Death by calcium

Bax and Bak, which mediate apoptosis *via* permeabilization of the outer mitochondrial membrane, are also expressed in the endoplasmic reticulum (ER), but their function in this organelle is unclear. In *Science*, Korsmeyer and colleagues show that Bax and Bak are required to maintain homeostatic ER Ca^{2+} concentrations. Mouse embryo fibroblasts deficient for both Bax and Bak had decreased resting Ca^{2+} concentrations in their ER, which subsequently reduced mitochondrial uptake of Ca^{2+} on release from the ER. Selective mitochondrial Bax expression restored apoptosis induced by BH3-only signals, but not by agents such as arachidonic acid and oxidative stress that induce release of intracellular Ca^{2+} stores. Conversely, overexpression of SERCA, an ER-associated calcium pump, could not restore BH3-only-induced cell death but did render cells susceptible to lipid second messengers and oxidative stimuli. Apoptosis mediated by other signals, such as staurosporine, required both ER Ca^{2+} release and mitochondrial Bax and Bak expression. These data show that Bax and Bak function in the ER and mitochondria to control apoptosis by regulating Ca^{2+} dynamics.

Science **300**, 135–139 (2003)

NF-κB to the rescue

The fate of a mature T cell after activation depends on multiple signaling pathways. Among them is the NF-κB pathway, which is thought to signal the survival of T cells *via* Akt. In the *Journal of Experimental Medicine*, Zheng *et al.* show that cells deficient in the two critical components of NF-κB, p50 and c-Rel, which have a disabled NF-κB pathway, have increased apoptosis and do not undergo cell cycling when stimulated through the T cell receptor (TCR). Secretion of IL-2 and expression of the anti-apoptotic gene Bcl-x_L are also markedly lower in the mutant cells. Retroviral transduction of an active NF-κB mutant prevents the death of T cells that are deprived of TCR signaling, suggesting that NF-κB is both necessary and sufficient for T cell survival. Constitutively active Akt also rescue T cells in $p50^{-/-}cRel^{-/-}$ mice, implying that the anti-apoptotic signals induced by Akt are independent of NF-κB. Thus, NF-κB is critical in TCR-mediated survival of T cells and functions through a pathway distinct from Akt.

J. Exp. Med. **197**, 861–874 (2003)

SETting death traps

The CTL protease granzyme A (GzmA) initiates apoptosis of target cells in a caspase-independent pathway. GzmA targets the SET complex during cell death. This 270- to 420-kDa ER-associated complex contains pp32 and three GzmA substrates, SET, HMG-2 and Ape1. In addition, the SET complex contains an unidentified GzmA-activated DNase (GAAD). In *Cell*, Lieberman and colleagues show that the tumor metastasis suppressor NM23-H1 functions as a GAAD. SET binding negatively regulates the nuclease activity of GAAD. During CTL-mediated apoptosis, GzmA cleavage of SET abrogates GAAD inhibition, allowing NM23-H1 to nick chromosomal DNA. Consistently, NM23-H1 overexpression enhanced GAAD activity, whereas NM23-H1 RNA interference reduced GzmA-induced DNA breaks. These data suggest GzmA mediates caspase-independent cell death *via* cleavage of SET, releasing NM23-H1 from inhibition.

Cell **112**, 659–672 (2003)

BAP break-up

Disruption of mitochondria is central to the cell death pathway. However, the events leading to mitochondrial fragmentation are unclear. In the *Journal of Cell Biology*, Brekenridge *et al*. show that the cleavage product of BAP31, which is an integral membrane protein of the endoplasmic reticulum, may be the key. Mitochondria are normally in a dynamic state of fusion and fission with associated microtubules. Caspase-8 activated by the death receptors cleaves BAP31, yielding the p20 pro-apoptotic fragment that causes release of Ca^{2+} from the ER and uptake of Ca^{2+} by the mitochondria. Calcium uptake by mitochondria recruits the protein Drp1, which mediates mitochondria fission. Full commitment to cell death then relies on the Bcl-2 family members to release cytochrome c from the fragmented mitochondria. Thus, BAP31 facilitates the cross-talk between ER and mitochondria, orchestrating the final death pathway.

J. Cell. Biol. **160**, 1115–1127 (2003)

Ku70 blocks Bax

Intrinsic apoptotic stimuli induce translocation of cytosolic Bax to mitochondria, triggering release of cytochrome c. But how inactive Bax remains sequestered in the cytoplasm was unclear. In *Nature Cell Biology*, Sawada *et al*. show that Ku70 binds inactive cytoplasmic Bax, suppressing apoptosis initiated through intrinsic apoptotic pathways, but not that triggered by death-receptor pathways. Initially identified as a thymic autoantigen, Ku70 exists in both the nucleus—as a DNA repair factor in complex with Ku80—and the cytoplasm, shown here to specifically form a complex with Bax. In resting cells, the majority of Bax protein is complexed with Ku70. Cytosolic, but not nuclear, Ku70 disappears upon induction of apoptosis. Ku70 overproduction reduces cell death, but *Ku70* antisense RNA sensitized cells to intrinsic death signals. The new data explains the hypersensitivity of Ku70-deficient cells to non-DNA–damaging cell stresses. What remains unknown is how death signals activate and release Bax from Ku70.

Nat. Cell Biol. **5**, 320–329 (2003)

GRIM tales

The transcriptional transactivator STAT3 induces anti-apoptotic gene expression in response to cytokines or growth factor signals. Constitutive activation of STAT3 has been implicated in tumorigenesis, resulting in part from loss of sensitivity to normal apoptotic signals. In the *EMBO Journal*, Lufei *et al*. identify GRIM-19 (one of a family of genes associated with retinoid–IFN-induced mortality) as a natural inhibitor of STAT3. GRIM-19 forms a protein complex with STAT3, but not other STAT molecules. STAT3 is localized in perinuclear aggregates but translocates to the nucleus upon growth factor stimulation. GRIM-19 primarily localizes to mitochondria, but N-terminal mutants fail to accumulate in mitochondria and are defective in blocking STAT3 nuclear localization. Excess GRIM-19 production reduced STAT3-dependent gene expression and nuclear localization in response to growth factors. Thus, GRIM-19 acts as a physiological tether of STAT3, which is released upon mitogenic stimulation.

EMBO J. **22**, 1325–1335 (2003)