Now I know my IKKs

The function of NF-κB in T cell development is controversial because targeted disruption of individual NF-κB or IKK subunits (IKK1 or IKK2) does not abrogate T cell development, whereas p50-p52 or p50-p65 deletion does. In *Immunity*, Pasparakis and colleagues generated mice with conditional deletions of NEMO or Ikk2, or carrying a kinase-dead IKK2 mutant. IKK2 deficiency allowed persistence of peripheral naive T cells, but disrupted regulatory and memory cell generation. Expression of IKK2ΔK (which functions as a dominant negative inhibitor of NF-κB) or T cell–specific ablation of NEMO abolished peripheral T cell development completely. Thus IKK1- or IKK2-induced NF-κB activation is required for T cell development and survival, whereas only IKK2 has an additional nonredundant function in the generation of regulatory and memory cells. *JDKW*

Immunity **19**, 377–389 (2003)

Smart surfactant

Recognition of pathogen-associated molecular patterns (PAMPs) by surfactant proteins induces the secretion of inflammatory mediators by macrophages. Conflicting data, however, indicate that these proteins could be anti-inflammatory. In *Cell*, Gardai *et al.* show that in steady-state conditions, surfactant protein A (SP-A) or SP-D binds the ITIM-containing membrane receptor SIRPα via its globular head. This interaction maintains quiescence. However, the recognition of PAMPs or necrotic cells by the same globular head of SP-A or SP-D induces its collagenous tail to bind CD91, which triggers a proinflammatory response. Thus, these surfactant proteins have an intrinsic ability to help maintain homeostasis. *PTL*

Cell **115**, 13–23 (2003)

Translating Vif effects

HIV-1 requires Vif (viral infectivity factor) to neutralize APOBEC3G, an mRNA-editing enzyme that terminates the virus life cycle after incorporation into newly formed virions. Two articles in *Nature Medicine* by Sheehy *et al.* and Marin *et al.* and one paper in *Molecular Cell* by Greene and colleagues show how Vif protects HIV from APOBEC3G-mediated inactivation. All three groups show that Vif induces APOBEC3's rapid degradation, thereby preventing its incorporation into progeny virions. Vif impairs APOBEC3 mRNA translation and accelerated APOBEC3G turnover by promoting its ubiquitination and proteosome-dependent degradation. Greene and colleagues also show that Vif has a conserved SLQ(Y/F)LA motif that is required for this degradation. Drugs that interfere with Vif-mediated APOBEC3G degradation could therefore prove useful as antiviral agents. *JDKW*

Nat. Med. **9**, 1398–1403 & 1404–1407 (2003); *Mol. Cell* **12**, 591–601 (2003)

Bacterial (in)digestion

Neutrophils can cause substantial collateral tissue damage if unchecked. In the *Proceedings of the National Academy of Science*, Kobayashi *et al.* show that engulfment of many bacterial pathogens triggers expression of proapopotic genes in neutrophils. Thus, the act of bacterial phagocytosis induces an apoptotic differentiation program in neutrophils that limits inflammatory responses. However, similar changes in neutrophil gene expression were not elicited by the bacterium *Streptococcus pyrogenes*. Carlsson *et al.*, in the *Journal of Experimental Medicine*, provide insights as to why this might be so: the *S. pyrogenes* M protein binds to complement-inhibitor protein C4BP and IgA-Fc, thereby conferring resistance to phagocytosis. *LAD*

Proc. Natl. Acad. Sci. USA **100**, 10948–10953 (2003); *J. Exp. Med.* **198**, 1057–1068 (2003)

RSSs position nucleosomes

Strict lineage-specific and temporal regulation governs the accessibility of the recombination signal sequences (RSSs) used during V(D)J recombination. Changes in DNA methylation and histone modification are associated with activation of individual antigen receptor loci. However, additional mechanisms must be involved to prevent recombination from occurring at cryptic RSS sites elsewhere in the genome. In the *EMBO Journal*, Boyes and coworkers show the conserved nonamer sequence can specifically position nucleosomes over the RSS, thereby repressing accessibility of the site to the RAG recombination enzymes. Such nucleosomes are resistant to remodeling enzymes that slide nucleosomes along DNA. Thus, precise nucleosomal positioning prevents aberrant recombination. A key question then arises as to how specific nucleosomes poised over targeted RSSs are modified in developing lymphocytes. *LAD*

EMBO J. **22**, 5197–5207 (2003)

Activation versus tolerance

The intracellular signaling pathways in antigen-presenting cells (APCs) that mediate T cell activation versus T cell tolerance are unclear. In *Immunity*, Cheng *et al.* investigate whether the transcription factor STAT3, which negatively regulates inflammatory responses, is involved. Disruption of STAT3 signaling using pharmacological inhibitors or by genetic targeting restored the responsiveness of tolerant $CD4^+$ T cells to cognate antigen presented by APCs *in vitro* and *in vivo*. Conversely, STAT3 overexpression impaired T cell priming. STAT3-deficient APCs had an inflammatory phenotype, producing little interleukin 10 (IL-10) and more IL-12 compared with APC controls. Supernatants derived from STAT3-deficient APCs also restored the responsiveness of tolerant T cells. Thus, STAT3 signaling is essential in the ability of APCs to determine immune activation versus tolerance. *JDKW*

Immunity **19**, 425–436 (2003)

Controlling niche size

Limited numbers of hematopoietic stem cells (HSCs) reside in protected niches in bone marrow, where they maintain pluripotency and self-renewal properties. In *Nature*, Calvi *et al.* and Zhang *et al.* show osteoblasts are the key bone marrow stromal cell responsible for maintaining HSC renewal. Osteoblasts line the endosteal bone surface, intimately engaging HSCs and promoting self-renewal through Jagged1-Notch interactions. Increased numbers of HSCs result when either parathyroid hormone is administered or signaling through bone morphogenetic protein is blocked. Both treatments increase the number of osteoblasts present, but paradoxically reduce the actual physical space and total bone marrow cell numbers due to increased bone density. Thus, the stem cell 'niche' reflects available access to the osteoblast cells. *LAD*

Nature **425**, 836–841 & 841–846 (2003)

Research notes written by Laurie A. Dempsey, Peter T. Lee and Jamie D.K. Wilson.