Death with CI-MPR

Apoptosis of virus-infected cells or tumor cells by cytotoxic T cells (CTLs) is initiated by granule-mediated exocytosis of cytolytic molecules or by Fas-Fas ligand interaction. The serine proteinase granzyme B is crucial for inducing granule-mediated apoptosis and is perforin-independent, which suggests the existence of a cell surface receptor. In *Cell*, Bleackley *et al.* show that cation-independent mannose 6-phosphate receptor (CI-MPR) functions as a receptor for granzyme B. Inhibition of granzyme B-CI-MPR binding prevented granzyme B uptake and induction of apoptosis. In addition, by using CI-MPR$^-$ and CI-MPR$^+$ cells as targets, they showed that CI-MPR was essential for CTL-mediated apoptosis *in vitro* and for transplant rejection of allogeneic cells *in vivo*. Thus, CI-MPR functions as a death receptor for granzyme B.

Cell **103**, 491–500 (2000)

Bones are not lazy

Two main cell populations, osteoblasts and osteoclasts, are continually remodeling bone tissue according to physiological circumstances. T cells express RANK ligand and play a role in bone resorption by signaling through RANK, which is expressed on osteoclasts. In *Nature,* Taniguchi and colleagues show that IFN-γ strongly suppresses osteoclastogenesis by interfering with the RANK-RANKL signaling pathway. IFN-γ induces rapid degradation of the RANK adaptor protein TRAF-6 resulting in strong inhibition of signaling molecules downstream of TRAF-6. However, osteoclastogenesis can be rescued by overexpression of TRAF-6, indicating that TRAF-6 is the critical target for IFN-γ action.

Nature **408** (in the press, 2000)

Monkey business with Ebola

Ebola virus causes outbreaks of hemorrhagic fever in humans. Its rapid progression prevents the development of natural immunity, so vaccine development is a priority. In *Nature*, Sullivan *et al.* have developed an effective vaccine strategy for Ebola virus infection in cynomologus macaques. A prime-boost strategy that consisted of DNA plasmids that encode multiple virion glycoprotein (gp) subtypes and a recombinant adenoviral vector that also directs gp expression was used. Immunized monkeys generated both humoral and cellular immune responses to Ebola. Monkeys challenged with Ebola virus remained asymptomatic for more than 6 months, whereas unimmunized macaques died within a week after challenge. These findings suggest it should be possible to develop a human vaccine to this pathogen.

Nature **408** (in the press, 2000)

Tyk2 and cytokine signaling

Binding of many cytokines to their specific cell surface receptors activates the Janus family of protein tyrosine kinases (Jaks). The Jak family consists of four members, Jak1 to 3 and Tyk2. In *Immunity*, two groups have analyzed the *in vivo* function of Tyk2 to determine whether it plays a redundant role in cytokine signaling. Karaghiosoff *et al.* found that *Tyk2*$^{-/-}$ mice display reduced responses to IFN-α, IFN-β and IL-12 and a selective deficiency in STAT3 activation within these pathways. IFN-γ signaling was also impaired and lipopolysaccharide-stimulated macrophages failed to produce nitric oxide. These mice also demonstrated an increased susceptibility to certain viral pathogens in the absence of Tyk2. Shimoda *et al.* also showed that Tyk2-deficient mice are unresponsive towards IFN-α but respond normally to IL-5 and IL-10, both of which activate Tyk2 *in vitro*. In addition, they also show Tyk2 is essential for IL-12–mediated T cell responses. These results suggest Tyk2 plays a selective role in mediating cytokine signaling and other signaling events associated with various stimuli.

Immunity **13**, 549–560 and 561–571 (2000)

IgA deficiency

Transforming growth factor (TGF) cytokines are implicated in the control of many processes, including cell cycle and differentiation and leukocyte development and function. To determine the role of TGF-β in B cells, Cazac and Roes generated mice with TGF-β receptor type II–deficient B cells using the Cre/*loxP* system. These deficient B cells have reduced life span and show an expansion in the peritoneal B1 cell compartment. The absence of the receptor also leads to hyperplasia in Peyer's patches, elevated serum immunoglobulin and hyperresponsive IgG3 responses. This abnormal response is associated with a virtually complete serum IgA deficiency. The data establish the importance of TGF-β receptor ligand interaction in the induction of IgA responses *in vivo*.

Immunity **13**, 443–451 (2000)

Chemotaxing with HIV

Hemofiltrate CC chemokine 1 (HCC-1) was originally isolated from the hemofiltrate of patients with chronic renal failure. Surprisingly, HCC-1 is constitutively expressed in a large variety of tissues and at a high concentration. A report in the *Journal of Experimental Medicine* describes the purification from hemofiltrate of a new high-affinity CCR5 ligand, which was identified as a truncated form of HCC-1. This ligand, which results from proteolytic processing of HCC-1, was shown to activate and recruit monocytes, T cells and eosinophils. It was also found to be highly active on other chemokine receptors, CCR1 and CCR5, and blocked HIV entry. It is thought that the processing activity of HCC-1 to the active ligand may be mediated by a serine protease. This process may affect HIV-1 replication in infected patients and play an important role in AIDS pathogenesis.

J. Exp. Med. **192**, 1501–1508 (2000)

Energetic macrophages

A protein thought to be involved in control of obesity plays a role in innate immunity. Uncoupling proteins (UCPs) are mitochondrial membrane proton transporters that uncouple respiration from oxidative phosphorylation by dissipating the proton gradient across the membrane. They have been implicated in the development of obesity because of their role in energy dissipation. However, a study in *Nature Genetics* shows that UCP2-deficient mice have normal body fat mass. Macrophages from these mice generate increased reactive oxygen species (ROS) and, consequently, *Ucp2*$^{-/-}$ mice are resistant to the intracellular parasite *Toxoplasma gondii.* UCP-2 appears to function as a controller of the redox state, thus playing an important role in innate immunity by regulating ROS production in macrophages.

Nature Genet. **26**, 435–439 (2000)