Tolling for *Drosophila*

The discovery of *Drosophila* Toll prompted a search for mammalian homologs. The most conserved region in these molecules is a signaling domain that is also shared with members of the IL-1R family, referred to as Toll-IL-1R (TIR) domain. In *Proceedings of the National Academy of Science*, Tauszig *et al.* identified Toll-3 to Toll-8 in *Drosophila*, which contain TIR domains. Some of these molecules are expressed at early stages suggesting that they may be involved in development. Conversely, Toll-5 is expressed only in larvae and adults and, like Toll, can activate a *Drosophila* antifungal Drosomycin peptide promoter. None of the Toll molecules were able to activate antibacterial peptide promoters. This study and one by Rutschman *et al*. in this issue of *Nature Immunology* suggest that antifungal and antibacterial responses follow distinct pathways.

Proc. Natl Acad. Sci. USA **97**,10520–10525 (2000); *Nature Immunol.* **1**, 342–347 (2000)

AID for antibody diversity

Antibody diversity is increased by class switch recombination (CSR) and somatic hypermutation (SHM). In the September issue of *Cell*, two papers by Honjo and colleagues show that activation-induced cytidine deaminase (AID) plays a crucial role in these processes. CSR is abolished in AID$^{-/-}$ mice, which also display a hyper-IgM phenotype with enlarged germinal centers (GCs) before and after immunization. In addition, SHM was abrogated in immunized AID$^{-/-}$ mice. Mutations in human AID occur in patients with the recessive form of hyper-IgM syndrome (HIGM2). Such patients exhibit hyperplastic lymphoid GCs and defective CSR and SHM. Thus, AID plays a crucial role in the generation of a normal antibody response.

Cell **102**, 553–563 and 565–575 (2000)

Autodestructive IL-18

Myelin oligodendrocyte glycoprotein (MOG) peptide–induced experimental autoimmune encephalitis (EAE) is an animal model for multiple sclerosis (MS). Although neither the exact sequence of events nor the molecular mediators of this CNS-inflammatory disease are clearly defined, it is known that EAE is a T_H1 cell–mediated disease. In the *Journal of Immunology,* Shi *et al*. investigated the development of EAE in IL-18 knockout mice. Compared to controls, IL-18$^{-/-}$ mice are defective in mounting autoreactive T_H1 or autoantibody responses and are resistant to MOG peptide–induced EAE. The study also showed that IL-18 promotes autoreactive T_H1 cell development, in part *via* induction of IFN-γ by NK cells. Selective targeting of IL-18 may prevent the development of such autoimmune responses and provide a possible therapy for MS.

J. Immunol. **165**, 3099–3104 (2000)

Two GEMs

B cell linker protein (BLNK), Src homology 2 domain–containing leukocyte protein (SLP-76) and linker for activation of T cells (LAT) are required for BCR and TCR function. Two papers in *Journal of Experimental Medicine* show how these proteins relate to glycolipid-enriched microdomains (GEMs). Kurosaki and colleagues show that in BLNK^{-} B cells, SLP-76 alone cannot reconstitute BCR function. However, function is restored when a membrane-associated SLP-76 chimera was localized to GEMs. Addition of other signaling molecules allowed SLP-76 to be recruited to GEMs. BLNK did not require these molecules for its recruitment to GEMs. These data show functional overlap of BLNK and SLP-76, although these molecules show differences in GEM-targeting requirements. Koretzky and colleagues found that a fraction of SLP-76 in T cells localizes to GEMs after TCR stimulation, and identified amino acids important for SLP-76 recruitment to GEMs. A mutated LAT–SLP-76 chimera precludes its recruitment to GEMs and diminishes its ability to support TCR signaling. Collectively, optimal TCR signaling relies on the compartmentalization of SLP-76, and a critical function of LAT is to bring SLP-76 to the membrane.

J. Exp. Med. **192**, 847–856 and in the press (2000)

Exploiting *Lactococcus lactis*

Inflammatory bowel disease (IBD) is a significant public health problem in the West. Its etiology remains unclear; IBD is characterized by chronic inflammation in the intestine, and it may involve abnormal T cell responses to the gut flora. Anti-inflammatory approaches can ameliorate the disorder. Because IL-10 has a central role in down-regulating inflammatory cascades and has shown promise in IBD clinical trials, Steidler *et al.* utilized this cytokine as a therapeutic modality by engineering *L. lactis* to secrete IL-10. Administration of these bacteria to mice with colitis reduced disease by 50% as well as preventing onset of colitis in IL-10 knockout mice. This could be a promising approach for long-term management of IBD.

Science **289**, 1352–1355 (2000)

Supersonic thymocytes

The hedgehog (Hh) signaling pathway is involved in the development of many mammalian tissues. In *Immunity,* Outram *et al.* show that Hh regulates the double positive (DP) to single positive stage of T cell development. Sonic hedgehog (Shh) is produced in the thymic epithelium, whereas its receptor molecules, patched (Ptc) and smoothened (Smo), are expressed by double negative (DN) thymocytes. An antibody to Shh increases differentiation from DN to DP, and recombinant Shh protein arrests thymocyte development at the CD25^{+} DN stage after rearrangement of the gene encoding TCRβ. Shh signaling up-regulates Smo on DN thymocytes, and pre-TCR signaling down-regulates this molecule on DN cells. Hh signaling, therefore, plays an important regulatory role in thymocyte development.

Immunity **13**, 187–197 (2000)

The great CTL escape

The appearance of SIV- and HIV-specific cytotoxic T cells (CTL) after primary infection is concurrent with a dramatic fall in viral load. In *Nature*, Watkins and colleagues have shown that Tat-specific CD8^{+} T lymphocyte responses select for SIV variants during resolution of viremia in the acute phase of infection. Sequence analysis of the entire virus immediately after the acute phase revealed amino acid replacements primarily accumulated in Tat epitopes recognized by CTLs. This suggests that Tat-specific CTLs are important in the control of wild-type virus replication. Cellular immune responses against viral proteins that are expressed early in the viral lifecycle could be important targets for HIV vaccine development.