THE ENDOPLASMIC RETICULUM

- All eukaryotic cells have an endoplasmic reticulum (ER).
- Its membrane typically constitutes more than half of the total membrane of an average animal cell.
- The ER is organized into a netlike labyrinth of branching tubules and flattened sacs extending throughout the cytosol , to interconnect
- The ER has a central role in lipid and protein biosynthesis

- Its membrane is the site of production of all the transmembrane proteins and lipids for most of the cell's organelles (the ER itself, the Golgi apparatus, lysosomes, endosomes, secretory vesicles, and the plasma membrane).
- The ER membrane makes a major contribution to mitochondrial and peroxisomal membranes by producing most of their lipids.
- Almost all of the proteins that will be secreted to the cell exterior plus those destined for the lumen of the ER, Golgi apparatus, or lysosomes are initially delivered to the ER lumen

TRANSLOCATION OF PROTIENS IN E.R

- Translocation of the proteins into the ER is mainly guided by the signal hypothesis
- It was proposed by the Blobel and Sabatini
- Proteins synthesized on the membrane bound polyribosomes contained a peptide extension called signal peptide
- Responsible for mediating their attachment with the ER membrane
- In contrast the protein being synthesized on the free polyribosomes lack this signal peptide .

- Insertion of resident proteins into the ER is dependent on the specific signal eg KDEL

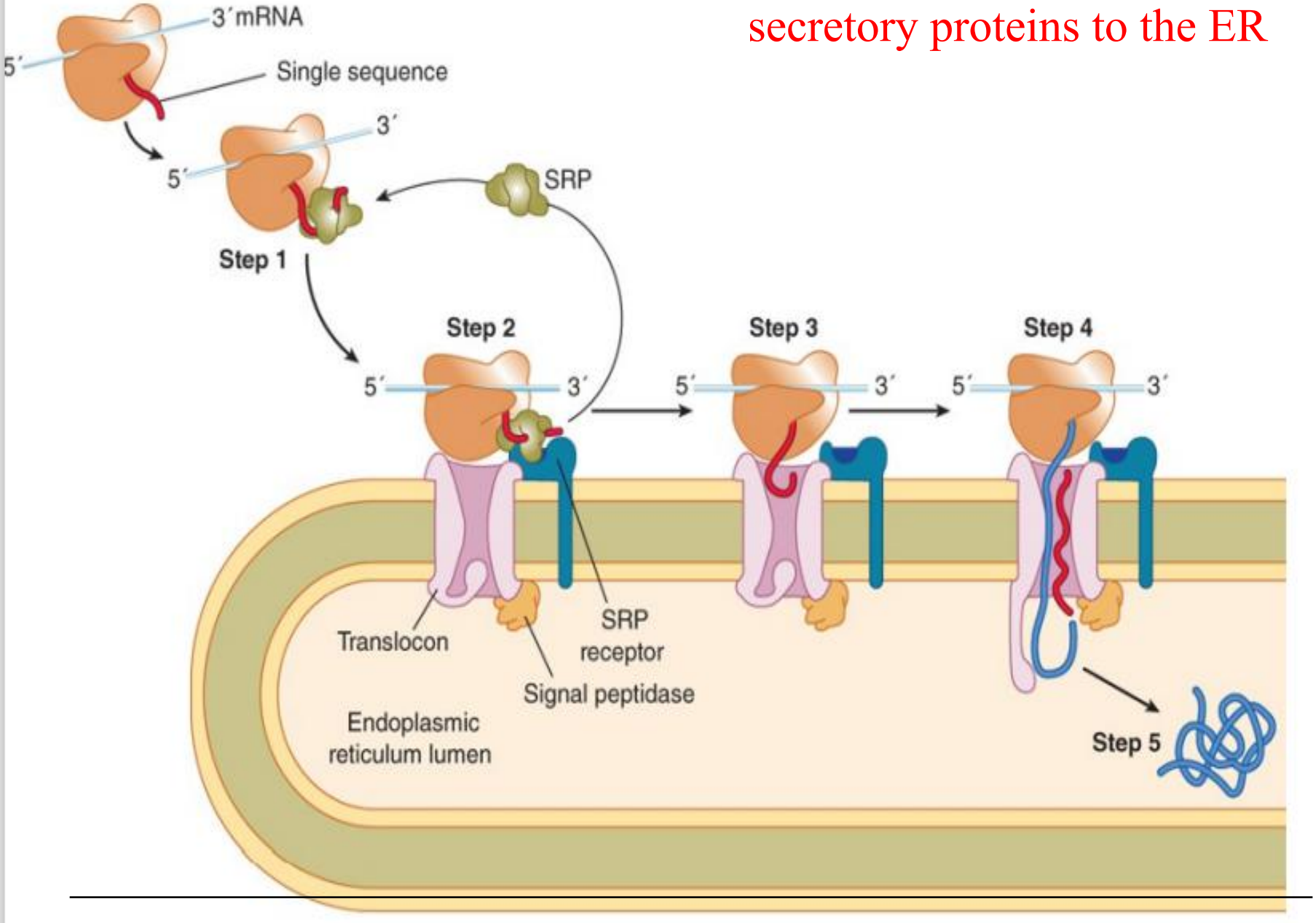
- But the membrane flow of certain proteins from the ER to the cell membrane is designated as bulk flow as this transport is non selective, occurs without any targeting signal involved

- But on the way back to the membrane if the proteins are destined to the lysosme or the secretory vesicles , the movement is mediated by the targeting sequence

Properties of Signal Peptides Directing Proteins to the ER

- Usually, but not always, located at the amino terminal
- Contain approximately 12-35 amino acids
- Methionine is usually the amino terminal amino acid
- Contain a central cluster (~6-12) of hydrophobic amino acids
- The region near the N-terminus usually carries a net positive charge
- The amino acid residue at the cleavage site is variable, but residues −1 and −3 relative to the cleavage site must be small and neutral

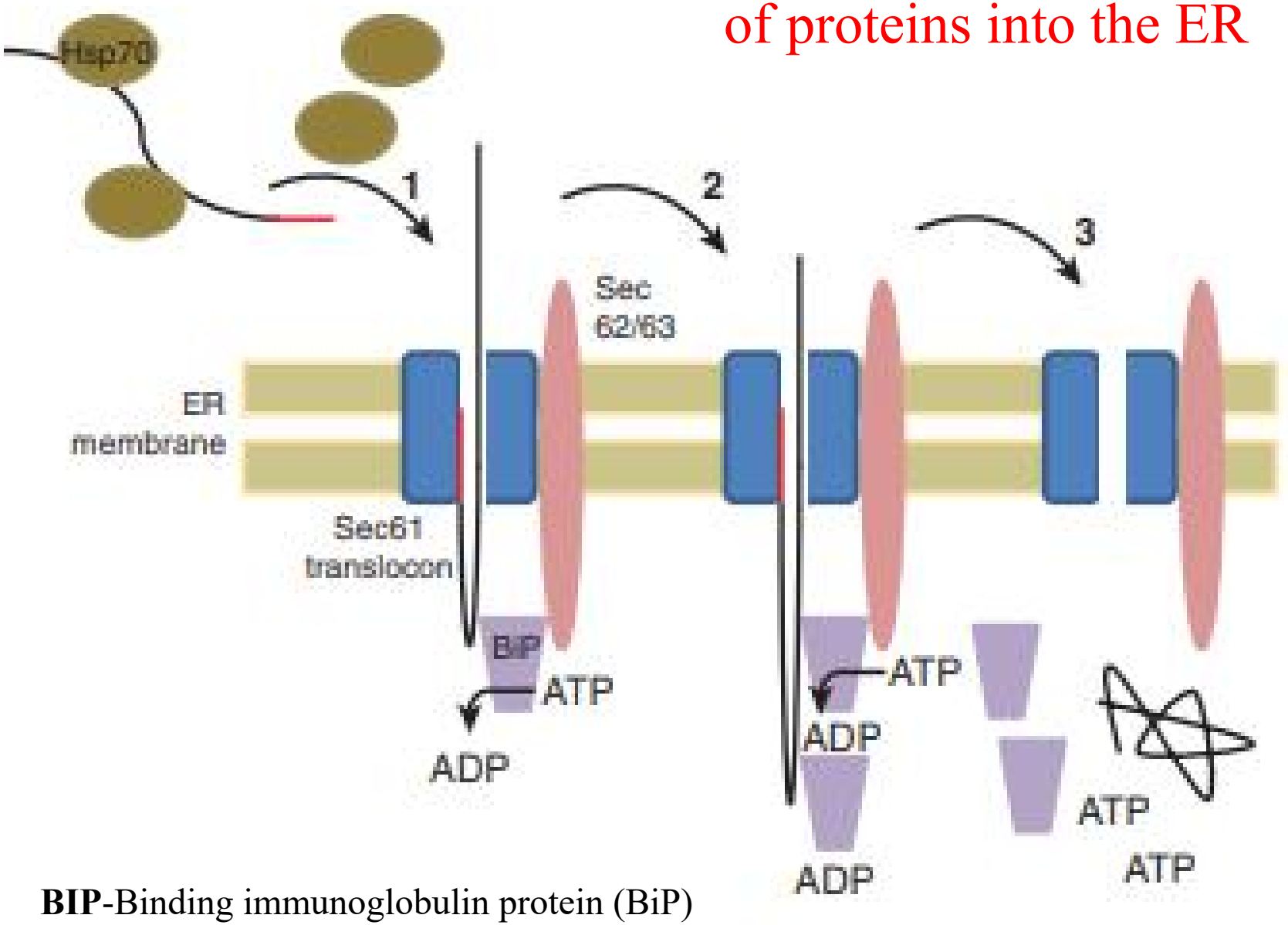
Cotranslational targeting of secretory proteins to the ER



Cotranslational targeting of secretory proteins to ER

- Step 1: As the signal sequence emerges from the ribosome, it is recognized and bound by the signal recognition particle (SRP).
- Step 2: The SRP escorts the complex to the ER membrane where it binds to the SRP receptor (SR).
- Step 3: The SRP is released, the ribosome binds to the translocon, and the signal sequence is inserted into the membrane channel.
- Step 4: The signal sequence opens the translocon. Translation resumes and the growing polypeptide chain is translocated across the membrane.
- Step 5: Cleavage of the signal sequence by signal peptidase releases the polypeptide into the lumen of the ER.

Posttranslational translocation of proteins into the ER

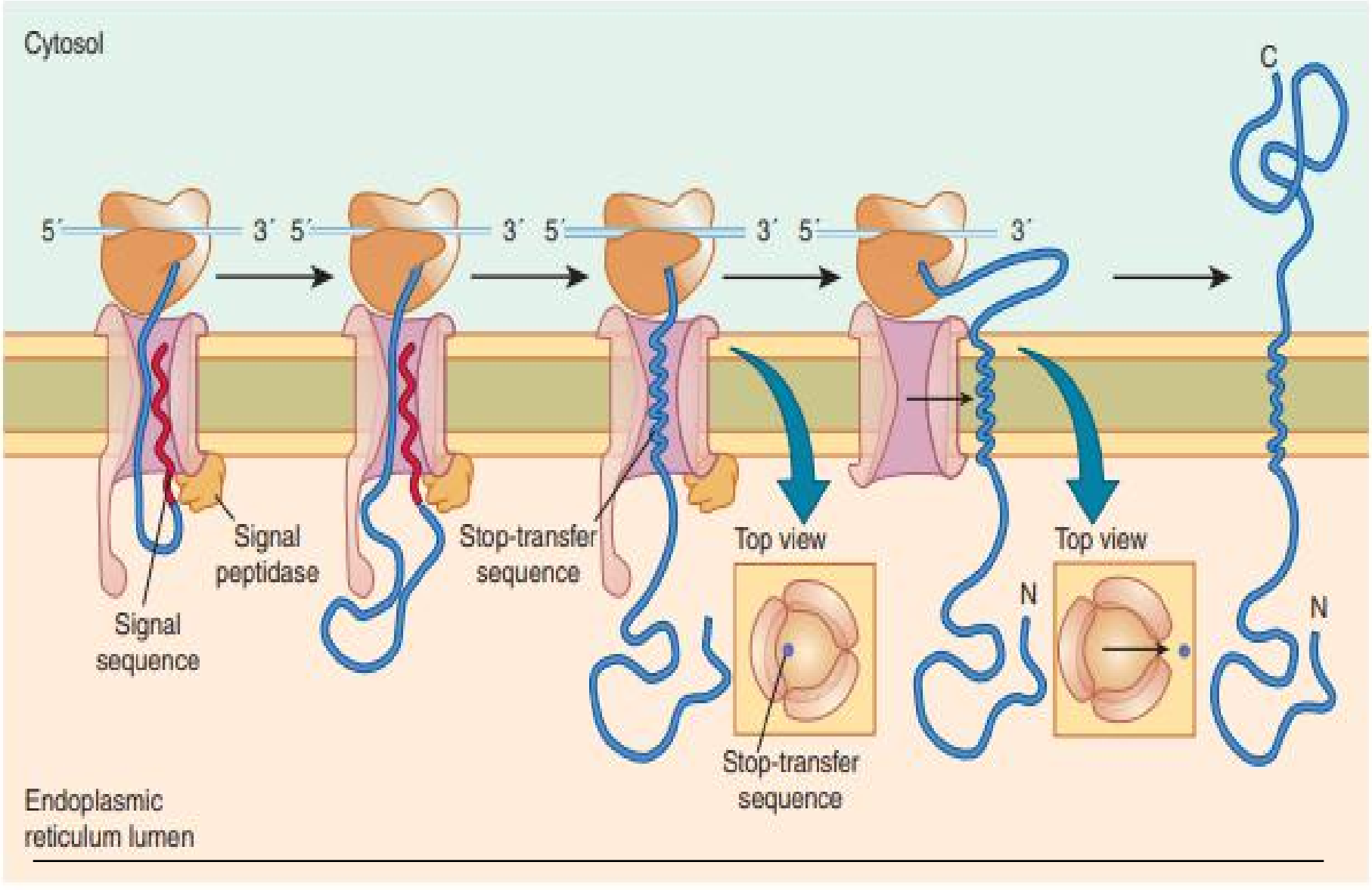


BIP-Binding immunoglobulin protein (BiP)

Posttranslational translocation of proteins into the ER

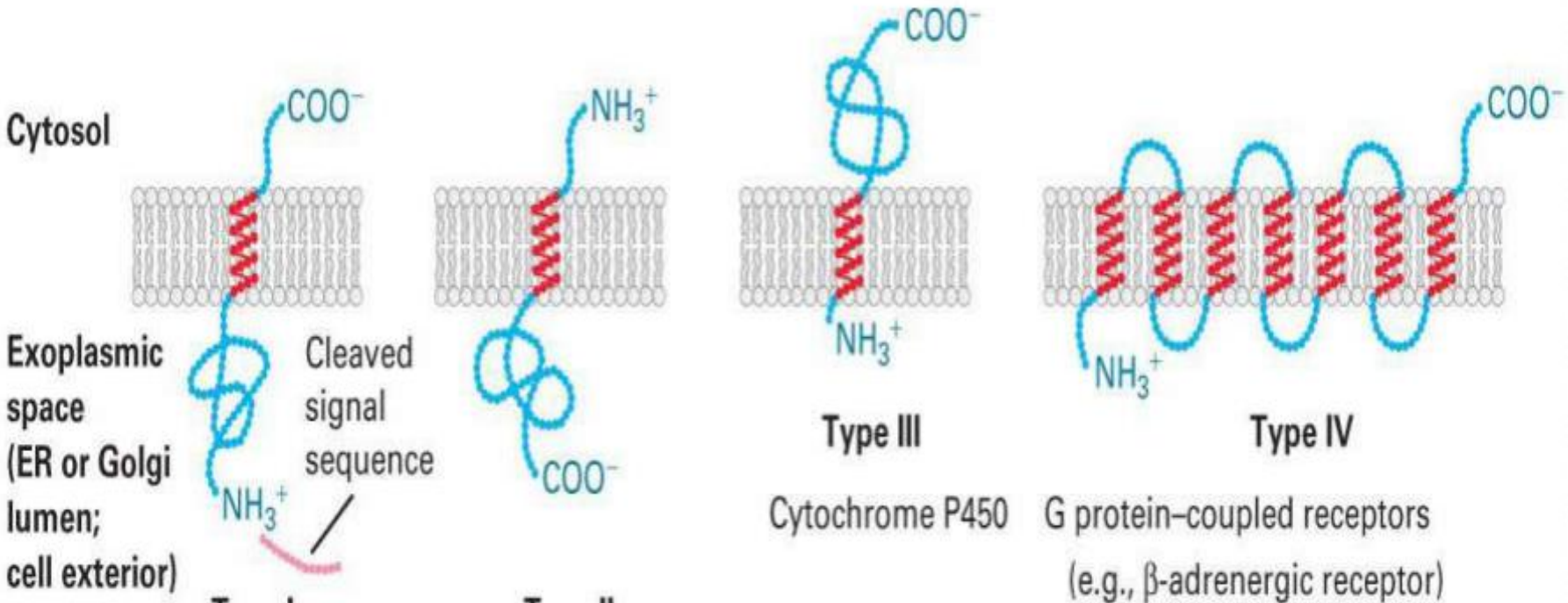
- Proteins synthesized in the cytosol are prevented from folding by chaperone proteins such as members of the Hsp70 family.
- The N-terminal signal sequence inserts into the Sec61 translocon complex and the cytosolic chaperones are released.
- BiP interacts with the protein and the Sec62/63 complex and its bound ATP is hydrolyzed to ADP.
- The protein is prevented from moving back into the cytosol by the bound BiP and successive binding of BiP and ATP hydrolysis pulls the protein into the lumen.
- When the whole protein is inside, ADP is exchanged for ATP and BiP is released

Insertion of a membrane protein with a cleavable signal sequence and a single stop-transfer sequence

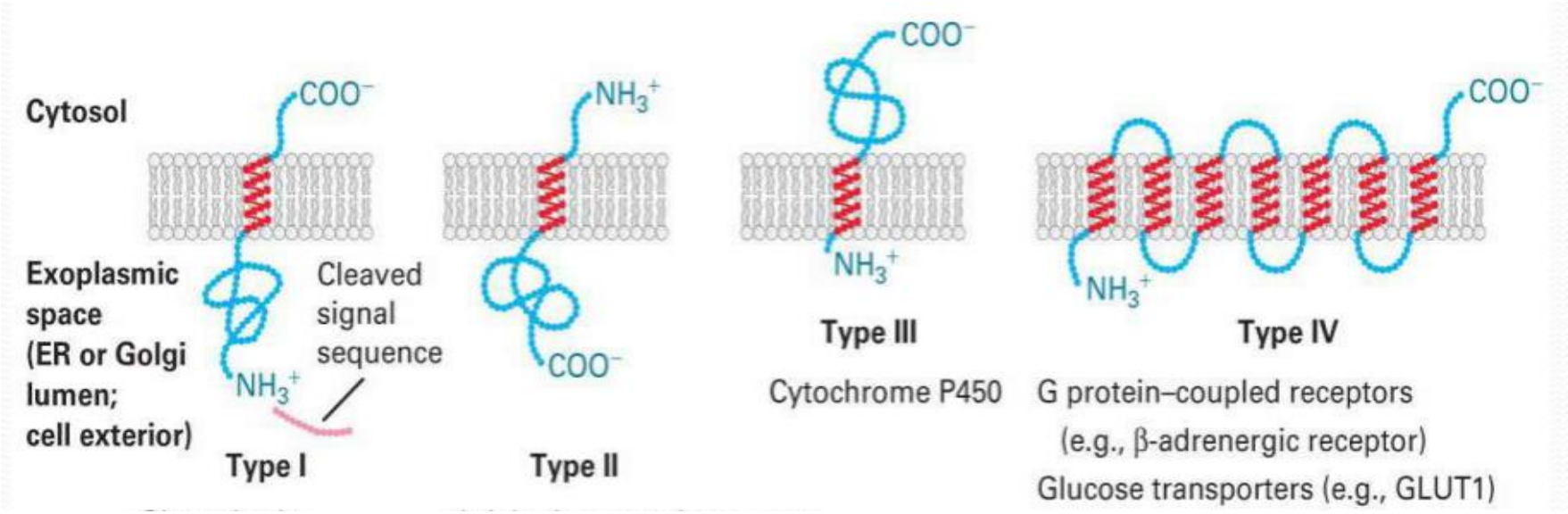


- The signal sequence is cleaved as the polypeptide chain crosses the membrane, so the amino terminus of the polypeptide chain is exposed in the ER lumen.
- However, translocation of the polypeptide chain across the membrane is halted when the translocon recognizes a transmembrane stop-transfer sequence.
- This allows the protein to exit the channel via a lateral gate and become anchored in the ER membrane.
- Continued translation results in a membrane-spanning protein with its carboxy terminus on the cytosolic side.

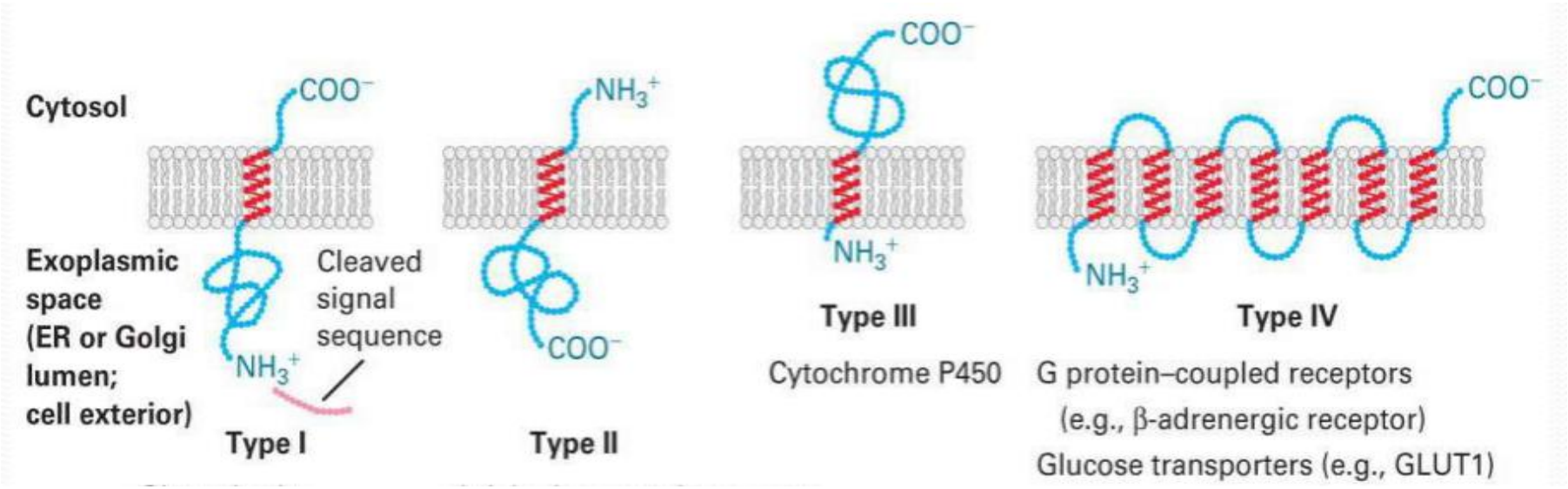
Variations in the way in which proteins are inserted into membranes



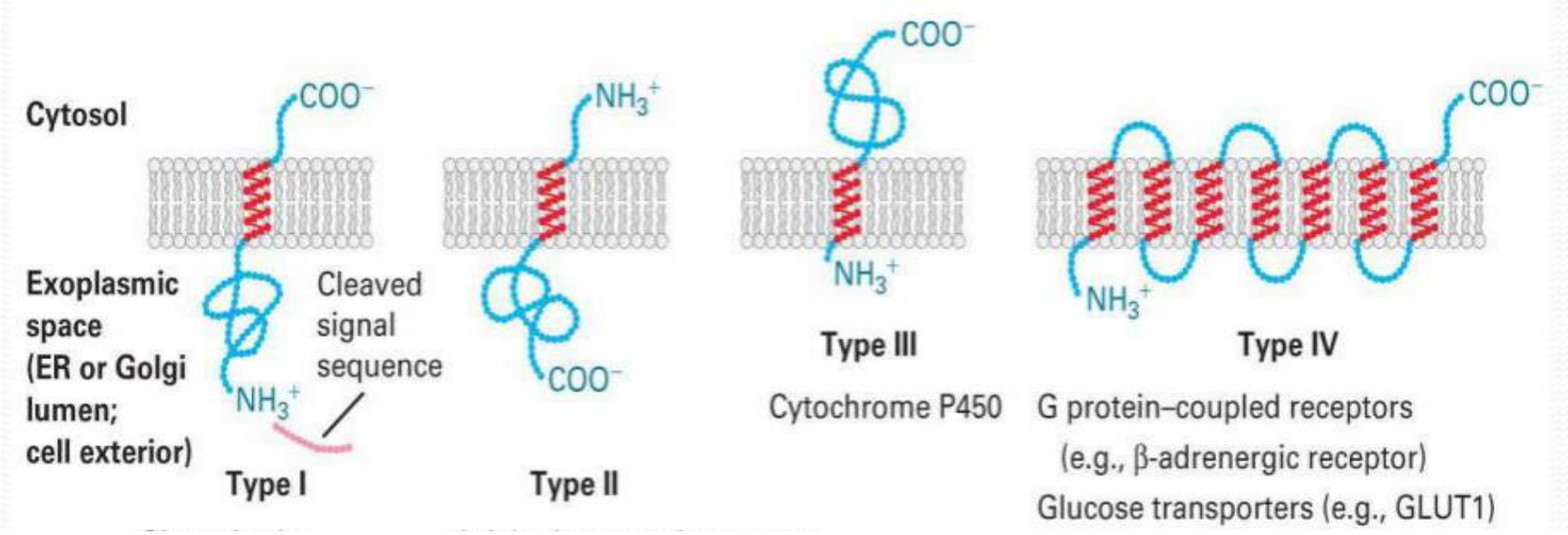
Type I	Type II	Type III	Type IV
Glycophorin	Asialoglycoprotein receptor	Cytochrome P450	G protein–coupled receptors (e.g., β-adrenergic receptor)
LDL receptor	Transferrin receptor		Glucose transporters (e.g., GLUT1)
Influenza HA protein	Sucrase–isomaltase precursor		Voltage-gated Ca_2^+ channels
Insulin receptor	Golgi galactosyltransferase		ABC small molecule pumps
Growth hormone receptor	Golgi sialyltransferase		CFTR (Cl^-) channel
	Influenza HN protein		Sec61
			Connexin



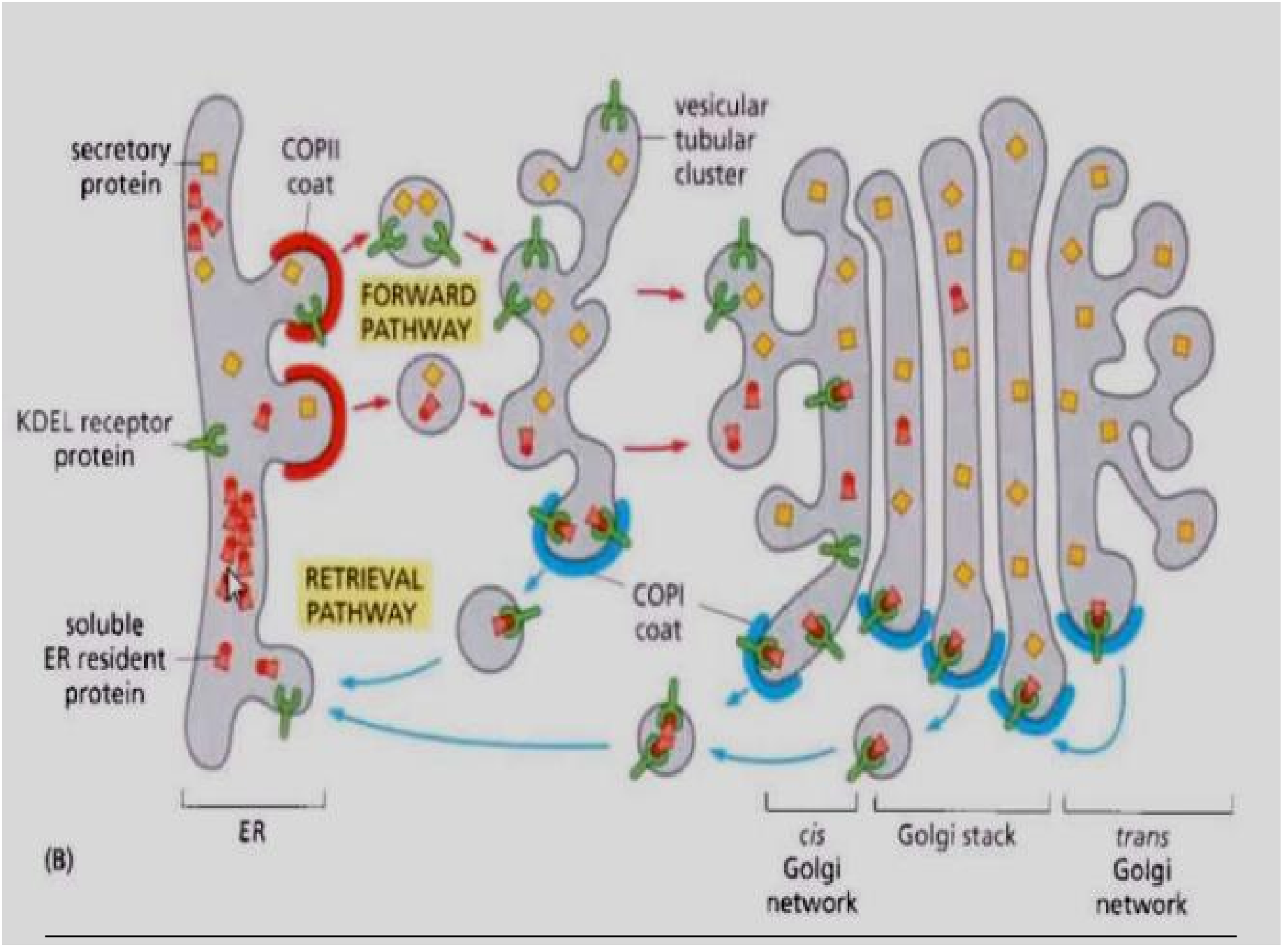
- The orientations form initially in the ER membrane, but are retained when vesicles bud off and fuse with the plasma membrane so that the terminal initially facing the ER lumen always faces the outside of the cell.
- Type I transmembrane proteins (eg, the LDL receptor and influenza hemagglutinin) cross the membrane once and have their amino termini in the ER lumen/cell exterior.



- Type II transmembrane proteins (eg, the asialoglycoprotein and transferrin receptors) also cross the membrane once, but have their C-termini in the ER lumen/cell exterior.
- Type III transmembrane proteins (eg, cytochrome P450, an ER membrane protein) have a disposition similar to type I proteins, but do not contain a cleavable signal peptide.



- Type IV transmembrane proteins (eg, G-protein-coupled receptors and glucose transporters) cross the membrane a number of times (7 times for the former and 12 times for the latter); they are also called polytopic membrane proteins
- Sequences that determine the structure of a protein in a membrane are called topogenic sequences.



- A number of proteins possess the amino acid sequence KDEL (Lys-Asp-Glu-Leu) at their carboxyl terminal
- KDEL-containing proteins first travel to the GA in vesicles coated with coat protein II (COPII)
- This process is known as anterograde vesicular transport.
- In the GA they interact with a specific KDEL receptor protein, which retains them transiently.
- They then return to the ER in vesicles coated with COPI (retrograde vesicular transport), where they dissociate from the receptor, and are thus retrieved
- Certain other non-KDEL-containing proteins also pass to the Golgi and then return, by retrograde vesicular transport, to the ER to be inserted therein.