

Molecular Biology of **THE CELL**

Fifth Edition

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Proteins Leave the ER in COPII-Coated Transport Vesicles

To initiate their journey along the biosynthetic–secretory pathway, proteins that have entered the ER and are destined for the Golgi apparatus or beyond are first packaged into small COPII-coated transport vesicles. These vesicles bud from specialized regions of the ER called *ER exit sites*, whose membrane lacks bound ribosomes. Most animal cells have ER exit sites dispersed throughout the ER network.

Originally, it was thought that all proteins that are not tethered in the ER enter transport vesicles by default. It is now clear, however, that entry into vesicles that leave the ER is usually a selective process. Many membrane proteins are actively recruited into such vesicles, where they become concentrated. It is thought that these cargo proteins display exit (transport) signals on their cytosolic surface that components of the COPII coat recognize (**Figure 13–20**); these coat components act as cargo receptors and are recycled back to the ER after they have delivered their cargo to the Golgi apparatus. Soluble cargo proteins in the ER lumen, by contrast, have exit signals that attach them to transmembrane cargo receptors, which in turn bind through exit signals in their cytoplasmic tails to components of the COPII coat. At a lower rate, proteins without exit signals can also enter transport vesicles, so that even proteins that normally function in the ER (so-called *ER resident proteins*) slowly leak out of the ER and are delivered to the Golgi apparatus. Similarly, secretory proteins that are made in high concentrations may leave the ER without the help of exit signals or cargo receptors.

The exit signals that direct soluble proteins out of the ER for transport to the Golgi apparatus and beyond are not well understood. Some transmembrane proteins that serve as cargo receptors for packaging some secretory proteins into COPII-coated vesicles are lectins that bind to oligosaccharides. The ERGIC53 lectin, for example, binds to mannose and is thought to recognize this sugar on two secreted blood-clotting factors (Factor V and Factor VIII), thereby packaging the proteins into transport vesicles in the ER. ERGIC53's role in protein transport was identified because humans who lack it owing to an inherited mutation have lowered serum levels of Factors V and VIII, and they therefore bleed excessively.

Only Proteins That Are Properly Folded and Assembled Can Leave the ER

To exit from the ER, proteins must be properly folded and, if they are subunits of multimeric protein complexes, they may need to be completely assembled. Those that are misfolded or incompletely assembled remain in the ER, where they are bound to chaperone proteins (discussed in Chapter 6), such as *BiP* or *calnexin*. The chaperones may cover up the exit signals or somehow anchor the proteins in

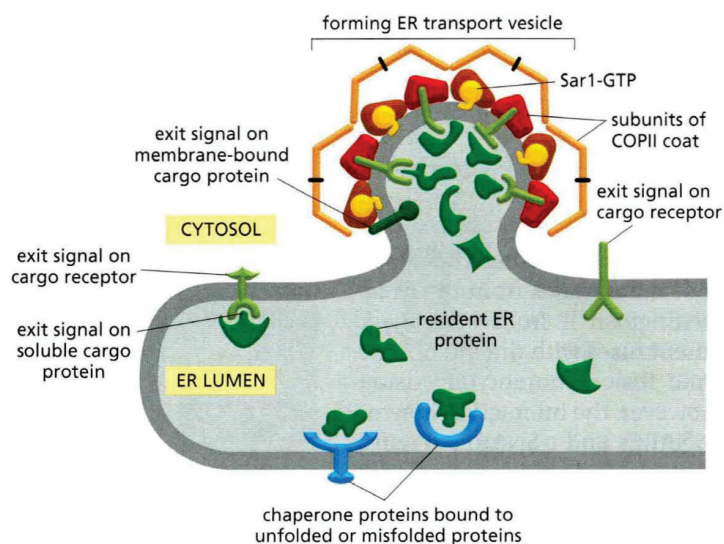


Figure 13–20 The recruitment of cargo molecules into ER transport vesicles. By binding directly or indirectly to the COPII coat, membrane and soluble cargo proteins, respectively, become concentrated in the transport vesicles as they leave the ER. Membrane proteins are packaged into budding transport vesicles through interactions of exit signals on their cytosolic tails with the COPII coat. Some of the membrane proteins that the coat traps function as cargo receptors, binding soluble proteins in the lumen and helping to package them into vesicles. A typical 50-nm transport vesicle contains about 200 membrane proteins, which can be of many different types. As indicated, unfolded or incompletely assembled proteins are bound to chaperones and retained in the ER compartment.

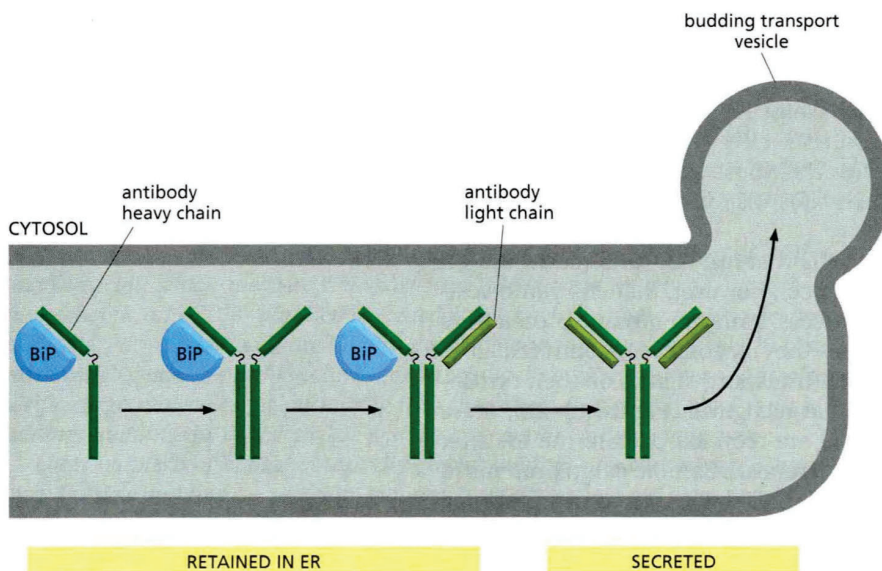


Figure 13–21 Retention of incompletely assembled antibody molecules in the ER. Antibodies are made up of two heavy and two light chains (discussed in Chapter 25), which assemble in the ER. The chaperone BiP is thought to bind to all incompletely assembled antibody molecules and to cover up an exit signal. Thus, only completely assembled antibodies leave the ER and are secreted.

the ER (**Figure 13–21**). Such failed proteins are eventually transported back into the cytosol, where they are degraded by proteasomes (discussed in Chapters 6 and 12). This quality-control step prevents the onward transport of misfolded or misassembled proteins that could potentially interfere with the functions of normal proteins. There is a surprising amount of corrective action. More than 90% of the newly synthesized subunits of the T cell receptor (discussed in Chapter 25) and of the acetylcholine receptor (discussed in Chapter 11), for example, are normally degraded without ever reaching the cell surface where they function. Thus, cells must make a large excess of many protein molecules to produce a select few that fold, assemble, and function properly.

The process of continual degradation of a portion of ER proteins also provides an early warning system to alert the immune system when a virus infects cells. Using specialized ABC-type transporters, the ER imports peptide fragments of viral proteins produced by proteases in the proteasome. The foreign peptides are loaded onto class I MHC proteins in the ER lumen and then transported to the cell surface. T lymphocytes then recognize the peptides as non-self antigens and kill the infected cells (discussed in Chapter 25).

Sometimes, however, there are drawbacks to the stringent quality-control mechanism. The predominant mutations that cause cystic fibrosis, a common inherited disease, result in the production of a slightly misfolded form of a plasma membrane protein important for Cl^- transport. Although the mutant protein would function perfectly normally if it reached the plasma membrane, it remains in the ER. This devastating disease thus results not because the mutation inactivates the protein but because the active protein is discarded before it reaches the plasma membrane.

Vesicular Tubular Clusters Mediate Transport from the ER to the Golgi Apparatus

After transport vesicles have budded from ER exit sites and have shed their coat, they begin to fuse with one another. This fusion of membranes from the same compartment is called *homotypic fusion*, to distinguish it from *heterotypic fusion*, in which a membrane from one compartment fuses with the membrane of a different compartment. As with heterotypic fusion, homotypic fusion requires a set of matching SNAREs. In this case, however, the interaction is symmetrical, with both membranes contributing v-SNAREs and t-SNAREs (**Figure 13–22**).

The structures formed when ER-derived vesicles fuse with one another are called *vesicular tubular clusters*, because they have a convoluted appearance in