TCR lures CTLA-4

T cell activation is regulated by signals provided by CD28 and CTLA-4, which bind to B7 expressed by antigen-presenting cells (APCs). Whereas CD28 is constitutively expressed by T cells and enhances proliferation, CTLA-4 is localized mainly in the endosomal compartment and suppresses T cell expansion. In *Immunity,* Egen and Allison tracked the movement of CTLA-4. CTLA-4 accumulated at the immunological synapse in proportion to the strength of the TCR signal, which suggests that CTLA-4 preferentially inhibits T cell responses under conditions of stronger T cell stimulation. The recruitment of CTLA-4 to the immunological synapse in response to potent TCR signaling may represent a new feedback control mechanism and have broad consequences for antigen-specific T cell responses, such as expanding the diversity of a T cell response.

Immunity **16**, 23–35 (2002)

Alloendothelium activates CD8s

Activation of T cells by graft-resident professional APCs, such as DCs, is thought to mediate direct allograft recognition pathways. However, human nonhematopoietic cells, such as the vascular endothelium, can activate allogeneic T cells *in vitro*. In *Nature Medicine*, Kreisel *et al.* showed, using a murine transplant model, that mouse nonhematopoietic cells could activate alloreactive $CD8^+$ T cells *in vitro* and *in vivo*. Direct activation of these cells resulted in the acute rejection of vascularized cardiac allografts, even when alloantigen was not presented by hematopoietic professional APCs of donor origin. This implies that donor nonhematopoietic cells can continue to activate alloreactive $CD8^+$ T cells for the life of the allograft.

Nature Med. **8**, 233–239 (2002)

Reciprocating cells

Before activated T cells are generated, NK cells arrive at the site of infection where they encounter activated DCs. But what controls the activation of resting NK cells at this stage is unclear. In the *Journal of Experimental Medicine* Gerosa *et al.*, Ferlazzo *et al.* and Piccioli *et al.* shed some light on this. Gerosa *et al.* showed that resting NK cells were activated by immature DCs in the presence of inflammatory stimuli. In the absence of inflammatory stimuli, Piccioli *et al.* showed that NK cell activation could be achieved only when DCs predominated. Ferlazzo *et al.* showed that mature DCs activated with inflammatory cytokines promoted NK cell activation. Conversely, Piccioli *et al.* and Gerosa *et al.* also showed that activated NK cells could promote DC maturation. Together these data show how DCs and NK cells cooperate to regulate the innate immune response.

J. Exp. Med. **195**, 335–341, 327–333 & 343–351 (2002)

Mutating with AID

Somatic hypermutation (SHM) of expressed immunoglobulin genes is restricted to activated germinal center (GC) B cells. Activation-induced cytidine deaminase mutants fail to undergo SHM. However the exact role played by AID in SHM is unknown, as is the requirement for other GC-specific proteins. In *Nature*, Scharff and colleagues expressed AID in human hybridoma cells and showed the SHM can be induced in non-GC B cells. The rates of Ig mutation correlated with the degree of AID expression in transfected cell lines. The mutation pattern, which targeted variable regions and hot-spot RGYW or WRCY nucleotide motifs, in the AID-expressing hybridomas resembled that found in GC cells. Thus, AID appears to be the only GC-specific factor required for the SHM process.

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KRC regulates TRAF2

TNF-α controls inflammation and apoptosis *via* the NF-κB and Jnk-SAPK signal transduction pathways. In *Molecular Cell*, Glimcher and colleagues have demonstrated a role for KRC (the mammalian homolog of *Drosophila schnurri*) in regulating gene activation patterns in these signaling pathways after proinflammatory stimulation. KRC over-expression inhibited, but antisense or dominant-negative KRC increased, NF-κB transactivation and Jnk phosphorylation. This resulted in apoptosis and cytokine gene expression. KRC mediated its effects by interacting with TRAF2, which intersects both the NK-κB and Jnk-SAPK pathways. Thus, the balance between KRC and TRAF2 may regulate the inflammatory and apoptotic response to TNF-α, with KRC acting as a negative regulator of TRAF signaling.

Mol. Cell **9**, 121–131 (2002)

Dual roles for DC-SIGN

DC-SIGN is a C-type lectin receptor expressed exclusively by DCs; it regulates transmigration through tissues by functioning as an adhesion receptor to ICAM-2 and ICAM-3. DC-SIGN also binds HIV gp120 to facilitate HIV transmission from DCs to T cells. In the *Journal of Immunology*, Engering *et al*. show DC-SIGN undergoes rapid ligand-specific internalization to deliver its cargo to the acidic late endosome-lysosome compartments, where subsequent antigen-processing and presentation to T cells could occur. Internalization of soluble DC-SIGN ligands triggered antigen-specific T cell activation. Importantly, such ligand internalization points to a mechanism by which HIV may cloak itself for delivery to T cell–rich areas in peripheral lymphoid tissues.

J. Immunol. **168**, 2118–2126 (2002)

Tyr-less SAP SH2 binding

The X-linked lymphoproliferative (*XLP*) disease gene encodes SAP, a 128-aa SH2 protein that lacks other effector domains. Unlike other SH2 proteins, SAP can bind to non-phosphorylated proteins, such as SLAM in T cells and 2B4 in NK cells, which suggests alternative modes of SH2 peptide recognition. In the *EMBO Journal*, Hwang *et al*. identify the structural peptide motif, T(S)-x-x-x-x-V(I), responsible for SAP's unconventional SH2 recognition properties. Solution NMR data support the three-pronged model for SAP protein recognition, whereby significant binding affinity is conferred by two of three possible target contacts involving the –2 threonine or serine, the +3 valine or isoleucine or tyrosine (phosphorylated or not) at the relative "0" position. Notably, the XLP mutant T53I, which alters contact with the –2 hydroxyl position, cannot bind to non-phosphorylated substrates. This highlights the physiological relevance of SAP's unusual SH2 recognition properties.

EMBO J. **21**, 314–323 (2002)