8⁺ T cells primed earlier in the course of infection. Chronic infection thus produces a heterogeneous CD8⁺ T cell population that includes both newly primed and older memory T cells. The production of such heterogeneous CD8⁺ T cells may occur in other situations with persistent antigen, such as cancer. **DCB**
J. Exp. Med. (11 September 2006) doi:10.1084/jem.20060995

Understanding Jnk

Experiments with fibroblasts deficient in the kinase Jnk1 or Jnk2 suggest that Jnk1 is a positive regulator whereas Jnk2 is a negative regulator of the transcription factor c-Jun. However, kinase assays indicate that both can activate c-Jun. In *Molecular Cell*, Davis and colleagues alter the Jnk2 ATP-binding pocket, rendering Jnk2 susceptible to chemical inhibition, to investigate that discrepancy. Analysis of fibroblasts expressing the mutant Jnk2 in the presence or absence of Jnk1 shows that the kinases are redundant in their ability to upregulate and phosphorylate c-Jun. Why is there a difference between conventional Jnk2-knockout fibroblasts and fibroblasts expressing this Jnk2 mutant? Only conventional Jnk2-knockout cells, which completely lack Jnk2 protein, show a compensatory gain of Jnk1 function. These data emphasize the advantages of chemical genetic approaches, which allow ablation of protein function without altering protein amount. **CB**
Mol Cell. 23, 899–911 (2006)

Blocking complement

Complement activation triggers inflammatory responses against invading organisms. However, many inflammatory diseases also arise from persistent complement activation or dysregulation. In *Nature Biotechnology*, MacKay and coworkers use humanized C5a receptor (C5aR) 'knock-in' mice to generate a panel of antagonistic monoclonal antibody (mAb) reagents that, in addition to their therapeutic potential, provide new insights into C5aR activation. Unexpectedly, human C5aR is fully functional in C5aR-deficient mice. Epitope mapping of the most potent C5aR mAbs demonstrates binding to the second extracellular loop of C5aR, specifically to the hexapeptide EEYFPP. Alteration of that motif produces constitutively active C5aR, suggesting structural changes after ligand binding regulate the activity of this receptor. Administration of the blocking C5aR mAbs in the K/BxN mouse model of arthritis prevents disease after serum transfer, thereby demonstrating the efficacy of targeting C5aR in an inflammatory autoimmune disease. **LAD**
Nat. Biotechnol. (17 September 2006) doi:10.1038/nbt1248

Degrading chemokines

Certain strains of *Streptococcus pyogenes* cause a rapid, necrotizing, 'man-eating' bacterial disease with high mortality. Infected tissues have a high bacterial burden but fail to recruit infiltrating leukocytes. In the *EMBO Journal*, Hidalgo-Grass *et al.* use a bioinformatics approach to identify streptococcal chemokine protease (ScpC), which is responsible for the degradation of host CXC chemokines such as IL-8, thereby 'silencing' the innate immune response to the invading pathogen. ScpC is responsible for the highly virulent phenotype of *S. pyogenes*, as mutants lacking ScpC fail to cleave IL-8 and cannot elicit tissue destruction in infected mice. Thus, this work identifies a key bacterial target for therapeutic intervention. **LAD**
EMBO J. 25, 4628–4637 (2006)

Specific deficiency

Four of five adults are infected with herpes simplex virus 1 (HSV-1), but for unknown reasons only a few develop HSV-1 encephalitis (HSE). In *Science*, Casanova and colleagues demonstrate that susceptibility to HSE is inherited as an autosomal recessive mutation in a single gene. Like cells from mice lacking the endoplasmic reticulum protein UNC-93B, cells from patients with HSE have impaired production of interferon- α (IFN- α), IFN- β and IFN- λ after stimulation with agonists of Toll-like receptor 3 (TLR3), TLR7, TLR8 or TLR9, but normal interferon production after TLR4 stimulation. The patients with HSE are found to be homozygous for mutations in *UNC93B1*. Fibroblasts from these patients cannot control HSV-1 replication and frequently undergo cytolysis, but those defects are 'rescued' after provision of recombinant IFN- α . These data emphasize a potential new therapy for HSE. Also, because patients with HSE resist other viral infections, these results expand the realm of primary immunodeficiency beyond disorders that predispose to infection with multiple pathogens. **CB**
Science (14 September 2006) doi:10.1126/science.1128346

Improving transplantation

Preserving graft-versus-tumor activity without the appearance of graft-versus-host disease (GVHD) is the goal of allogeneic stem cell transplantation. In *Blood*, Caligiuri and colleagues evaluate the effect of abrogating interleukin 15 (IL-15) production and *trans* presentation by donor bone marrow-derived cells in the clinically relevant C57BL/6 \rightarrow B6D2F1 mouse model of GVHD. Recipients of IL-15-deficient bone marrow cells have a substantial delay in the onset of GVHD, yet retain beneficial graft-versus-tumor activity. Mixed bone marrow chimera experiments with cells deficient in either IL-15 or IL-15R α demonstrate that cells must coordinately express both IL-15R α and IL-15, which supports the known model of presentation of IL-15 *in trans*. Expression of the transcription factor T-bet by donor cells is also required for IL-15-dependent acute GVHD. Thus, expression of IL-15 by donor cells seems to determine whether GVHD occurs after bone marrow transplantation. **DCB**
Blood 108, 2463–2496 (2006)

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