How the ER gets its shape

Two proteins are sufficient to form tubules at the ER, say Junjie Hu, Tom Rapoport (Harvard Medical School, Boston, MA), and William Prinz (National Institutes of Health, Bethesda, MD).

The ER often appears as a tubular network. Previous work showed its tubular shaping involves a class of integral membrane proteins, comprising the reticulons and a protein family that includes DP1 in mammals and Yop1p in yeast. To investigate the tubule-forming abilities of these proteins, the authors purified Yop1p or a reticulum from yeast cells, mixed each with lipids, and reconstituted artificial membranes. The resulting proteoliposomes had the shape of tubules with a constant diameter (~15–17 nm). These tubules were narrower than normal ER tubules because they contain a higher concentration of tubule-inducing proteins.

“The reticulons and DP1/Yop1p were known to be required for ER tubule formation,” Rapoport says. “This study shows they are sufficient.” The structure of these proteins is not known yet, but they form hairpin bends in the membrane and have the propensity to form oligomers. These characteristics suggest that they may form tubules via two effects: external wedging to induce local curvature, and protein linking to form a scaffold that enforces a smooth bend. “The synthesis of the two is most efficient,” says Rapoport. “We think this is a paradigm for how membranes are shaped in general.” JCB

Hu, J., et al. 2008. Science. 319:1247–1250.

Lipid is new Star in nuclear regulation

A lipid known for its cytoplasmic duties jacks up mRNA levels by activating a polyadenylating enzyme, say Richard Anderson and colleagues (University of Wisconsin, Madison, WI).

The PtdIns4,5P2 phosphoinositide is generated by PIPK-α, which is activated by an as-yet uncharacterized stress–response pathway and which links to mRNA-processing complexes called nuclear speckles. In their new study, the authors used the enzyme’s speckle-targeting region as bait to find PIPK-α–associated proteins, which they reasoned might be regulatory targets of PtdIns4,5P2. This strategy led them to a new polyadenylating enzyme they named “speckle-targeted PIPK-α–regulated poly(A) polymerase,” or Star-PAP. The close proximity of PIPK-α and Star-PAP might facilitate the lipid’s ability to turn on the polymerase.

A knockdown of either Star-PAP or PIPK-α reduced the polyadenylation and subsequent expression levels of about 2,000 mRNAs, many of which are involved in response to oxidative stress. Treatment of cells with an oxidative stressor increased the association of Star-PAP with PIPK-α and the RNA polymerase machinery and thereby increased Star-PAP’s activity. Together, the data show the Star-PAP assembly is positioned to extend poly(A) tails on transcripts that are needed for surviving oxidative stresses.

“This is a novel gene expression regulatory mechanism,” says Anderson. “It’s also the first poly(A) polymerase [found to be] regulated by a signaling pathway. This suggests that other PAPs may be regulated as well.” JCB

Mellman, D.L., et al. 2008. Nature. 451:1013–1018.

New exit: caspase-1 for secretion

Caspase activates secretion of many inflammatory response proteins without signal sequences, say Martin Keller, Hans-Dietmar Beer, and colleagues (Swiss Federal Institute of Technology, Zürich, Switzerland), revealing a new pathway for secretion.

The cytokine interleukin-1α (IL-1α) has no secretion signal peptide but is nonetheless secreted as part of the inflammatory response. IL-1α is also not a substrate for caspase-1, but its secretion is reduced in macrophages that do not express the protease.

In the new work, the authors showed that caspase-1 inhibition reduced secretion of IL-1α and almost 80 other inflammatory response proteins, many of which lack secretion signal peptides, including FGF-2. Many of the transported proteins were not caspase-1 substrates, yet catalytic activity of the enzyme was required for their secretion, for reasons that are not yet clear. Both IL-1α and FGF-2 bound to caspase-1, suggesting that the enzyme may carry them directly.

“Unlike signal sequence–driven secretion, which is regulated at the level of transcription,” says Beer, “unconventional secretion can rapidly release a wide variety of proteins.” The proteins involved trigger detoxification, tissue repair, and cell survival, suggesting caspase-1 is helping to regulate the entire inflammatory response. JCB

Keller, M., et al. 2008. Cell. 132:818–831.