Functional allelic exclusion

Most T cells express a single TCR at the cell surface. Once a functional TCR is expressed, suppression of further TCR recombination events mediates monoclonality of T cells. However, the identification of T cells bearing two different TCRs has shown such genetic allelic exclusion to be "leaky". In the *Proceedings of the National Academy of Science USA*, Sant'Angelo *et al.* demonstrate an additional mechanism by which T cells maintain monoclonality. Despite transcribing all four mRNA species, T cells from double TCR-transgenic mice do not simultaneously express both available TCRs at the cell surface. Thus, cell surface expression of a second TCR may be blocked after translation. This process is likely controlled during the assembly of the αβ heterodimer.

Proc. Natl Acad. Sci. USA **98**, 6824–6829 (2001)

A snug fit: CR2-C3d

Deposition of activated serum complement proteins on foreign surfaces links adaptive and innate humoral immune responses. The complement receptor CR2 amplifies signals received through the BCR and contributes to B cell tolerance. As reported in *Science*, Szakonyi *et al.* used X-ray structure determination to resolve the issue of how CR2 recognizes its ligand C3d, which covalently attaches to antigen. The CR2 binding interface formed by two membrane-proximal consensus repeats are fixed in space by hydrophobic interactions, which fold into V-shaped β barrels that have extensive shape complementarity with the binding surface of C3d. The structure explains previous observations for this receptor-ligand interaction and reveals potential therapeutic interaction sites.

Science **292**, 1725–1728 (2001)

Avoiding graft-versus-host disease

Effective cancer immunotherapy strategies have been hampered by problems associated with bolstering patients' immune recognition of tumor-specific neo-self antigens and, when allogeneic bone marrow transplantation is used, development of graft-versus-host disease (GVHD). In *Nature Medicine*, Perreault and colleagues show effective elimination of malignant leukemic cells, without provoking GVHD, by adoptive transfer of primed T lymphocytes specific for a single immunodominant minor histocompatibility antigen (MiHA) into allogeneic recipients. Avoidance of GVHD required that no other minor host-reactive T cells were present at time of transplantation, as epitope spreading primes these cells against host tissues. The strategy of selective transfer of *ex vivo*–primed cytolytic T cells targeted to a single MiHA may lead to effective anti-cancer therapies in the clinic.

Nature Med. **7**, 789–794 (2001)

Life in the marginal zone

Trapping of blood-borne particulate antigens by marginal zone (MZ) B cells is thought to bridge innate immune responses with the acquisition of long-term adaptive humoral immunity. Two reports in *Immunity* describe how MZ B cells arise and demonstrate the active role played by these cells in generating early antibody responses. Cariappa *et al.* show that signals received through the BCR act as a rheostat in recent bone marrow emigrants to develop into either MZ cells or follicular B cells. Thus, endogenous antigen interactions drive naïve B cell development in the periphery. Martin *et al.* show that MZ B cells become antibody-producing plasma cells within hours of antigen interaction, thus play a direct early role in clearing blood-borne pathogens.

Immunity **14**, 603–615 and 617–629 (2001)

Human regulatory T cells

Immunological self-tolerance is critical for the prevention of autoimmunity. In rodents, one mechanisms by which self-tolerance is maintained is *via* $CD4^+CD25^+$ regulatory T cells. In the *Journal of Experimental Medicine*, three groups—Levings *et al.*, Dieckmann *et al.* and Jonuleit *et al.*—have isolated human regulatory $CD4^+CD25^+$ T cells and confirmed that these cells resemble their murine counterparts. For example, these cells express CTLA-4 and are hyporesponsive to stimulation with allogeneic dendritic cells. In addition, they can suppress $CD25^-$ T cell responses to anti-CD3 stimulation. They produce IL-10 and TGF-β, but these are not directly required for the suppressor activity. The identification of regulatory $CD4^+CD25^+$ T cells has important implications for therapy and study of tolerance in humans.

J. Exp. Med. **193,** 1285–1294, 1295–1302 and 1303–1310 (2001)

Two opposites attract

Chemokine receptors undergo ligand-mediated homodimerization to trigger Ca^{2+} flux and chemotaxis. In *EMBO Journal*, Martinez-A. and colleagues show that the chemokine receptors CCR2 and CCR5 can also heterodimerize. Simultaneous stimulation with CCL2 and CCL5 induces heterodimerization of CCR2-CCR5 and triggers a Ca^{2+} response at lower ligand concentrations than either chemokine alone. Although this process recruits both receptor-associated signaling complexes, the heterodimer activates another signaling pathway involving $G_{q/11}$. This delays activation of PI3K, causes a pertussis toxin–resistant Ca^{2+} flux and triggers cell adhesion instead of chemotaxis. This may explain chemokine signaling desensitization and regulation of cell migration during immune and inflammatory responses.

EMBO J. **20**, 2497–2507 (2001)

Pten in T cell homeostasis

The tumor suppressor gene *Pten* encodes a multifunctional phosphatase that dampens proliferation and survival signals generated through phosphatidyl inositol-3,4,5-triphosphate. $Pten^{-/-}$ mice are nonviable, whereas mice heterozygous for Pten expression often develop lymphoid malignancies and autoimmune disorders. In *Immunity*, Suzuki *et al.* generate T cell lineage–specific $Pten^{-/-}$ mice that display multiple defects in T cell tolerance and homeostasis. Mutant mice have increased $CD4^+$ cells in the periphery, develop $CD4^+$ T cell lymphomas and have increased autoantibody production. $Pten^{-/-}$ T cells hyperproliferate, secrete more T_H1 and T_H2 cytokines and resist apoptosis. $Pten^{-/-}$ T cells show increased PKB (Akt) and Erk phosphorylation in response to T cell receptor stimulation. Thus, Pten is an important regulator of T cell tolerance and homeostasis.

Immunity **14**, 523–534 (2001)