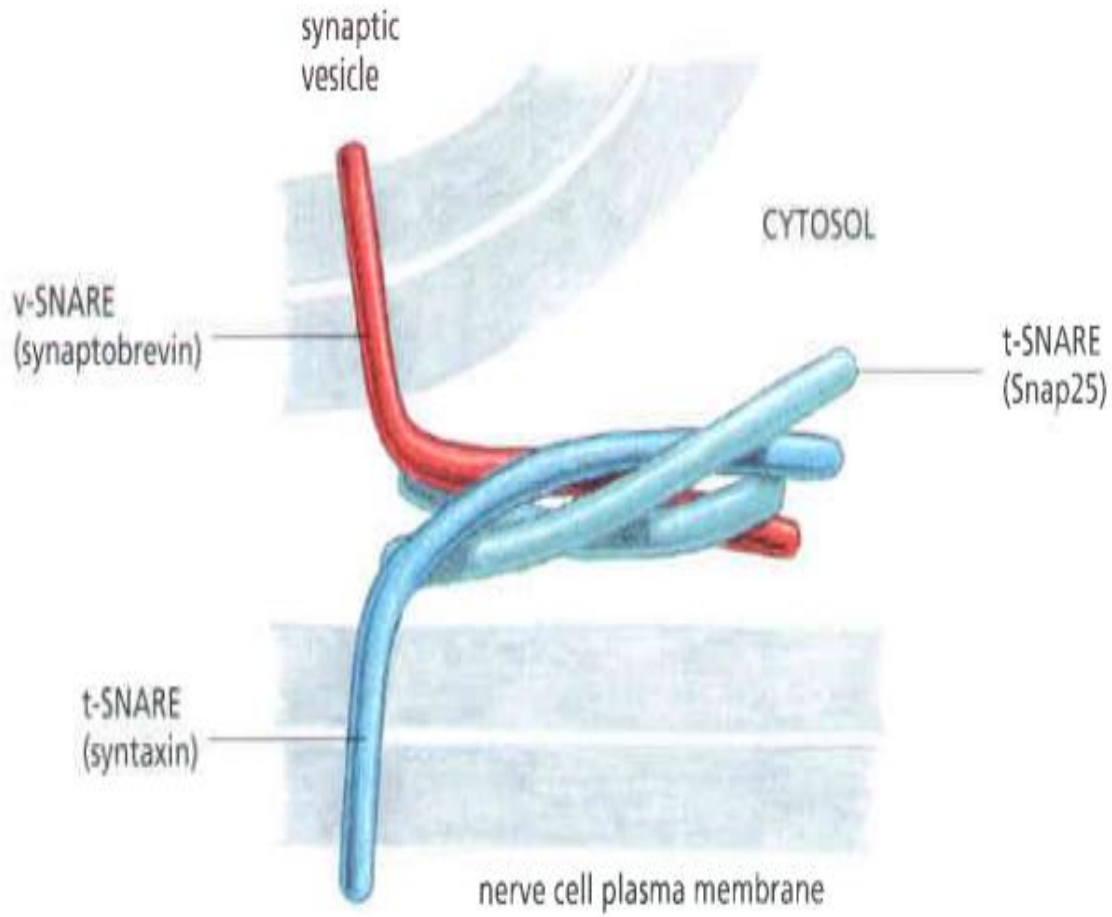
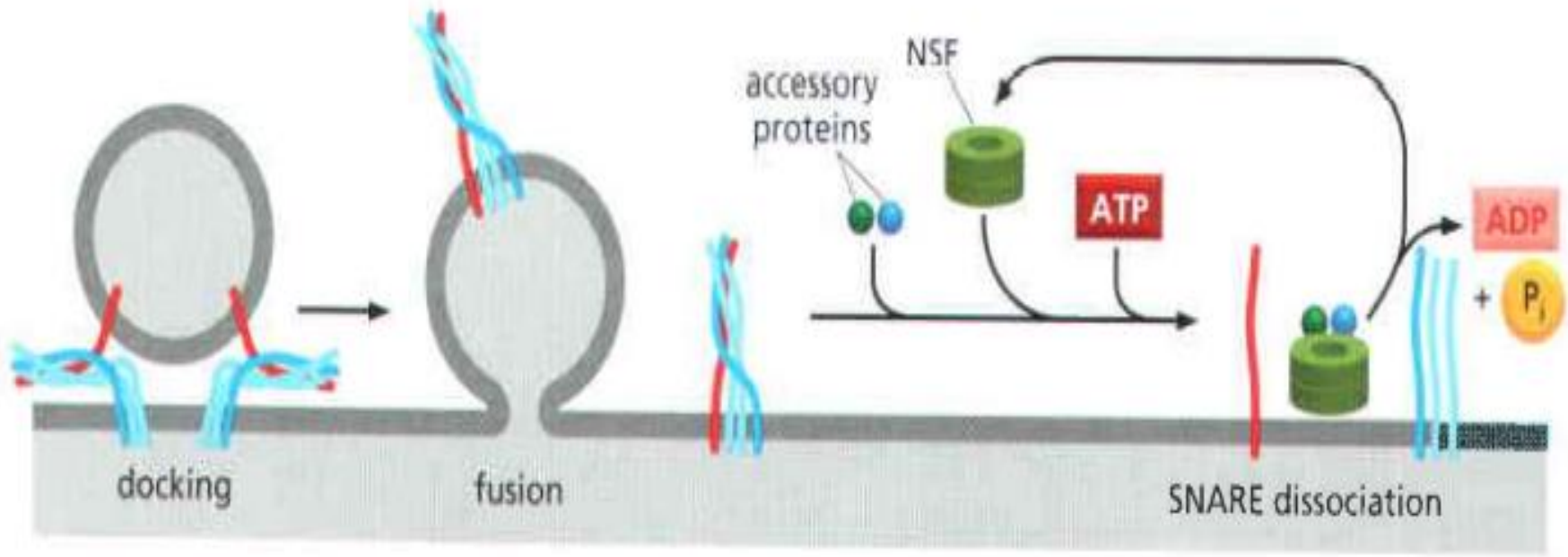
Protein Trafficking


synaptic
vesicle
CYTOSOL
v-SNARE
(synaptobrevin)
t-SNARE
(Snap25)
t-SNARE
(syntaxin)
nerve cell plasma membrane

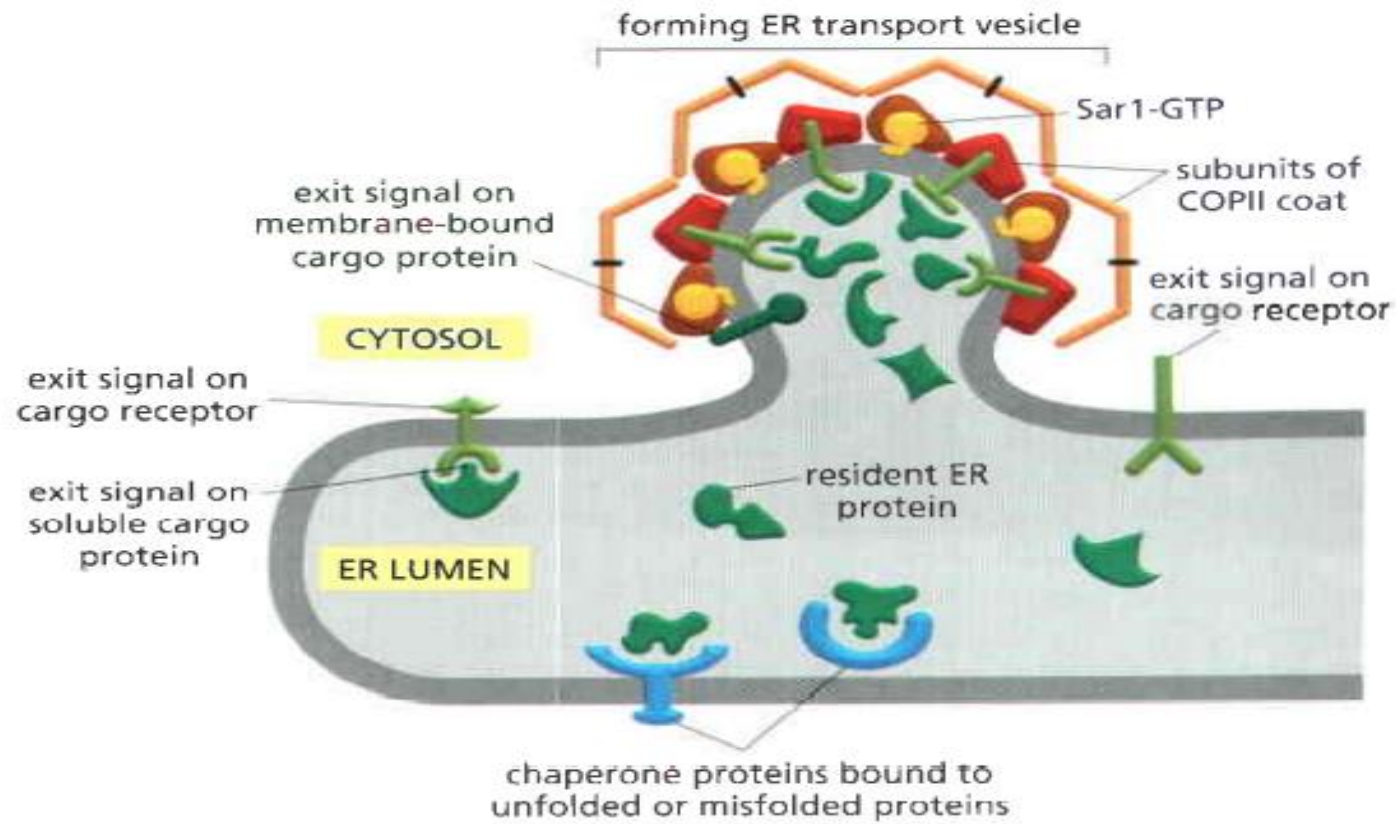

accessory
proteins
NSF
ATP
ADP
+ P_i
docking
fusion
SNARE dissociation

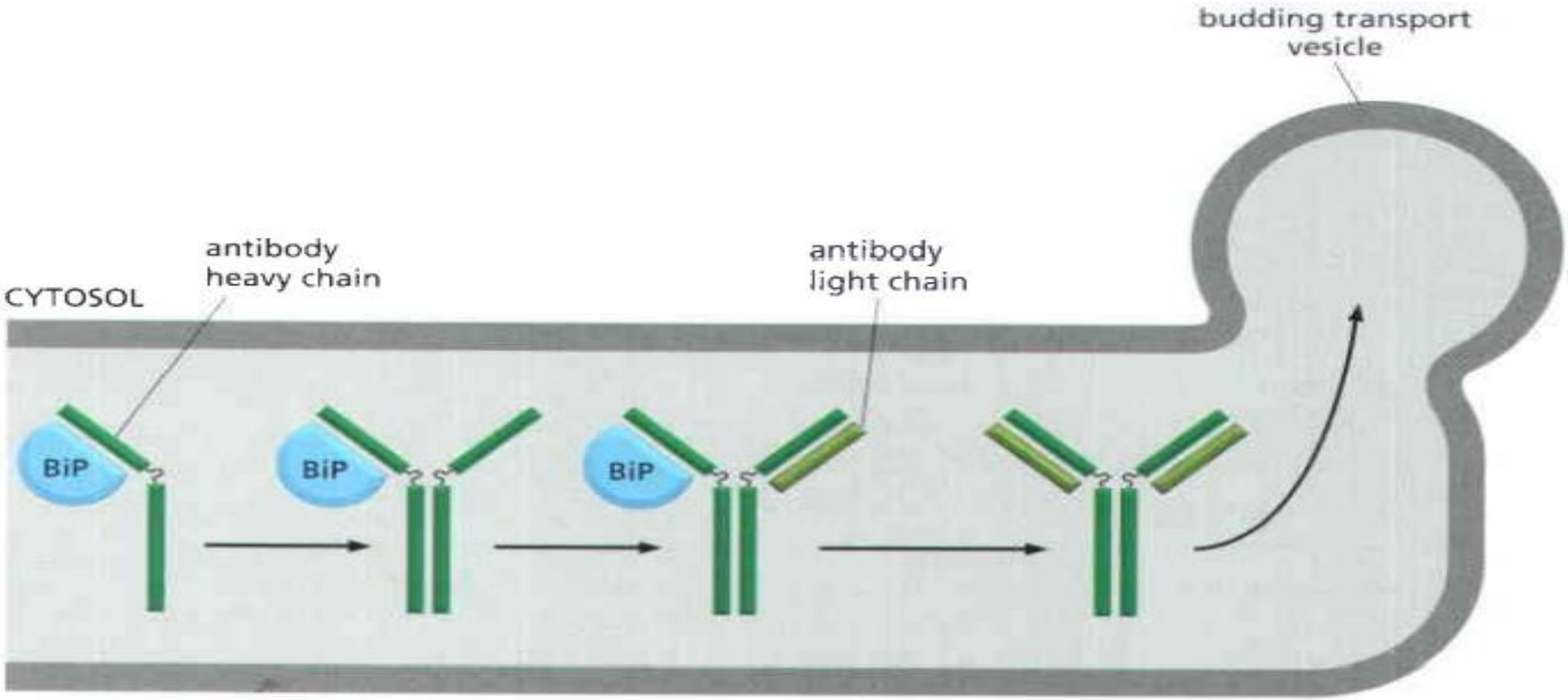
TRANSPORT FROM THE ER THROUGH THE GOLGI APPARATUS

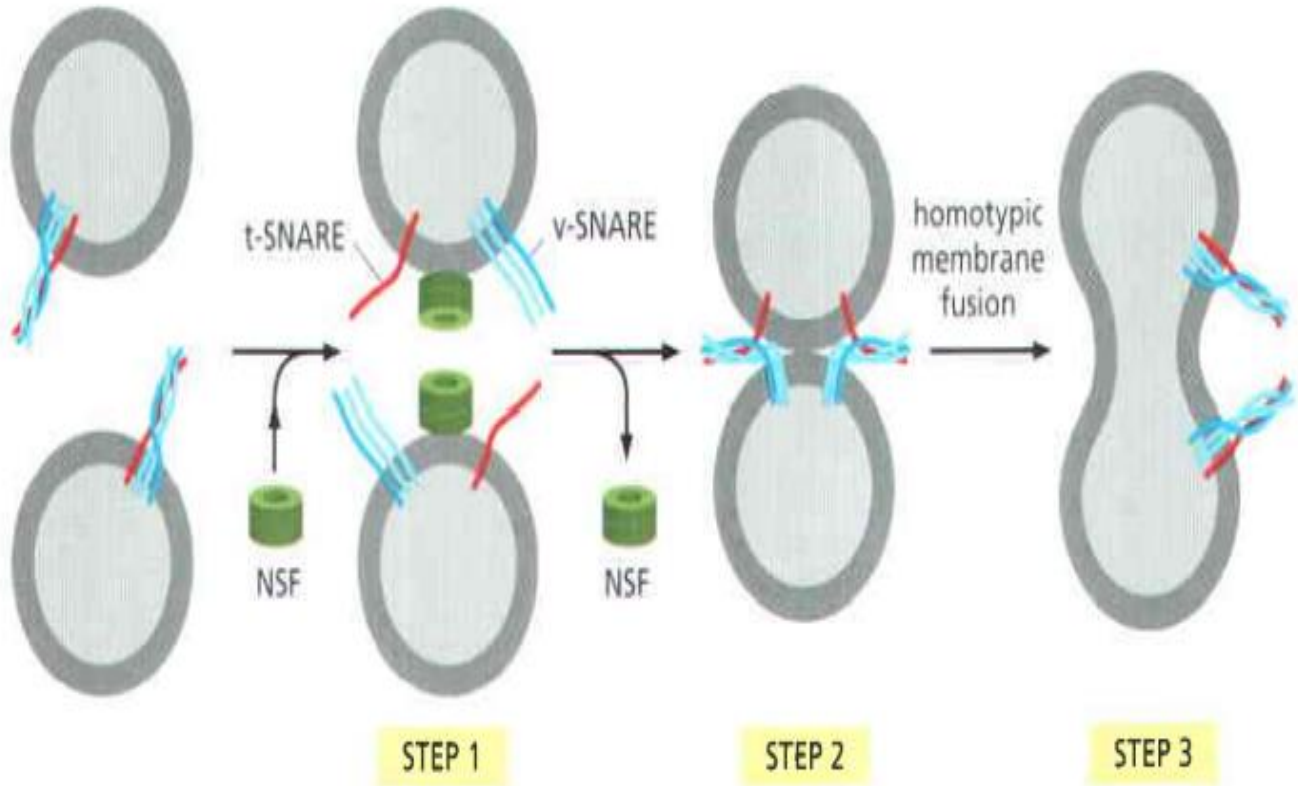
- ER to the cell surface consists of many sorting steps, which continuously select membrane and soluble lumenal proteins for packaging and transport-in vesicles or organelle fragments that bud from the ER and Golgi apparatus.
- Golgi apparatus also lies on the exit route from the ER, and a large proportion of the carbohydrates that it makes are attached as oligosaccharide side chains to the many proteins and lipids that the ER sends to it.
- A subset of these oligosaccharide groups serve as tags to direct specific proteins into vesicles that then transport them to lysosomes.

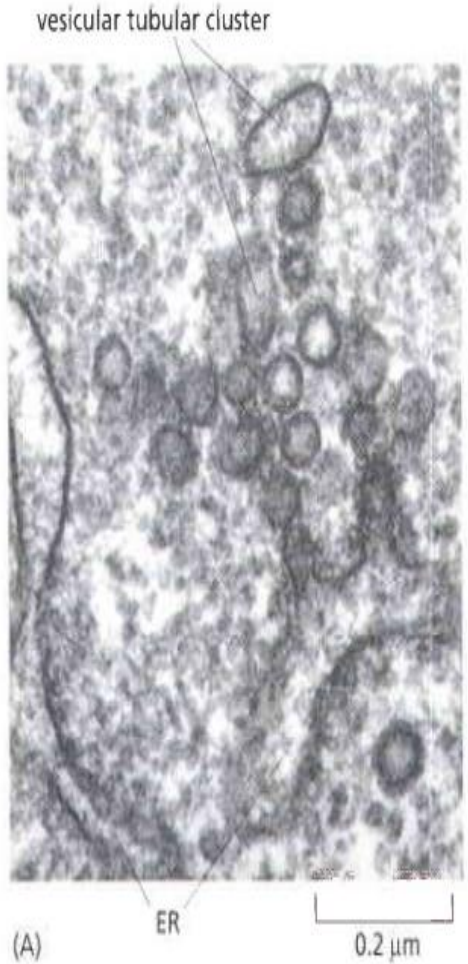
Proteins Leave the ER in COPI|-Coated Transport Vesicle

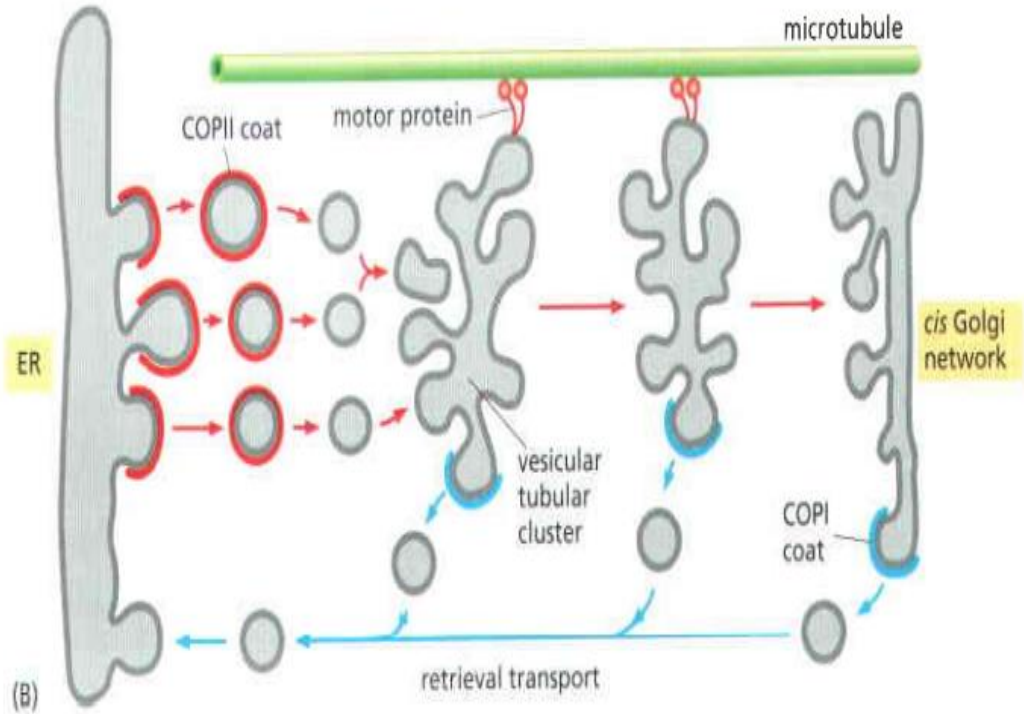
- Proteins that have entered the ER and are destined for the Golgi apparatus or beyond are first packaged into small COPII-coated transport vesicles.
- These vesicles bud from specialized regions of the ER called ER exit sites, whose membrane lacks bound ribosomes
- coat components act as cargo receptors and are recycled back to the ER after they have delivered their cargo to the Golgi apparatus


forming ER transport vesicle
Sar1-GTP
subunits of COPII coat
exit signal on membrane-bound cargo protein
exit signal on cargo receptor
CYTOSOL
exit signal on cargo receptor
exit signal on soluble cargo protein
resident ER protein
ER LUMEN
chaperone proteins bound to unfolded or misfolded proteins


budding transport vesicle
antibody heavy chain
antibody light chain
CYTOSOL
BiP
BiP
BiP
RETAINED IN ER
SECRETED

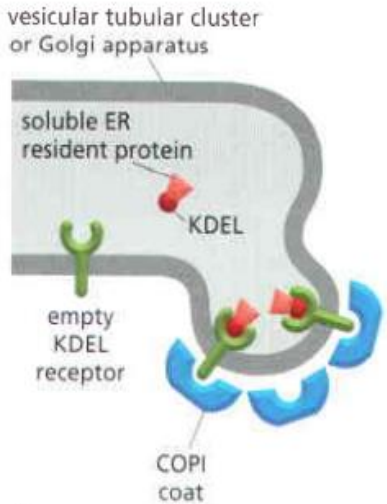

t-SNARE
v-SNARE
NSF
NSF
homotypic
membrane
fusion
STEP 1
STEP 2
STEP 3


vesicular tubular cluster
ER
0.2 µm
(A)

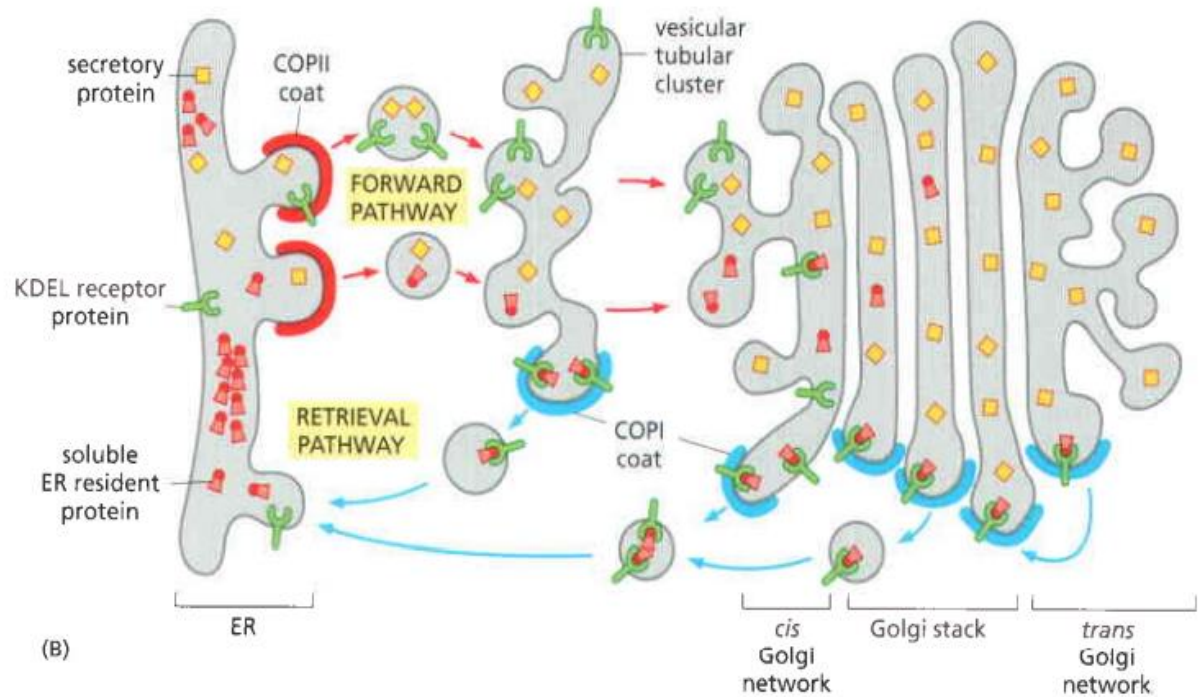

microtubule
COPII coat
motor protein
ER
cis Golgi network
vesicular tubular cluster
COPI coat
retrieval transport
(B)

The Retrieval Pathway to the ER Uses Sorting Signal

- The retrieval pathway for returning escaped proteins back to the ER depends on ER retrieual signals. Resident ER membrane proteins, for example, contain signals that bind directly to COPI coats and are thus packaged into CoPl-coated transport vesicles for retrograde delivery to the ER. The best-characterized retrieval signal of this type consists of two lysines, followed by any two other amino acids, at the extreme c-terminal end of the ER membrane protein. It is called a KKXX sequence, based on the single-letter amino acid code.
- Soluble ER resident proteins, such as BiB also contain a short retrieval signal at their c-terminal end, but it is different: it consists of a Lys-Asp-Glu-Leu or a similar sequence. If this signal (KDEL sequence) is removed from Bip by genetic engineering, the protein is slowly secreted from the cell. If the signal is transferred to a protein that is normally secreted, the protein is now efficiently returned to the ER

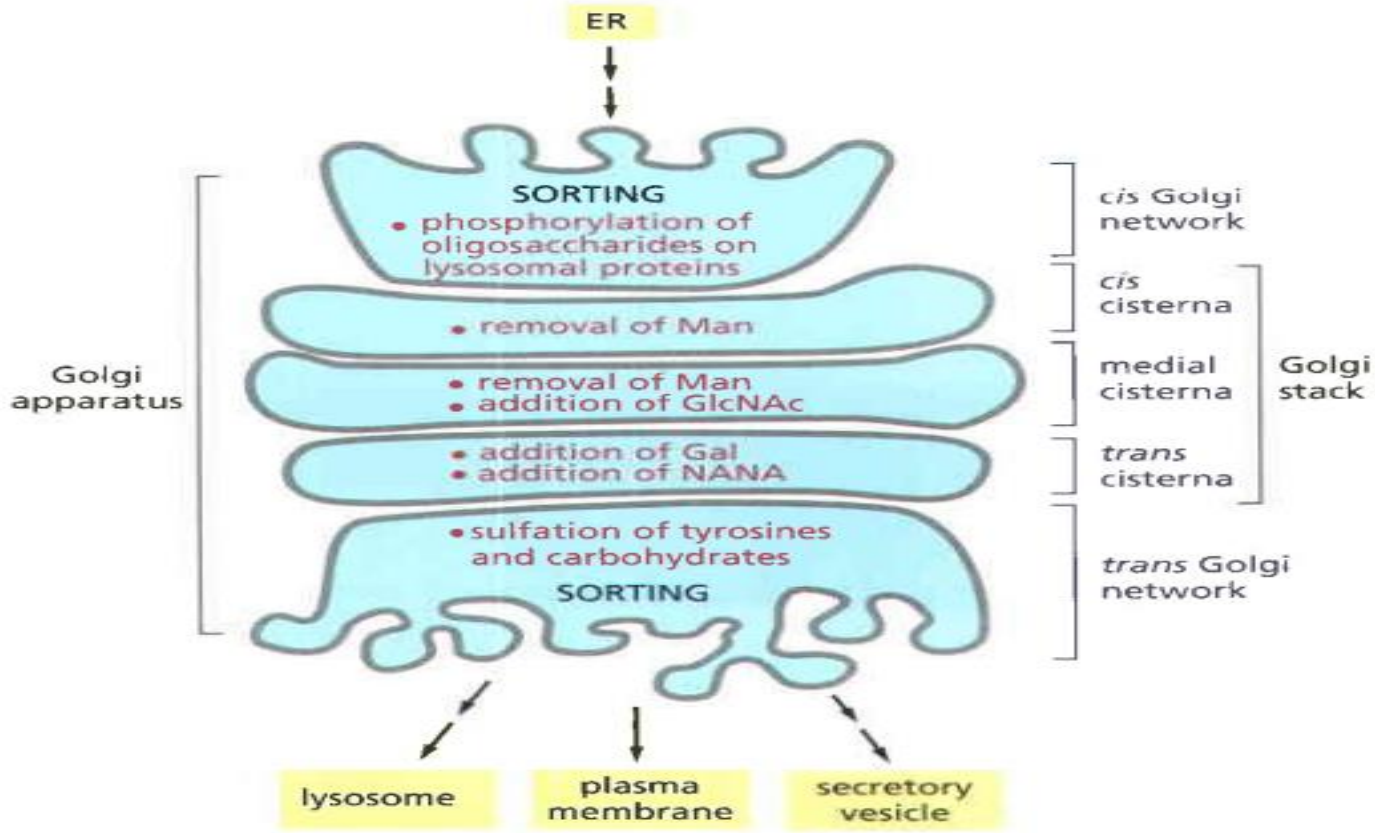

vesicular tubular cluster
or Golgi apparatus
soluble ER
resident protein
KDEL
empty
KDEL
receptor
COPI
coat

(A)

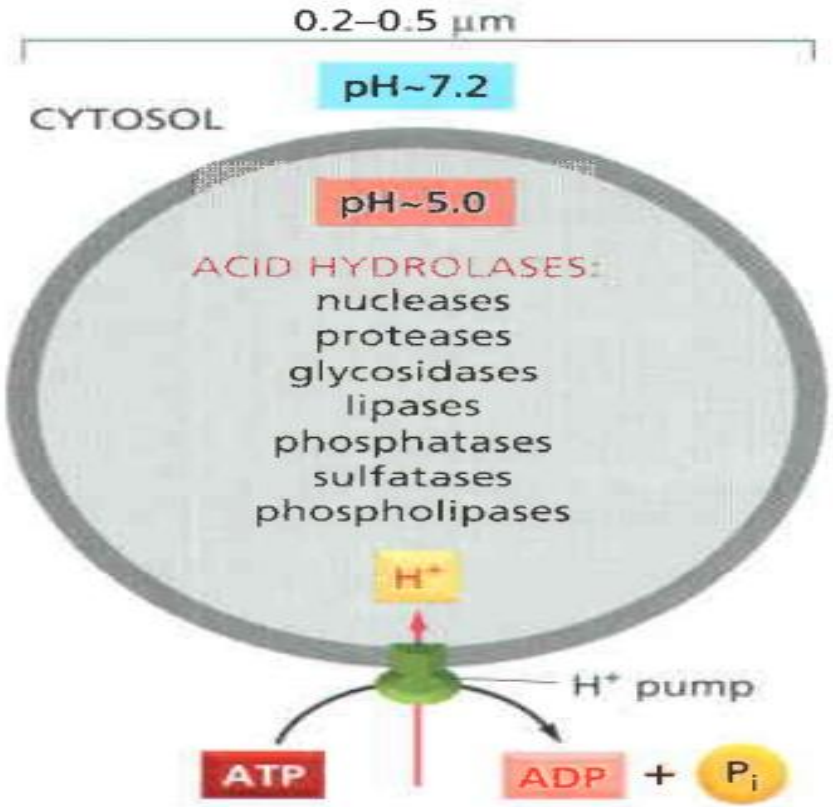

secretory
protein
COPII
coat
vesicular
tubular
cluster
FORWARD
PATHWAY
KDEL receptor
protein
RETRIEVAL
PATHWAY
COPI
coat
soluble
ER resident
protein
ER
cis
Golgi
network
Golgi stack
trans
Golgi
network

(B)

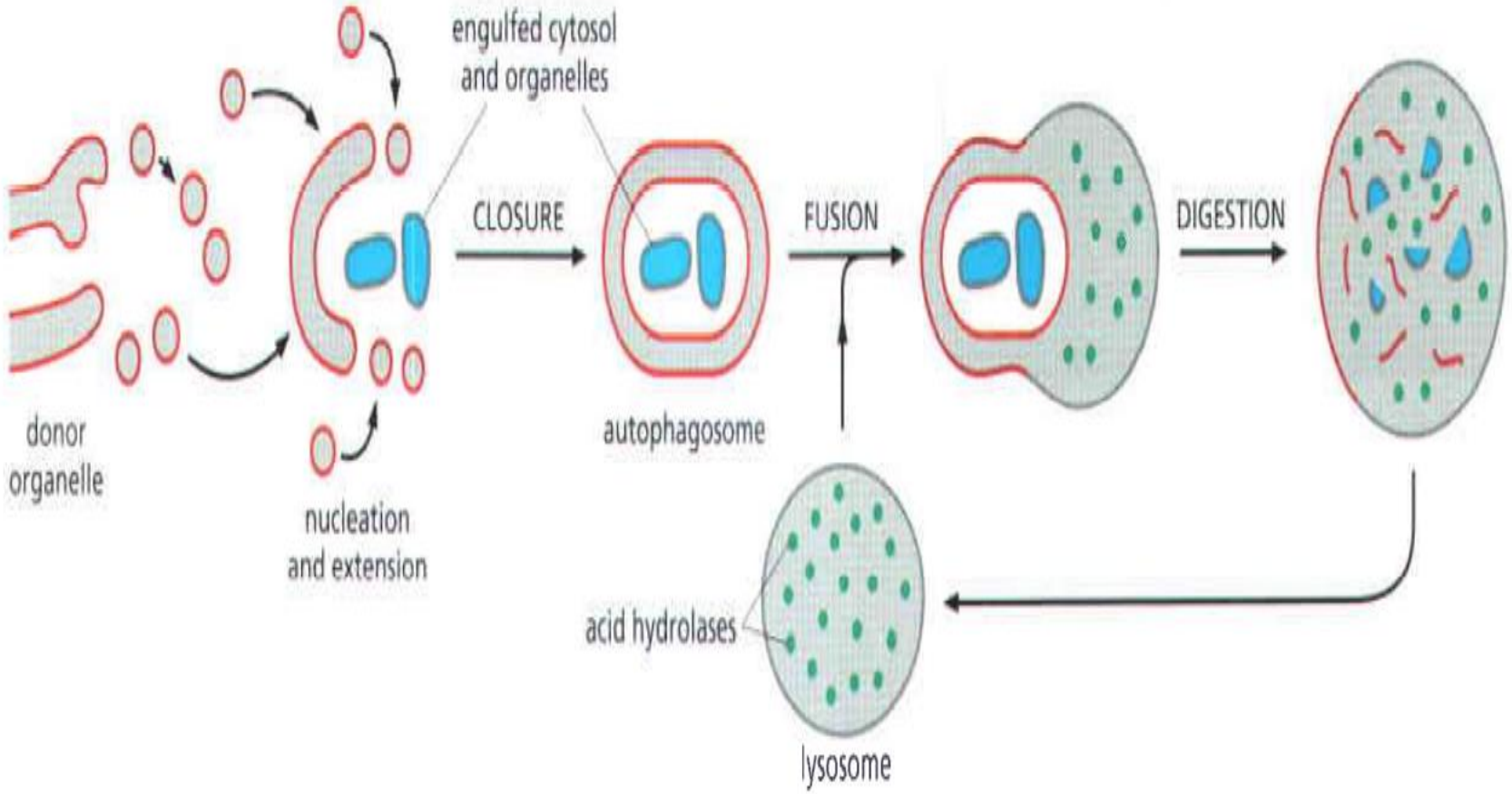
Oligosaccharide processing in Golgi compartments



Lysosomes Are the Principal Sites of Intracellular Digestion



A model of autophagy



A Mannose 6-Phosphate Receptor Recognizes Lysosomal Proteins in the Trans Golgi Network

- Both classes of proteins are co-translationally transported into the rough ER and then transported through the Golgi apparatus to the TGN.
- The transport vesicles that deliver these proteins to endosomes (from where the proteins are moved on to lysosomes) bud from the TGN.
- The vesicles incorporate the lysosomal proteins and exclude the many other proteins being packaged into different transport vesicles for delivery elsewhere.
- They carry a unique marker in the form of mannose 6 phosphate (M6P) groups, which are added exclusively to the N linked oligosaccharides of these soluble lysosomal enzymes as they pass through the lumen of the cis Golgi network.
- Transmembrane M6P receptor proteins, which are present in the TGN, recognize the M6P group

Transport of lysosomal hydrolases to lysosome