Processing lymphocyte survival

Cytokine signaling through Janus kinases prevents lymphocyte apoptosis. In *Nature*, Ihle and colleagues document a crucial function for the Bcl-2-like protein Hax1 in the survival of lymphocytes and their progenitors. Like mice lacking the mitochondrial proteases Parl and HtrA2, Hax1-deficient mice develop progressive lymphocyte apoptosis and die prematurely. By interacting with Parl, Hax1, whose expression is induced by cytokine stimulation and is diminished by cytokine withdrawal, enhances the processing of HtrA2 to its active form in the mitochondria. Impaired HtrA2 protease activity permits the accelerated appearance of the activated form of Bax, which precipitates permeabilization of the mitochondrial outer membrane and lymphocyte apoptosis after cytokine withdrawal. Elucidation of the molecular mechanism by which HtrA2 protease function delays Bax activation awaits further study. ***CB***

***Nature* 452, 98–102 (2008)**

Dicer in B cells

Researchers are devoting increasing attention to post-transcriptional regulation mediated by microRNA generated by the endoribonuclease Dicer. In *Cell*, Rajewsky and colleagues examine the effect of Dicer ablation in developing B lineage cells. Loss of Dicer results in an early block at the pro-B cell–to–pre-B cell stage, due in part to higher expression of the proapoptotic protein Bim and more apoptosis. This phenotype can be partially 'rescued' by transgenic expression of the antiapoptotic protein Bcl-2. Wild-type and Dicer-deficient pre-B cells show differences in D_H segment usage during *Igh* recombination. This result is reflected in 'sterile' transcription that occurs before the recombination event and thus affects targeting in the *Igh* locus. TdT expression is not extinguished after the pro-B cell stage in Dicer mutants, leading to more 'N addition' in the recombination joints of light-chain genes. More functions for Dicer will probably be identified, as expression arrays note differences in hundreds of genes expressed in pro-B cells. *LAD*

Cell **132**, 860–874 (2008)

Foxp3 and RORα

The transcriptional repressor Foxp3 is important for the function of regulatory T cells. In the *Journal of Immunology*, Ziegler and colleagues demonstrate that Foxp3 interacts with RORα, another transcription factor that functions in many cell types. Mapping studies of full-length Foxp3 show that exon 2 of *Foxp3* is required for RORα interaction, which is consistent with the failure of a natural variant of Foxp3 lacking exon 2 to bind RORα. Other assays demonstrate that the Foxp3-RORα interaction inhibits RORα transcriptional activity, requires the AF2 domain of RORα known to be essential for its interaction with coactivators or corepressors, and requires an 'LxxLL' motif in Foxp3. Finally, endogenous gene targets of RORα are inhibited by Foxp3 expression. These data identify a protein-protein interaction probably important for the function and development of regulatory T cells. ***DCB***

***J. Immunol.* 180, 4785–4792 (2008)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Length matters

Double-stranded DNA in the cytoplasm triggers cellular 'danger signals' and induces type I interferon responses. DNA-dependent activator of interferon responses (DAI) has been identified as one such intracellular sensor. In the *Proceedings of the National Academy of Sciences*, Wang *et al.* examine the molecular interactions between DAI and double-stranded DNA. Interferon activation occurs only when DNA molecules larger than 500 base pairs are present in the cytosol; longer DNA molecules trigger stronger responses. DAI contains three DNA-binding motifs, including two Z domains that recognize GC-rich DNA and a central D3 domain. Deletion of either Z domain still allows DNA binding, but mutants lacking D3 do not bind DNA. All three domains are needed to signal interferon expression, presumably to trigger higher-order protein assemblies, as shown by DAI mutants that can spontaneously form dimers and signal. Notably, 'knockdown' of DAI by small interfering RNA in primary mouse embryonic fibroblasts indicates that other sensors of cytosolic double-stranded DNA must exist. Their identity awaits future work. *LAD*

Proc. Natl. Acad. Sci. USA **105**, 5477–5482 (2008)

TIR mimics from pathogens

Toll-like receptor signaling initiates key immune responses to pathogens. In *Nature Medicine*, Miethke and colleagues identify two genes in a database search of bacterial genomes; these genes are homologs of the human Toll–interleukin 1 receptor (TIR) domain. Mutant bacterial strains lacking these TIR-containing protein (Tcp) genes stimulate much more proinflammatory tumor necrosis factor and interleukin 6. *TcpB* from *Brucella melitensis* blocks adaptor MyD88–induced activation of transcription factor NF-κB but not adaptor TRIF–mediated activation of interferon-β. The TIR domain of *TcpC* from *Esherichia coli* strain CFT073 binds to endogenous TIR-containing MyD88, is important for virulence in a mouse model of urinary tract infection, is secreted from *E. coli* CFT073 and then taken up by host cells, and is neutralized by treatment with the efflux pump inhibitor PAβN. These data demonstrate a unique way that pathogenic bacteria can subvert the host innate immune response, as well as a possible pharmacological countermeasure. ***DCB***

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Negative regulator of Nod signals

By a mechanism independent of its catalytic activity, caspase 12 suppresses intracellular caspase 1 inflammasomes, which process and activate interleukins 1 and 18. In *Cell Host & Microbe*, Saleh and colleagues extend this negative regulatory function of caspase 12 to cytosolic Nod proteins, which are crucial in the host defense against enteric bacteria. Caspase 12–deficient mice more efficiently eliminate the intestinal bacteria *Citrobacter rodentium*, and intestinal epithelial cells from these mice produce more antimicrobial peptides. Nod protein expression is required for this enhanced antimicrobial peptide production. By competing with the ubiquitin ligase TRAF6 for binding to the Nod adaptor protein RIP2, caspase 12 suppresses NF-κB activation induced by Nod stimulation. These findings may help clarify previous observations of links between polymorphisms in human caspase 12 and susceptibility to severe sepsis. *CB*

Cell Host Microbe **3**, 146–157 (2008)