DC progenitor is myeloid

Dendritic cells (DCs) are specialized antigen-presenting cells that initiate and orchestrate immune responses as well as playing a role in tolerance induction. The molecule CD8α is used to define DC subsets. There is much debate over the origin of these DC subsets, one idea being that $CD8\alpha^-$ DCs are myeloid-derived, whereas $CD8\alpha^+$ are lymphoid-derived. In *Science*, Weissman and colleagues show that this is not the case and that both $CD8\alpha^+$ and $CD8\alpha^-$ DCs can arise from clonogenic common myeloid progenitors in both thymus and spleen. Therefore, DC expression of CD8α is not indicative of lymphoid origin but may reflect DC maturation status.

Science **290,** 2151–2154 (2000)

Restricted exports

MHC class I molecules present peptides to cytotoxic T lymphocytes. Peptide is loaded onto MHC molecules (pMHC), in association with TAP, in the ER. After dissociation from TAP, pMHCs were thought to exit the ER by nonselective bulk flow. In *Immunity*, Edidin and colleagues show that, in fact, pMHCs exit by association with cargo receptors. Loading of class I with peptide triggers dissociation from TAP but has no effect on rates of ER-to-Golgi transport. Also, pMHC accumulates at ER exit sites from which TAP molecules are excluded. ER-to-Golgi transport of class I molecules is independent of their cytoplasmic tails, which themselves lack ER export motifs. The paper also demonstrates that class I molecules associate with the putative cargo receptor, BAP31.

Immunity **13**, 841–851 (2000)

Lymphangiogenesis

The lymphatic vasculature transports tissue fluid, macromolecules and cells back into the blood circulation. In the February issue of *Nature Medicine*, Alitalio and colleagues shed further light on the mechanisms of lymphangiogenesis: the process of building the lymphatic vasculature. Vascular endothelial growth factor C (VEGF-C) and VEGF-D stimulate lymphangiogenesis and their receptor, VEGFR-3, has been linked to hereditary lymphedema. In this study in mice, the soluble form of VEGFR-3 strongly inhibited VEGF-C and VEGF-D signaling, resulting in the inhibition of fetal lymphangiogenesis and the regression of lymphatic vessels already formed. However, the mice survive the neonatal period without lymphatic vessels in several tissues and later show regeneration of the lymphatic vasculature, suggesting that induction of lymphatic generation in humans may be possible.

Nature Med. **7**, 199–205 (2001)

Regulating CD45 ...

The molecule CD45 is found on all nucleated cells and is required for signal transduction through antigen receptors. It is a member of the receptor-like transmembrane protein tyrosine phosphatase (RPTP) family. A current model for regulation of CD45, and other RPTP family members, proposes that dimerization inhibits phosphatase activity through symmetrical interactions between an inhibitory structural wedge and the catalytic site. In *Cell*, Weiss and colleagues show strong data in support of this model. With a single point mutation inactivating the inhibitory wedge of CD45, mice transgenic for the mutated CD45 suffer from polyclonal lymphocyte activation. This leads to lymphoproliferation and severe autoimmune nephritis with autoantibody production and eventually death. This dramatic phenotype illustrates the importance of negative regulation of CD45 by dimerization.

Cell **103**, 1059–1070 (2000)

...CD45 regulates

The transmembrane protein tyrosine phosphatase (PTPase), CD45, is an important regulator of antigen receptor signaling in lymphocytes. This molecule is highly expressed on all hematopoietic lineages throughout all stages of development. In *Nature*, Penninger and colleagues investigated whether CD45 could be involved in cytokine receptor signaling. They generated CD45 gene-targeted cell lines, which resulted in enhanced cytokine and IFN receptor-mediated activation of JAKs and STATs. Functionally, CD45 suppresses JAK kinases and negatively regulates cytokine receptor signaling, erythropoietic-dependent hematopoiesis and antiviral responses *in vitro* and *in vivo*. These data provide an unexpected role for CD45 as a JAK phosphatase and negative regulator of cytokine receptor signaling.

Nature **409**, 349–354 (2001)

Diabetes susceptibility gene

The pathogenesis of insulin-dependent diabetes mellitus (IDDM) depends on environmental and genetic causes. The MHC region is the major genetic contributor to susceptibility, although a number of other unidentified genes are also required. In *Nature Genetics*, Morahan *et al.* used NOD mice to identify human homologs of loci associated with IDDM development. They identified a susceptibility locus, *IDDM18*, located near the interleukin-12 (IL-12) p40 gene, *IL12B*. A single base change in the 3′-untranslated region (UTR) of *IL12B* exhibited strong linkage disequilibrium with the IDDM susceptibility locus. The allele was associated with greater expression of *IL12B* in cell lines. This suggests that individuals with the susceptibility allele probably produce more IL-12p40, which is likely to enhance IL-12–dependent T_H1 responses important in mediating this autoimmune disease.

Nature Gen. **27**, 218–221 (2001)

IL-15 role in fatal leukaemia

Interleukin 15 (IL-15) is a proinflammatory cytokine and growth factor required for lymphocyte homeostasis. It is thought that inflammation may play a role in the genesis of certain cancers. To investigate the role of IL-15 in possible malignant transformation of lymphocytes, Caligiuri and colleagues engineered mice to overexpress IL-15. In a report in the *Journal of Experimental Medicine*, they show that these transgenic mice exhibit early expansions of the NK and $CD8^+$ T cell populations. Later, they develop fatal lymphocytic leukemia with a T-NK phenotype. This study provides new evidence that leukemia, like other cancers, can arise as a result of chronic stimulation by a proinflammatory cytokine.

J. Exp. Med **193**, 207–217 (2001)