Puma pathway

If the phosphatidylinositol-3-OH kinase (PI(3)K)–Akt signaling pathway, which can inhibit the activity of the FOXO transcription factors, is made constitutively active, lymphocytes are rendered resistant to apoptosis induced by cytokine withdrawal. In the *Journal of Experimental Medicine*, Tak Mak and colleagues show that the PI(3)K-Akt-FOXO pathway controls expression of the BH3-only protein Puma, shown before to be upregulated following cytokine withdrawal. Interleukin 2 withdrawal stimulates binding of FOXO3a to the promoter of the gene encoding Puma. Puma-deficient T lymphocytes are more resistant than wild-type T lymphocytes to apoptosis induced by interleukin 2 withdrawal. Deletion of the genes encoding Puma and Bim (another FOXO target) renders T lymphocytes even more resistant to apoptosis, suggesting a synergistic relationship between BH3-only proteins. These data pinpoint FOXO-induced Puma expression as a mechanism underlying PI(3)K-Akt–induced protection from cytokine deprivation–induced apoptosis in T lymphocytes. ***CB***
***J. Exp. Med.* (26 June 2006) doi:10.1084/jem.20060353**

Seeing antigen

B cells and T cells 'see' antigen differently: B cells can recognize structurally intact native antigens, whereas T cell recognize dendritic cells (DCs) presenting processed peptides. In *Science*, Germain and colleagues show that B cells also 'see' antigen presented by DCs. B cells contact antigen-laden DCs in extrafollicular sites shortly after entering lymph nodes but before entering lymphoid follicles. These antigen-specific interactions lead to calcium fluxes and upregulation of activation markers in B cells. Such antigen-specific interactions also alter the migration properties of responding B cells. Nonspecific B cells do not change their velocity or direction after encountering DCs. These results also suggest that 'free' antigen draining into lymph nodes is not readily available and that like T cells, B cells must interact with antigen-presenting DCs to become primed before follicle entry. *LAD*
Science **312**, 1672–1676 (2006)

Pinning down Btk

Btk is a tyrosine kinase required for signaling from the B cell receptor. In the *Journal of Biological Chemistry*, Yu *et al.* demonstrate that Btk in B cells is regulated by the prolyl isomerase Pin1 in different phases of the cell cycle. Binding of Pin1 to Btk alters both tyrosine phosphorylation of Btk and its half-life. Differential regulation of Btk during the cell cycle occurs via binding of Pin1 at one of two phosphorylated serine residues of Btk, S21 or S115. Phosphorylation of S21 leads to Pin1 binding and regulation only during mitosis, whereas phosphorylation of S115 leads to Pin1 binding and regulation specifically in the resting cells. Regulation of Btk phosphorylation and its half-life is confirmed in cells from Pin1-deficient mice. Thus, a key regulator of Btk activity and half-life, Pin1 prolyl isomerase controls a critical non–receptor tyrosine kinase for normal B cell biology. ***DCB***
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Research notes written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey

Gating by S1P

Sphingosine 1-phosphate (S1P) can induce systemic lymphopenia by altering lymphocyte and thymocyte egress. In *Nature Chemical Biology*, Rosen and colleagues investigate the molecular basis underlying S1P-induced lymphopenia by using S1P derivatives. Two enantiomers (*R* and *S*) that differ only by the position of an amino group at the chiral center, are specifically recognized by the $S1P_1$ receptor. Yet only the *R* form is biologically active as a $S1P_1$ antagonist. Administration of the *R* enantiomer alone enhances capillary leakage but does not alter bloodstream lymphocyte numbers. Intravital imaging of lymph nodes in animals demonstrates altered motility of medullary (but not cortical) lymphocytes after administration of $S1P_1$ agonists. There are no migration defects when the *R* enantiomer is given alone, but it substantially inhibits the function of $S1P_1$ agonists when co-administered. These data challenge the model of S1P 'functional antagonism'; instead, the authors suggest S1P regulates endothelial cell gating properties. *LAD*
Nat. Chem. Biol. (9 July 2006) doi:10.1038/nchembio804

Saving coding ends

Ataxia-telangiectasis mutated (ATM) protein kinase mediates cellular responses to DNA double-strand breaks (DSBs). In *Nature*, Bredemeyer *et al.* find that ATM is required for maintaining the integrity of coding ends produced in recombination-activating gene–induced DSBs. Pre–B cell lines from $Atm^{+/+}$ and $Atm^{-/-}$ mice were retrovirally transduced with specific recombination substrates and treated with a v-Abl kinase inhibitor to induce rapid RAG expression and a G1-to-S transition block. Evaluation of subsequent recombination products shows that ATM deficiency increases 'unrepaired' coding ends, which are normally sealed hairpins during the recombination process. Unrepaired ends were also found in aberrant rearrangements, suggesting that the ends had 'dissociated' from post-cleavage recombination complexes. ATM, therefore, maintains both the integrity of coding ends and their association with recombination complexes, which helps explain ATM deficiency in humans, a syndrome associated with genome instability and lymphoid malignancies. ***DCB***
***Nature* (14 June 2006) doi:10.1038/nature04866**

Antiviral AID

By deaminating retroviral DNA, some cytidine deaminases inhibit retrovirus replication. In *Immunity*, Papavasiliou and colleagues identify a new function for the cytidine deaminase AID in preventing retrovirus-induced B cell transformation. AID-deficient bone marrow cells infected with Abelson murine leukemia virus (Ab-MLV) proliferate faster and to a greater extent than their infected wild-type counterparts. This effect is cell autonomous, as wild-type recipients of Ab-MLV-infected AID-deficient bone marrow cells die faster than recipients of Ab-MLV-infected wild-type cells. Ab-MLV infection induces expression of enzymatically active AID, which inflicts genotoxic damage on the host cell genome and triggers surface expression of the Rae-1 NKG2D ligand, thus rendering infected wild-type cells susceptible to natural killer cell lysis *in vitro*. In addition, Ab-MLV-induced AID expression results in phosphorylation of the kinase Chk1, which is known to inhibit cell cycle entry. The mechanism by which Ab-MLV induces AID expression remains to be identified. *CB*
Immunity **24**, 779–786 (2006)