Silencing CD8+ lineage commitment

In the absence of the transcription factor Th-POK, thymocytes bearing T cell receptors restricted to major histocompatibility complex (MHC) class II engender CD8+ T cells. In *Science*, Taniuchi and colleagues show that Runx transcription factors actively suppress Th-POK during the process of T cell lineage commitment. Mice lacking wild-type Runx1 and Runx3 in the T cell lineage have few CD8+ T cells but contain abundant CD4+ T cells that have helper T cell–like characteristics and appear even in the absence of MHC class II proteins. Unlike true CD8+ T cells, these 'redirected' MHC class I–restricted CD4+ T cells express Th-POK. A Runx-binding site in the Th-POK locus is essential for silencing Th-POK expression in CD69−CD4+CD8+ and CD4−CD8+ thymocytes, and mice lacking this silencer show a nearly complete lack of CD8+ T cells. Additional work is needed to determine how signals inducing CD4+ lineage commitment antagonize Runx-mediated silencing. ***CB***

Science **319, 822–825 (2008)**

New target identified

Cystatin F is a cysteine protease inhibitor expressed by immune cells whose relevant protease targets remain unknown. In the *EMBO Journal*, Watts and colleagues show that cystatin F is a potent inhibitor of cathepsin C, a protease required for the activation of lytic granule enzymes. Cystatin F is synthesized as a glycosylated disulfide-linked dimer; however, recombinant cystatin F fails to inhibit cathepsin C activity *in vitro*. The new work shows this is because of blockade of the cystatin F–cathepsin C interaction by steric hindrance. Removal of an amino-terminal peptide of monomeric cystatin F by the endocytic pathway is required before it can associate with cathepsin C and thereby block its catalytic active site. How cystatin F amino-terminal processing is regulated remains an open question. *LAD*

EMBO J. **27**, 499–508 (2008)

SOCS-ing flu immunity

Host inflammatory and antiviral responses to influenza virus infection require Toll-like receptor 3 (TLR3) and the RNA helicase RIG-I. In *Journal of Immunology*, Si-Tahar and colleagues show that the inhibitor proteins SOCS1 and SOCS3 are upregulated after influenza infection. The 'knockdown' of various factors by small interfering RNA indicates that this upregulation is independent of TLR3 but is dependent on RIG-I, mitochondrial antiviral signaling protein (MAVS) and the interferon-α receptor, whose 'knockdown' prevents induction of SOCS1 and SOCS3. Both SOCS proteins inhibit type I interferon antiviral responses but differentially affect proinflammatory signaling. Thus, type I interferon signaling promotes a negative feedback loop that depends on suppression of antiviral immunity by SOCS1 and SOCS3. This regulatory pathway may be broadly important during infection, as several viruses signal the induction of type I interferon through a RIG-I-dependent pathway and viruses such as HIV-1 and hepatitis C induce SOCS3. ***DCB***

J. Immunol. **180, 2034–2038 (2008)**

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

Collateral damage & selective repair

Activation-induced cytidine deaminase (AID) induces somatic hypermutation and immunoglobulin class-switch recombination in antigen-activated B cells. Although immunoglobulin genes have the most mutations, other genes are also mutated in an AID-dependent way. In *Nature*, Schatz and colleagues have done a genome-wide analysis of the mutation frequencies generated by AID activity. AID targets many more genes than previously appreciated but are not fixed in the genome because of high-fidelity repair mechanisms that correct the lesions. Immunoglobulin genes undergo error-prone repair, resulting in higher fixed mutation frequencies. Loss of either Ung, required for base-excision repair, or the mismatch repair enzyme Msh2 'unmasks' other nonimmunoglobulin genes targeted by AID. Notably, mutation frequencies are not higher in triple-mutant (AID-deficient) or unactivated Ung−Msh2− mature B cells. Genes with E box–binding motifs have higher frequencies of mutation, which indicates that E2A proteins may recruit AID to its target. These data suggest selective means of recruiting repair enzymes to genes in mutating B cells. *LAD*

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IL-22 versus mucosal bugs

Interleukin 22 (IL-22) is a mediator of innate immunity in epithelial cells. In *Nature Medicine*, Zheng *et al.* and Aujla *et al.* find that IL-22 production in response to bacterial infection leads to the induction of antimicrobial responses in epithelial cells. Studying the lung pathogen *Klebsiella pneumoniae*, Aujla *et al.* show that T cell production of IL-22 protein occurs 16 hours after infection, requires IL-23 and is associated with bacterial infection in patients with cystic fibrosis. Studying the gut pathogen *Citrobacter rodentium,* Zheng *et al.* find that CD11c+ dendritic cells, not T cells, produce IL-22 that protects the gut epithelium. Both groups show that IL-22 expression stimulates epithelial cells that uniquely express the IL-22 receptor to produce antimicrobial proteins and peptides, including the secreted C-type lectin proteins RegIIIβ and RegIIIγ, during *C. rodentium* infection, and iron-sequestering lipocalin 2 during *K. pneumonia* infection. These studies emphasize the importance of IL-22 in host defense against mucosal bacterial infection. ***DCB***

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Backup defense

Whether the cytosolic bacterial detectors Nod1 and Nod2 are required for host defense in mice that also express TLRs is not known. In *Immunity*, Nunez and colleagues show that Nod1 and Nod2 are important for protective immune responses when TLR signaling is disabled because of chronic TLR stimulation. Macrophages exposed to the TLR4 ligand lipopolysaccharide (LPS) produce proinflammatory cytokines and activate the transcription factor NF-κB after secondary stimulation with the Nod2 ligand MDP but not after restimulation with LPS. Because of LPS-induced upregulation of RICK, an adaptor protein involved in Nod2 signaling, MDP induces more production of proinflammatory cytokines and expression of a broader array of genes in macrophages pretreated with LPS than in naive macrophages. LPS-treated mice lacking Nod1 and Nod2 show impaired survival after *Listeria monocytogenes* infection relative to that of LPS-treated wild-type mice. Thus, Nod proteins maintain host defense in the face of chronic TLR stimulation. *CB*

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