PROTEIN FOLDING

Handling the stress

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BAX and BAK are mitochondrial proapoptotic proteins that function in intrinsic cell-death pathways. However, a report in *Science* now shows that BAX and BAK also function at the endoplasmic reticulum (ER) membrane, and reveals a new role for these members of the core apoptotic machinery in the stress-associated unfolded-protein response (UPR).

In higher eukaryotes, ER stress stimulates three distinct UPR-signalling pathways through sensors that include IRE1α (inositol-requiring transmembrane kinase and endonuclease-1α), PERK (protein kinase-like ER kinase) and ATF6 (activation of transcription factor-6). Cells from mice that are deficient in both *Bax* and *Bak* are resistant to proapoptotic agents that induce the UPR, which prompted the authors to further investigate the connection between these proapoptotic proteins and UPR signalling events *in vivo*.

Hetz *et al.* generated conditional *Bax Bak* double-knockout mice and used an *in vivo* model for ER stress, which involved the intraperitoneal injection of tunicamycin into the liver and kidney. *Bax Bak* double-knockout mice responded abnormally to tunicamycin-induced ER stress in the liver; they displayed extensive tissue damage and decreased expression of the IRE1α-substrate X-box-binding protein-1 (XBP1) and its target genes. Hetz *et al.* next showed that this phenotype was associated with cellular dysfunction rather than cell death. This finding led the authors to postulate that BAX and BAK might have an important role in adaptation responses to ER stress *in vivo* through the modulation of IRE1α signalling.

How can these mitochondrial proteins modulate an ER response? The authors analysed different signalling pathways in *Bax Bak* double-knockout cells and first showed that these cells display a phenotype that is similar to that of IRE1α-deficient cells after ER-stress induction. Then, using organelle-specific reconstitution assays and ER-targeted versions of BAK, Hetz *et al.* not only found that BAK expression at the ER membrane is required for IRE1α signalling, but also showed that both BAK and BAX directly interact with the cytosolic domain of IRE1α, probably stabilizing its active form.

Whether these proteins function as stress sentinels that connect stress signals to the proapoptotic machinery — under circumstances when cellular homeostasis is irreversibly altered — remains to be seen.

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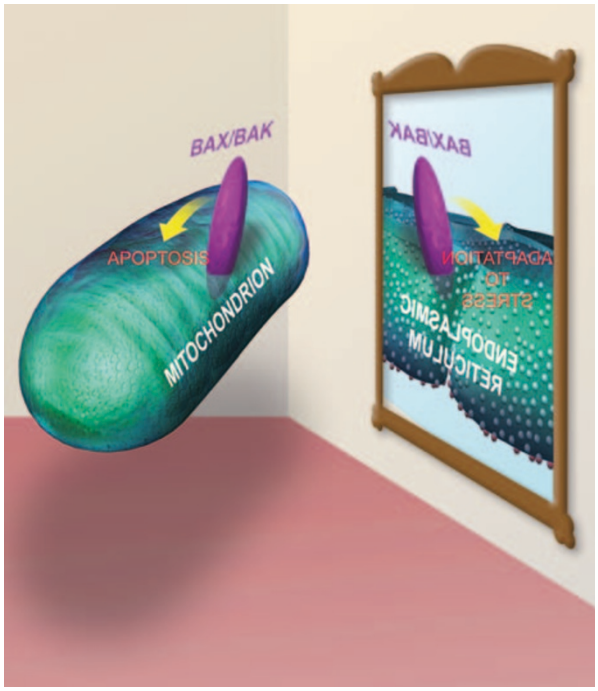

Image courtesy of E. Smith, Dana Farber Cancer Institute, Boston, USA.

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ORIGINAL RESEARCH PAPER Hetz, C. *et al.* Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1α. *Science* **312**, 572–576 (2006)