Common p73 pathway

Stimulation of the T cell receptor (TCR) on cycling peripheral T cells causes their apoptosis by a process called TCR–activation-induced cell death (TCR-AICD). In two papers in *Nature*, Kaelin and colleagues show that T cells undergoing TCR-AICD induce the p53-related gene p73, a mediator of apoptosis. T cells were protected from TCR-AICD by introduction of either the transcription factor E2F-1 or p73 dominant-negative proteins. They also show that E2F-1 induces the transcription of p73 and that disruption of p73 function inhibited E2F-1–induced apoptosis in p53-defective cells. These data indicate that p73 may serve to integrate receptor-mediated apoptotic stimuli and that activation of p73 provides a means for E2F-1 to induce death in the absence of p53.

Nature **407**, 642–645 and 645–648 (2000)

Flip side of death

CD28 is a major costimulator required for efficient activation of mature T cells. Krammer and colleagues in the *European Journal of Immunology* investigated the anti-apoptotic activity of CD28 in activation-induced cell death (AICD) using freshly isolated primary T cells in prolonged interleukin 2 culture. This *in vitro* model showed that CD28 costimulation acts on the CD95 pathway to reduce AICD of restimulated T cells. Costimulation up-regulated Bcl-x_L, down-regulated FasL mRNA and increased the expression of the short form of the anti-apoptotic FLICE-inhibitory protein c-$FLIP_{short}$. Thus, c-$FLIP_{short}$ is an inhibitor of ACID under physiological conditions.

Euro. J. Immunol. **30**, 2765–2774

Perforin as immunoregulator

Shustov *et al.* in the *Journal of Clinical Investigation* investigated the role of perforin-mediated CTL effector function in immune regulation. They induced acute graft-*versus*-host disease (GVHD) using perforin-deficient donor T cells (pfp→F1). This resulted in classic features of acute GVHD such as up-regulation of Fas and FasL, production of anti-host CTL and secretion of both T_H1 and T_H2 cytokines. However, pfp donor cells failed to eliminate host B cells despite intact Fas-FasL–mediated CTL activity. After 4 weeks of disease these mice developed features of chronic GVHD such as T_H2 cytokine production, increased numbers of B cells, persistence of donor $CD4^+$ T cells, autoantibody production and lupus-like renal disease. Thus, perforin plays an important immunoregulatory role in the prevention of humoral autoimmunity though the elimination of autoreactive B cells and antigen-specific T cells.

J. Clin. Invest. **106**, R39–R47 (2000)

Visualizing CTLA-4

Additional signals, provided by engagement of CD28 on T cells with its B7 ligands CD80 and CD86, are required to sustain and enhance T cell activation. Conversely, the interaction of B7 molecules with CTLA-4 inhibits T cell signaling. In *Science,* Ostrov *et al.* have resolved the crystal structure of the extracellular domain of CTLA-4 to 2.0 Å. The CTLA-4 molecule is a member of the immunoglobulin superfamily and displays a strand topology similar to V_α domains, with an unusual mode of dimerization that places the B7 binding sites distal to the dimerization interface. This allows each CTLA-4 dimer to bind two bivalent B7 molecules and suggests that a periodic arrangement of these components within the immunological synapse may contribute to the regulation of T cell responsiveness.

Science **290**, 816–819 (2000)

Adhering erythrocytes

The lack of an adequate animal model for malaria has made it difficult to determine whether infected erythrocytes interact *in vivo* in microvessels. In the *Journal of Experimental Medicine,* Kubes and colleagues visualized *Plasmodium falciparum*–endothelial interactions in human microvasculature. Human skin grafted onto SCID mice enabled direct observation of the human vasculature by epifluorescence intravital microscopy. The adhesion molecules CD36 and intracellular adhesion molecule 1 (ICAM-1) were sufficiently expressed to allow infected erythrocytes under physiological shear to roll on and adhere to postcapillary venules and arteriole vasculature. Anti-CD36 reversed the firm adhesion of infected erythrocytes, suggesting that anti-adhesive therapy could be used in malaria.

J. Exp. Med. **192**, 1205–1211 (2000)

Tip of the ICEBERG

Caspase-1 converts the 34-kD inactive precursor of interleukin 1β (IL-1β) to the mature 17-kD proinflammatory cytokine. RIP2 and caspase-1 interact through their caspase-recruitment domains (CARDs) at the COOH-terminus of RIP2 and within the prodomain of caspase-1. Their binding causes oligomerization, which promotes caspase-1 autoactivation. In *Cell*, Humke *et al.* show that ICEBERG, a member of the death-domain-fold superfamily, is an inhibitor of IL-1β generation. After induction by proinflammatory stimuli, this CARD-containing protein binds the corresponding CARD motif present in the prodomain of caspase-1, preventing association with RIP2, which ultimately attenuates caspase-1 activation, IL-1β generation and inflammation. Thus, ICEBERG functions as a 'decoy' molecule to control IL1-β generation.

Cell **103**, 99–111 (2000)

DAP12-deficent mice

Two papers in *Immunity* investigate the role of DAP12, an immunoreceptor tyrosine-based activation motif (ITAM)–bearing adaptor molecule implicated in the activation of natural killer (NK) and myeloid cells. Lanier and colleagues generated DAP12-deficient mice. Ly49 on NK cells was down-regulated and nonfunctional. $DAP12^{-/-}$ mice were resistant to peptide-induced EAE; myelin-specific $CD4^+$ T cells had reduced interferon γ production, due to inadequate T cell priming. Vivier and colleagues generated DAP12 loss-of-function mice in which the ITAM was nonfunctional. Although NK cells were present, the spectrum of natural cytotoxicity towards tumor cells was restricted. Dendritic cells accumulated in mucocutaneous epithelia, and contact sensitivity was impaired. Thus, DAP12 plays a specific role in innate immunity and suggest that DAP12 signaling may be required for optimal antigen presenting cell function or inflammation.