## Protective glycolipids

Deficiency in NKT cells may be causal to type 1 diabetes. $V_\alpha14^+$ NKT cells recognize α-galactosylceramide (α-GalCer) glycolipid presented by MHC class I–like molecule CD1d. In *Nature Medicine* Sharif *et al.* and Hong *et al.* and Wang *et al.* in the *Journal of Experimental Medicine* analyze the protective effect of α-GalCer treatment on the development of diabetes in NOD mice. Even when initiated after the onset of insulitis, α-GalCer treatment protects NOD mice from type 1 diabetes in a CD1d-dependent manner. Both Sharif *et al.* and Hong *et al.* also show protection is correlated with a polarized $T_H2$-like response as well as suppression of islet-specific T and B cell responses. These studies suggest α-GalCer may be useful in the treatment of human type 1 diabetes.

*Nature Med.* **7**, 1052–1056 & 1057–1062 (2001)
*J. Exp. Med.* **194**, 313–319 (2001)

## Mimicry or nonspecific stimuli?

The association between viral infections and induction or exacerbation of autoimmune disease is poorly understood. In *Immunity*, Cantor and colleagues examine the relative roles of molecular mimicry and nonspecific inflammatory stimuli in the transition from infection to autoimmune disease. They use a replication-competent murine herpes virus 1 (HSV-1 KOS) point mutant, which contains a single amino acid exchange in the putative mimicry epitope, and mice expressing a TCR transgene specific for the self-peptide mimic. They show that viral mimicry is critical for disease induction after low-level viral infection of mice containing limited numbers of autoreactive T cells, whereas innate immune mechanisms are sufficient to provoke disease in animals containing expanded numbers of autoreactive T cells. Thus, both viral mimicry and nonspecific innate immune mechanisms have dominant roles in the generation of autoimmunity under particular conditions.

*Immunity* **15**, 137–147 (2001)

## Deviating $T_H1$ cells

DNA vaccines can be used to elicit immunity or tolerance. To modulate the immune response to DNA vaccines, preparations that contain cytokine genes and genes to certain pathogens have been used in "covaccines." In *Immunity*, Steinman and colleagues show covaccination of mice with a construct encoding IL-4 and residues 139–151 of the self-peptide proteolipid protein, PLP(139–151), protects against experimental autoimmune encephalomyelitis (EAE) induction by PLP(139–151). IL-4–dependent STAT6 phosphorylation induced autoreactive T cells to shift their cytokine profile to $T_H2$. In addition, DNA covaccination with the genes encoding myelin basic protein and IL-4 can reverse established EAE. Thus, this method of protective immunity using DNA vaccination and local gene delivery could prove beneficial in the treatment of multiple sclerosis and other autoimmune diseases caused by $T_H1$ autoreactive cells.

*Immunity* **15**, 15–22 (2001)

## Spontaneous autoimmunity

Animal models of autoimmune diseases often require repeated immunizations with self-antigen to recapitulate disease development, frequently without complete penetrance. Shevach and colleagues report in the *European Journal of Immunology* the development of a mouse model of organ-specific autoimmune disease that occurs spontaneously with complete penetrance in young animals. Mice transgenic for TxA23 (a CD4 TCR), which recognizes the gastric parietal cell protein H/K ATPase α-chain, develop severe autoimmune gastritis that resembles the disease pernicious anemia in humans. Adoptive transfer of $10^3$ lymphocytes conferred severe disease development in immunocompromised hosts, but transfer of $10^7$ cells into wild-type recipients only induced mild gastritis, consistent with the of loss of immunoregulatory cells in immunocompetent hosts. This mouse model should prove insightful for determining the regulatory factors responsible for autoimmune disease development, progression and suppression.

*Eur. J. Immunol.* **31**, 2094–2103 (2001)

## Key genes in end-stage arthritis

Arthritis, like many autoimmune diseases, develops in distinct stages that may be influenced by multiple independent disease susceptibility traits. In the *Journal of Experimental Medicine*, Ji *et al.* identify the genes that underlie these susceptibilities to discrete phases of arthritic disease in inbred mice. Transfer of serum or immunoglobulin from arthritic animals into healthy recipients can provoke rapid end-stage destructive joint disease with high penetrance in susceptible strains. Using this model and back-crossing disease-prone animals with unaffected animals, Ji *et al.* were able to identify several genetic loci by that predisposed mice to arthritic disease. Genomic scans of a responder–nonresponder pair (C57BL/6 × NOD) localized the dominant susceptibility locus to the complement *C5* gene. Other susceptibility loci resided on murine *chr1*, coinciding with *Sle1* but not *fcgr2*, *chr12* or *chr18*. The power of genomics, teamed with dissection of disease stages, should provide ample cues to understanding the multifactorial contributions that lead to overt autoimmune disease.

*J. Exp. Med.* **194,** 321–330 (2001)

## RAGE in diabetic nephropathy

Nephropathy is a fatal disease complication common to end-phase diabetes. Pathogenesis involves mesangial cell expansion followed by glomerulosclerosis. Although mouse models have been developed that recapitulate the pathology of diabetic islet destruction, no models exist for advanced diabetic kidney disease. In the *Journal of Clinical Investigation*, Yamamoto *et al.* describe mice that show kidney pathologies similar to the lesions observed in human diabetic disease. Vascular damage due to prolonged hyperglycemia is thought to involve interactions between advanced glycation end products (AGEs) interacting with their receptor (RAGE) on endothelial cells. Mice expressing the human RAGE receptor in vascular cells crossed with those that develop insulin-dependent diabetes show increased AGE serum concentrations. Subsequent kidney damage—as revealed by glomerular hypertrophy, increased albuminuria and mesangial sclerosis—occurs in the RAGE Tg-diabetic mice, but not those lacking the transgene. Importantly, these symptoms could be prevented by administration of the AGE inhibitor, 2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide (OPB-9195). Thus, therapeutic intervention of AGE-RAGE interactions may prove beneficial in human disease.

*J. Clin. Invest.* **108**, 261–268 (2001)