A Is For . . .

Translocase

translocase *— A heterotrimeric protein complex that changes shape to allow transport of newly formed polypeptides across cell membranes.*

All cellular proteins are synthesized in the cytosol, but many must then be transported through phospholipid membranes to reach their final destinations. While ion channels are highly specific in allowing one kind of ion through while preventing the passage of others, the protein-translocation channel must allow the passage of chemically and sterically varied substrates, representing any segment from a translocating protein, without compromising the permeability of the membrane.

Almost 30 years ago, Günter Blobel proposed that the translocation of proteins across membranes would occur through a proteinaceous channel, and that newly made proteins are targeted for export by a signal peptide at one end, which ultimately is removed during transport.

It was originally proposed that translocation occurred as the protein was being made (co-translationally), with a tight seal between the protein-synthesis machinery (ribosomes) and the translocation channel ensuring osmotic integrity. However, electron microscopic studies show a gap of about 15 Å separating the ribosomal exit site from the translocation channel during co-translational transport, and some translocation also occurs post-translationally, after the polypeptides are completed in the cytosol. The solution is a flexible channel that expands to accommodate larger protein segments as they pass through the membrane.

Transport occurs through a *translocase*, a highly conserved, heterotrimeric complex of membrane proteins, called the Sec61 complex in eukaryotes and the SecY complex in bacteria and archaea. It consists of α-, β-, and γ-subunits, with the α-subunit forming the protein-translocation channel.

The α-subunit has two linked halves, transmembrane (TM) segments 1–5 and 6–10, joined by the γ-subunit. This creates a funnel- or hourglass-shaped channel. In the resting state, the channel is plugged by a short α-helix, which moves aside during translocation, opening the channel to reveal a ring of hydrophobic isoleucine residues that form a pore at its constriction.

Because the channel is a passive conduit, it must associate with other components that provide energy to drive the polypeptide through the channel. Translocation is initiated by the binding of this partner molecule. In co-translational transport, the ribosome is the partner, and the elongating polypeptide chain moves directly from the ribosome into the membrane channel. In post-translational transport, in bacteria, the cytosolic ATPase SecA pushes polypeptides into the channel, whereas in eukaryotic cells, the Hsp70-family chaperone BiP performs this role.

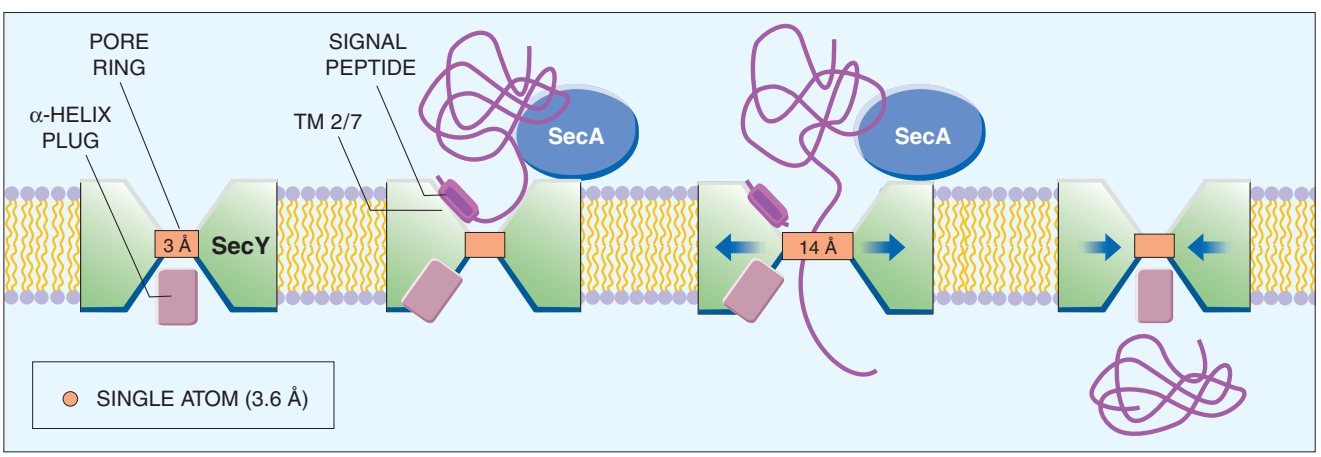
The next step is the binding of the signal sequence from the translocating polypeptide to the TM2 and 7 segments on the α-subunit. This causes the α-helix plug to swing out of the way, exposing the channel and the ring pore at its constriction. However, this pore has a diameter of only 3 Å, whereas translocating protein segments can range up to 12 to 14 Å. Flexibility is provided largely by conformational changes in the α-subunit helices to which the pore residues are attached. Rearrangements of the loops between TM 4 and 5 and between TM 9 and 11 in the opposing α-subunits allow the pore width to expand as needed.

With the signal sequence intercalated between TM 2 and 7, the polypeptide inserts as a loop into the channel. The polypeptide chain then is transported through the pore, and the signal sequence is cleaved. As the polypeptide chain moves from the cytoplasm to the external site, the pore ring forms a gasket-like seal around the chain, hindering the permeation of other molecules and preserving osmotic integrity. Finally, after the polypeptide has passed through the channel, the plug returns to its closed position.

RECENT REVIEWS

J. de Keyzer, C. van der Does, and A.J.M. Driessen: The bacterial translocase: a dynamic protein channel. *Cell Mol Life Sci* 60:2034-2052, Oct 2003.

J. Benach and J.F. Hunt: Shape-shifting protein channel. *Nature* 427:24-26, 1 Jan 2004.



ADAPTED FROM VAN DEN BERG ET AL: *NATURE* 427:36-44, 1 JAN 2004.