

# Prolonged stress sparks ER to release calcium stores and induce cell death in aging-related diseases

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Li et al. explain how prolonged stress sparks the endoplasmic reticulum (ER) to release its calcium stores, inducing cells to undergo apoptosis in several aging-related diseases. The study will appear in the September 21, 2009 issue of the *Journal of Cell Biology* (online September 14).

Stressful conditions cause misfolded proteins to accumulate in the ER. Cells try to recover by slowing down translation and increasing production of their protein folding machinery. But if the [stress](#) continues, prolonged expression of a transcription factor called CHOP promotes cell death instead. The apoptotic machinery is triggered by calcium released from the ER, but how CHOP induces this step wasn't known.

Li et al. zoomed in on two ER proteins—an oxidase called ERO1-alpha and the [calcium channel](#) IP3R—to connect the dots between CHOP induction and calcium release. ERO1-alpha is a transcriptional target of CHOP, and its reexpression in cells lacking CHOP restored the cell death pathway. On the other hand, knocking down ERO1-alpha or IP3R prevented calcium release and apoptosis in response to ER stress. Insulin-resistant obese mice—known to suffer increased ER stress—showed elevated IP3R-dependent calcium release, indicating that the pathway operates in vivo.

The researchers think that ERO1-alpha oxidizes the ER lumen,

promoting the formation of a key disulphide bond in IP3R that makes the channel more active. Senior author Ira Tabas points out the importance of understanding this mechanism further: mice lacking CHOP are protected against cell death arising from a variety of pathologies, including advanced atherosclerosis, diabetes, and neurodegeneration.

More information: Li, G., et al. 2009. *J. Cell Biol.*  
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