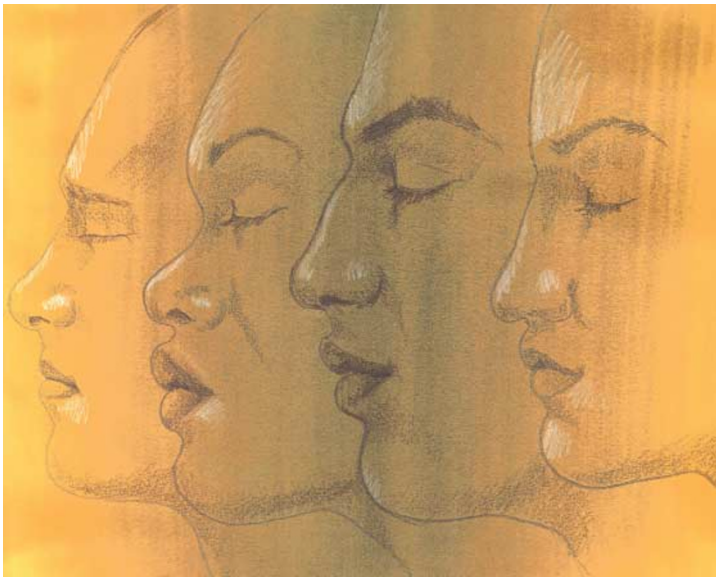
APOPTOSIS

Managing stress



In today's hectic society, it's important to manage our stress levels so that we remain healthy and, not surprisingly, stress management is also crucial at the cellular level. Stress in the endoplasmic reticulum (ER) has been linked to the induction of apoptosis. This link could be important in ischaemia–reperfusion injury when Ca^{2+} escapes from the ER at a time of ATP deficiency, and in neurodegenerative diseases when protein folding/secretion in the ER is defective. But what mechanisms control this apoptotic process? Reed and colleagues shed light on the matter in *Molecular Cell*.

They focused on mammalian Bax inhibitor-1 (BI-1) — a known anti-apoptotic protein that is localized to ER membranes. They generated *Bi-1* knockout mice, and tested the sensitivity of BI-1-deficient cells to ER stress. Compared to *Bi-1*$^{+/+}$ and *Bi-1*$^{+/-}$ cells, *Bi-1*$^{-/-}$ fibroblasts, hepatocytes and neurons were more sensitive to the apoptosis that is induced by ER-stress agents (thapsigargin, tunicamycin and brefeldin A). However, cells that lacked BI-1 showed a normal sensitivity to agents that induce the classic, intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways.

Next, Reed and co-workers showed that BI-1-deficient mice were more sensitive to ER-dependent tissue injury — tunicamycin injection into *Bi-1*$^{-/-}$ mice resulted in increased signs of apoptosis in kidney cells and neurons compared with wild-type mice. Furthermore, using a mouse stroke model, they showed that BI-1 is needed to prevent the apoptotic brain damage that is caused by ischaemia–reperfusion injury.

As the loss of BI-1 increases sensitivity to ER-stress-induced apoptosis, the authors investigated whether BI-1 overexpression has a protective effect. Indeed, they showed that BI-1-overexpressing cells are more resistant to ER-stress-induced apoptosis, but retain a similar sensitivity to the intrinsic and extrinsic apoptotic pathways.

So, at which point does BI-1 exert its protective function and how does it function? Reed and colleagues found that BI-1 inhibits the activation and mitochondrial translocation of Bax, prevents depolarization of the mitochondrial membrane and reduces the activation of caspases that function downstream of mitochondria. It therefore seems that BI-1 blocks apoptotic signalling between the ER and mitochondria. Furthermore, they showed that BI-1 seems to function by altering ER Ca^{2+} regulation — BI-1 overexpression reduced the release of Ca^{2+} from the ER.

This work has therefore shown that "BI-1 regulates a cell death pathway important for cytopreservation during ER stress". As ER stress is relevant to conditions such as stroke, Alzheimer's disease and Parkinson's disease, it will be interesting to determine whether the function of BI-1 is of relevance to these disorders and whether it can be exploited therapeutically to preserve cells in such disease situations.

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References and links

ORIGINAL RESEARCH PAPER Chae, H.-J. *et al.* BI-1 regulates an apoptosis pathway linked to endoplasmic reticulum stress. *Mol. Cell* **15**, 355–366 (2004)

WEB SITE
John Reed's laboratory:
http://www.burnham.org/FacultyAndResearch/Faculty/john_reed_report.asp