Brave new thymi

In *Nature Biotechnology*, Poznansky *et al*. describe a new procedure to mimic human thymic development through the engineering of an artificial thymic "organoid". By using a 3-D matrix of tantalum-coated carbon seeded with murine thymic stroma, it was possible to recreate the conditions necessary for T lymphopoiesis from human $CD34^+$ progenitors. By day 14 there were discrete populations of $CD4^+$ and $CD8^+$ single positive, as well as double positive, thymocytes. These T cells exhibited diverse TCR V_β expression and, on functional analysis, the T cells were able to respond to a number of stimuli (IL-2, PHA, Con A) in an appropriate manner. Artificial thymic organoids may provide an ideal source of T cells to restore immune function in patients undergoing allogeneic stem cell transplantation, or in those infected with HIV.

Nature Biotech., **18**, 729–734 (2000)

Toxic flagellin

Enteroaggregative *E. coli* (EAEC) causes acute and persistent diarrhea, often associated with intestinal inflammation and impairment of growth in children. A soluble, heat-stable factor released by these bacteria rapidly induces IL-8 production from the intestinal epithelial cell line, Caco-2. In the *Journal of Clinical Investigation*, Steiner *et al*. show how they cloned and identified this Il-8–releasing factor as a flagellin, which is different from known *E.coli* flagellar proteins. Flagella purified from several EAEC isolates cause potent IL-8 release from Caco-2 cells, whereas an engineered aflagellar EAEC mutant does not cause this release. Finally, the cloned flagellin expressed in nonpathogenic *E.coli* causes release of IL-8 from Caco-2 cells. These findings may lead to a better understanding of how EAEC induces intestinal pathogenesis.

J. Clin. Invest., **105**, 1769–1777 (2000)

B cells: paying the Toll

B cells play an important role in host responses against Gram-negative bacteria. B cell responses to LPS are mediated by the Toll-like receptor (TLR)-4, a molecule also present on macrophages and neutrophils. In the *Journal of Experimental Medicine*, Ogata *et al*. show that another TLR, RP105, which is predominantly expressed on mature B cells, is involved in B cell responses to LPS. Gene targeting of RP105 in mice revealed impaired B cell responses to LPS. The group also showed functional cooperation between TLR-4 and RP105 in LPS-induced NF-κB activation. The important role of RP105 in B cell activation by LPS makes it a possible target for enhancement of the humoral response against Gram-negative bacteria.

J. Exp. Med., **192**, 23–29 (2000)

Avoiding death with TRADD

Functions of the TNFR superfamily are mediated by TNFR-associated factors (TRAFs). TNF-α induces apoptosis, but TRAF-2 can suppress this by the recruitment of cIAPs for the direct inhibition of caspase activation. In *Cell*, Park *et al*. reveal a newly identified mechanism for TRAF-2 signaling. TRAF-2 can be recruited to activated TNFR-1 directly or indirectly via the adaptor protein TRADD. They show that TRAF-2–TRADD binding is mediated by an extensive protein-protein interface and that this binding is of a much higher affinity than the TRAF-2–TNFR-1 interaction. They also show that TRAF-2 signaling is more readily initiated by TRADD than by direct receptor–TRAF-2 interactions, and that TRADD mutations result in highly potent apoptosis induction. This indicates that TRAF-2-TRADD interactions are extremely sensitive to affinity changes.

Cell, **101**, 777–787 (2000)

Dominating chemokines

Chemokine gradients are involved in directing T cell migration. In the *Journal of Immunology*, Bromley *et al.* reasoned that a chemokine gradient leading past, rather than towards, the APC may disrupt T cell activation by preventing the T cell from stopping long enough to form the immune synapse (IS). Using a transmigration assay, this group show that migration signals produced by receptors CCR7 (SLC and MIP-3) and CXCR3 (IP-10) are dominant over TCR signals and block or prevent IS formation, whereas signals produced by CXCR4 (SDF-1), CCR2 (MCP-1), CCR4 (MDC) and CCR5 (RANTES and MIP-1) are submissive to TCR signals. Thus, dominant chemokine gradients represent another mechanism for T cell ignorance of agonist MHC-peptide complexes.

J. Immunol., **165**, 15–19 (2000)

T cells low on perforin

In the *Journal of Experimental Medicine*, Appay *et al*. have used class I MHC–peptide tetrameric complexes in conjunction with intracellular staining to dissect the functional phenotype of circulating HIV-1– and CMV-specific $CD8^+$ T cells. $CD8^+$ T cells, specific for both HIV and CMV antigens, produce antiviral cytokines and chemokines (IFN-γ, TNF-α and MIP-1β), although a subset of tetramer-reactive $CD8^+$ T cells secretes only IFN-γ and MIP-1β. Importantly, HIV-specific $CD8^+$ T cells expressed significantly less perforin than CMV-specific $CD8^+$ T cells. Reduced perforin expression is linked with persistent CD27 expression and poor specific lysis *ex vivo*. This suggests that HIV-1–specific $CD8^+$ T cells show impaired maturation and cytolytic activity.

J. Exp. Med., **192**, 63–76 (2000)

Inhibition of angiogenesis

Most tumor cells do not express MHC class II molecules, but in the June issue of *Immunity* Qin and Blankenstein show that $CD4^+$ T cells can play a role in rejecting class II tumors. Immunity against a class II tumor in mice is IFN-γ–dependent, but IFN-γR expression is not required on tumor cells, T cells or hematopoietic cells in the priming phase. However, successful immunity requires IFN-γR expression on nonhemapoietic cells for the effector phase and involves inhibition of tumor-induced angiogenesis, the mechanism of which is not yet elucidated. This shows that an effective antitumor response involves communication between $CD4^+$ T cells and nonhematopoietic cells.