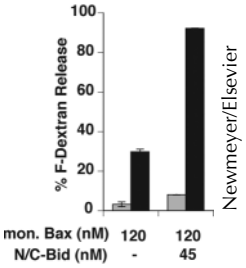
TEXT BY NICOLE LEBRASSEUR
LEBRASN@ROCKEFELLER.EDU

Poking a hole in mitochondria

Proapoptotic Bcl-2 proteins release death proteins such as cytochrome *c* by poking holes directly in mitochondria, according to Tomomi Kuwana, Donald D. Newmeyer (La Jolla Institute for Allergy and Immunology, San Diego, CA), and colleagues.

Earlier in vivo studies of the large protein family were stymied by the number of family members, and in vitro assays were inconclusive. The Newmeyer group has now successfully developed a minimal cell-free membrane model that behaves like mitochondrial outer membranes (OMMs). Adding recombinant Bid and Bax to the membranes allowed the exit of molecules over 100 times bigger than cytochrome *c*. With further minimalism, the authors showed that Bid and Bax also released large molecules from protein-free liposomes, as long as the liposomes contained cardiolipin, a signature mitochondrial lipid. Thus, Bax, Bid, and cardiolipin seem to be all a cell needs to induce mitochondria to spill their death-inducing guts. "That we can permeabilize membranes with Bid and Bax alone means we don't need to invoke any more complicated mechanism," says Newmeyer.



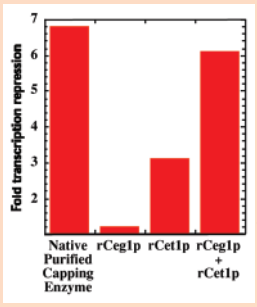
Bax and Bid release dextrans from liposomes that contain cardiolipin (black bars).

The mechanism of hole formation is probably not simple, however. Tetramers of Bax were sufficient for the release of the macromolecules, but a Bax tetramer would not form a conventional protein channel of adequate size. Newmeyer hypothesizes that the insertion of Bax into the OMM may cause a rearrangement in or change the curvature of lipids, particularly cardiolipin, such that Bax and the lipids might both line the newly made opening. ■

Reference: Kuwana, T., et al. 2002. *Cell.* 1111:331–342.

Putting a cap on reinitiation

The transcription apparatus barely gets started before shutting itself down, according to Lawrence Myers (Dartmouth Medical School, Hanover, NH), Paul Tempst (Memorial Sloan-Kettering Cancer Center, New York, NY), and colleagues.



Native and recombinant capping enzymes block transcription in vitro.

The authors have found that the two yeast mRNA capping enzymes, Cet1p and Ceg1p, are potent in vitro inhibitors of transcription. Cet1p, stimulated by its Ceg1p binding partner, stalled transcription by blocking reinitiation at already activated promoters. Conversely, elimination of Cet1p in vivo stimulated transcription. Although Cet1p is the first general repressor found to act at reinitiation, this step is well suited for transcription inhibition. "If 100 transcripts are made from a promoter," says Myers, "only one is made at initiation—the remaining 99 are made by reinitiation."

A block by the capping enzyme could ensure that RNA polymerase does not make more transcripts than can be properly processed. It is still unclear how capping enzymes block reinitiation. Possibly, the interaction of Cet1p with proteins in the reinitiation scaffold may prevent further polymerase subunits from entering. The inhibition must be lifted to allow multiple rounds of transcription. Here, Myers speculates that the final step of capping (methylation, which does not occur in the in vitro system) might release repression and allow reinitiation. ■

Reference: Myers, L., et al. 2002. *Mol. Cell.* 10:883–894.

Dendritic cells can be self sustaining

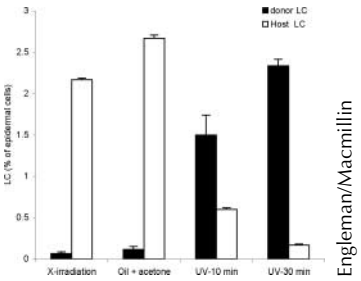
Langerhans cells (LCs) are antigen-presenting cells that explore the skin for signs of infection. Whether or not they find an infection, LCs are continually replaced. Miriam Merad (Stanford University School of Medicine, Stanford, CA), Edgar Engleman, and colleagues show that LCs maintain their numbers through two sources: a local supply for normal upkeep, and an emergency store in the blood.

LCs are the first example of a dendritic cell type that is maintained locally. Merad and colleagues examined LCs in mice that had received a bone marrow transplant. Although LCs in the bloodstream were replaced by cells from the donor, LCs in the skin remained of host origin. "Langerhans were thought to be constantly reproduced by the bone marrow," says Merad. "But LCs in skin are replacing themselves with a local store of precursors." Thus, precursor pools in the skin are probably set during embryogenesis.

Despite the local source, LCs were also recruited from the blood, but only when the need was great. Both minor and severe injuries depleted LCs in the skin, but bone marrow–derived LC precursors were recruited from the blood only after severe injuries, such as exposure to UV light. Recruitment required the chemokine receptor CCR2 and secretion of its ligands by the injured skin.

The results fuel the argument that bone marrow–derived stem cells may provide a source of repair cells that can be rapidly mobilized after injury. Muscle mesenchymal cells and microglia brain cells likewise maintain themselves via local stores and might recruit new stem cells from the blood only upon injury or inflammation, perhaps to minimize outside influences on sensitive tissues. ■

Reference: Merad, M., et al. 2002. *Nat. Immunol.* 10.1038/ni852.



LCs are recruited from the blood (black bars) after severe (UV-induced), but not minor, injures.