Chapter 1: Vesicular traffic
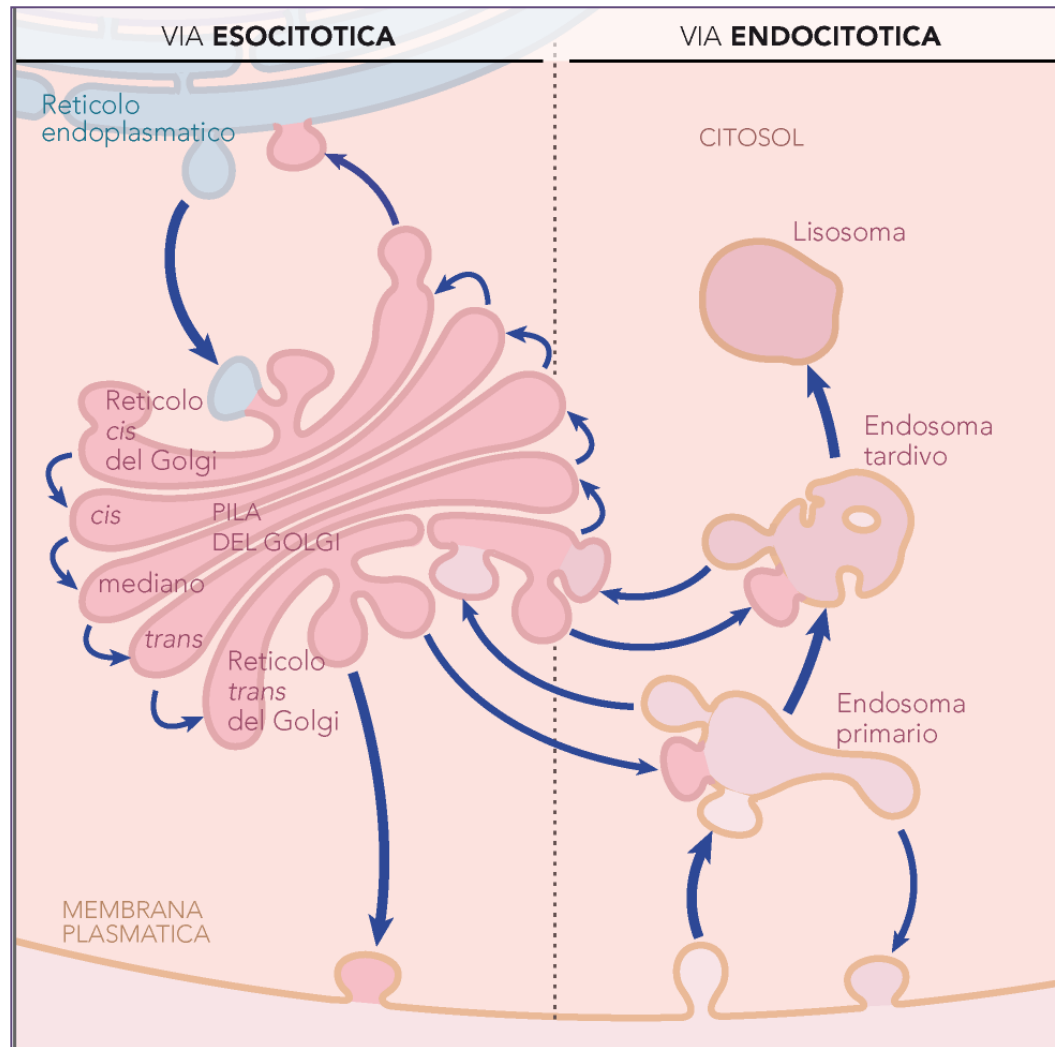
Major Protein-sorting pathways in eukaryotic cells
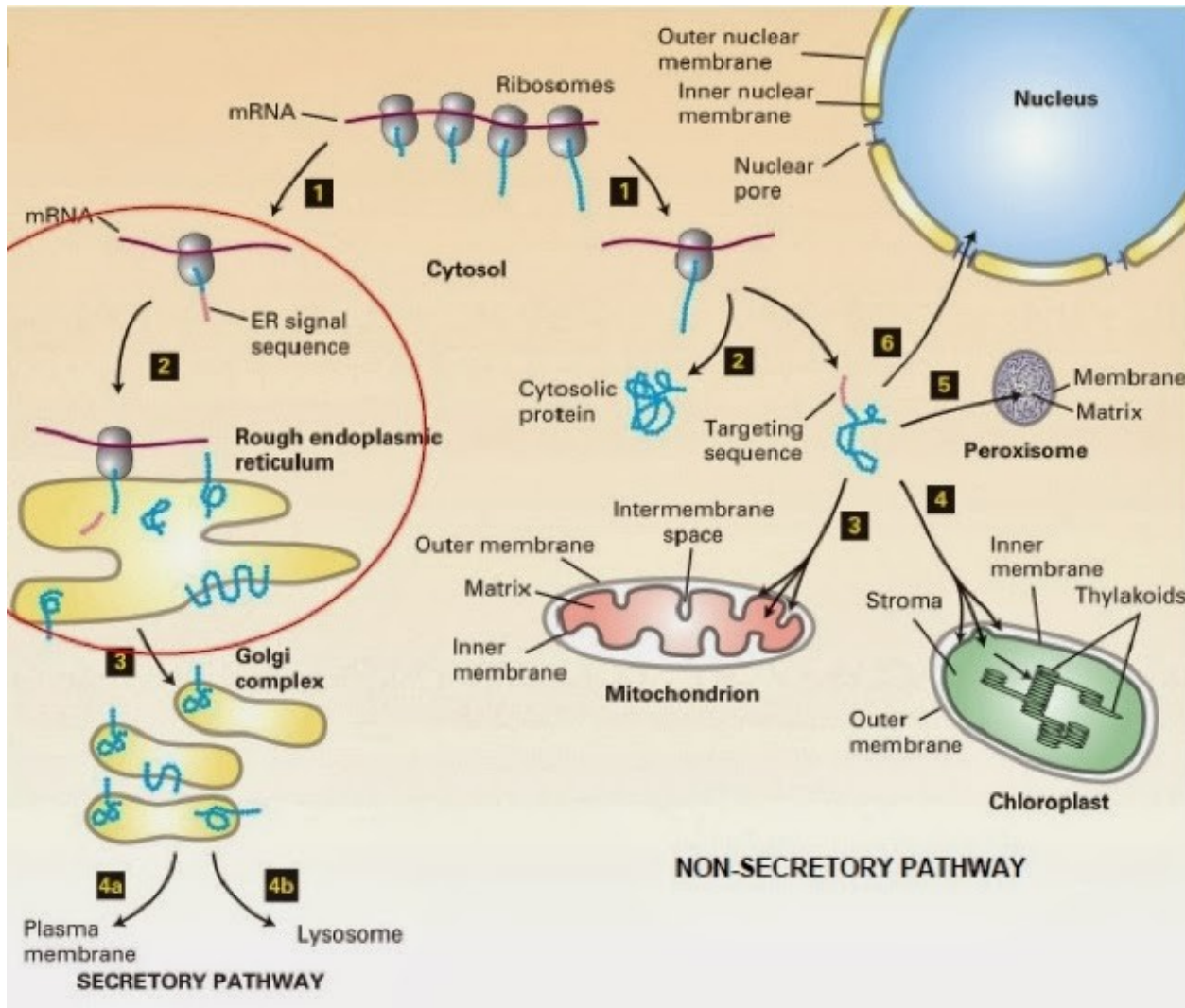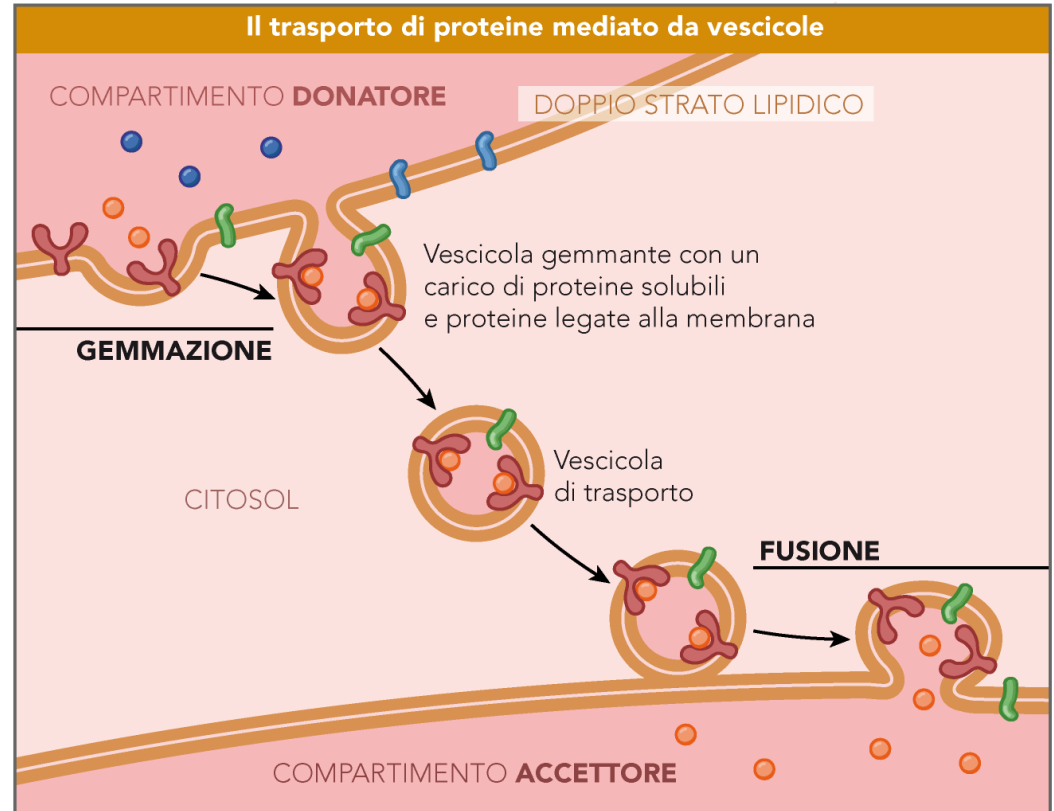
Secretory and endocytic pathways

Vesicular transport

✓Unifying principle governs all protein trafficking in **secretory** and **endocytic pathways**: transport of membrane and soluble proteins from one membrane-bounded compartment to another is mediated by **transport vesicles.**
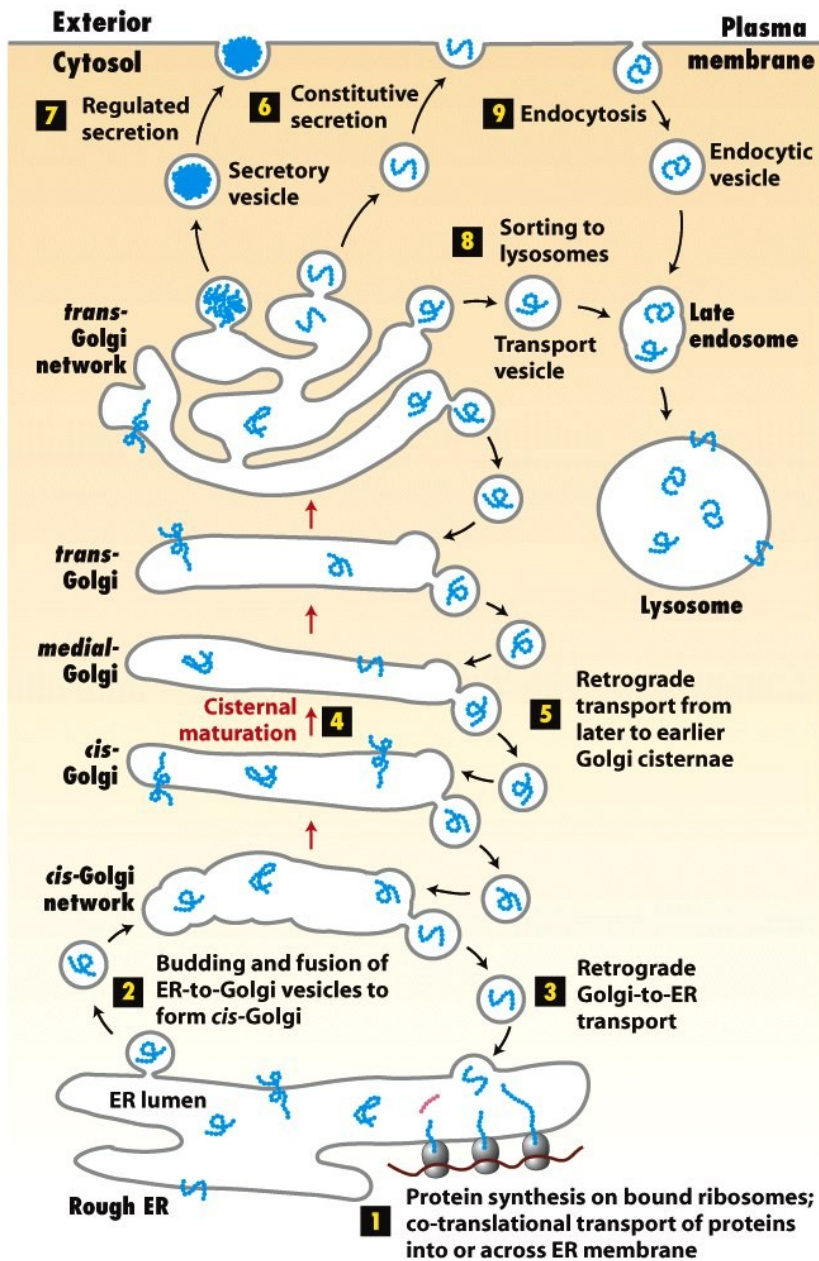
✓Vesicles collect **"cargo" proteins** in buds arising from the membrane of one compartment and then deliver these cargo proteins to the next compartment by fusing with the membrane of that compartment

✓The same face of the membrane remains oriented toward the cytosol

Il trasporto di proteine mediato da vescicole

COMPARTIMENTO **DONATORE**

DOPPIO STRATO LIPIDICO

GEMMAZIONE

Vescicola gemmante con un carico di proteine solubili e proteine legate alla membrana

CITOSOL

Vescicola di trasporto

FUSIONE

COMPARTIMENTO **ACCETTORE**

Each step in the secretory and endocytic pathways employs a different type of vesicle, but each of the different vesicular transport steps is simply a variation on a common theme.

Major routes for protein trafficking in the secretory pathway

Exterior

Cytosol

Plasma membrane

7 Regulated secretion

6 Constitutive secretion

9 Endocytosis

Endocytic vesicle

Secretory vesicle

8 Sorting to lysosomes

trans-Golgi network

Transport vesicle

Late endosome

trans-Golgi

Lysosome

medial-Golgi

Cisternal maturation **4**

5 Retrograde transport from later to earlier Golgi cisternae

cis-Golgi

cis-Golgi network

Budding and fusion of ER-to-Golgi vesicles to form *cis*-Golgi **2**

3 Retrograde Golgi-to-ER transport

ER lumen

Rough ER

Protein synthesis on bound ribosomes; **1** co-translational transport of proteins into or across ER membrane

Anterograde and retrograde transport vescicles

cis-Golgi network

2 Budding and fusion of ER-to-Golgi vesicles to form cis-Golgi

3 Retrograde Golgi-to-ER transport

ER lumen

Rough ER

1 Protein synthesis on bound ribosomes; co-translational transport of proteins into or across ER membrane
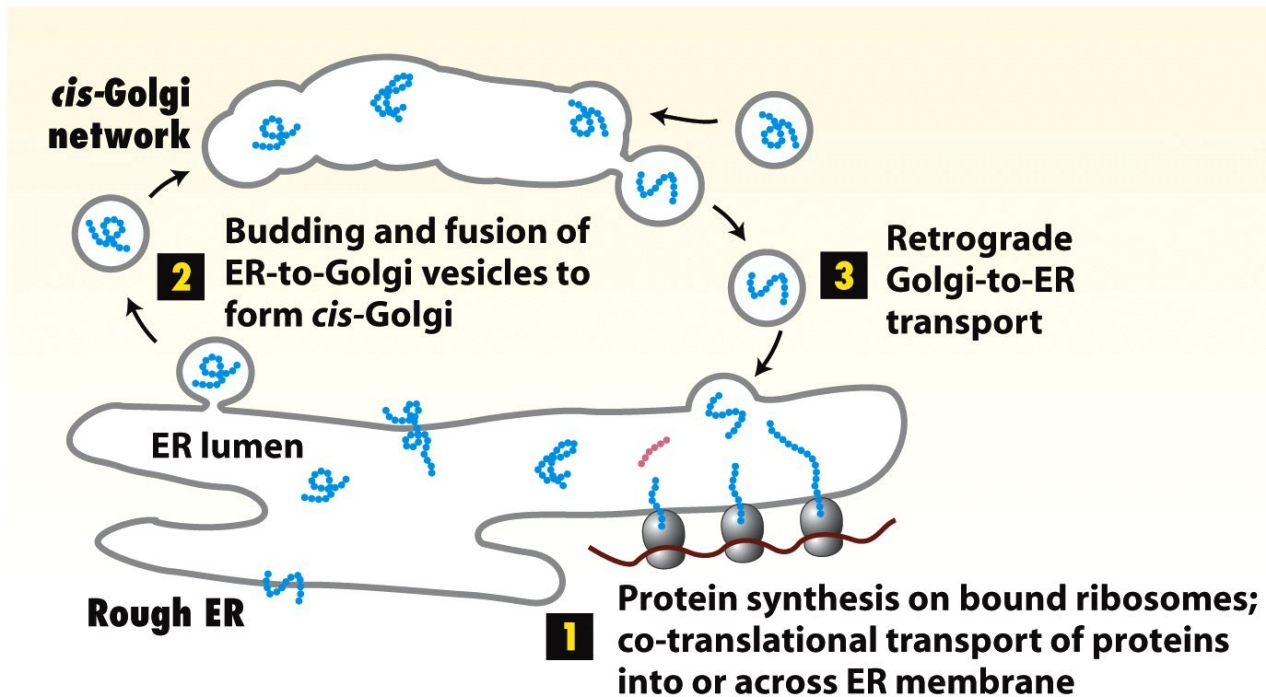
Figure 14-1 part 1
Molecular Cell Biology, Sixth Edition
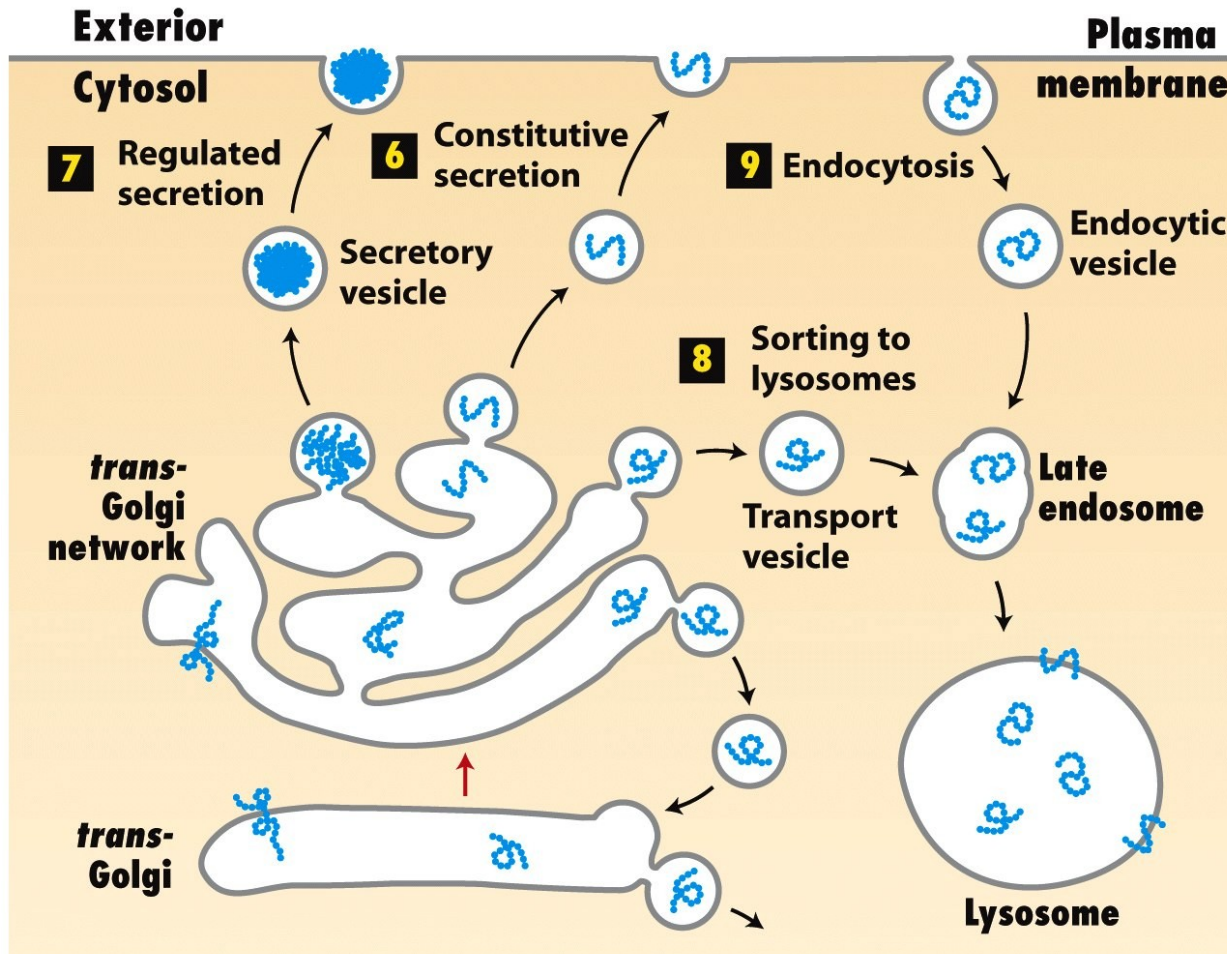© 2008 W. H. Freeman and Company

Exocytosis and endocytosis

Figure 14-1 part 3
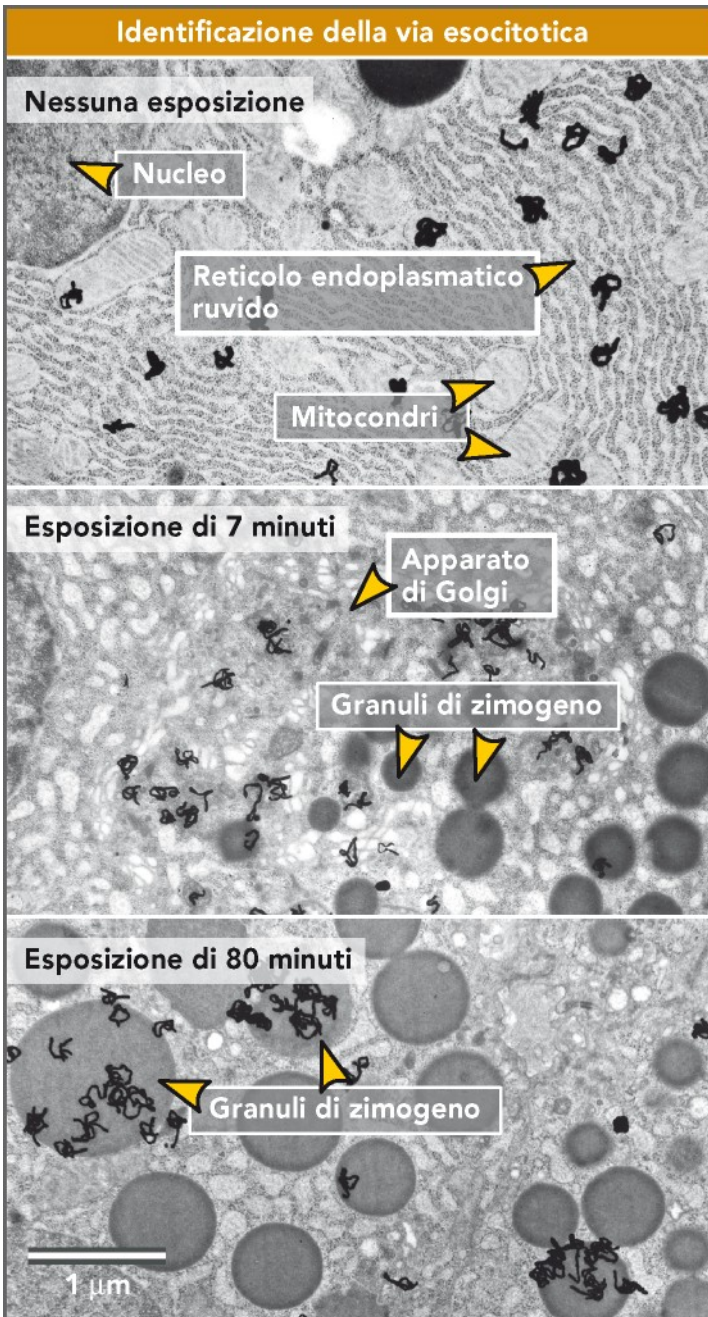*Molecular Cell Biology, Sixth Edition*
© 2008 W. H. Freeman and Company

Identificazione della via esocitotica

Nessuna esposizione
- Nucleo
- Reticolo endoplasmatico ruvido
- Mitocondri

Esposizione di 7 minuti
- Apparato di Golgi
- Granuli di zimogeno

Esposizione di 80 minuti
- Granuli di zimogeno

1 μm

Studies to establish the order in which proteins move from organelle to organelle in the secretory pathway.

Many components required for the formation and fusion of transport vesicles have been identified in the past decade by a remarkable convergence of genetic and biochemical approaches.

pulse-chase labeling on pancreatic acinar cells

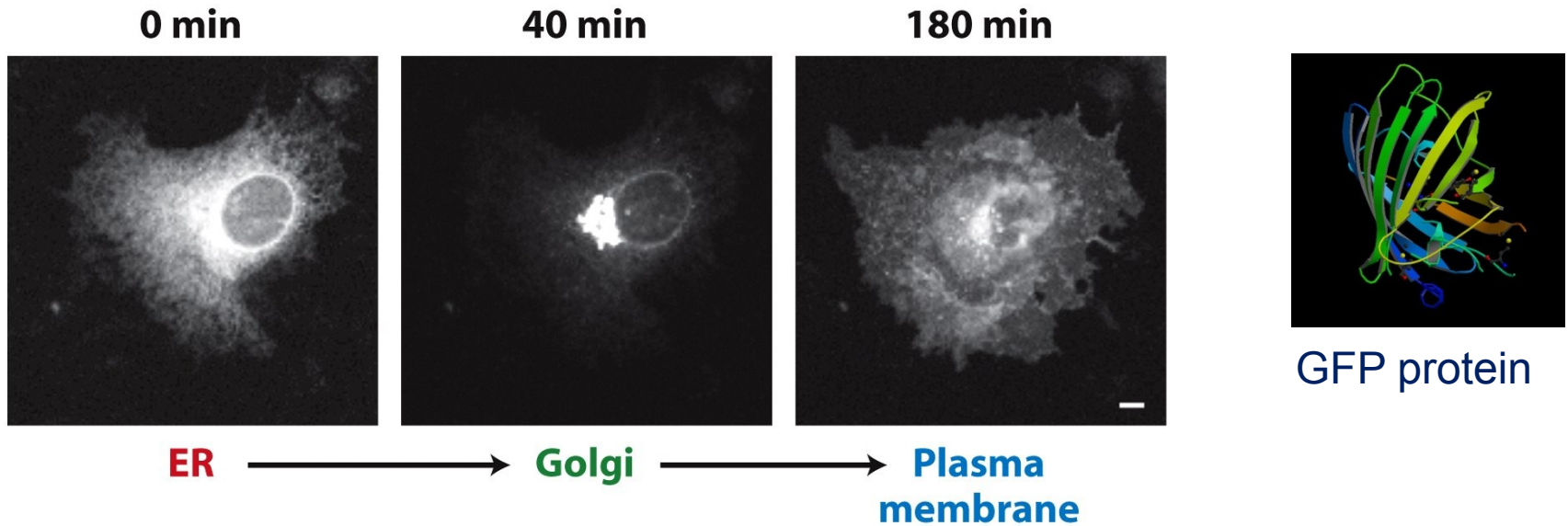# Fluorescence microscopy of VSVG-GFP fusion protein

0 min **40 min** **180 min**

ER ⟶ Golgi ⟶ Plasma membrane

Figure 14-2a
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

GFP protein

Gene encoding **a temperature-sensitive mutant** of the membrane **glycoprotein G** from vesicular stomatitis virus (VSV), fused to GFP protein has been introduced into cultured mammalian cells by transfection (VSVG-GFP).
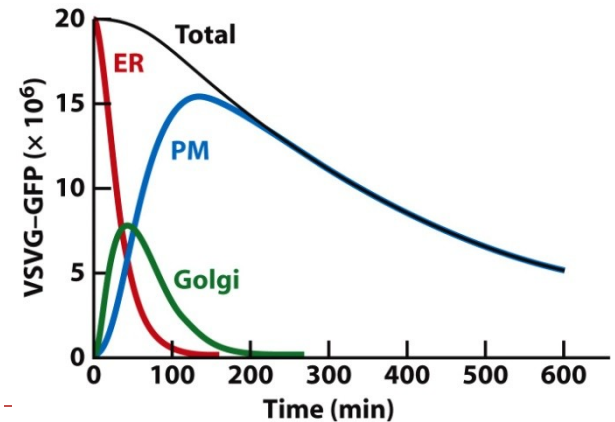

Figure 14-2b
Molecular Cell Biology, Sixth Edition
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Transport from the ER to the Golgi can be assayed based on sensitivity to cleavage by endoglycosidase D
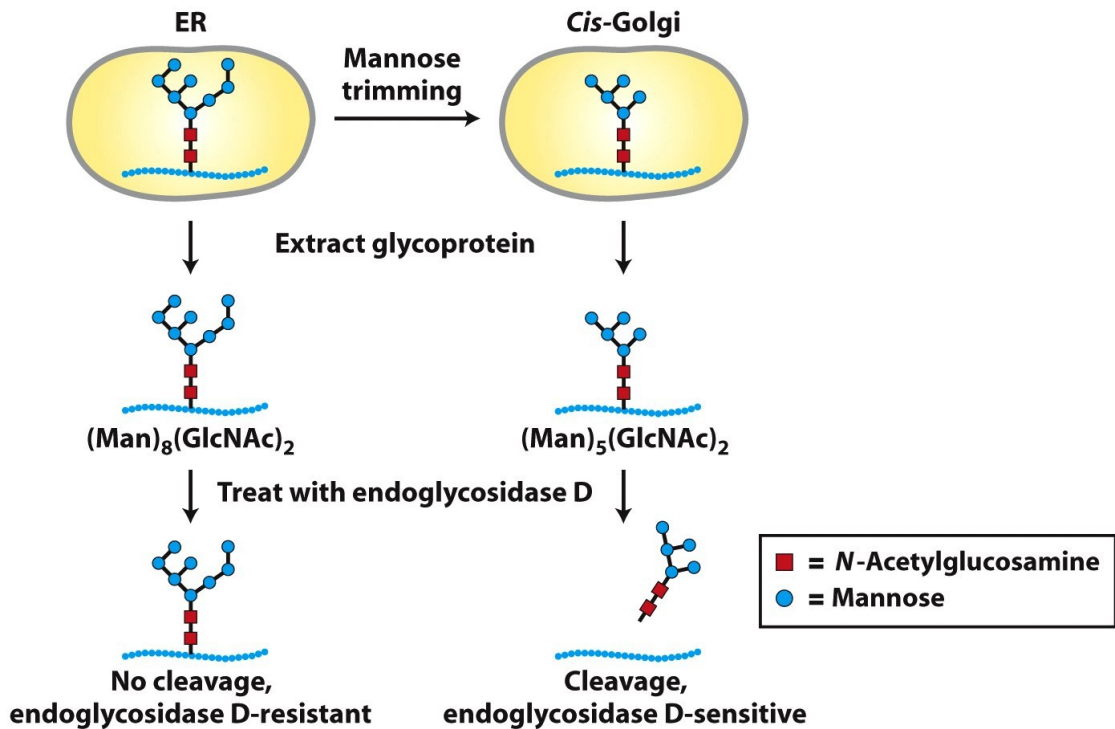

Figure 14-3a
Molecular Cell Biology, Sixth Edition
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Cis-Golgi maturation of VSV-G protein from vesicular stomatitis virus (VSV)
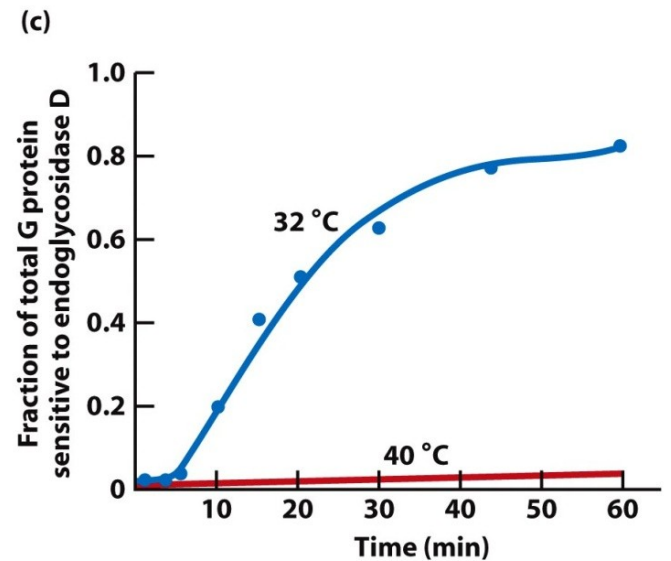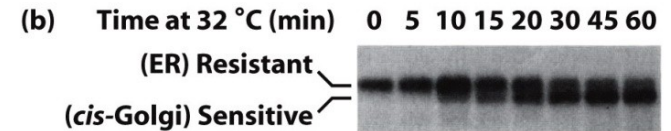

Figure 14-3bc
Molecular Cell Biology, Sixth Edition
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Tracking movement of VSV-G protein in virus-infected cells pulse-labeled with radioactive amino acids.

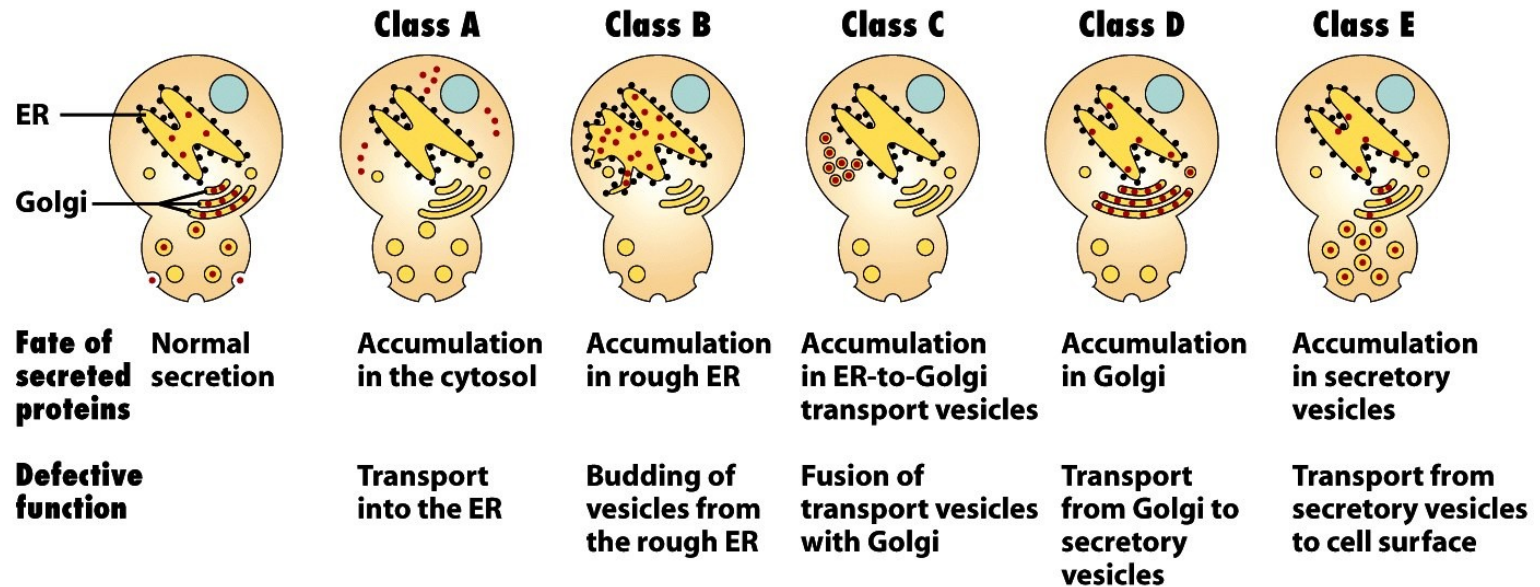# Phenotypes of yeast *sec* mutants identified stages in the secretory pathway

		Class A	Class B	Class C	Class D	Class E
Fate of secreted proteins	Normal secretion	Accumulation in the cytosol	Accumulation in rough ER	Accumulation in ER-to-Golgi transport vesicles	Accumulation in Golgi	Accumulation in secretory vesicles
Defective function		Transport into the ER	Budding of vesicles from the rough ER	Fusion of transport vesicles with Golgi	Transport from Golgi to secretory vesicles	Transport from secretory vesicles to cell surface

Figure 14-4
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Many of the components required for intracellular protein trafficking have been identified in yeast by analysis of **temperature-sensitive sec mutants** defective for the secretion of proteins at the **nonpermissive** temperature.

These studies (double mutants) confirmed that as a secreted protein is synthesized and processed it moves sequentially from the cytosol → rough ER → ER-to-Golgi transport vesicles → Golgi cisternae → secretory vesicles and finally is exocytosed.

Basic mechanisms underlying vesicle budding and fusion.
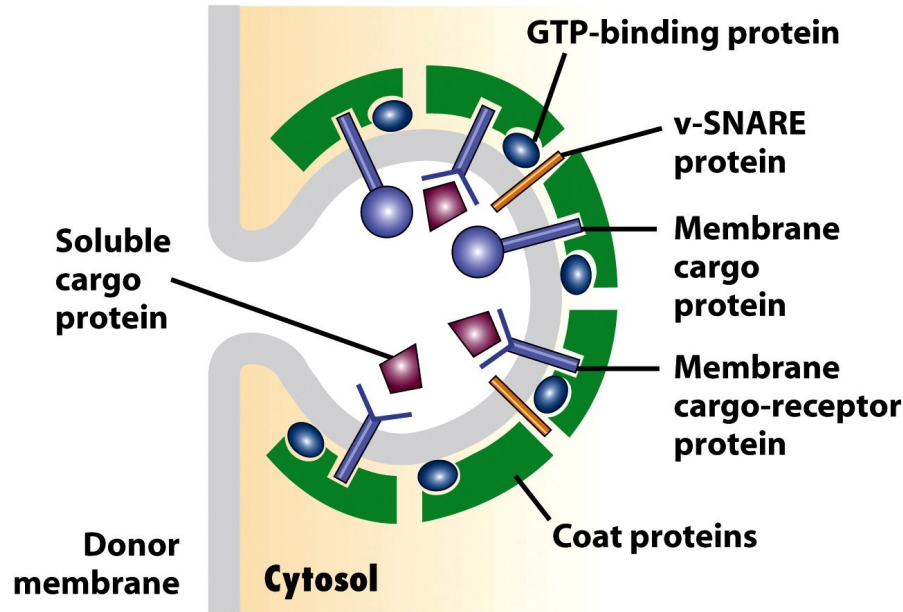

Coated vesicle budding

GTP-binding protein

v-SNARE protein

Soluble cargo protein

Membrane cargo protein

Membrane cargo-receptor protein

Coat proteins

Donor membrane

Cytosol

Figure 14-6a
Molecular Cell Biology, Sixth Edition
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Uncoated vesicle fusion

Cytosol

Target membrane

t-SNARE proteins

v-SNARE protein

SNARE complex
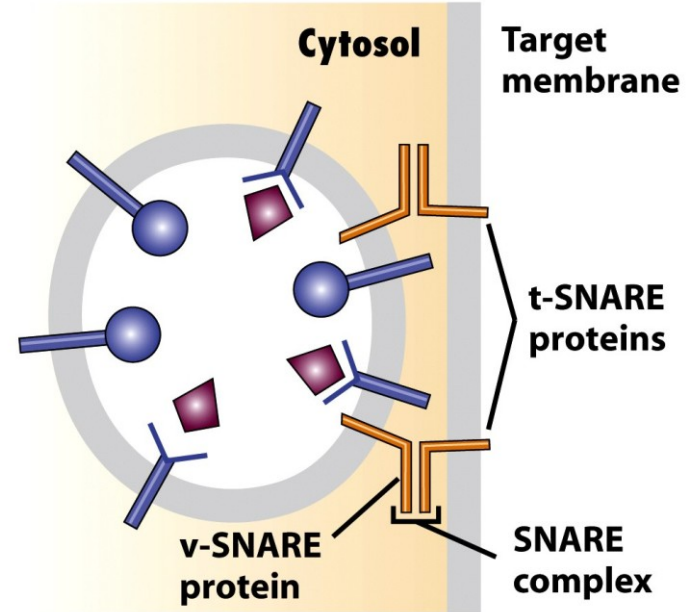
Figure 14-6b
Molecular Cell Biology, Sixth Edition
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Basic mechanisms underlying vesicle budding and fusion. Each step in the secretory and endocytic pathways employs **a different type of vesicle**, studies employing genetic and biochemical techniques have revealed that each of the different vesicular transport steps is simply a **variation on a common theme.**

In vitro budding reactions of a coated vescicle
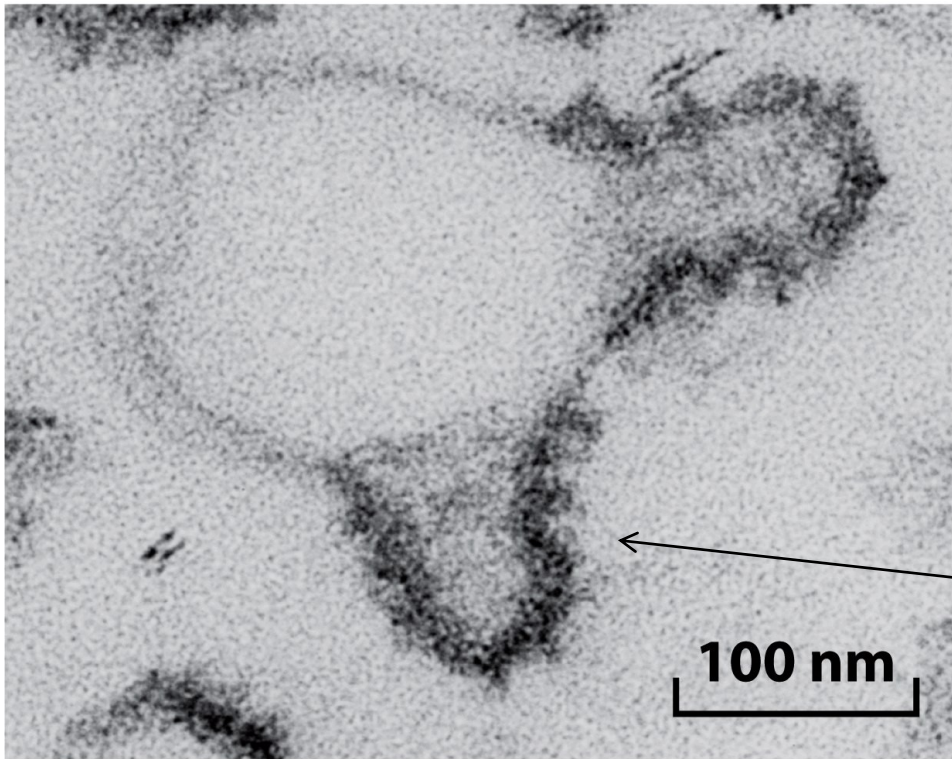
Isolated or artificial membranes and purified coat proteins. Polymerization of the coat proteins onto the cytosolic face of the parent membrane is necessary to produce the high curvature of the membrane

Vesicle buds

100 nm

Figure 14-7
Molecular Cell Biology, Sixth Edition
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Types of coated vesicles

TABLE 17-1	Coated Vesicles Involved in Protein Trafficking		
Vesicle Type	**Coat Proteins**	**Associated GTPase**	**Transport Step Mediated**
COPII	Sec23/Sec24 and Sec13/Sec31 complexes, Sec16	Sar1	ER to *cis*-Golgi
COPI	Coatomers containing seven different COP subunits	ARF	*cis*-Golgi to ER Later to earlier Golgi cisternae
Clathrin and adapter proteins*	Clathrin + AP1 complexes	ARF	*trans*-Golgi to endosome
	Clathrin + GGA	ARF	*trans*-Golgi to endosome
	Clathrin + AP2 complexes	ARF	Plasma membrane to endosome
	AP3 complexes	ARF	Golgi to lysosome, melanosome, or platelet vesicles

*Each type of AP complex consists of four different subunits. It is not known whether the coat of AP3 vesicles contains clathrin.

# Major types of coat proteins in vesicular traffic in the secretory and endocytic pathways.
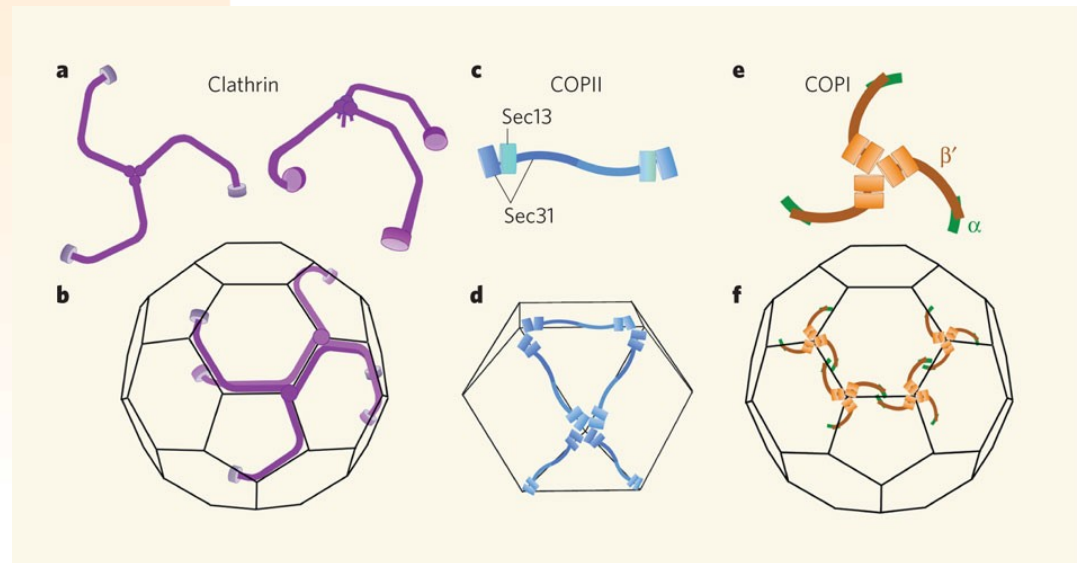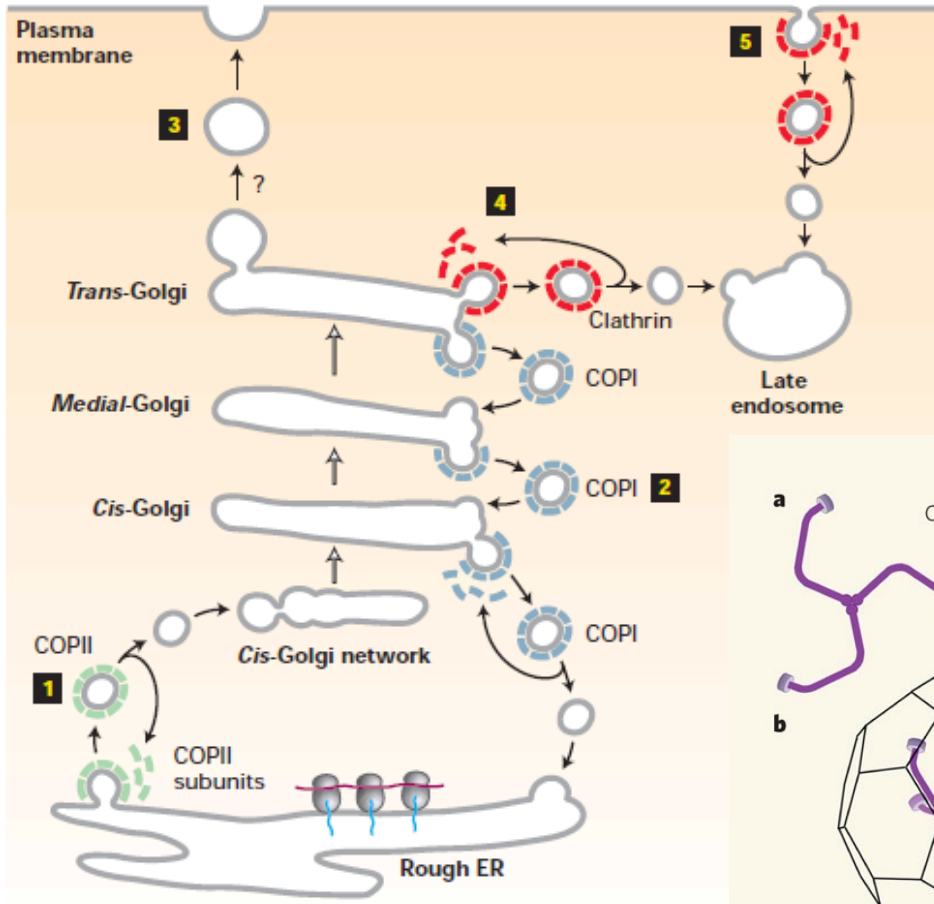
Budding Vesicles Wear Coats

1 When coat proteins assemble at the membrane, they force the lipid bilayer to begin to bend.

2 As they gather at the membrane, coat proteins may also select the cargo that is packaged into the forming vesicle.

3 As more coat proteins are added, they shape the surrounding membrane into a sphere.

4 Once a coated vesicle pinches off, the coat falls off, and the cargo-filled vesicle is ready to travel to its destination.
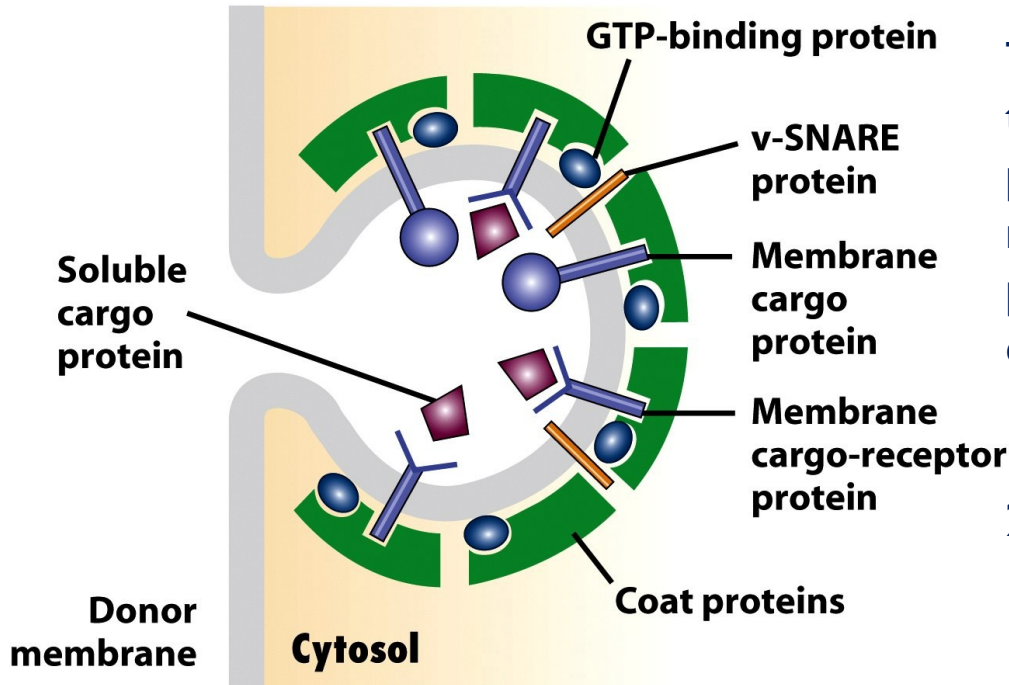
Golgi   Cytosol
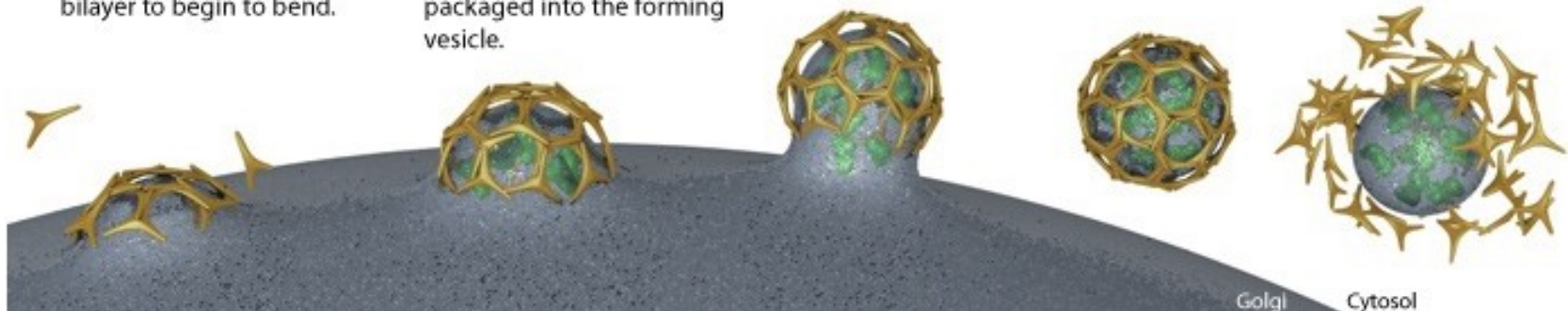
Some vesicles form with the help of coat proteins. Geometrically arranged coat proteins on the surface of the membrane help the vesicle to bud off.

http://learn.genetics.utah.edu/content/cells/vesicles/

The budding of vesicles from their parent membrane

Coated vesicle budding

The budding of vesicles is driven by the polymerization of soluble protein complexes onto the membrane to form a **proteinaceous vesicle coat** The coat functions:

1) adds curvature to the membrane to form a vesicle
2) also **acts as the filter** to determine which proteins are admitted into the vesicle.

Figure 14-6a
Molecular Cell Biology, Sixth Edition
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The integral membrane proteins in a budding vesicle include **v-SNAREs,** which are crucial to eventual fusion of the vesicle with the correct target membrane

A Set of GTPase Switch Proteins Controls Assembly of Vesicle Coats

The coats of all three vesicles contain a **small GTP-binding protein:** acts as a **regulatory subunit** to control coat assembly.

Sar1 is present in the coat of COPII vesicles. **ARF** is the GTPase used by COPI and clathrin vesicles.
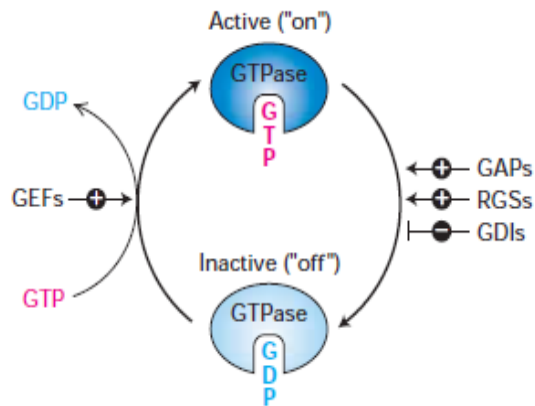
Both ARF and Sar1 are **monomeric GTPase** of **switch proteins** that exchange GDP/GTP.

Cycling of GTPase switch proteins between the active and inactive forms. Activation is promoted by GEFs (guanine nucleotide–exchange factors).

Binding of GTP to Sar1 (ARF) promoted by Sec12 causes a conformational change in **Sar1** that exposes its hydrophobic N-terminus,
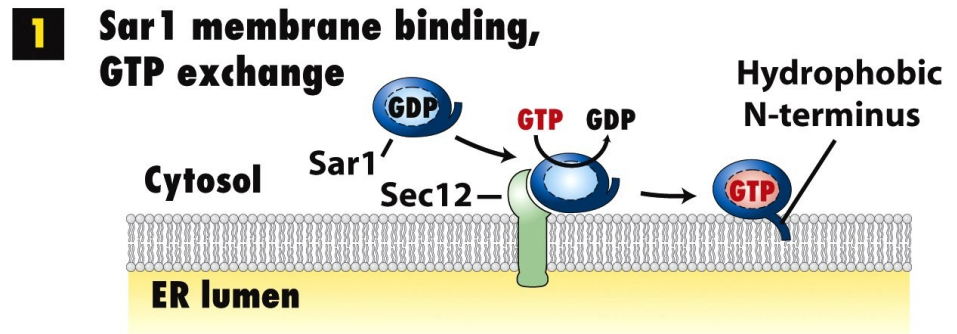
Sar1 couples a cycle of GTP binding and hydrolysis to the formation and then dissociation of the COPII coat

Sec23/Sec24
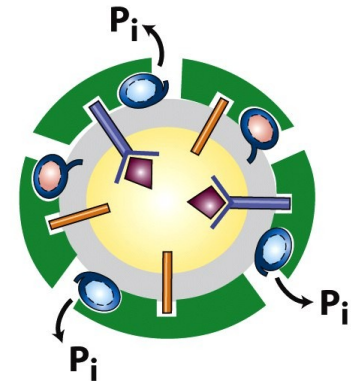
2 **COPII coat assembly**
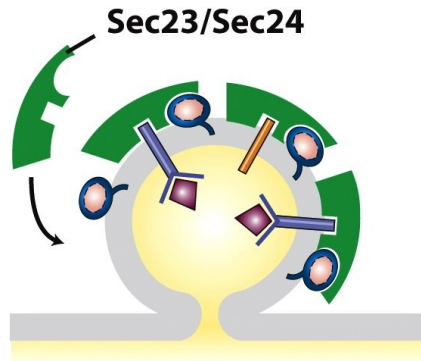
2. The membrane-attached Sar1 GTP drives polymerization of cytosolic complexes of COPII subunits on the membrane, eventually leading to formation of vesicle buds.
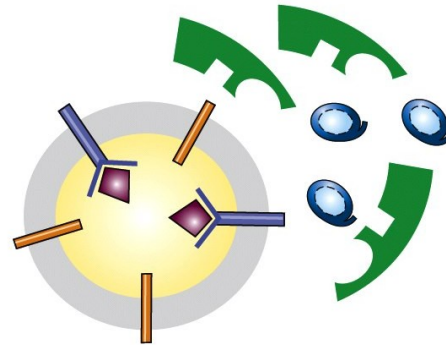
3. Once COPII vesicles are released from the donor membrane, the Sar1 GTPase activity hydrolyzes Sar1 GTP in the vesicle membrane to Sar1 GDP

3 **GTP hydrolysis**

P_i
P_i
P_i

Disassembly of COPII coat

4 **Coat disassembly**

Uncoated vesicle

4. This hydrolysis triggers disassembly of the COPII coat.

With mutant versions of Sar1 that **cannot hydrolyze GTP**, vesicle coats form and vesicle buds pinch off. However, all available coat subunits eventually become permanently assembled into coated vesicles that are unable to fuse with target membranes.

  ARF protein undergoes a similar cycle of nucleotide exchange and hydrolysis coupled to the assembly of vesicle coats composed either of COPI or of clathrin and other coat proteins.
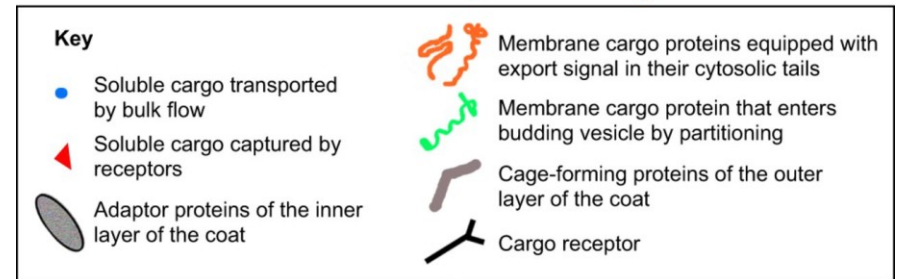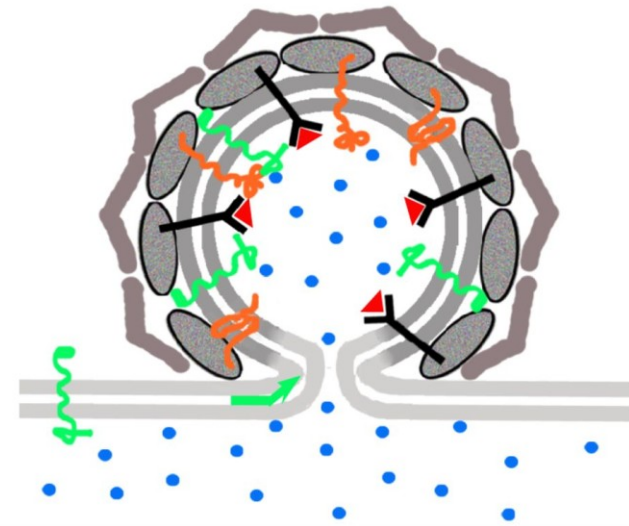
Different mechanisms of recruitment of cargo to transport vesicles

Vesicle buds must be able to discriminate among potential membrane and soluble cargo proteins.

Membrane cargo proteins: the mechanism by which the vesicle coat selects cargo molecules is by directly binding to specific sequences, or **sorting signals,** in the cytosolic portion of membrane cargo proteins.

Soluble proteins within the lumen of parent organelles can in turn be selected by binding to the luminal domains of certain membrane cargo proteins, which act as receptor.

Key

- Soluble cargo transported by bulk flow
- Soluble cargo captured by receptors
- Adaptor proteins of the inner layer of the coat
- Membrane cargo proteins equipped with export signal in their cytosolic tails
- Membrane cargo protein that enters budding vesicle by partitioning
- Cage-forming proteins of the outer layer of the coat
- Cargo receptor

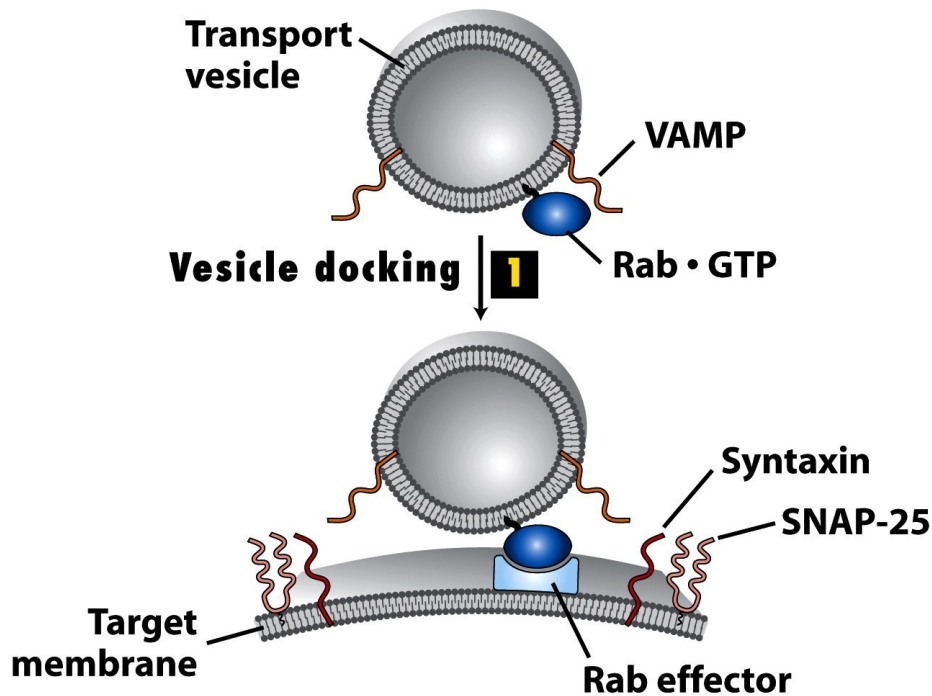Nica Borgese J Cell Sci 2016;129:1537-1545

Targeting Sequences on Cargo Proteins Make Specific Molecular Contacts with Coat Proteins

TABLE 17-2 Known Sorting Signals That Direct Proteins to Specific Transport Vesicles

Signal Sequence*	Proteins with Signal	Signal Receptor	Vesicles That Incorporate Signal-bearing Protein
Lys-Asp-Glu-Leu (KDEL)	ER-resident luminal proteins	KDEL receptor in *cis*-Golgi membrane	COPI
Lys-Lys-X-X (KKXX)	ER-resident membrane proteins (cytosolic domain)	COPI α and β subunits	COPI
Di-acidic (e.g., Asp-X-Glu)	Cargo membrane proteins in ER (cytosolic domain)	COPII Sec24 subunit	COPII
Mannose 6-phosphate (M6P)	Soluble lysosomal enzymes after processing in *cis*-Golgi	M6P receptor in *trans*-Golgi membrane	Clathrin/AP1
	Secreted lysosomal enzymes	M6P receptor in plasma membrane	Clathrin/AP2
Asn-Pro-X-Tyr (NPXY)	LDL receptor in the plasma membrane (cytosolic domain)	AP2 complex	Clathrin/AP2
Tyr-X-X-Φ (YXXΦ)	Membrane proteins in *trans*-Golgi (cytosolic domain)	AP1 (μ1 subunit)	Clathrin/AP1
	Plasma membrane proteins (cytosolic domain)	AP2 (μ2 subunit)	Clathrin/AP2
Leu-Leu (LL)	Plasma membrane proteins (cytosolic domain)	AP2 complexes	Clathrin/AP2

*X = any amino acid; Φ = hydrophobic amino acid. Single-letter amino acid abbreviations are in parentheses.

Rab proteins are required for the targeting of vesicles to the target membrane

Transport vesicle

VAMP

Vesicle docking 1

Rab • GTP

Syntaxin

SNAP-25

Target membrane

Rab effector

Figure 14-10a part 1
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Targeting of vesicles to the appropriate target membrane is mediated by **Rab proteins,** GTPase superfamily of **switch proteins.**

Conversion of cytosolic Rab GDP to Rab GTP, enables it to interact with a particular transport vesicle and insert its isoprenoid anchor into the vesicle membrane.

Once Rab GTP is tethered to the vesicle surface, it interacts with one of a number of different large proteins, known as **Rab effectors,** attached to the target membrane.

After vesicle fusion occurs, the GTP bound to the Rab protein is hydrolyzed to GDP, triggering the release of Rab -GDP, which then can undergo another cycle of GDP-GTP exchange, binding, and hydrolysis.

A different type of Rab and Rab effector appears to function for each vesicle type

Each type of vescicles and organelles has at least one **Rab** protein on its cytosolic surface. Sec4 mutant (yeast cells) accumulate secretory vesicles that are unable to fuse with the plasma membrane (class E mutants).
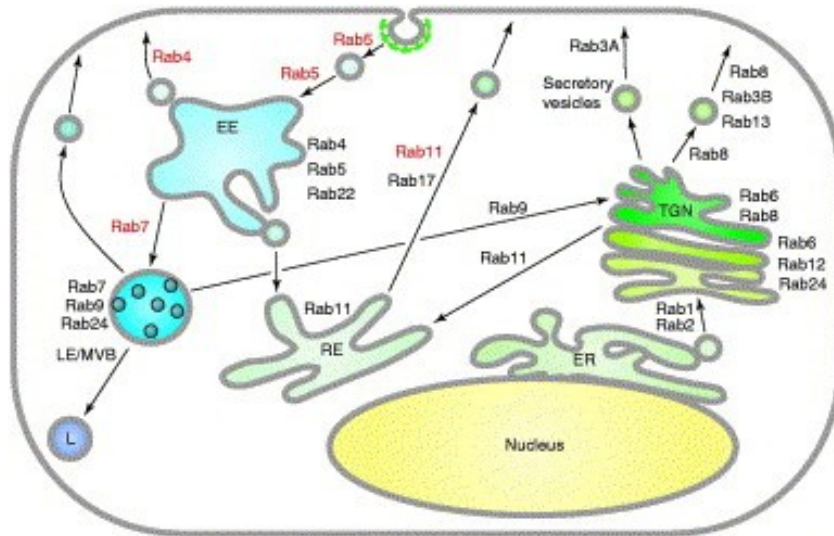
Z. Gáborik , L. Hunyady Trends in Endocrinology and Metabolism, V. 15, 2004, 286 -93

Rab1 is essential for ER-to-Golgi transport reactions, **Rab7** associate with late endosome.

Model for the role of EEA1 in endocytic membrane docking/fusion
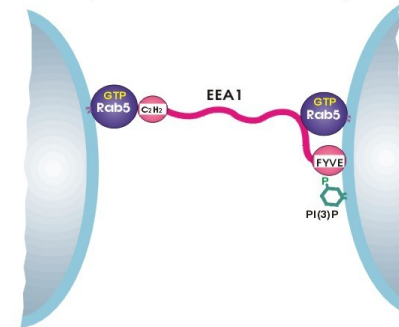
Example: **Rab5 protein** is localized to endocytic vesicles (EE). A long coiled protein known as **EEA1** (early endosome antigen 1), which resides on the membrane of the early endosome, functions as the **Rab effector** for Rab5.

Paired Sets of SNARE Proteins Mediate Fusion of Vesicles with Target Membranes

After Rab-mediated docking of a vesicle on its target membrane, the interaction of cognate **SNAREs** brings the two membranes close enough together that they can fuse. They provide a layer of specificity.
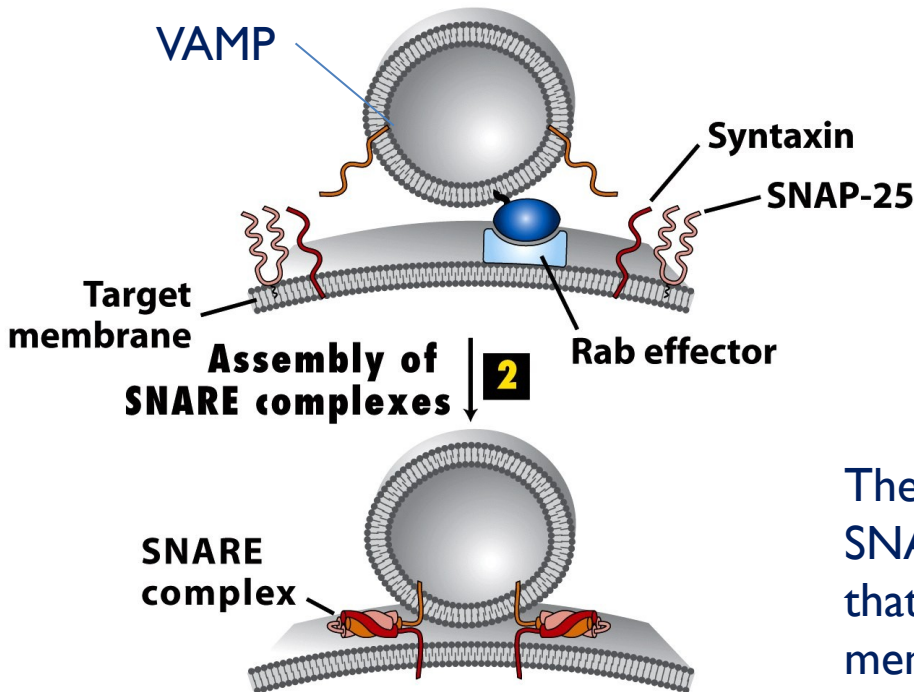
The best-understood examples of SNARE-mediated fusion occurs during **exocytosis of secreted proteins.**
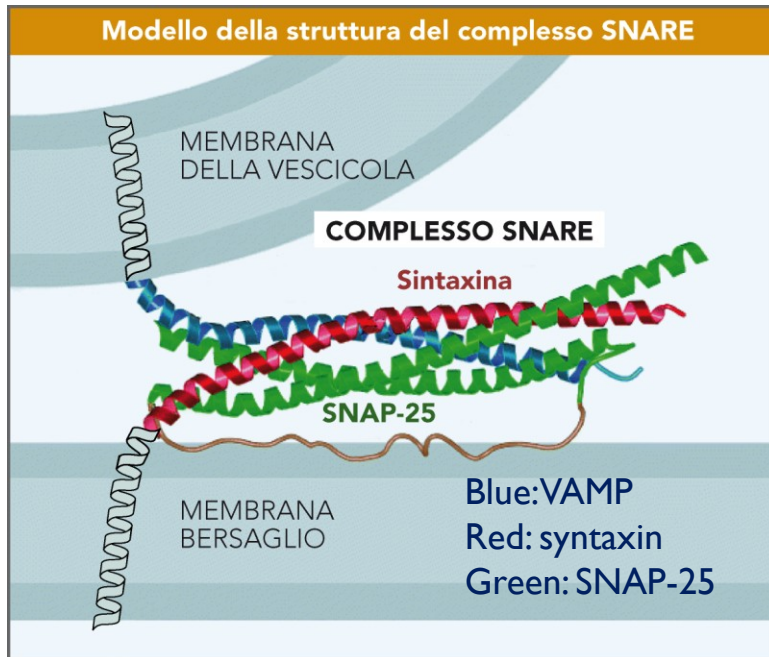
The cognate **SNAREs:**
V-SNARE: = VAMP (*vesicle-associated membrane protein*)
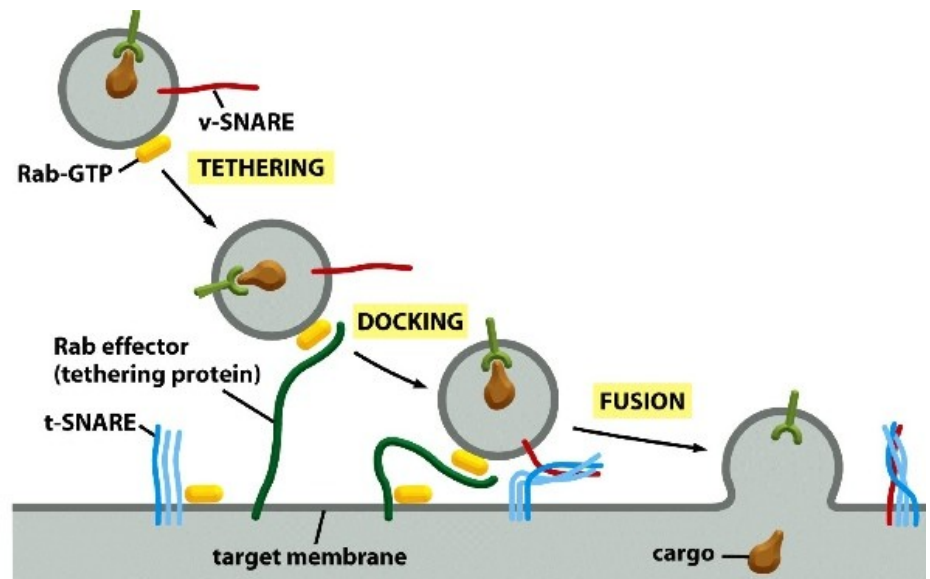T-SNARE: Syntaxin and SNAP-25.

The cytosolic region in each of these three SNARE proteins form a **four-helix bundle** that anchor vesicles to the target membrane.

VAMP
Syntaxin
SNAP-25
Target membrane
Rab effector
Assembly of SNARE complexes 2
SNARE complex

Figure 14-10a part 2
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Model of the structure of the SNARE complex

Modello della struttura del complesso SNARE

MEMBRANA DELLA VESCICOLA

COMPLESSO SNARE

Sintaxina

SNAP-25

MEMBRANA BERSAGLIO

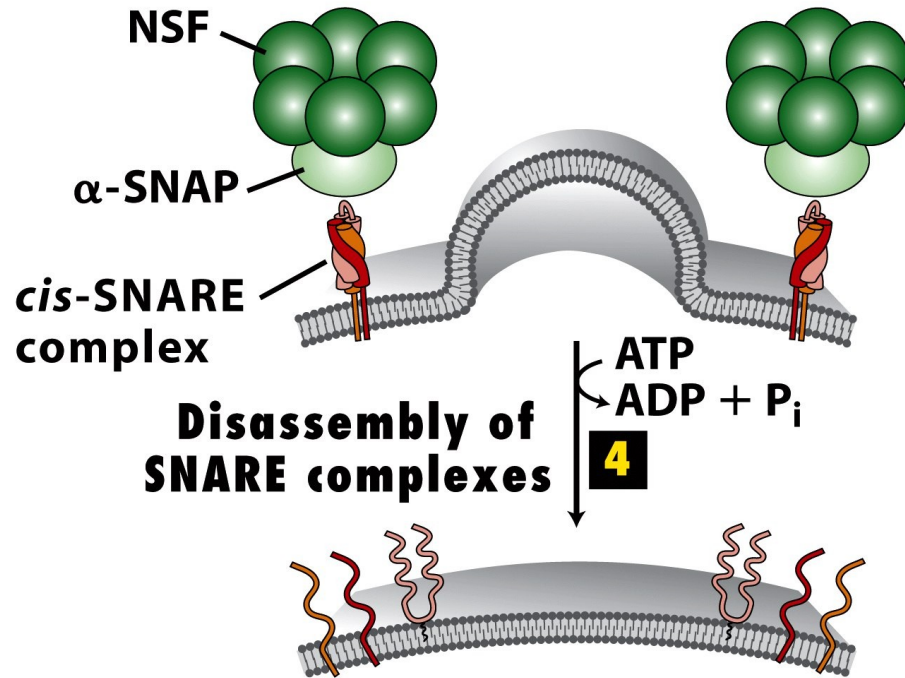Blue: VAMP
Red: syntaxin
Green: SNAP-25

The cytosolic region in each of these three SNARE proteins contains a repeating **heptad sequence** that allows four helices—one from VAMP, one from syntaxin, and two from SNAP-25 to coil around one another to form a **four-helix bundle** with unusual stability **.**

In **liposomes,** formation of SNARE complexes is sufficient to bring about **membrane fusion**

Rab-GTP

v-SNARE

TETHERING

Rab effector (tethering protein)

t-SNARE

DOCKING

FUSION

target membrane

cargo

Dissociation of SNARE complexes is driven by ATP Hydrolysis

NSF
α-SNAP
cis-**SNARE complex**

Disassembly of SNARE complexes

ATP
ADP + P$_i$

4

Figure 14-10a part 4
Molecular Cell Biology, Sixth Edition
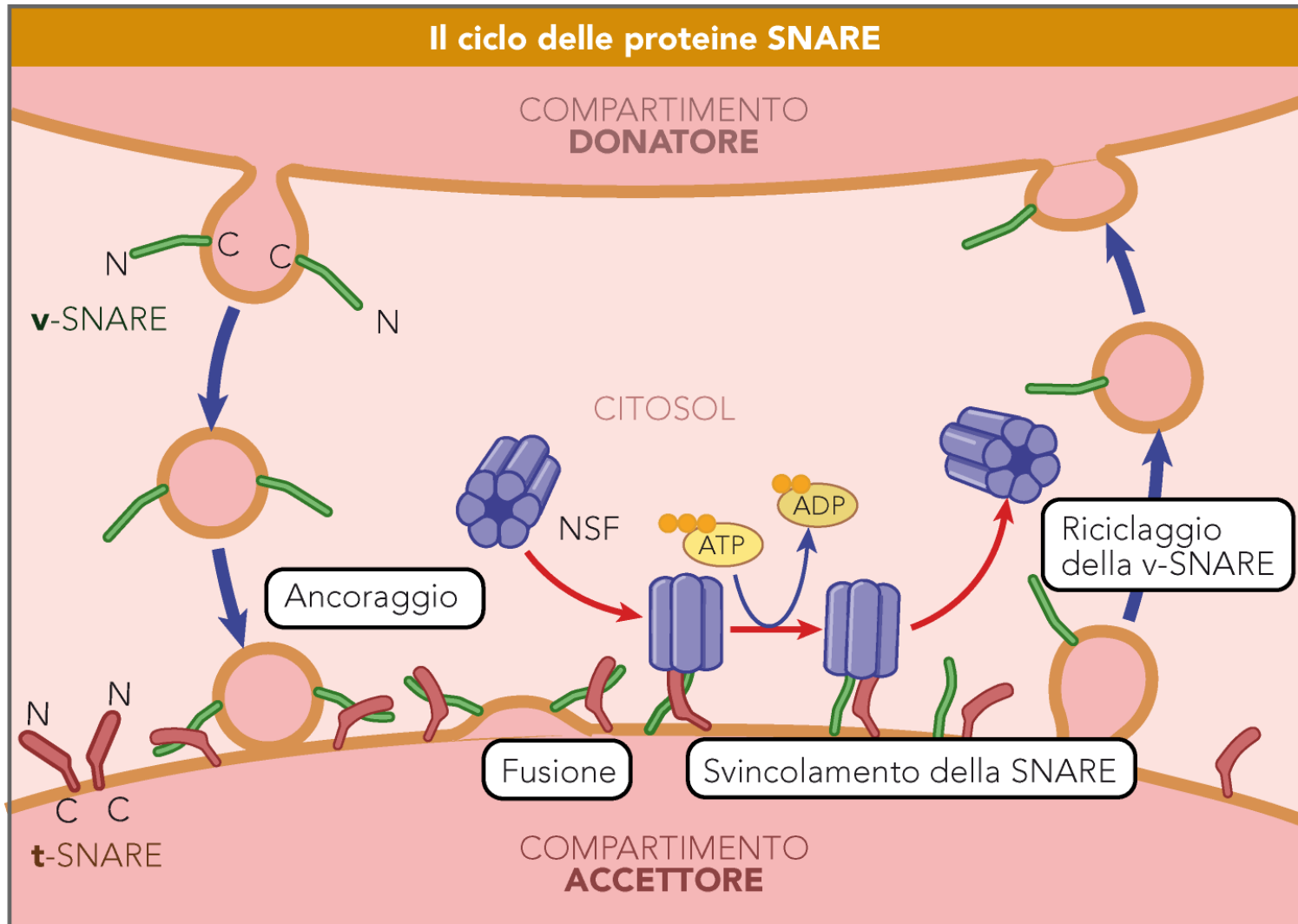© 2008 W. H. Freeman and Company

Because of the stability of SNARE complexes, their dissociation depends on additional proteins and the input of energy.

NSF examer and **α-SNAP**, are required for regeneration of free SNARE proteins and not for ongoing vesicle fusion

Sec yeast mutants homologues to NSF and alpha-SNAP belong to the mutants of class C. NSF and -SNAP proteins are not necessary for actual membrane fusion, but rather are required for **regeneration** of free SNARE proteins.

NSF is required to recycling of SNARE proteins

Il ciclo delle proteine SNARE

COMPARTIMENTO DONATORE

CITOSOL

v-SNARE

NSF

ATP

ADP

Ancoraggio

Riciclaggio della v-SNARE

Fusione

Svincolamento della SNARE

t-SNARE

COMPARTIMENTO ACCETTORE

Early Stages of the Secretory Pathway
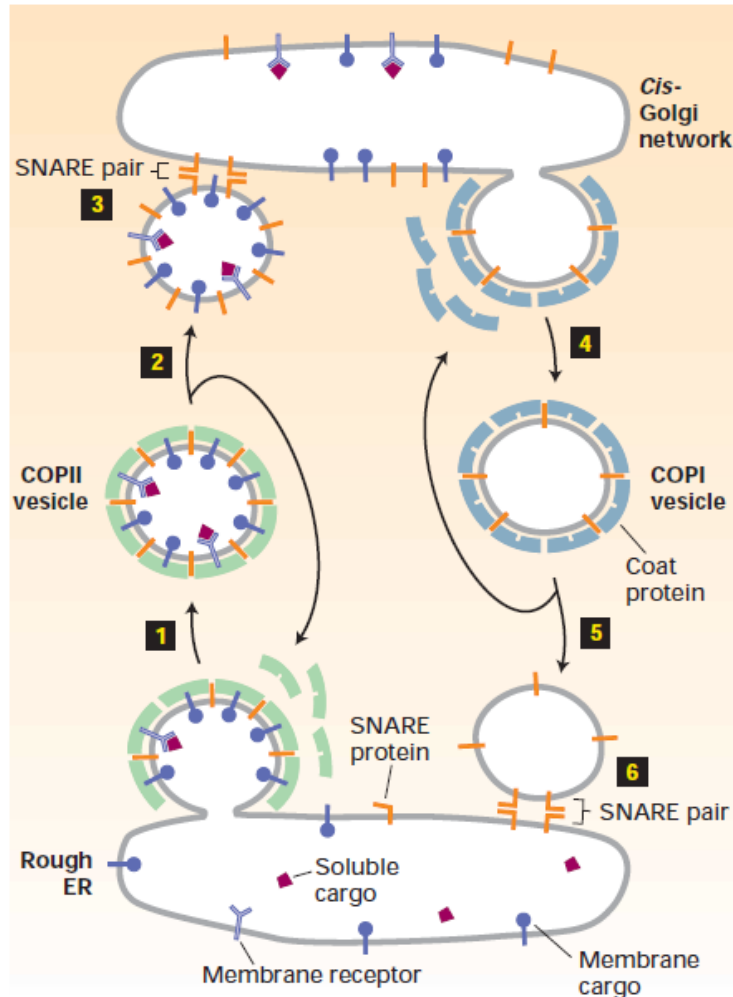
Take a closer look at vesicular traffic through the ER and Golgi stages of the secretory pathway

Vesicular traffic through the ER and Golgi stages of the secretory pathway is mediated by COPII (anterograde transport) and by COPI vesicles (retrograde transport)

COPII Vesicles Mediate Transport from the ER to the Golgi

COPII vesicles were first recognized when cell-free extracts of yeast rough ER membranes were incubated with cytosol, ATP, and a nonhydrolyzable analog of GTP.
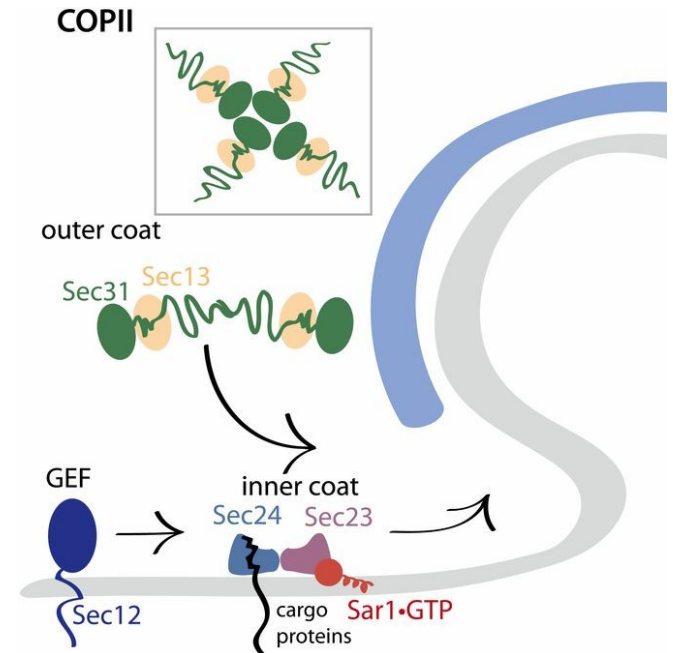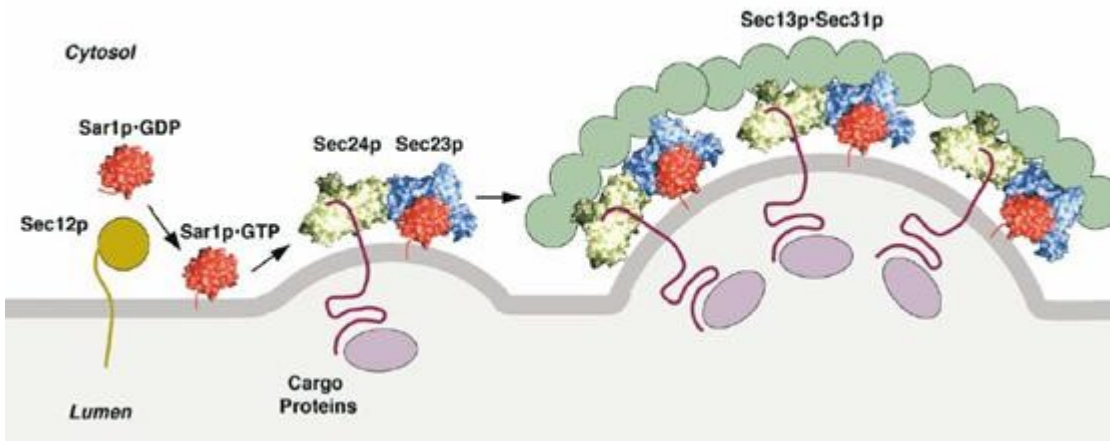
The cytosolic segments of Integral ER membrane proteins are specifically recruited into **COPII** contain a **di-acidic** sorting signal (**Asp-X-Glu**) which binds to the **Sec24** subunit of the COPII coat and is essential for the selective export of certain membrane proteins from the ER.

Few receptors for soluble cargo proteins are known.

The COPI coat assembles upon activation of Arf1

Genetics 2013 vol. 193 no. 2 383-410
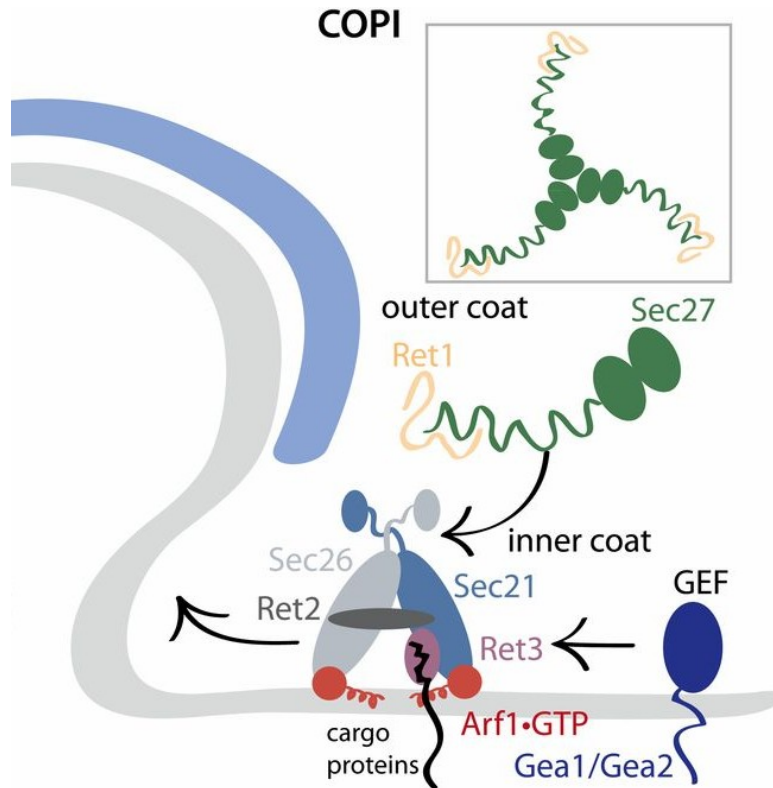
Arf1 in turn recruits the **inner coat complex** (Sec21/Sec26/Ret2/Ret3) (similar to AP-2 adaptor complex).

The COPI outer coat is formed by **3** proteins which assembles in a triskelion structure via interactions of three domains of Sec27

COPI Vesicles Mediate Retrograde Transport within the Golgi and from the Golgi to the ER

Yeast cells containing temperature sensitive mutations in COPI proteins have been categorized as class B *sec mutants*
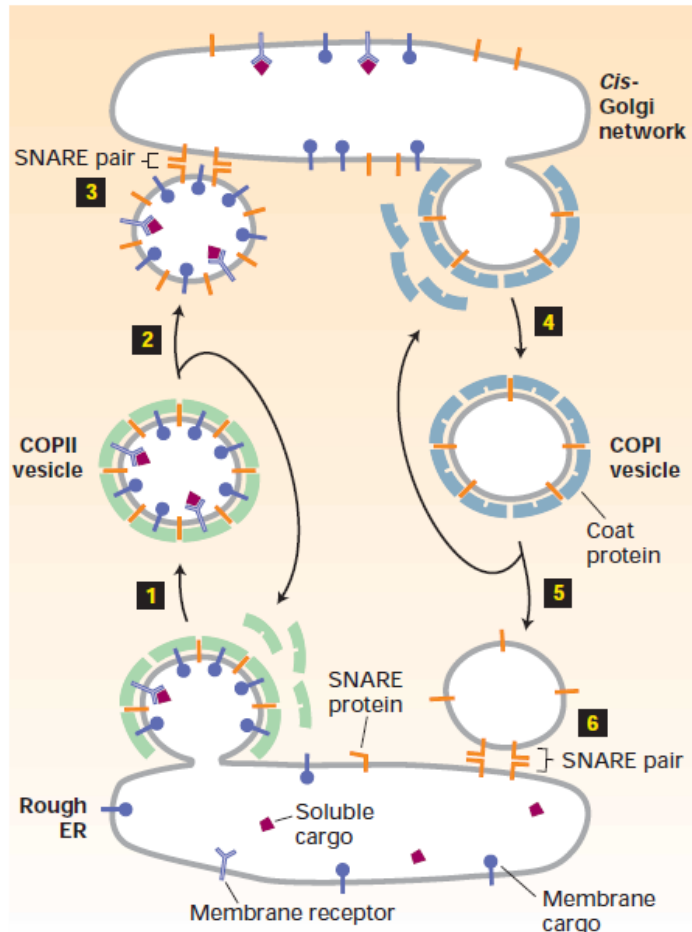
Functions of retrograde transport from the cis-Golgi to the ER:

✓Recycling of vesicle membranes

✓Recycling of v-SNARE

- COPI mutants cannot recycle key membrane proteins back to the rough ER, the ER gradually becomes depleted of ER proteins such as v-SNAREs and eventually vesicle formation from the rough ER is halted.

✓Retrieval of missorted ER-resident proteins (sorting mistakes).

•ER contains several soluble resident proteins (chaperone BIP and protein disulfide isomerase) loaded passively into vesicles destined for the cis-Golgi.

Retrograde transport from the cis-Golgi rescues missorted ER-resident proteins (sorting mistakes).
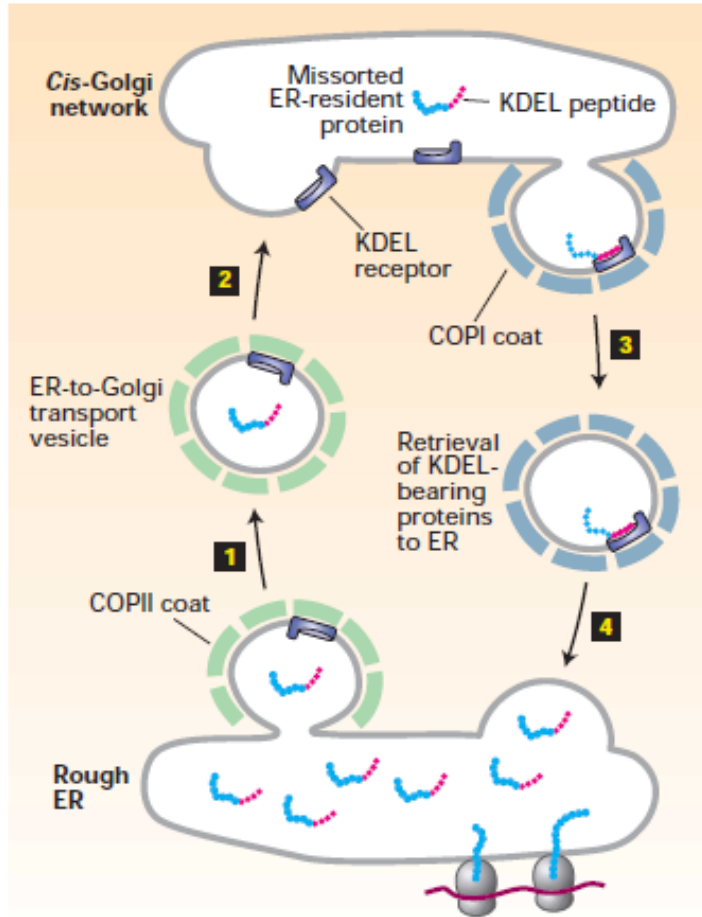

Most soluble ER-resident proteins carry a Lys-Asp-Glu- Leu (KDEL) sorting signal at their C-terminus. KDEL is recognized and bound by the **KDEL receptor**, found on transport vesicles shuttling between the ER and the cis-Golgi and on the cis-Golgi reticulum.

The KDEL receptor and other membrane proteins that are transported back to the ER from the Golgi contain a **Lys-Lys-X-X** sequence at the very end of their C-terminal segment, which faces the cytosol. This is necessary and sufficient to incorporate proteins into COPI vesicles for retrograde transport.

Mutant protein disulfide isomerase lacking these four residues is synthesized in fibroblasts is secreted

Anterograde Transport Through the Golgi could occur by Cisternal Progression
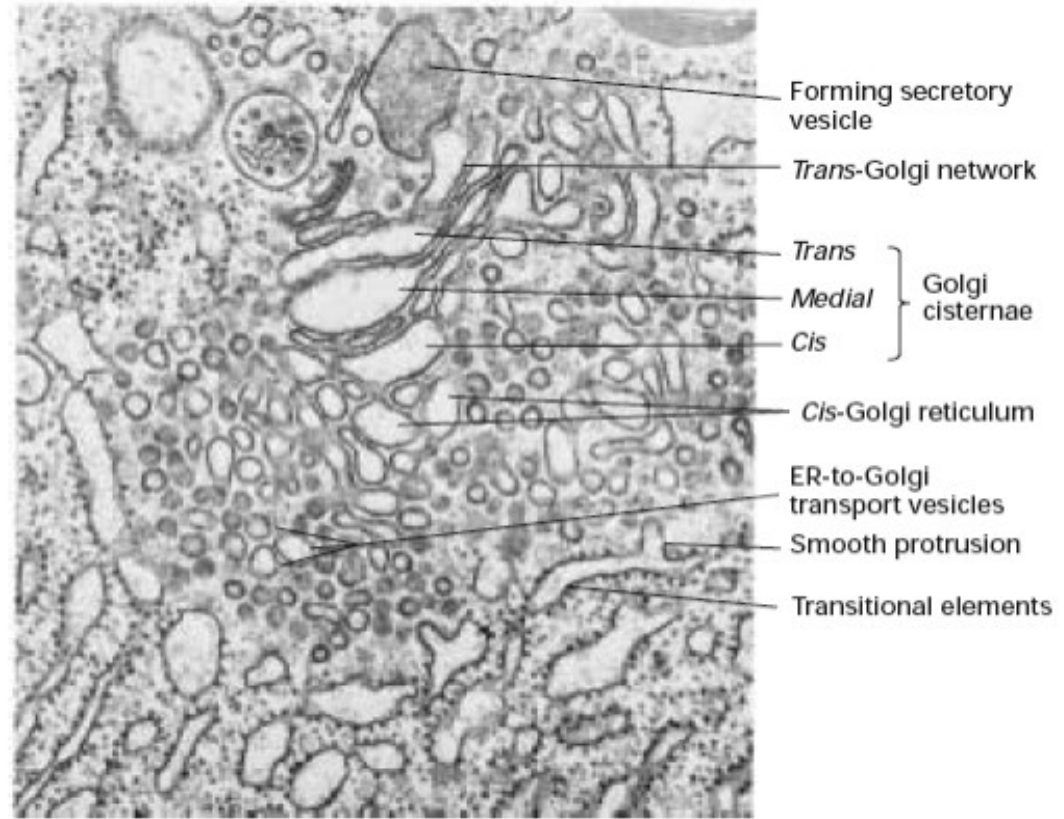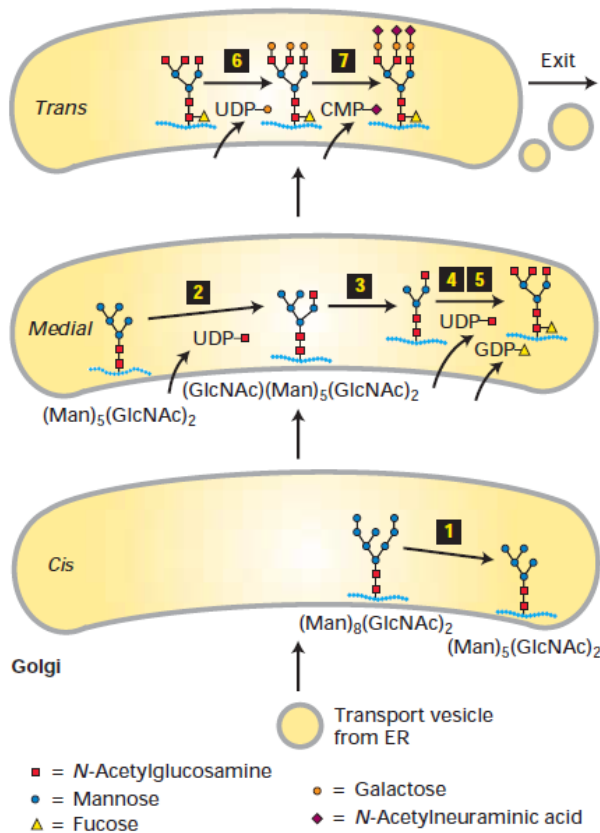
Some protein aggregates (e.g. collagen) are too large to be incorporated into small transport vesicles, and aggregates have never found in transport vesicles. It has been suggested that the forward movement of these and perhaps all secretory proteins from one Golgi compartment to another does not occur via small vesicles.
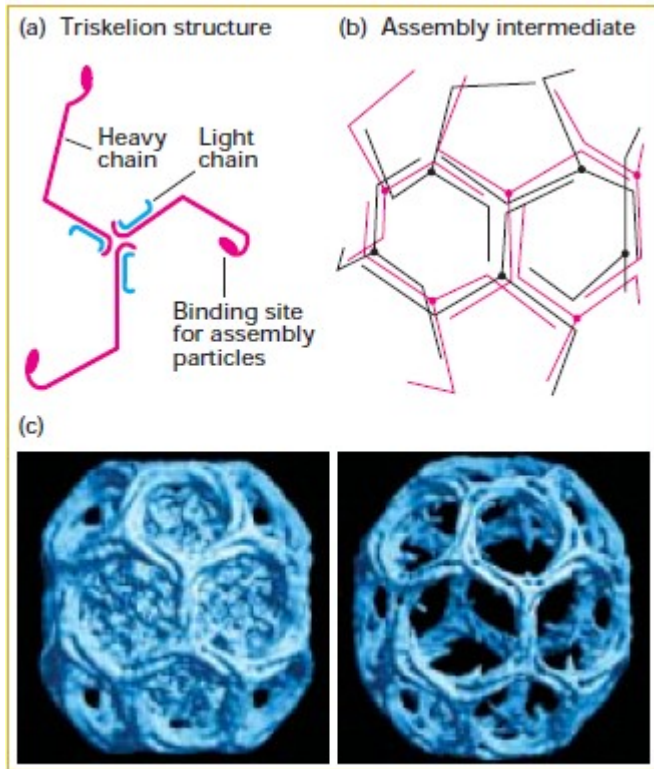
Later Stages of the Secretory Pathway
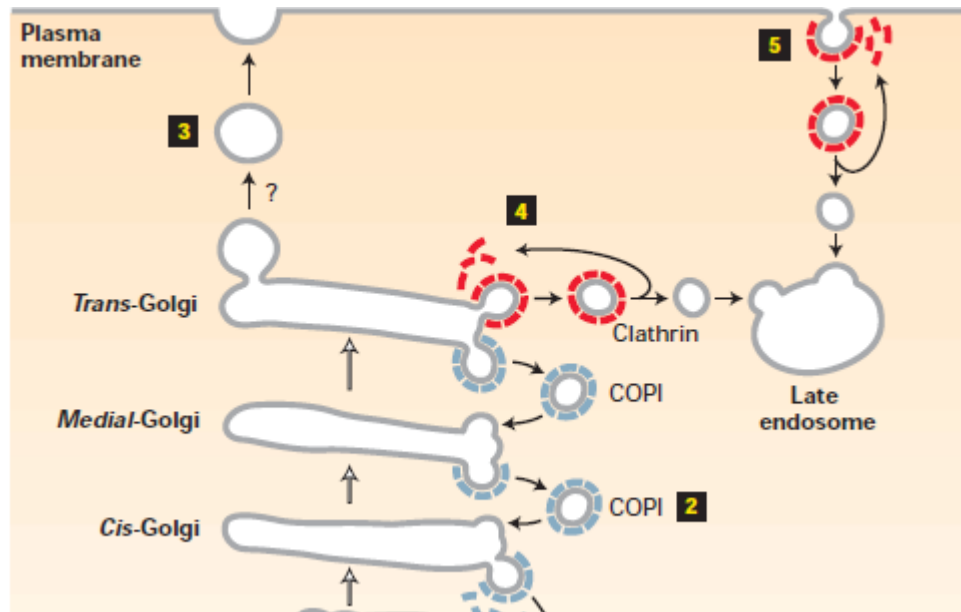
Properly processed cargo proteins reach the *trans-Golgi network, the* most-distal Golgi compartment where they are sorted into vesicles for delivery to their final destination.

Vesicles Coated with Clathrin and/or Adapter Proteins Mediate Several Transport Steps


Structure of clathrin coats

The best-characterized vesicles that bud from the **trans-Golgi network** (TGN) have a two-layered coat:
- an outer layer composed of the **fibrous protein clathrin** and
- an inner layer composed of **adapter protein (AP)** complexes.

Clathrin: three branched shape, called **triskelion.** Each branch: 1 heavy chain of 180 kDa forming legs from α-helical zigzags and 1 light chain of 35-40 kDa;
Triskelions polymerize to form a polyhedral cage **with intrinsic curvature**. The clathrin triskelions determine the geometry of the clathrin vescicles.

A clathrin-coated pit on the cytosolic face of the plasma membrane

La clatrina forma reticoli

RETICOLO PIATTO — RETICOLI CURVI
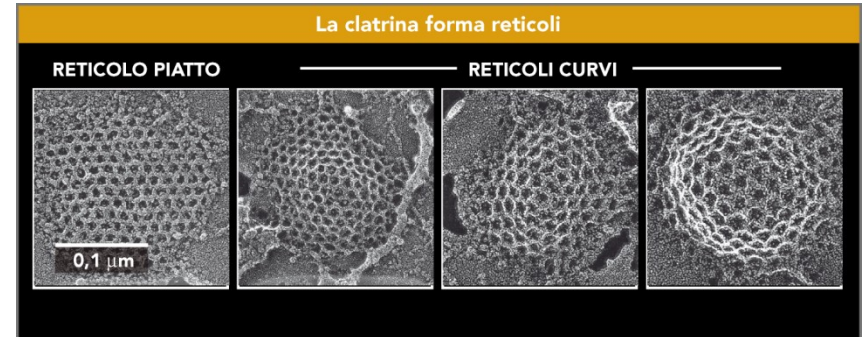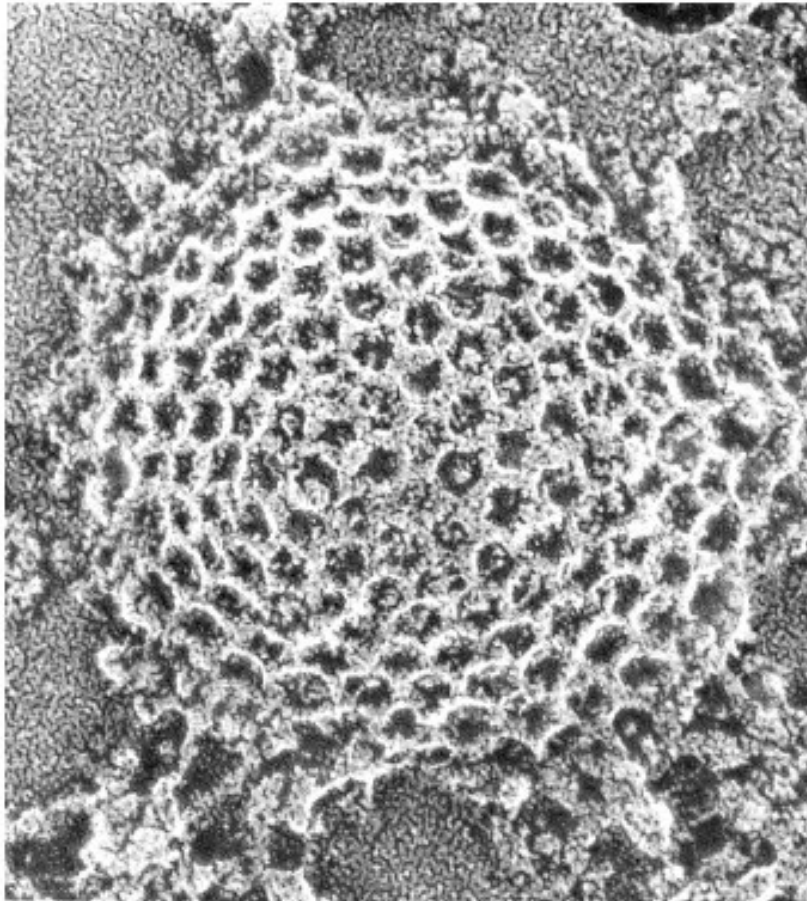
0,1 μm

Triskelions assemble in vitro to form empty lattice cages with open hexagonal and pentagonal faces.
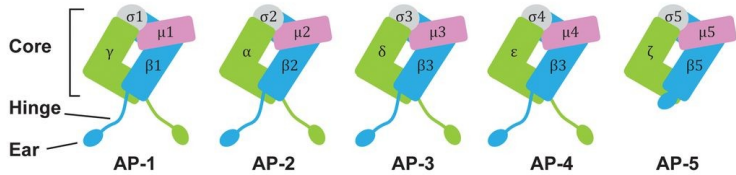
They are very similar to those observed in vivo.

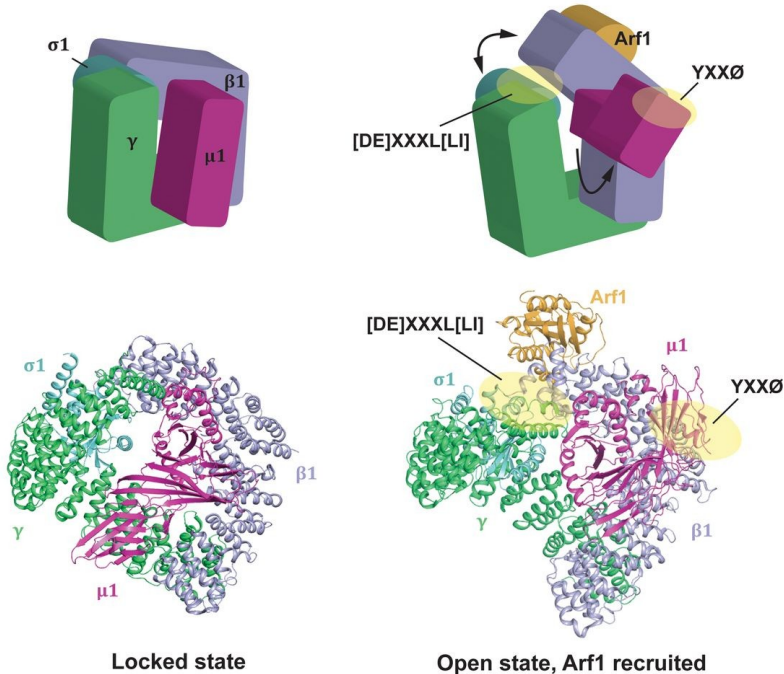Assembly does not require ATP and direct binding to membranes

0.1 μm   Figure 17-35

The adapter complexes (AP)

A

B

Locked state   Open state, Arf1 recruited

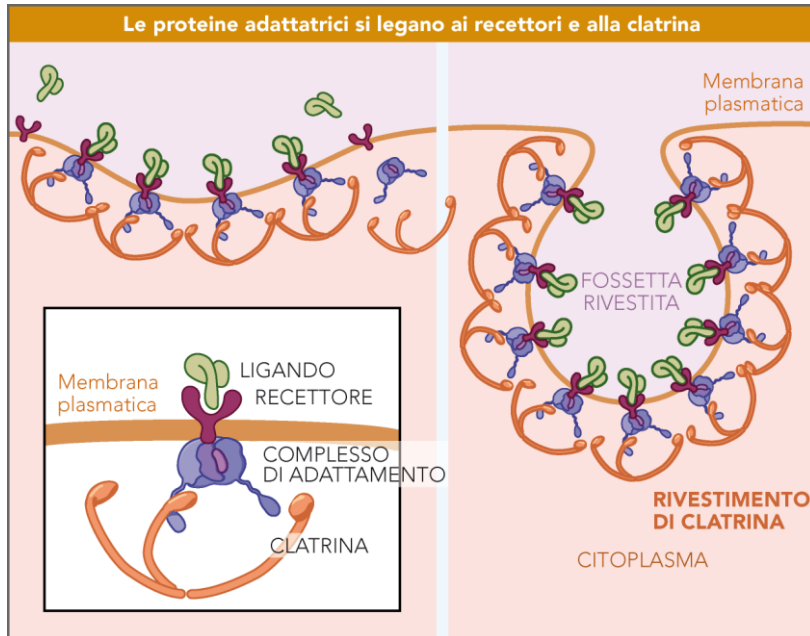Locked and open structure of AP-1 core complexes

Clathrin polymerization occurs on a donor membrane in association with **AP complexes** (340,000 MW), which assemble between the clathrin lattice and the membrane.

AP complexes are heterotetramers containing one copy each of 4 different adapter subunits.
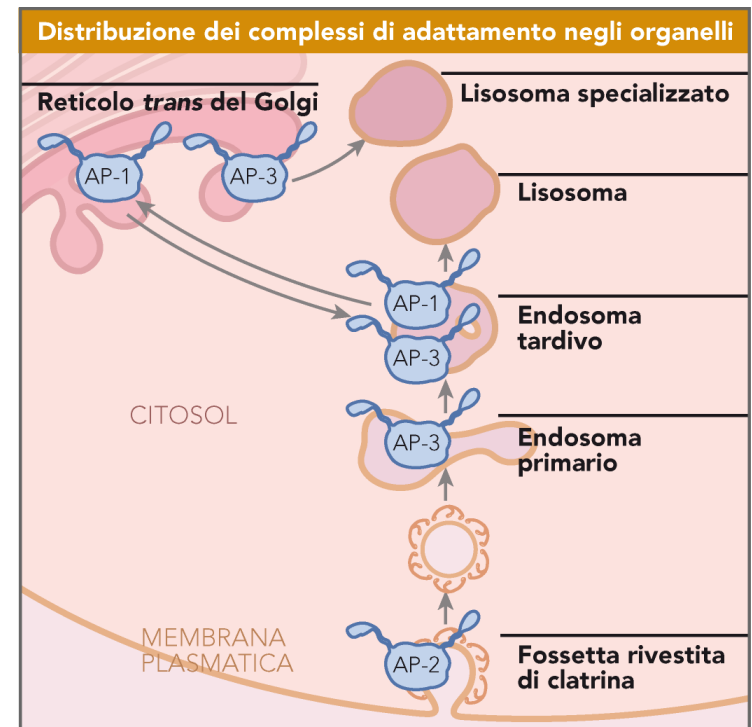
In the presence of **Arf1** binding, AP-1 undergoes a large conformational change to the open state exposing the binding sites for cargo proteins

clathrin/AP1: Proteins containing a **Tyr-XX**-Φ, (where Φ is a bulky hydrophobic amino acid), are recruited into clathrin/AP1 vesicles

Adapter proteins determine which cargo proteins are specifically included in clathrin vesicle

Le proteine adattatrici si legano ai recettori e alla clatrina

Membrana plasmatica

FOSSETTA RIVESTITA

Membrana plasmatica

LIGANDO
RECETTORE

COMPLESSO DI ADATTAMENTO

CLATRINA

RIVESTIMENTO DI CLATRINA

CITOPLASMA

Adapter proteins determine which cargo proteins are specifically included in (or excluded from) a budding transport vesicle.

Distribuzione dei complessi di adattamento negli organelli

Reticolo *trans* del Golgi

Lisosoma specializzato

AP-1   AP-3

Lisosoma

AP-1

Endosoma tardivo

AP-3

CITOSOL

AP-3

Endosoma primario

MEMBRANA PLASMATICA

AP-2

Fossetta rivestita di clatrina

Vesicles containing different adapter complexes have been found to mediate specific transport steps:

AP1 complex: cargo selection from the TGN and endosomes.

AP2 complex: cargo selection from plasma membrane

AP3 complex: cargo selection to lysosomes

Dynamin Is Required for Pinching Off of Clathrin Vesicles

Dynamin is a cytosolic protein that polymerizes around the neck portion and then hydrolyzes GTP.
The energy derived from GTP hydrolysis is thought to drive "contraction" of dynamin around the vesicle neck until the vesicle pinches off.

As with COPI and COPII vesicles, clathrin/AP vesicles normally lose their coat soon after their formation


Incubation of cell extracts with a nonhydrolyzable derivative of GTP provides leads to accumulation of clathrin coated vesicle buds with excessively long necks surrounded by polymeric dynamin but do not pinch off
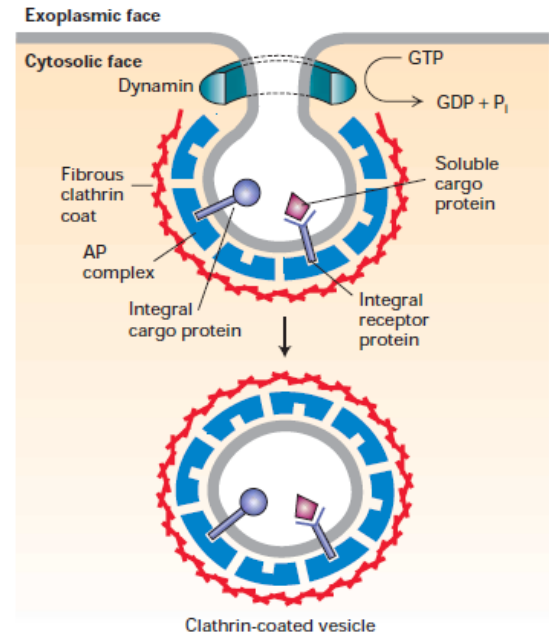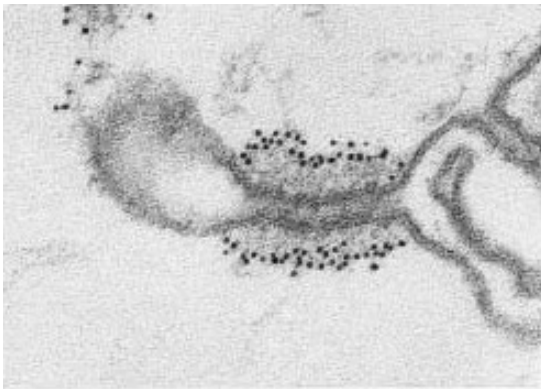
COPI and COPII vesicles appear to pinch off from donor membranes without the aid of a GTPase.

Mannose 6-phosphate (M6P) residues targets soluble enzymes to lysosomes
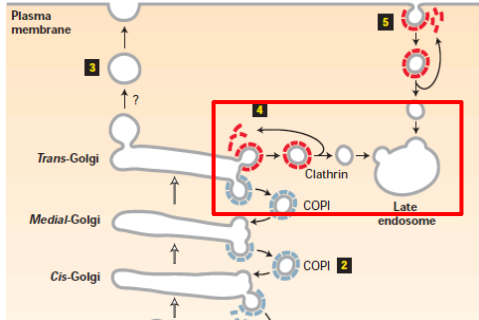
The sorting signal that directs soluble lysosomal enzymes from the trans-Golgi network to the late endosome is a carbohydrate residue, **mannose 6-phosphate (M6P),** which is formed in the cis-Golgi. The N-linked Man8(GlcNAc)2 oligosaccharide present on most lysosomal enzymes undergo a two-step reaction sequence that generates M6P residues.
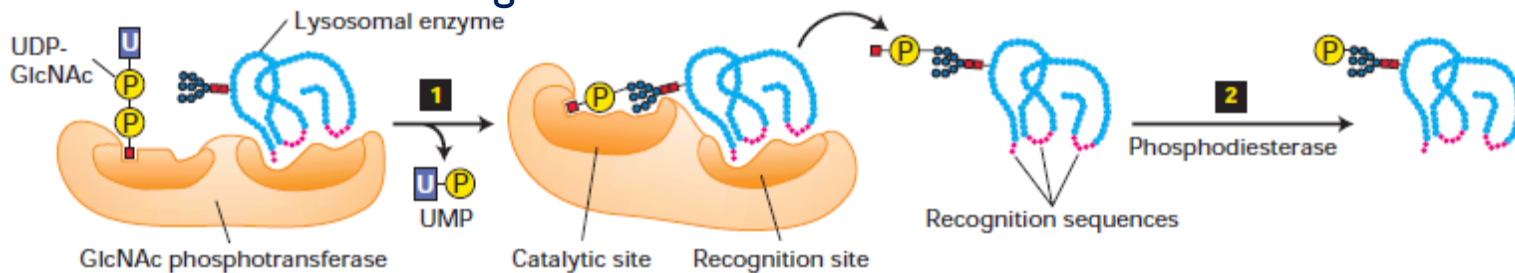

1) A *GlcNAc phosphotransferase* transfers a phosphorylated GlcNAc group to C6 of one or more mannose residues.
2) A *phosphodiesterase* removes the GlcNAc group, leaving a phosphorylated mannose residue on the lysosomal enzyme.

The addition of M6P prevents lysosomal enzymes from undergoing the further processing reactions as other secreted and membrane proteins: clathrin/AP1 vesicles contain the **M6P receptor** which bounds lysosomal enzymes then bud from the *trans-Golgi network*

Mannose 6-Phosphate Residues Target Soluble Proteins to Lysosomes
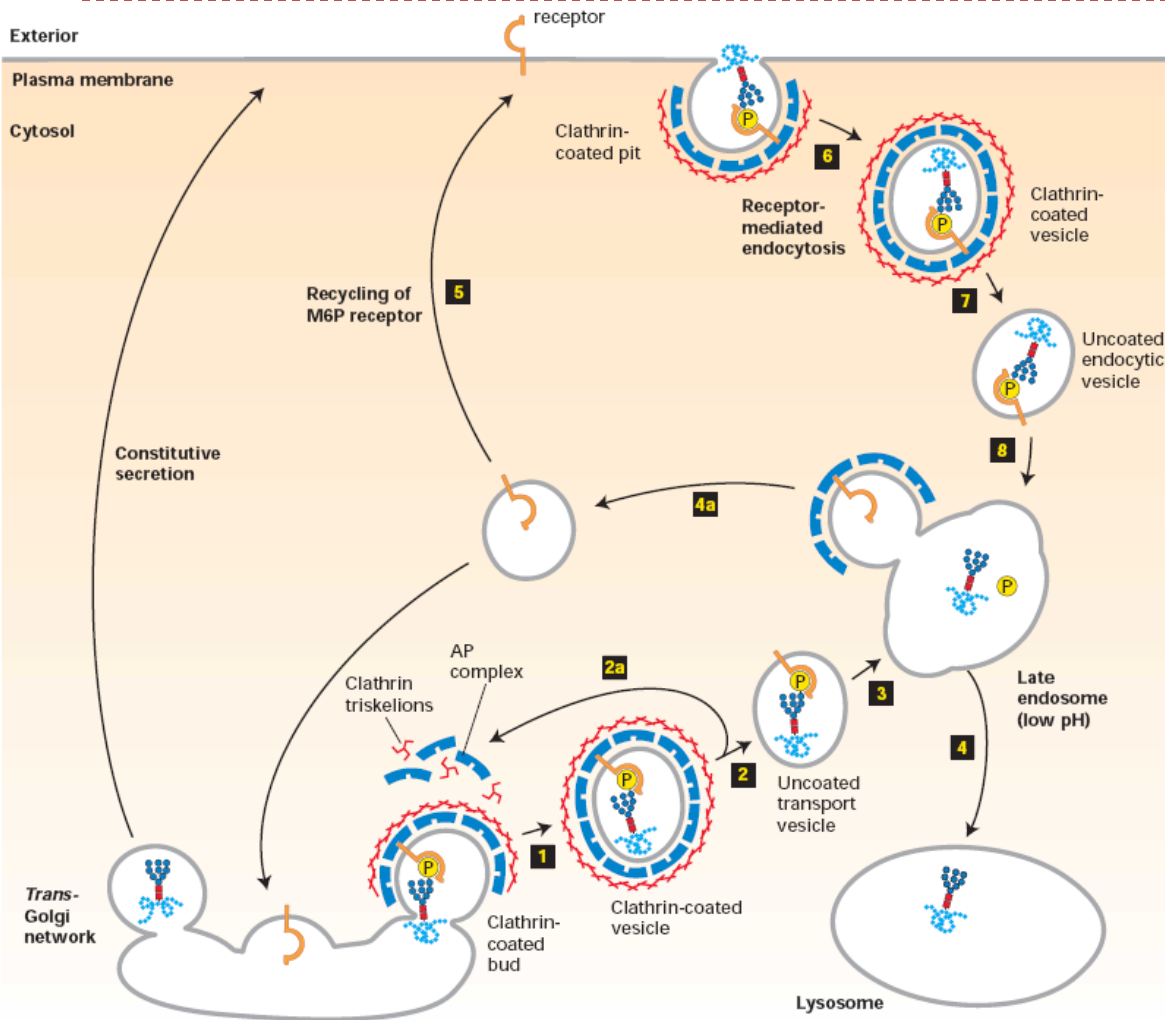
M6P receptor and bound lysosomal enzymes then bud from the *trans-Golgi network,* lose their coats, and subsequently fuse with the late endosome.

Because **M6P receptors** can bind **M6P** at the slightly acidic pH (≈6.5) of the trans-Golgi network but not at a pH less than 6, the bound lysosomal enzymes are released within **late endosomes** (pH of 5.0–5.5).

A phosphatase within late endosomes usually removes the phosphate from M6P residues on lysosomal enzymes.

Vesicles budding from late endosomes recycle the M6P receptor back to the *trans*-Golgi network.

Study of Lysosomal Storage Diseases Revealed Key Components of the Lysosomal Sorting Pathway

Lacking the M6P sorting signal, the lysosomal enzymes are secreted rather than being sorted to and sequestered in lysosomes.
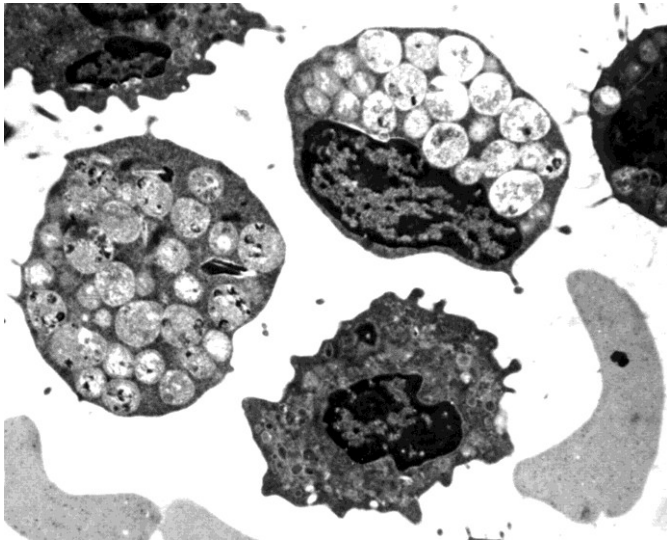
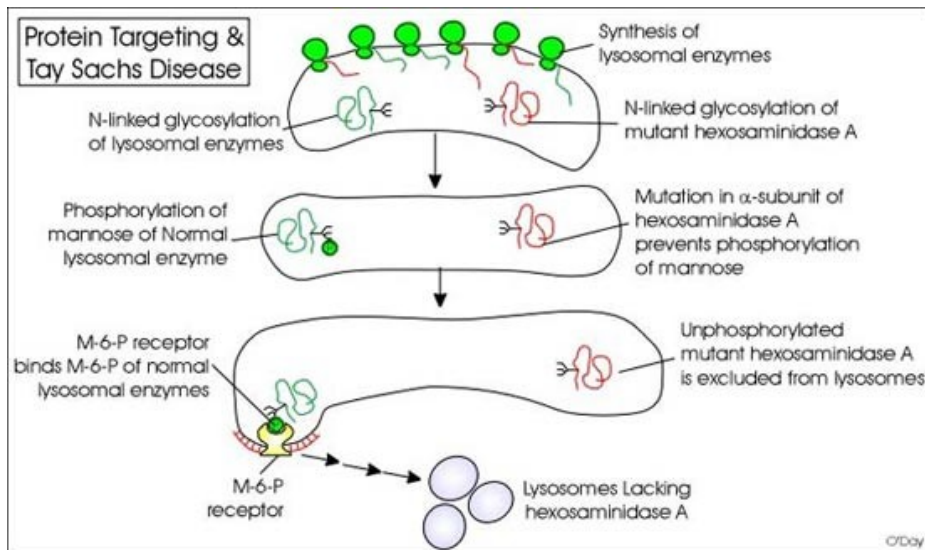van der Meer W et al. J Clin Pathol 2001;54:724-726

JCP

I-cell disease: lymphocytic vacuoles containing round osmiophilic structures

Lysosomal storage diseases, are caused by the absence of one or more lysosomal enzymes. As a result, undigested glycolipids and extracellular components that would normally be degraded by lysosomal enzymes **accumulate in lysosomes** as large inclusions.

I-cell disease: a severe lysosomal storage disease, in which cells from affected individuals lack the **N-acetylglucosamine phosphotransferase**
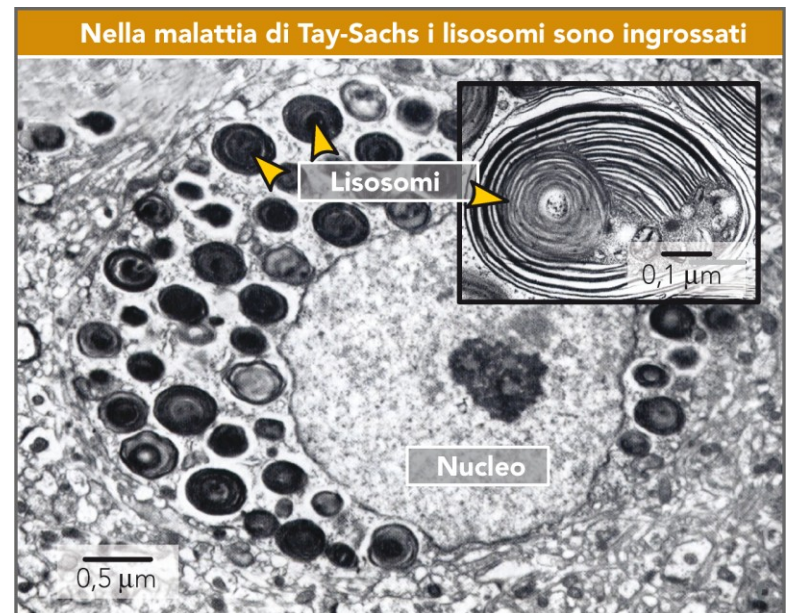
Lysosomal storage diseases are characterized by abnormal lisosomes.

Protein Targeting & Tay Sachs Disease

Synthesis of lysosomal enzymes

N-linked glycosylation of lysosomal enzymes

N-linked glycosylation of mutant hexosaminidase A

Phosphorylation of mannose of Normal lysosomal enzyme

Mutation in α-subunit of hexosaminidase A prevents phosphorylation of mannose

M-6-P receptor binds M-6-P of normal lysosomal enzymes

Unphosphorylated mutant hexosaminidase A is excluded from lysosomes

M-6-P receptor

Lysosomes Lacking hexosaminidase A

O'Day

http://drustapbio.wikia.com/wiki/Tay-_Sachs

Tay-Sachs GM2 gangliosidosis results in cell accumulation of harmful amounts of lipids (gangliosides) in the brain.

Tay-Sachs GM2 gangliosidosis is an inherited metabolic disorder that results from defects in lysosomal function (Lysosomal storage diseases) due to a **Hexosaminidase A** deficiency in lysosomes.

Nella malattia di Tay-Sachs i lisosomi sono ingrossati

Lisosomi

0,1 μm

Nucleo

0,5 μm