Maturing NKT cells

CD1d-restricted NKT cells have been implicated in various disease processes, including autoimmune diabetes and tumor rejection. However, their development is poorly understood. In *Science* and the *Journal of Experimental Medicine*, Benlagha *et al.* and Pellicci *et al.*, respectively, show that the initiation of NKT cell development is thymus dependent. NKT cells acquire NK markers as they mature with a concomitant switch from a T_H2- to a T_H1-type cytokine profile. These final maturation steps also occur extrathymically because recent thymic emigrants are of the immature NK1.1$^-$ phenotype. Knowledge of NKT cell development may help us to understand their dysregulation in various diseases.

J. Exp. Med. **195**, 835–844 (2002); *Science* 14 Mar 2002 (DOI: 10.1126/science.1069017)

Positively negative

Pattern recognition receptors are fundamental to the surveillance of pathogens by the innate immune system. This is exemplified by *Drosophila*, which lacks an elaborate adaptive immune system. In *Nature*, Gottar *et al.* and Ramet *et al.* show that a member of the *Drosophila* peptidoglycan recognition protein (PGRP) family specifically recognizes Gram-negative but not the expected Gram-positive bacteria. In *Science*, Choe *et al.* identify *PGRP-LC* as the isoform required to mediate these *in vivo* effects through activation of the NF-κB–like Relish pathway, leading to antibacterial responses triggered by either peptidoglycan or LPS. Thus, the PGRP family modulates diverse immune responses and may include receptors for distinguishing a spectrum of molecules that trigger the innate immune system.

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Salmonella safehouse

Merely examining the interaction between microbes and cells of the immune system may not help us to fully appreciate the basis of the morbidity and mortality caused by pathogens. Understanding the location of this interaction is just as important. In *Immunity*, McSorley *et al.* show that despite the rapid activation of CD4$^+$ T cells in the Peyer's patches after oral infection by *Salmonella*, *Salmonella*-specific T cells are not activated in the spleen and do not migrate efficiently to the liver. The lack of antigen-specific T cell migration into the major nonlymphoid sites of bacterial replication appears to be an immune evasion strategy of the bacteria that may ultimately be lethal to the host.

Immunity **16**, 365–377 (2002)

HAM-inducing mimicry

Certain autoimmune diseases may be caused by molecular mimicry. However, despite decades of research, direct evidence linking infectious agents to autoimmune diseases is scarce. In *Nature Medicine*, Levin *et al.* analyzed serum IgG from patients with HTLV-1–associated myelopathy (HAM) or tropical spastic parapesis (TST). This serum IgG recognized the antigen heterogeneous nuclear riboprotein-A1 (hnRNP-A1) and cross-reacted with HTLV-1-tax, to which HAM patients have an immunodominant response. HAM IgG specifically recognized the pyramidal motor neurons, Betz cells, which are preferentially damaged in HAM patients. Infusion of HAM IgG into the extracellular space of individual neurons inhibited neuronal firing further supporting the idea that the autoimmune response caused this neurological disease. Thus, these data show that mimicry between a viral and neuronal protein is involved in the pathogenesis of HAM.

Nature Med. **8**, 509-513 (2002)

Negative inhibition

Members of the NF-κB and IκB transcription factor family are implicated in thymocyte development by providing survival and death signals. In *Molecular Cell*, Fiorini *et al.* have identified another family member, called IκBNS, that plays a role in negative selection. Induction of negative selection increased IκBNS expression, whereas positive selection signals did not affect IκBNS transcription. Functionally, IκBNS appears to act as an inhibitor of NFκB; this is shown by its ability to block transcription of NF-κB reporter constructs, affect NF-κB EMSAs and bind NF-κB proteins in nuclear lysates after TCR triggering. In addition, retroviral transduction of IκBNS disrupted thymocyte development at the double-positive stage and increased TCR-induced apoptosis in fetal thymic organ cultures. These data show that negative selection induces transcription of IκBNS, an inhibitor of NF-κB.

Mol. Cell **9**, 637–648 (2002)

Nuclear positioning

The accessibility of Ig genes to transcription and recombination machinery is subject to tissue-specific developmental regulation. In *Science,* Kosak *et al.* show the subnuclear positioning of IgH and κ genes shift before transcriptional activation in developing B lymphocytes. Inactive IgH and κ loci, found in T cells or in multipotential hematopoietic progenitor cells, localize with lamin B at the nuclear periphery. Nuclear repositioning of both loci away from the periphery initiates at the early pro-B cell stage. Contrary to expectation, the IgH locus appears to undergo large-scale compaction during this event, but remains distinct from centromeric heterochromatin. Both IgH repositioning and compaction require IL-7 signals. The compact, repositioned IgH locus may be required to facilitate the long-range interactions necessary for RAG-mediated V-to-DJ recombination.

Science **296**, 158–162 (2002)

Vav1 clusters integrins

TCR-dependent cytoplasmic signals activate integrins by inducing integrin clustering. This increases integrin avidity for its ligand and therefore facilitates T cell activation. Integrin avidity modulation requires cytoskeletal reorganization, which is controlled by a Vav1-WASP signaling pathway. However, it is not known whether this pathway also regulates integrin activation and cell adhesion. In *Immunity*, Penninger and colleagues show Vav1 controls TCR-dependent integrin-mediated adhesion. Vav1-deficient thymocytes and T cells were unable to form tight conjugates with APCs after TCR stimulation. However, WASP-deficient T cells showed normal TCR-dependent cell adhesion, but exhibited defective TCR clustering. These findings suggest Vav1 and WASP mediate two distinct pathways that control integrin clustering and TCR clustering, respectively.

Immunity **16**, 331–343 (2002)