T cell autophagy

Autophagy, or phagocytosis of a cell's own cytoplasm, is essential for cell survival during growth factor deprivation as well as for the elimination of some intracellular pathogens. In the *Journal of Experimental Medicine*, He and colleagues set out to determine whether autophagy, which can occur in T cells *in vitro*, influences T cell differentiation and function. Unmanipulated mouse thymocytes and mature T cells contain autophagosomes (whose size and/or frequency increases after CD3 crosslinking) and express genes encoding proteins required for autophagy. Cells lacking autophagy-related gene 5 show excessive apoptosis and impaired proliferation, and those defects are more severe in $CD8^+$ than in $CD4^+$ populations. In other cell types and systems, autophagy proteins have been shown to interact with antiapoptotic proteins Bcl-2 and Bcl-x_L and the FADD adaptor molecule. Whether such interactions occur in T cells and influence T cell survival and proliferation remains for future study. ***CB***
***J. Exp. Med.* (26 December 2006) doi:10.1084/jem.20061303**

Malaria susceptibility

Production of interferon-γ (IFN-γ) by natural killer (NK) cells soon after infection activates many cell types and can influence the outcome of adaptive immune responses. In *PLoS Pathogens*, Newman *et al.* show that monocytes or myeloid dendritic cells (but not plasmacytoid dendritic cells) are required for human NK cell activation in response to *Plasmodium falciparum*–infected red blood cells (iRBCs). Purified NK cells fail to respond to iRBCs, but iRBCs trigger robust myeloid cell responses. Myeloid cells responding to iRBCs provide both cytokine and cell contact–dependent signals to NK cells, leading to abundant secretion of IFN-γ. Those results suggest that the initial myeloid cell response to iRBCs influences the magnitude of subsequent NK cell production of IFN-γ and potential susceptibility to plasmodia infection. *LAD*
PLoS Pathogens **2**, e118 (2006)

Cooperative signaling

Integrin $\alpha_9\beta_1$ is expressed on neutrophils as well as other cell types, but investigation of its influence on neutrophil function has been hindered by the early postnatal death of α_9-deficient (*Itga9*$^{-/-}$) mice. In *Immunity*, Sheppard and coworkers circumvent that obstacle by analyzing 1-week-old *Itga9*$^{-/-}$ mice and find that $\alpha_9\beta_1$ and the G-CSF cytokine receptor (G-CSFR) work cooperatively in neutrophils. *Itga9*$^{-/-}$ mice have many fewer neutrophils in the bone marrow and peripheral blood. Although they have wild-type quantities of surface G-CSFR, *Itga9*$^{-/-}$ bone marrow cells show impaired G-CSF-induced colony formation and phosphorylation of transcription factor STAT3. Stimulation of $\alpha_9\beta_1$ and the presence of the α_9 cytoplasmic domain are essential for G-CSF-induced phosphorylation of G-CSFR, STAT3 and the kinase Erk, as well as for the formation of a physical complex of $\alpha_9\beta_1$ and G-CSFR. Further details of the molecular mechanism through which $\alpha_9\beta_1$ promotes G-CSFR signaling remain to be determined. ***CB***
***Immunity* 25, 895–906 (2006)**

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

Toxoplasma virulence

The protozoan parasite *Toxoplasma gondii* infects one quarter or more of the world's population. Two studies in *Science*, by Taylor *et al.* and Saeij *et al.*, provide new insight into the importance of secreted protozoan proteins associated with high parasite burdens and hyperproduction of T helper cell type I cytokines. Both studies use genetic crosses of virulent (type I) and avirulent (type III) strains and positional cloning to isolate virulence factors from a region of chromosome VII. The parasite gene encoding ROP18, a serine-threonine kinase, is evaluated because its expression and polymorphisms vary in virulent and avirulent strains. ROP18 is a member of a family of parasite effector proteins that are secreted from apical organelles called rhoptries. Complementation of avirulent strain III with *ROP18* from strain I confers considerable virulence. Saeji *et al.* also characterize the *ROP16* allele, which, in contrast, is associated with lower virulence. The two studies thus demonstrate that secreted rhoptry proteins determine toxoplasma virulence. *DCB*
Science **314**, 1776–1783 (2006)

Type B T cells

Type B $CD4^+$ T cells represent approximately 50% of the endogenous T cell repertoire for a given peptide and respond only to peptide–major histocompatibility complex (MHC) generated in the absence of the chaperone protein H2-DM (such as peptide added exogenously), whereas the more commonly known type A T cells respond to peptide-MHC complexes generated either in the absence of H2-DM or by intracellular processing of antigen and loading of peptide. In the *Journal of Immunology*, Lovitch *et al.* extend previous *in vitro* analyses by generating type B T cell receptor transgenic mice specific for the 48-62 epitope of hen egg-white lysozyme (HEL). Although transgenic type B T cells respond vigorously *ex vivo* to the 48-62 peptide and poorly to intact HEL, mice primed with either peptide or intact HEL plus adjuvant or with HEL-loaded allogeneic dendritic cells display type B responses that are independent of the adaptor protein MyD88. These data suggest that a unique antigen presentation pathway generates H2-DM-independent peptide-MHC complexes from intact protein that stimulate type B T cells. ***DCB***
***J. Immunol.* 178, 122–133 (2007)**

Palmitoylated Fas

Ligand-induced internalization of the death receptor Fas (CD95) can trigger lymphocyte apoptosis through a caspase 8–mediated pathway. In the *EMBO Journal*, Feig *et al.* and Chakrabandhu *et al.* report that palmitoylation of Fas cysteine residue 199 enhances the formation of high-molecular-weight aggregates and Fas internalization and recruitment of the death-domain signaling molecules FADD and pro–caspase 8. Inhibition of palmitoylation, either by alteration of membrane-proximal cysteine or by the use of chemical inhibitors, blocks Fas internalization and Fas-mediated apoptosis. Palmitoylation seems to facilitate the localization of Fas to lipid rafts and its aggregation in SDS-resistant complexes. Fas palmitoylation also links it to the actin cytoskeleton, which, after Fas ligation, undergoes ezrin-mediated internalization of the aggregated membrane complex. Receptor internalization has been shown to be required for assembly of the death signal. These data help to resolve the early signaling events involved in Fas-mediated apoptosis. *LAD*
EMBO J. (7 December 2006) doi:10.1038/sj.emboj.7601456 & doi:10.1038/sj.emboj.7601460