B cell rafting

CD19 and CD21 form a complex that plays a critical role in enhancing B cell responses to T cell–dependent antigens. In *Immunity,* Pierce and colleagues investigate the role this complex plays in signaling from lipid rafts. After coligation by complement-tagged antigens, and using the potent immunogen hen egg lysozyme bound to the complement component C3d, the CD19-CD21 complex significantly prolongs B cell receptor (BCR) residency in lipid rafts. This results in prolonged BCR signaling, compared to BCR cross-linking alone. When coligated to the BCR, the CD19-CD21 complex retards the internalization and degradation of the BCR. This newly identified mechanism for the enhancement of BCR signaling may explain why the CD19-CD21 complex enhances B cell responses.

Immunity **14**, 169–179 (2001)

Splicing CD40

CD40 is a member of the tumor necrosis factor receptor superfamily and is expressed on a wide range of immune cells. In the *Proceedings of the National Academy of Science*, Waldmann and colleagues have identified five CD40 isoforms generated by alternative splicing in the region between exons 5 and 9. At an early stage of activation, pre-CD40 RNA is spliced to a signal-transducible CD40 mRNA, whereas in the later stages of activation the mRNA is replaced by a nonsignal-transducible form. They show that expression of CD40 is regulated differently in dendritic cells and activated macrophages. Their data suggests that CD40 expression is controlled by post-transcriptional regulation through alternative splicing.

Proc. Natl Acad. Sci. USA **98**, 1751–1756 (2001)

Tumor therapy

Bone marrow (BM) is a major site for long-term persistence of tumor-specific memory cells and of small numbers of dormant tumor cells that are kept under active host T cell–control. In *Nature Medicine,* Feuerer *et al.* studied the specificity and functional activity of BM T cells from breast cancer patients and tested whether these T cells had therapeutic potential *in vivo.* Patients' T cells along with autologous dendritic cells were pulsed with tumor cell lysates. These T cells could be specifically reactivated to become IFN-γ–producing cytotoxic effector cells. In addition, these restimulated T cells from BM, but not from peripheral blood, were able to cause regression of autologous tumors xenotransplants in NOD-SCID mice. Thus, activated memory T cells may be useful for immunotherapy of cancer.

Nature Med. **7**, 452–458 (2001)

STAT3 in IBD

Proinflammatory cytokines, including IFN-γ and IL-6, play a crucial role in the pathogenesis of inflammatory bowel diseases. In the *Journal of Experimental Medicine,* Yoshimura and colleagues show that STAT3 plays a role in the maintenance of intestinal inflammation. STAT3 was strongly tyrosine phosphorylated in human ulcerative colitis, and in colitis in mice. In IL-6–deficient mice, STAT3 activation and the development of colitis was significantly reduced. Expression of the STAT inhibitor CIS3 (also known as SOCS3 or SSI3) was highly expressed in the colon of mice with colitis. Mice expressing a dominant-negative form of CIS3 suffered from a more severe form of colitis. These data suggest that hyperactivation of STAT3 results in severe colitis and that CIS3 plays a negative regulatory role in inflammation by down-regulating STAT3 activity.

J. Exp. Med **193**, 471–481 (2001)

Innate escape

Human cytomegalovirus (HCMV) has evolved a number of mechanisms to evade immune surveillance. HCMV can down-regulate MHC class I expression on infected cells and thereby escapes T cell recognition. However, this theoretically leaves the cell vulnerable to NK cell–mediated lysis. In *Immunity*, Cosman *et al.* have identified a mechanism by which HCMV might inhibit the NK cytolytic response. A HCMV glycoprotein, UL16, can bind the MHC class I–like molecules ULBP1 and 2. These molecules can bind the NKG2D-DAP10 receptor and stimulate NK cell activation. Expression of ULBPs in NK cell–resistant target cells confers susceptibility to NK cell cytolysis. Since UL16 can block ULBP recognition by NKG2D-expressing cells, HCMV-infected cells can escape attack by the innate immune system.

Immunity **14**, 123–133 (2001)

Nonlymphoid memory cells

Two groups in *Science* and *Nature* have analyzed the generation of antigen-specific memory T cells in lymphoid and nonlymphoid tissue. Lefrancois and colleagues show that in response to infection, antigen-specific CD8 T cells migrate to nonlymphoid tissues where they are present as long-lived memory cells. Compared to splenic and lymphoid memory T cells, nonlymphoid resident memory T cells exhibited potent *ex vivo* lytic activity. Jenkins and colleagues show that naïve CD4 T cells, specific for a model antigen, reside exclusively in secondary lymphoid tissues. However, exposure to antigen + LPS-induced T cell proliferation in secondary lymphoid tissue and migration of these cells into nonlymphoid organs. Two populations of CD4 memory T cells with different functional characteristics persisted in the lymph nodes and nonlymphoid tissue. For CD8 or CD4 memory cells, those most capable of responding immediately to an external threat sit as sentinels in nonlymphoid tissues.

Nature **410**, 101–105 (2001)
Science **291**, 2413–2416 (2001) (Available online 1 March 2001 at 10.1126/Science.1058867)

Receptor-specific NIK

A variety of cell surface receptors can activate NF-κB. The signals induced by these diverse receptors converge downstream into a common pathway that leads to the activation of IκB kinase (IKK) complex. The role of NF-κB–inducing kinase (NIK) in activating the IKK complex is controversial. In *Science*, Yin *et al.* have generated NIK$^{-/-}$ mice to determine whether NIK plays a critical role in signal-induced NF-κB activation. Normal NF-κB DNA-binding activity was observed using a variety of cytokines including lymphotoxin-β (LTβ) and TNF. However, LTβ-induced, but not TNF-induced, NF-κB failed to transactivate NF-κB–regulated genes. Thus, NIK is not a common upstream kinase as previously proposed but instead acts in a receptor-specific manner to promote the transcriptional activity of the NF-κB complex

Science **291**, 2162–2164 (2001)