Reversing tolerance

Peripheral T cell tolerance helps limit autoimmune responses. However, T cell tolerance represents a major obstacle in diseases such as cancer where a lack of T cell response can prevent immunity. Although great strides have been made to prevent induction of T cell tolerance, little progress has been made in defining targets that reverse established tolerance. In *Nature Medicine*, Croft and colleagues show that OX40 signals are effective in reversing established tolerance. Ligation of OX40 after antigen-specific tolerance has been established promotes T cell expansion and restores normal responsiveness to antigen. Thus, targeting of OX40, and perhaps other members of the TNF receptor family, may be useful for modulating T cell function in a variety of diseases.

Nature Med. **7**, 907–912 (2001)

To B or not to B?

Pax5 is continuously expressed during B lymphopoiesis. In Pax5-deficient mice, B cell development is arrested at the pro-B cell stage. In *Immunity*, Horcher *et al.* have studied the late function of Pax5 *in vivo*. Using conditional mutagenesis to inactivate Pax5 during late B lymphopoiesis, they show a preferential loss of mature B cells, inefficient lymphoblast formation and reduced amounts of serum IgG. The gene expression profile of the mature B cells was also altered. Most cell surface B cell antigens were down-regulated, whereas expression of non-B lymphoid genes was activated and B cell–specific genes were lost. Therefore, Pax5 is required to maintain the function, identity and survival of mature B lymphocytes during late B cell development.

Immunity **14**, 779–790 (2001)

Sulfated HEV homing receptors

Lymphocyte homing is mediated by L-selectin ligands expressed on high endothelial venules (HEVs). HEV-borne L-selectin ligands, such as GlyCAM-1, all have mucin-like domains that act as scaffolding for O-linked oligosaccharides, which can be sialylated, fucosylated and sulfated. 6-sulfo sLe^x structures on core2 branched O-linked oligosaccharide, formed by core2 β1,6-N-acetylglucosaminyltransferases (core2GlcNAcT), are implicated in L-selectin ligand activity. However, lymphocyte homing activity is normal in core2GlcNAcT-deficient mice. In *Cell*, Yeh *et al.* have identified a sulfated extended core1 mucin-type O-glycan as the L-selectin ligand required for lymphocyte homing in the absence of core2 structures. The HEV-expressed core1 extension-β1,3-N-acetylglucosaminyltransferase (Core1-β3GlcNAcT) promotes formation of 6-sulfo sLe^x on core1 oligosaccharides. Thus, Core1-β3GlcNAcT together with Core2GlcNAcT-1 play a prominent role in the homing of lymphocytes to secondary lymphoid organs.

Cell **105**, 957–969 (2001)

Making plasma cells

Little is known about transcription factors that control the transition of mature activated B cells to antibody-secreting plasma cells. In *Nature*, Glimcher and colleagues show that the basic-region leucine zipper transcription factor XBP-1 is required for the generation of plasma cells. XBP-1 transcript up-regulation correlated with plasma cell differentiation *in vitro*. Overexpression of XBP-1 in B lineage cells induced plasma cell differentiation. In addition, XBP$^{-/-}$RAG-2$^{-/-}$ chimeric mice had normal numbers of activated B cells and formed normal germinal centers, but secreted little immunoglobulin at baseline or in response to T-independent or T-dependent antigens. These mice also failed to control infection with the B cell–dependent polyoma virus. Thus, XBP-1 is required for the terminal differentiation of B lymphocytes to plasma cells.

Nature **412**, 300–307 (2001)

STAT1 for mycobacterial immunity

Susceptibility to mycobacterial infections has been observed in patients who harbor recessive genetic defects encoding IL-12 or IFN-γ cytokines or their respective receptors. In *Science*, Casanova and colleagues report finding a dominant-negative mutant of STAT1 that conferred susceptibility to mycobacterial infections, but not viral infections. IFN-α/β and INF-γ signaling induces STAT1 activation and nuclear localization, where it forms two distinct transcriptional activation factors, homodimeric GAF and heterotrimeric ISGF3. Mutation of Leu^{706} in STAT1 impaired its ability to be phosphorylated at Tyr^{701}, resulting in its cytoplasmic retention. Heterozygotic expression of this mutation impaired GAF-, but not ISGF3-, mediated transcriptional activation. This mutation conferred a selective defect in the ability to ward off mycobacterial infections.

Science **294**, 300–303 (2001)

PESTs inhibit lymphocytes

How do lymphocytes turn off or modulate signals received through their antigen receptors? In the *EMBO Journal*, Veillette and Davidson show that the protein tyrosine phosphatase PEST negatively regulates downstream signals generated by antigen receptors in B and T cells. PEST associates with several signaling molecules, including Shc, Pyk2, Fak and Cas, which are required for inducing Ras-MAPK activation pathways and actin cytoskeleton rearrangements. PEST appears to dampen lymphocyte signals by at least two mechanisms: catalytic dephosphorylation and noncatalytic association with its phosphorylated protein substrates. Thus, PEST negatively regulates lymphocyte activation by inhibiting activation of the Ras-MAPK signaling pathways.

EMBO J. **20**, 3414–3426 (2001)

Thymic neighborhoods

Thymocyte differentiation occurs through discrete stages that are characterized by phenotypic and biochemical changes. However, less well established are the anatomical sites at which differentiation occurs. In the *Journal of Experimental Medicine*, Lind *et al.* report spacially discrete thymic microenvironments that hematopoietic precursors travel through on their journey from the bloodstream to the thymic cortex, and *en route*, develop from DN multipotent precursors to committed DP thymocytes. Histological examination of thymic precursors was done in thymi that were not altered by irradiation, cell ablation or other inflammatory damage to the vasculature or thymic stroma. The nonhomogenous distribution of DN thymocytes suggests that stromal environments induce or support discrete steps in thymocyte differentiation.

J. Exp. Med. **194**, 127–134 (2001)