In This Issue

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How ER stress gives cells the CHOP

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.

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-α and the calcium channel IP3R—to connect the dots between CHOP induction and calcium release. ERO1-α 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-α 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-α 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.

Li, G., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200904060.

The long and short of mitochondrial fusion

Mitochondria still fuse in yeast with a GTPase-deficient l-Mgm1 (left) but fragment if the s-Mgm1 isoform lacks GTPase activity (right).

Two isoforms of a yeast GTPase combine—with the help of a special phospholipid—to drive mitochondrial inner membrane fusion, DeVay et al. report.

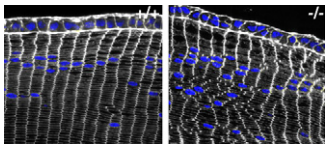
Mitochondria constantly merge and divide to distribute their activity appropriately throughout the cell. When coming together, these organelles use proteins related to the endocytic GTPase dynamin to fuse both their outer and inner membranes. In yeast, two different isoforms of a GTPase called Mgm1 drive inner membrane fusion: a short soluble form (s-Mgm1) that is proteolytically cleaved from a longer, transmembrane version (l-Mgm1). Both isoforms are required for fusion, but their precise contributions to the process were unclear.

DeVay et al. expressed the proteins and examined their association with liposomes mimicking either the mitochondrial inner or outer membranes. Both s-Mgm1 and l-Mgm1 preferred inner membrane liposomes—the key determinant was an inner membrane phospholipid called cardiolipin. Moreover, although s-Mgm1 on its own was monomeric and inactive, cardiolipin stimulated the protein's GTPase activity by promoting its oligomerization on the liposome surface. s-Mgm1 thus acts specifically at the inner membrane, despite its localization to the intermembrane space.

Cardiolipin didn't stimulate the activity of l-Mgm1, however, which fit the group's observation that yeast expressing GTPase-deficient l-Mgm1 were normal, as long as they expressed a separate version of s-Mgm1 that retained its enzymatic function. The researchers think that cardiolipin helps the two Mgm1 isoforms assemble together on the inner membrane, where the conformational changes in s-Mgm1 as it hydrolyses GTP are coupled to lipid bilayer deformation by l-Mgm1's transmembrane domain. In addition, l-Mgm1 dimers may tether opposing inner membranes together, as a prelude to fusion or to fold them into cristae.

DeVay, R.M., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906098.

Cell packing comes under the lens



The regular hexagonal arrangement of lens fiber cells is disrupted in the absence of tropomodulin1 (right).

A network of proteins underlying the plasma membrane keeps epithelial cells in shape and maintains their orderly hexagonal packing in the mouse lens, say Nowak et al.

Spectrin, F-actin, and associated proteins form a meshwork that supports and shapes the plasma membrane of red blood cells. A similar network underlies the membranes of other cell types, including lens fiber cells: elongated epithelial cells that encircle vertebrate lenses in concentric layers, appearing in cross section as tightly packed hexagons. Actin filaments within this membrane skeleton are stabilized by their association with members of the tropomyosin and tropomodulin families of actin-binding proteins.

In mice lacking tropomodulin1, γ-tropomyosin was also lost from the membrane skeleton of lens fiber cells. F-actin and spectrin remained associated with the cell membrane, but gaps appeared in the usually continuous protein network, suggesting that the two actin-binding proteins stabilize a subset of actin filaments required to link the network together. Scanning electron microscopy revealed that fiber cell membrane protrusions, which interlock with neighboring cells, were distorted and irregularly arranged in the absence of tropomodulin1. And although the fiber cells appeared hexagonal when first forming at the lens' equator, they often became misshapen and disorganized as they matured and moved toward the lens' center.

Senior author Velia Fowler thinks that disruption of the spectrin–actin network alters the adhesive interactions between neighboring cells, causing their shapes and packing to become disordered in response to the mechanical stresses associated with lens growth and eye movements.

Nowak, R.B., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200905065.