Weaklings unite to reorganize cell

Although normally seen as a branching network of membranes, the endoplasmic reticulum can quickly and dramatically reorganize into a variety of regular, tightly stacked arrays. Referring to these structures collectively as organized smooth endoplasmic reticulum (OSER), Snapp et al. report on page 257 that surprisingly weak protein interactions can induce their formation. The results undermine a previous model of OSER formation, suggest a general mechanism that could drive membrane stacking in organelle biogenesis, and raise a warning flag for users of green fluorescent protein (GFP) tags.

Previous work suggested that OSER biogenesis entailed the tight, zipper-like dimerization of the cytoplasmic domains of certain ER-resident proteins. However, the authors found that naturally occurring OSER-inducing proteins can diffuse freely between OSER and ordinary reticular ER, indicating that they are not tightly bound in zipper structures. Weakly dimerizing GFP, and chimeric ER proteins with GFP on their cytoplasmic tails, could also induce OSER formation, but similar proteins with nondimerizing GFP tags could not.

When any of the weakly dimerizing proteins are expressed above a threshold level in a cell, several different types of OSER structures can form, suggesting that a single mechanism produces the spiraling, stacked, and crystallloid ER shapes seen in earlier studies. Mutations that cause the genetic diseases Charcot-Marie-Tooth syndrome and early onset torsion dystonia have been linked to mutant protein accumulation in the ER leading to OSER formation. The function of OSER in healthy cells remains unknown, but Snapp et al. suggest that the structures may help sequester lipid-soluble toxins.

Mass action by weakly binding proteins might be a general way to organize stacked organelle structures, including chloroplast thylakoids and the Golgi apparatus. The striking morphological changes induced by dimerizing GFP domains also suggest that the popular fluorescent tag could have unintended consequences.

In polarized epithelial cells, the clathrin adaptor complex AP-1B targets many proteins to the basolateral membrane, but how does AP-1B separate its cargos away from the ubiquitous AP-1A complex, from which it differs only slightly? A pair of papers in this issue identify several unique components of the AP-1B targeting system, and show that AP-1B segregates into a distinct membrane domain that may connect two basolateral sorting pathways.

Folsch et al. (page 351) show that, despite their strong homology, AP-1A and AP-1B complexes segregate onto distinct populations of clathrin-coated membranes in MDCK cells. In the Golgi apparatus, AP-1B specifically recruits components of the exocyst complex, which is thought to target transport vesicles to the basolateral plasma membrane. AP-1B also localizes to perinuclear regions that appear to be in a post-Golgi compartment that is distinct from the trans-Golgi network but very close to transferrin-positive recycling endosomes.

The post-Golgi localization of AP-1B is especially intriguing, as polarized cells must sort both internalized receptors in the endosome recycling pathway and newly synthesized proteins from the Golgi apparatus. The two sorting pathways may intersect in the perinuclear region.

Although many basolateral proteins rely on AP-1B for targeting, not all do—a fact underscored by Ang et al. on page 339. These authors show that disrupting the function of either Rab8 or Cdc42 specifically blocks AP-1B–mediated transport, leaving AP-1B–independent basolateral proteins unaffected. Rab8, a mammalian homologue of yeast Sec4p, appears in the same perinuclear region where AP-1B, exocyst components, and recycling endosomes appear to congregate. The authors are now using an immobilized Golgi apparatus assay to identify additional components of the sorting system.