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Hitting the brakes

Ligation of the coreceptor CTLA-4 regulates T cell activity and is essential for preventing the development of T cell–mediated autoimmunity, but precisely how CTLA-4 shuts down T cell function remains unclear. In *Science*, Rudd and colleagues demonstrate that CTLA-4 stimulation counteracts T cell receptor (TCR)–induced 'stop' signals. In lymph nodes, after encountering cognate peptide, CTLA-4-deficient T cells arrest, but the motility of CTLA-4$^+$ cells remains unchanged. *In vitro*, CTLA-4$^+$ T cells engage in shorter interactions with antigen-presenting cells displaying cognate peptide, undergo less proliferation and produce less interleukin 2 than do CTLA-4-deficient T cells. Further work is needed to determine whether by reducing the contact time between T cells and antigen-presenting cells presenting low-affinity self antigens, CTLA-4 can 'encourage' potentially autoreactive T cells to 'move along' and thereby discourage the development of autoimmunity. ***CB***

***Science* (26 August 2006) doi:10.1126/science.1131078**

Mast cells in tolerance

With specific conditioning regimens, allograft recipients can be tolerized to their donor graft tissue. In *Nature*, Lu *et al.* show that mast cells are required for the establishment of tolerance. More mast cells are found in tolerized tissue grafts than in rejected grafts. Mast cell–deficient (W^{sh}) mice rapidly reject allogeneic skin grafts in conditions inducing tolerance in wild-type mice. Mast cell reconstitution in W^{sh} recipient mice could prolong graft survival. Activated regulatory T cells produce large amounts of the mast cell growth factor interleukin 9. Treatment with antibody to interleukin 9 also abolishes the establishment of tolerance in graft recipients. How mast cells influence T cell effector function and engender tolerance remains unknown. *LAD*

Nature (20 August 2006) doi:10.1038/nature05010

Shared equipment

The chemokine SDF-1α influences T cell function, and stimulation of the SDF-1α receptor CXCR4 induces activation of signaling molecules, including the tyrosine kinase Zap70, which transmit signals emanating from the TCR. In *Immunity*, Hedin and colleagues investigate the mechanism by which CXCR4 uses components of the TCR signaling pathway. After treatment with SDF-1α, CXCR4 and TCR complexes move within close proximity of each other. Transmission of CXCR4 signals requires surface expression of TCR-associated CD3ζ chains containing intact immunoreceptor tyrosine-based activation motifs (ITAMs), and seems to proceed via constitutively phosphorylated TCR-Zap70 complexes. SDF-1α 'costimulation' enhances some (AP-1 transcription factor activation) but not other (NF-κB and NFAT transcription factor activation) outcomes of TCR signaling. The complete picture of intertwining CXCR4 and TCR signaling cascades remains to be drawn, but these results emphasize a unique formation of heterodimers between the TCR and a chemokine receptor. ***CB***

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Research notes written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey

Altered acidification

Patients with cystic fibrosis develop recurrent bacterial lung infections because of defective clearance of inhaled microorganisms. In *Nature Cell Biology*, Di *et al.* report that macrophages from mice lacking the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel cannot acidify endosomal vacuoles. This defect prevents efficient killing of phagocytosed bacteria. CFTR is expressed in macrophages but not in neutrophils, where it localizes to endosomal membranes and counterbalances the influx of H^+ into acidifying endosomes with transport of Cl^-. Although CFTR-deficient macrophages show no defects in phagocytosis or the generation of reactive oxygen species, the lack of acidic vesicles prevents the activation of lysosomal enzymes required for the killing and degradation of internalized microbes. The more neutral vesicle environment of CFTR-deficient macrophages allows enhanced bacterial survival and replication. These findings could help explain why patients with cystic fibrosis are prone to lung infections. *LAD*

Nat. Cell Biol. **8**, 933–944 (2006)

TREM-ming macrophages

Several myeloid and natural killer cell receptors associate with and signal through the ITAM-containing adaptor DAP12. In the *Journal of Immunology*, Lanier and colleagues find that DAP12-mediated signaling in macrophages can be inhibitory when DAP12 associates with the receptor TREM-2. A chimeric TREM-2–DAP12 receptor but not a chimeric TREM-1–DAP12 receptor inhibits tumor necrosis factor production induced by Toll-like receptor (TLR) and Fc receptor signaling after expression in DAP12-deficient macrophages. 'Knockdown' of TREM-2 in wild-type macrophages increases TLR-induced production of tumor necrosis factor by stimulation with either CpG or zymosan. A TREM-2–Fc fusion protein binds macrophages, whereas an $F(ab')_2$ antibody to TREM-2 inhibits TREM-2–Fc binding, indicating that macrophages express a TREM-2 ligand. Thus, like other DAP12-associated receptors such as Siglec-H and NKp44, TREM-2 uses DAP12 for the inhibition of proinflammatory responses associated with TLR stimulation. ***DCB***

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Regulatory microRNA

MicroRNAs (miRNAs) are conserved regulatory RNAs of approximately 22 nucleotides that regulate post-transcriptional gene expression. In the *Proceedings of the National Academy of Sciences*, Baltimore and colleagues demonstrate that stimulation of the human acute monocytic leukemia cell line THP-1 with lipopolysaccharide specifically induces expression of three miRNAs: *miR-146*, *miR-155* and *miR-132*. Rapid induction of *miR-146* in particular indicates that it belong to the class of immediate-early response genes induced by proinflammatory mediators. Of the two human *miR-146* genes, *miR-146a* is dependent on the transcription factor NF-κB. Algorithm-based searches for predicted 'targets' of *miR-146* have identified potential sites in the 3′ untranslated regions of *Irak1*, *Traf6* and *Map3k8* mRNA. Expression of luciferase reporter constructs containing the 3′ untranslated regions of those mRNAs is much lower when *miR-146* is also expressed but not when a mutant *miR-146* is expressed. These data suggest that NF-κB regulates expression of miRNAs that control immune responses *in vivo*. *DCB*

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