Imagine inserting a piece of string into an inflated balloon without letting any of the air out. An analogous problem confronts cells in the production of integral membrane-spanning proteins, which must be inserted partway into the ER without letting the ER calcium stores leak into the cytoplasm. On page 261, Haigh and Johnson show that the ER luminal chaperone protein BiP controls one end of a double door system at the translocon, the pore through which nascent proteins enter the ER, and propose a model to explain how the cell accomplishes the daunting task of regulating this double door.

On the cytoplasmic side of the ER membrane, the ribosome binds to the translocon to seal it while translocating a nascent polypeptide into the ER lumen. But the ribosome must break this seal to allow a cytoplasmic domain to extend into the cytoplasm. Some mechanism must exist to seal the luminal side of the translocon when this happens.

Using a clever fluorescence quenching assay in isolated microsomes, the authors found that BiP is required to seal the luminal side of the translocon pore at certain stages during the integration of a transmembrane protein, and that BiP can do this even in the absence of other luminal proteins. This activity of BiP requires ATP hydrolysis, suggesting that the protein may use similar mechanisms in its diverse duties as a chaperone and pore sealer.

The authors propose that translation of a transmembrane sequence causes a BiP-mediated closure of the luminal side of a translocon, allowing the ribosomal seal to be opened on the cytoplasmic side without breaching the ER membrane. Future studies will focus on identifying the domains of BiP responsible for sealing the translocon, and determining how BiP and the ribosome coordinate their actions across the ER membrane.

Proteins that are destined to be secreted from a cell undergo a multistep sorting and transport process, but until recently a critical portion of the secretory pathway—the transport of cargo from the Golgi apparatus—has been difficult to dissect. On page 271, Harsay and Schekman show that one population of yeast secretory proteins apparently takes a detour through an endosomal compartment on its way from the Golgi apparatus to the cell surface. Although some types of mammalian cells appear to use a secretory pathway involving endosomes, the new work is the first demonstration of such a system in yeast, a model system that should help define additional steps in this poorly understood process.

Previous work demonstrated that yeast sec6 mutants exhibit a post-Golgi secretion defect that causes the accumulation of two populations of secretory vesicles, distinguished by their differing buoyant densities and cargos. In this genetic background, Harsay and Schekman found that mutations in VPS genes, affecting transport to an endosomal compartment, also block protein sorting to the high-density secretory vesicles. In these double mutants, proteins normally targeted to the high-density vesicles are instead sorted into the light-density vesicles.

This is the first time newly synthesized soluble exocytic proteins have been shown to move through an endosomal compartment on the way to being secreted. While it is still unclear why the cell would have two separate secretion pathways, one possibility is that the less abundant high-density vesicles, which are enriched in enzymes for particular metabolic processes, may allow rapid responses to environmental changes without causing membrane expansion. The cell’s ability to reroute secretory proteins from one pathway to another may also explain why it has been difficult to isolate mutants defective in the post-Golgi portion of the secretion process: both pathways would have to be shut down simultaneously to block secretion. Using mutations that block the high-density vesicle pathway, the authors are now trying to identify genes involved in the light-density vesicle pathway.