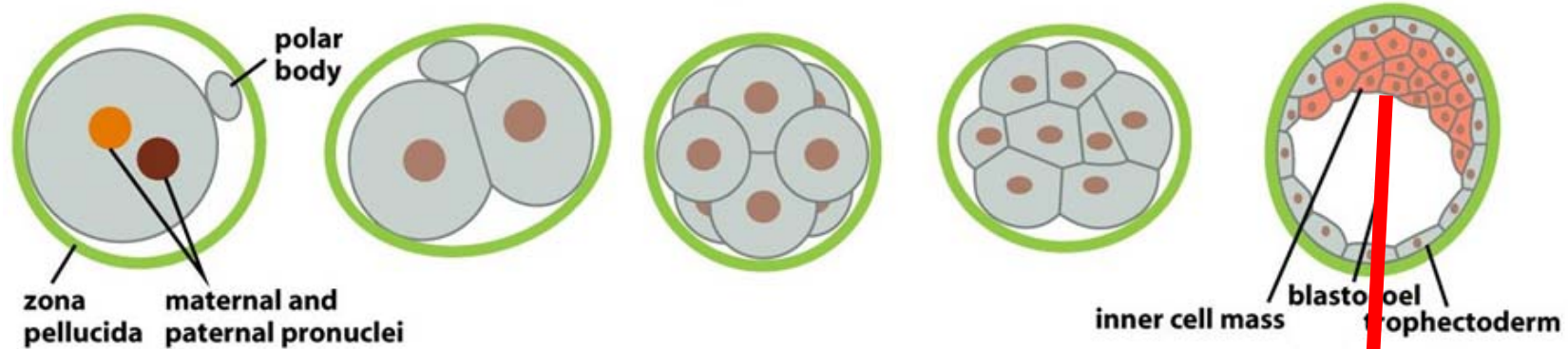


A fluorescence microscopy image showing a dense network of neurons. The cell bodies and processes are stained in red, while specific regions or structures are highlighted in blue. The background is dark, making the glowing structures stand out.

Cell Biology and Development

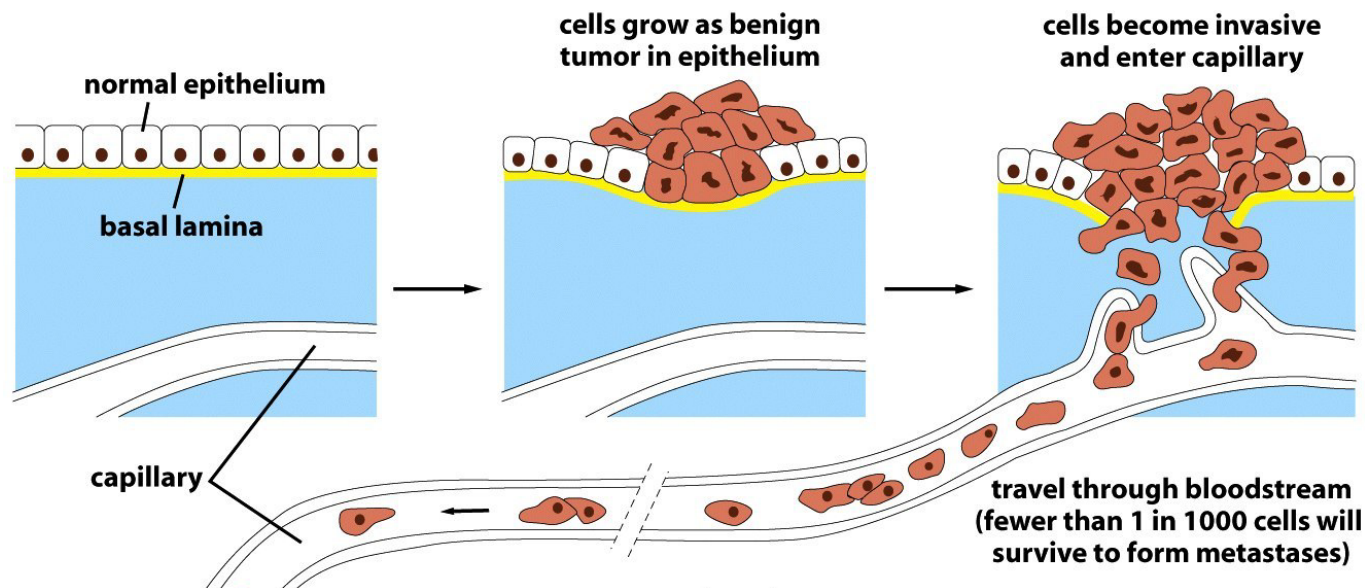
BIO230 *Section 2*
Prof. Tony Harris



How do cells change their shapes, functions, interactions and numbers to build tissues, organs and organisms?



What goes wrong
when cells lose control of their shapes,
functions, interactions and numbers
during cancer progression
or with degenerative disease?



To understand normal cell biology and disease we must understand the molecular machinery that functions inside cells to control their shapes, functions, interactions and numbers.

Lectures

1-3: How do cells and tissues organize themselves spatially?

4-6: How do multicellular organisms develop?

7-9: How do cells communicate with each other?

10-12: How are cell numbers controlled?

A few general points

- Please post questions on-line
- Fill-ins for web notes are in royal blue
- You are responsible for the lecture material for the exam (readings associated with the lectures provide a second source for the material).

To understand normal cell biology and disease we must understand the molecular machinery that functions inside cells to control their shapes, functions, interactions and numbers.

Lectures

1-3: How do cells and tissues organize themselves spatially?

1. Membrane trafficking
2. Cytoskeletal networks
3. Cell adhesion

Why is membrane trafficking important?

Cells must engage the extracellular space

- to communicate with other cells
- to acquire resources

These processes and changes to these processes require dynamic changes to the plasma membrane

the plasma membrane the outer surface, this is what separates environments.
membrane trafikking, everything inside the cell will affect the membrane

polarized cell
ends not the same

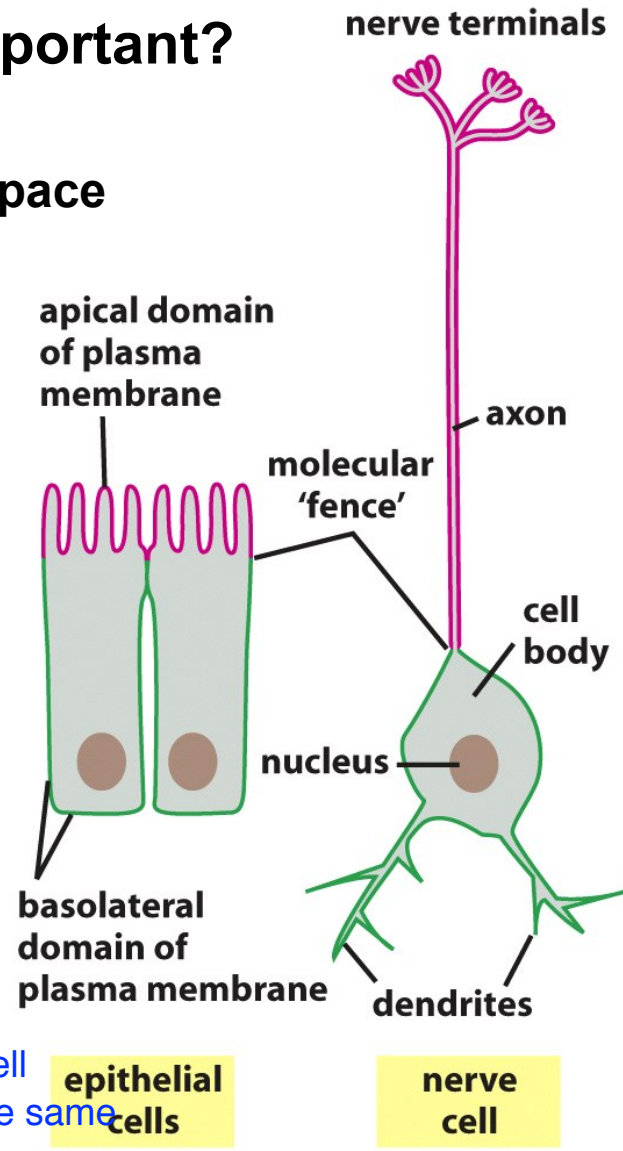
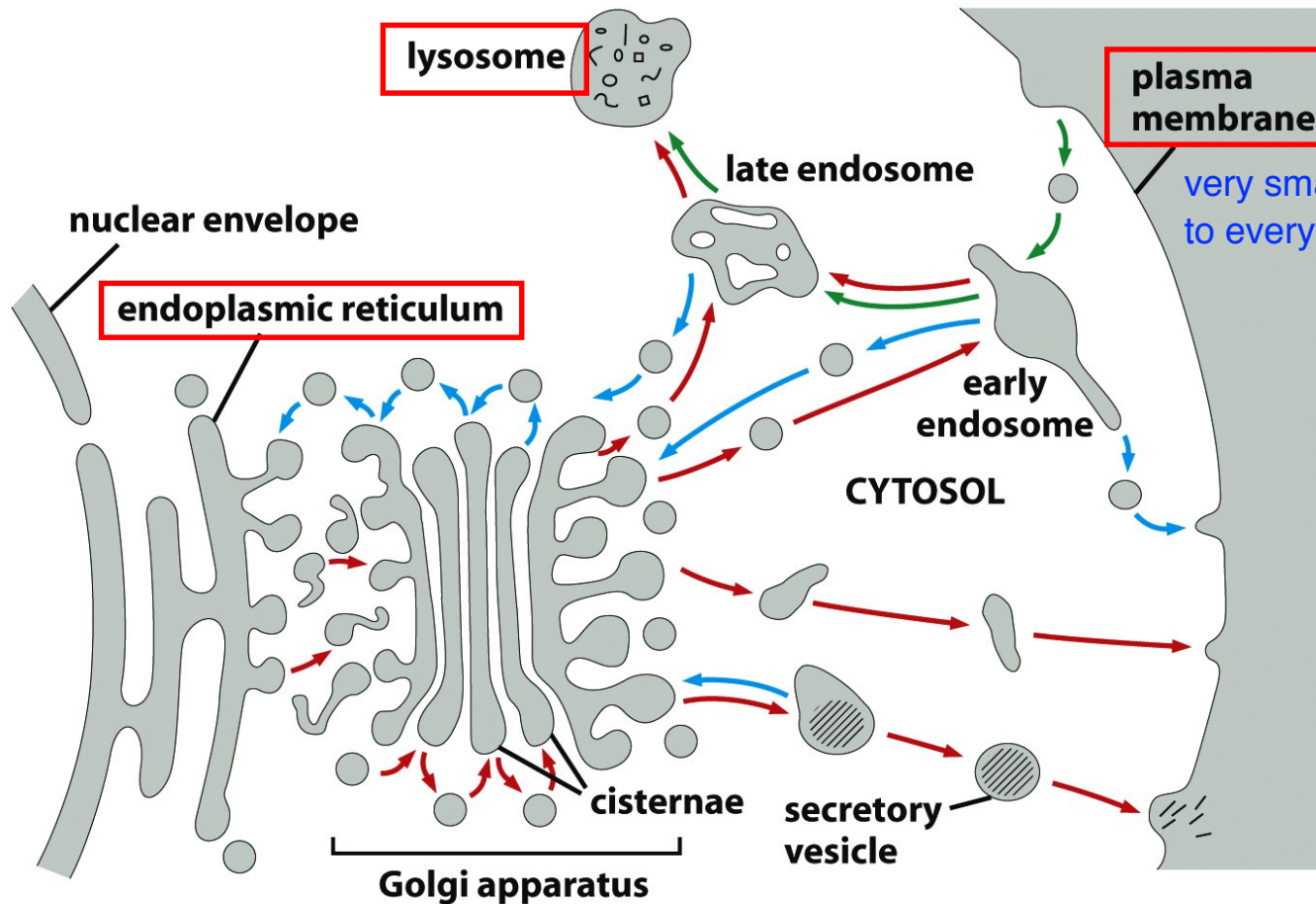


Figure 13-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Biosynthetic-Secretory and Endocytic Pathways Change the Plasma Membrane

Connections among the **endoplasmic reticulum** (makes proteins), the **plasma membrane**, and the **lysosome** (breaks down proteins)



8

Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Basic Principles of the Biosynthetic-Secretory and Endocytic Pathways

1. > Polarized Trafficking Routes
have a start and a stop

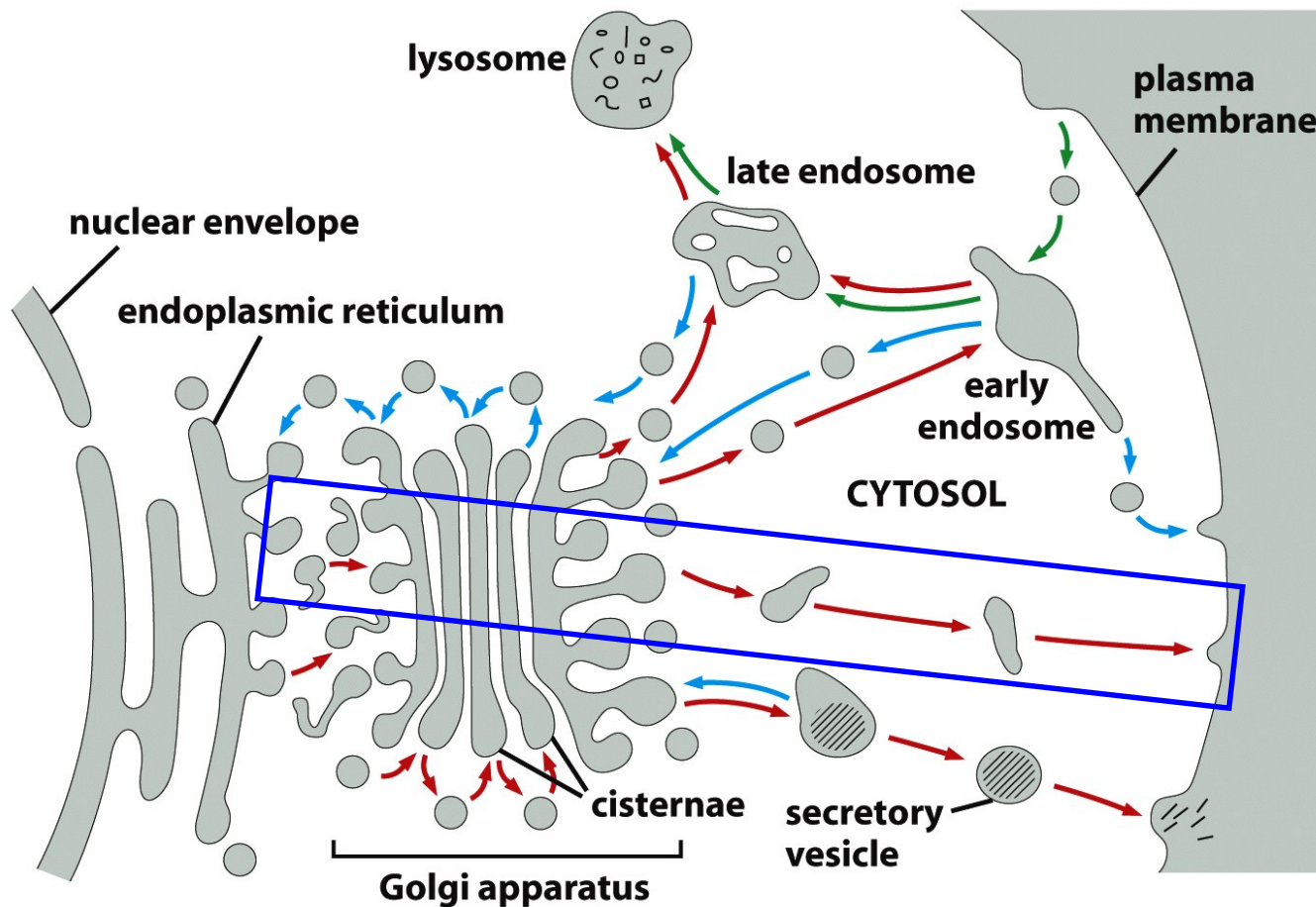
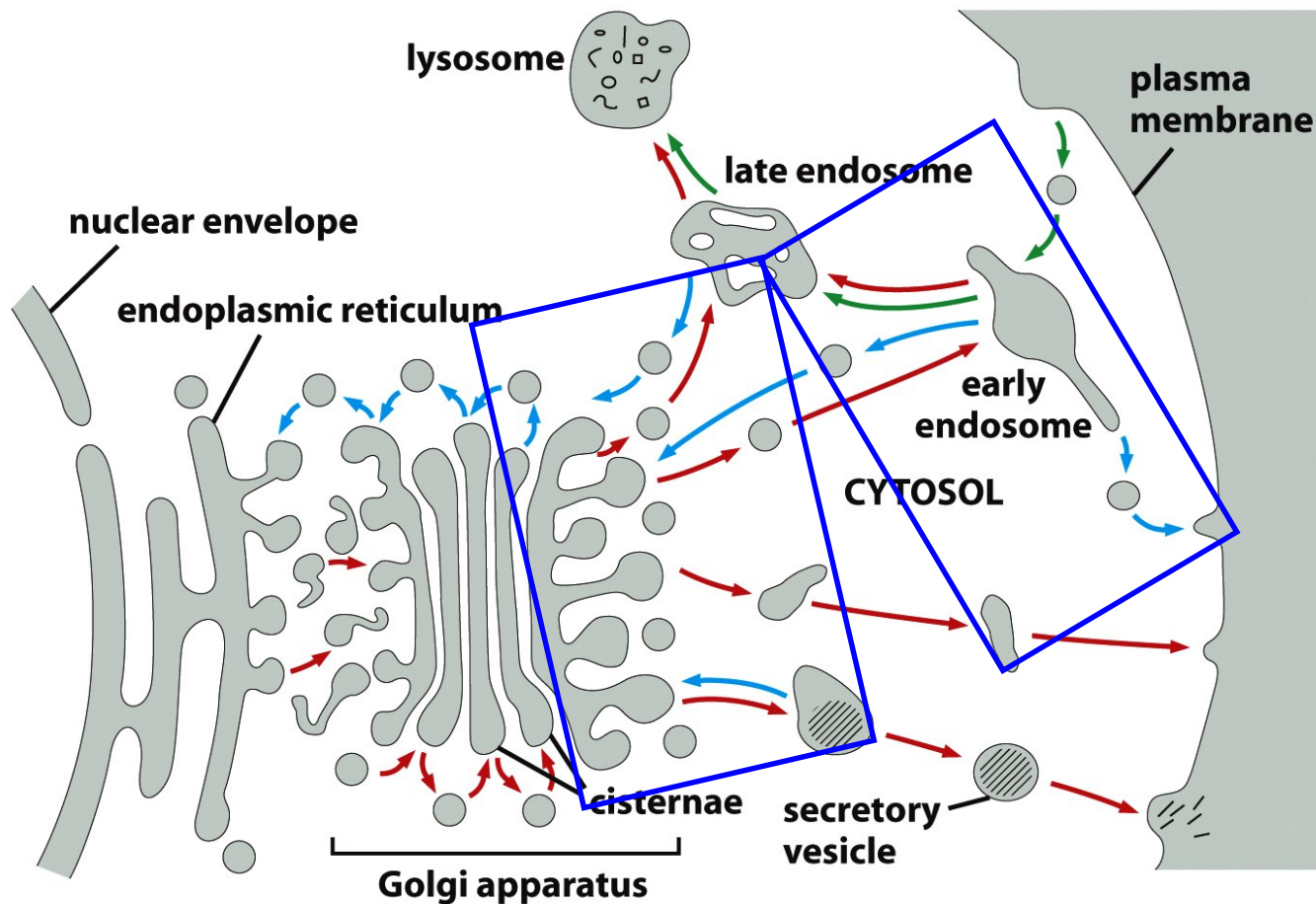


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Basic Principles of the Biosynthetic-Secretory and Endocytic Pathways

1. >
2. > Sorting stations, sites of arrival events from several places, also departure events
trans - golgi, endosome

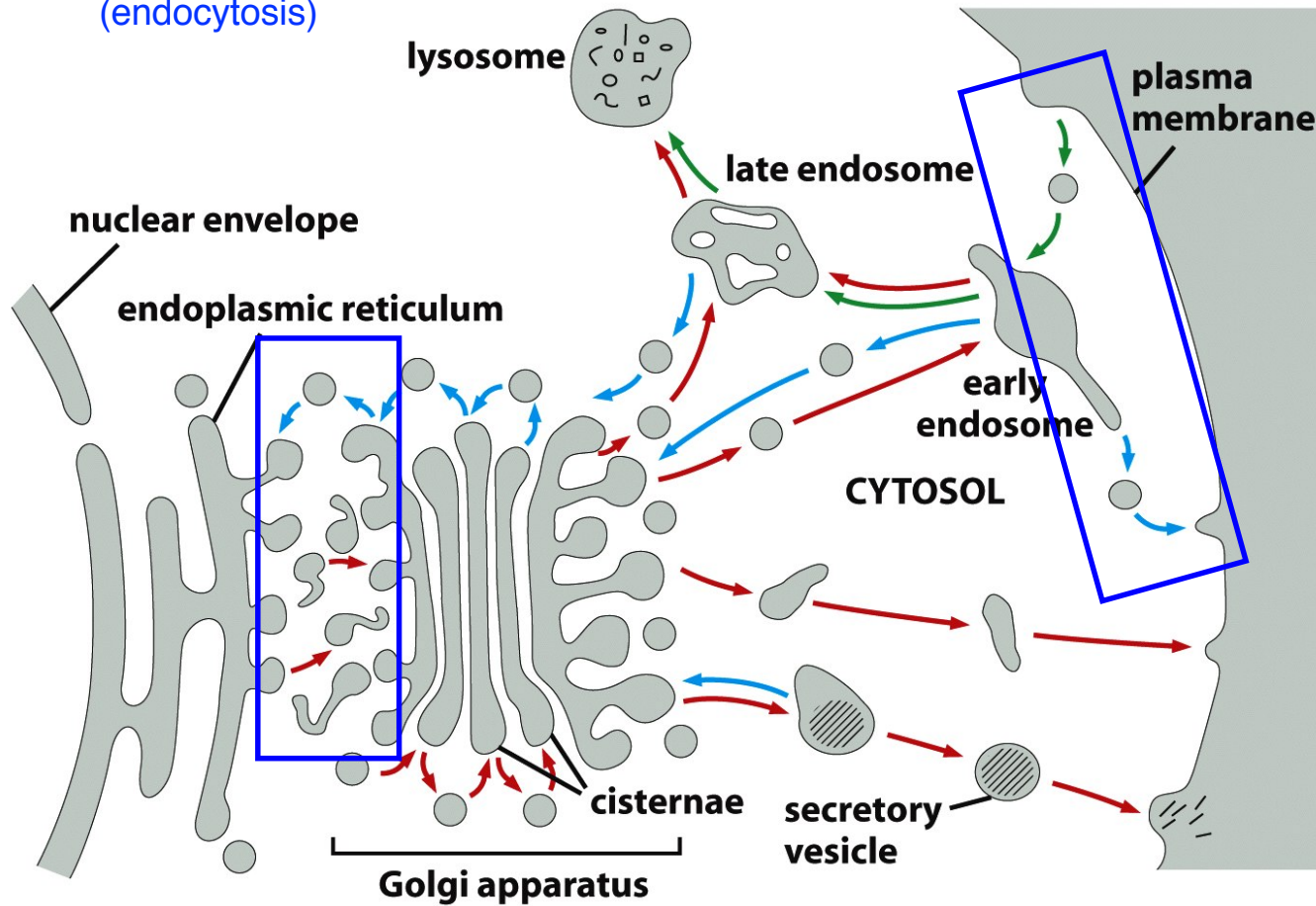


10

Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Basic Principles of the Biosynthetic-Secretory and Endocytic Pathways

1. >
2. >
3. > Retrieval mechanisms and general balance among routes, (avoid depletion) (endocytosis)



11

Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Secretory Pathways: Constitutive and Regulated

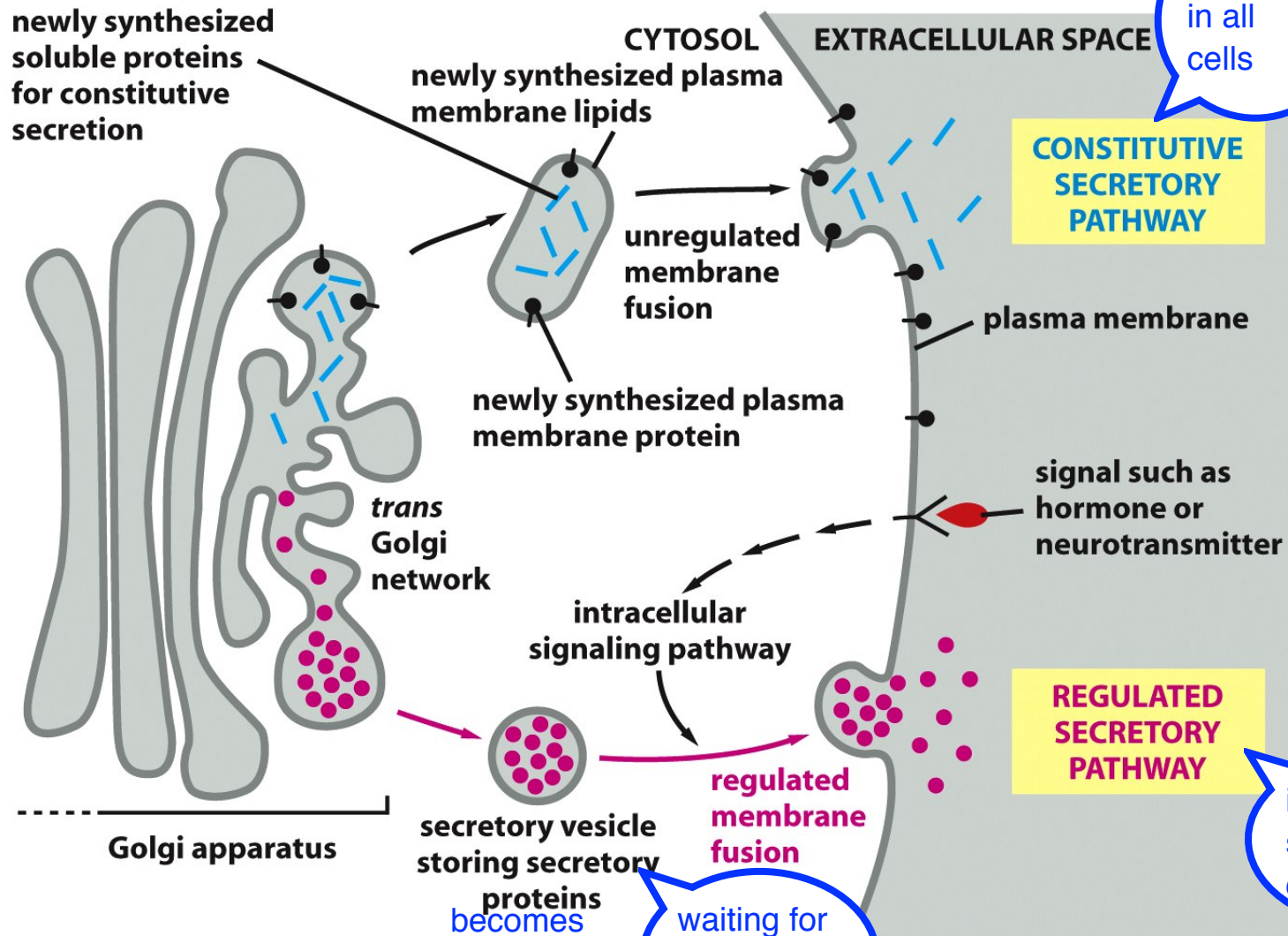


Figure 13-63 Molecular Biology of the Cell 5/e (© Garland Science 2008)

both begin at the same place, (biosynthetic pathway), leaves the golgi, very unregulated (both pts = constitutive), regulated is the one that is regulated

In the both pathways, a mature secretory vesicle is made by retrieving Golgi components and concentrating cargo

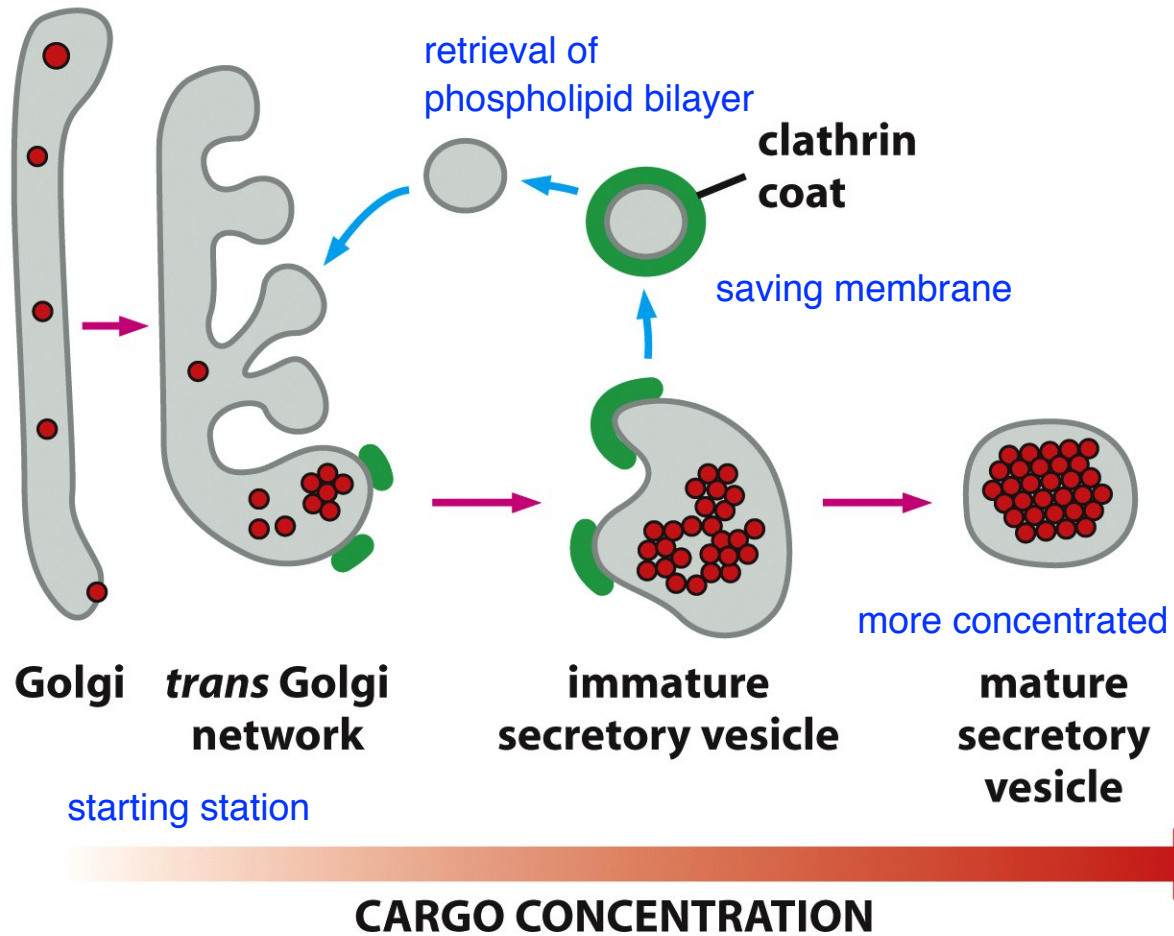
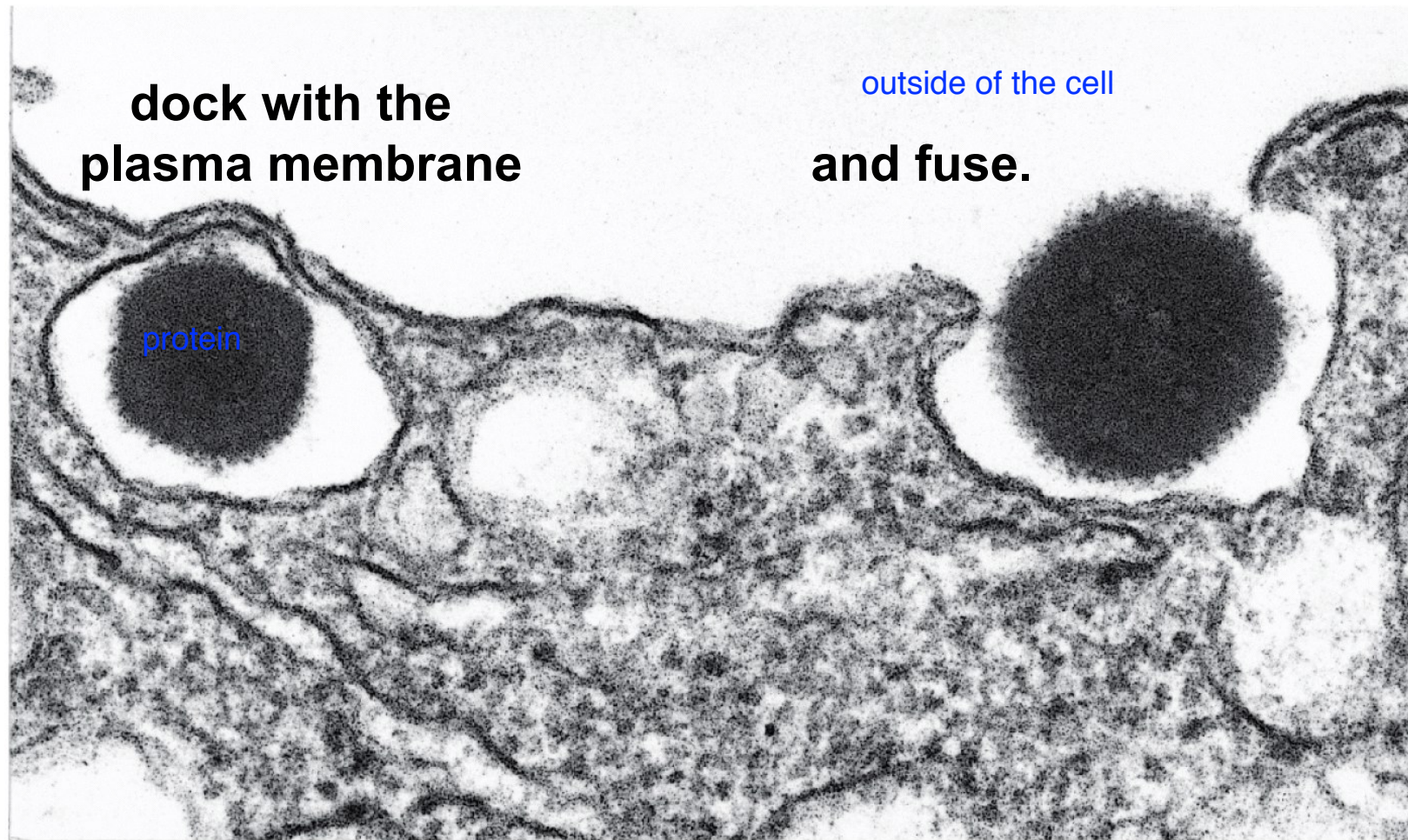


Figure 13-65a Molecular Biology of the Cell 5/e (© Garland Science 2008)

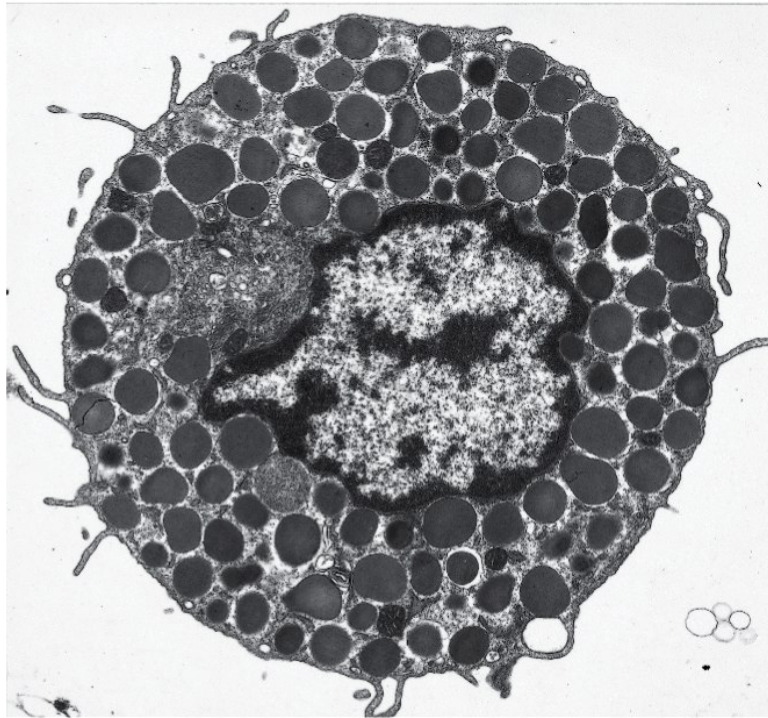
In the constitutive pathway, the vesicles then



0.2 μm

Figure 13-66b Molecular Biology of the Cell 5/e (© Garland Science 2008)

**In the regulated pathway,
the vesicles are stored until**



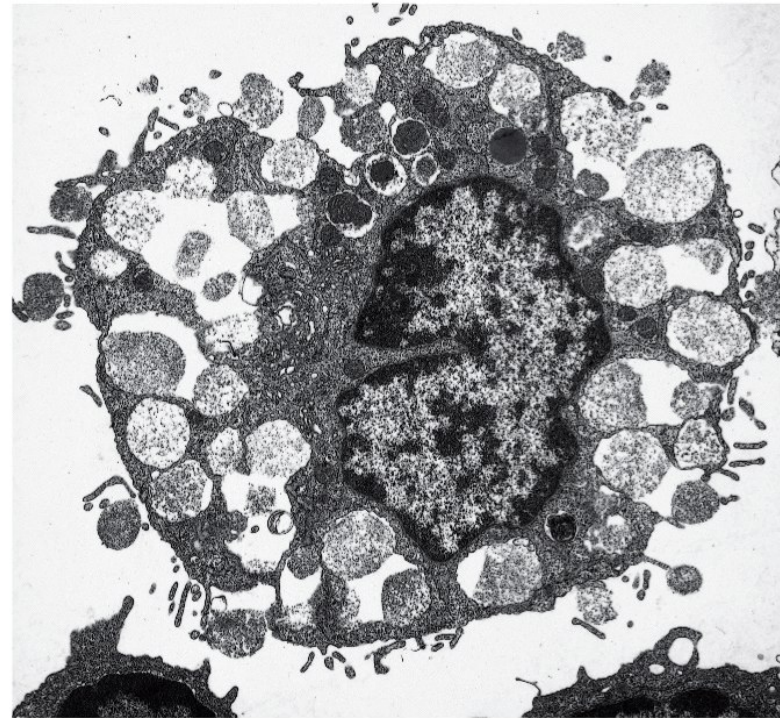
(A)

5 μm

Figure 13-68 Molecular Biology of the Cell 5/e (© Garland Science 2008)

vesicles, made and held
waiting for signal to be released,
all contents will be expelled

**a signal triggers
their docking and fusion**



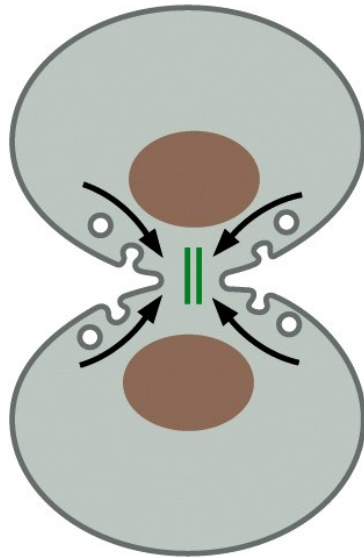
(B)

e.g. a Mast cell releasing stored
Histamine after induction by a
soluble extracellular stimulant

15

membrane is always continuous, cell is not exploding

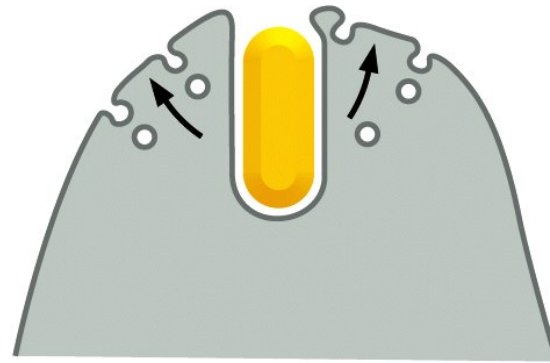
Regulated secretion provides extra plasma membrane when needed



(A) CLEAVAGE FURROW

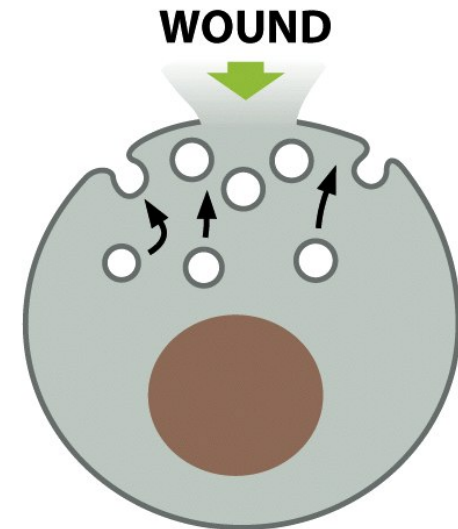
Figure 13-70 Molecular Biology of the Cell 5/e (© Garland Science 2008)

cell splitting in cytokinesis



(B) PHAGOCYTOSIS

enveloping something
from environment



(C) WOUND REPAIR

from lysosomes

a and b, cell membrane comes from
late/early endosomes

Regulated secretion provides extracellular signals

A specialized case:

The release of neurotransmitters at a nerve terminal

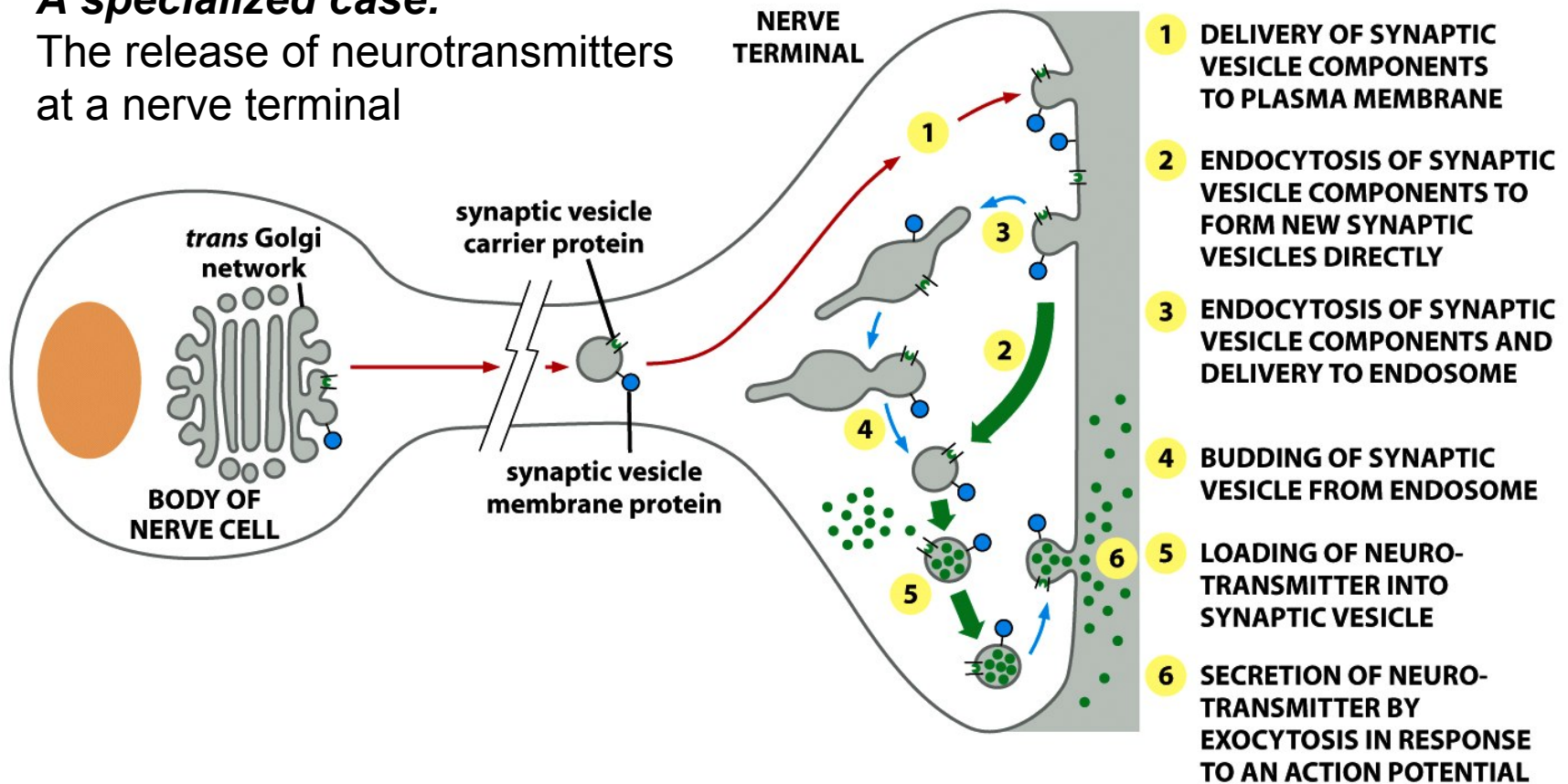


Figure 13-73 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Endocytic pathways counterbalance secretory pathways and perform specific functions

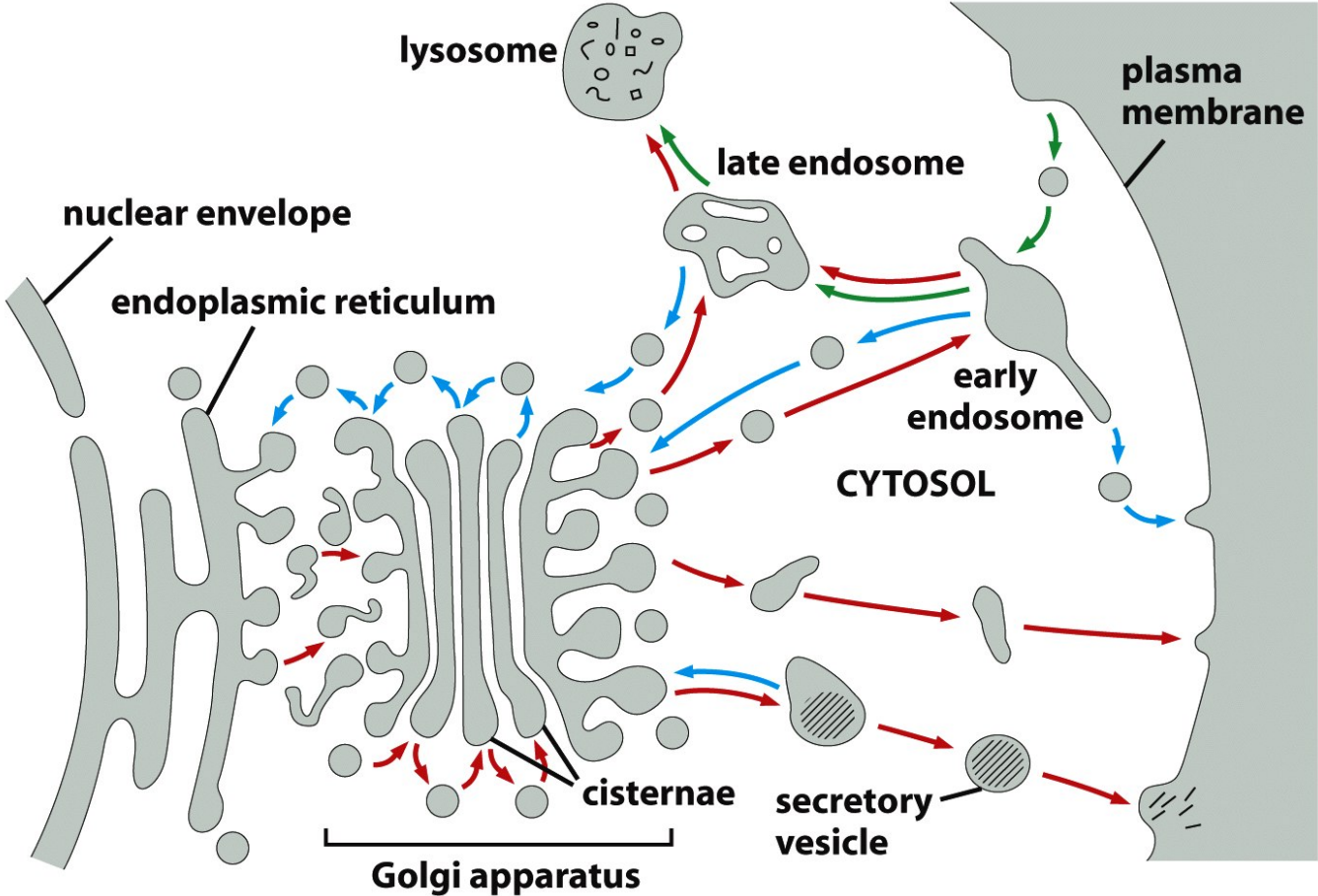


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

going into cell
The basic steps of endocytosis

extracel intrac Invagination

Fission

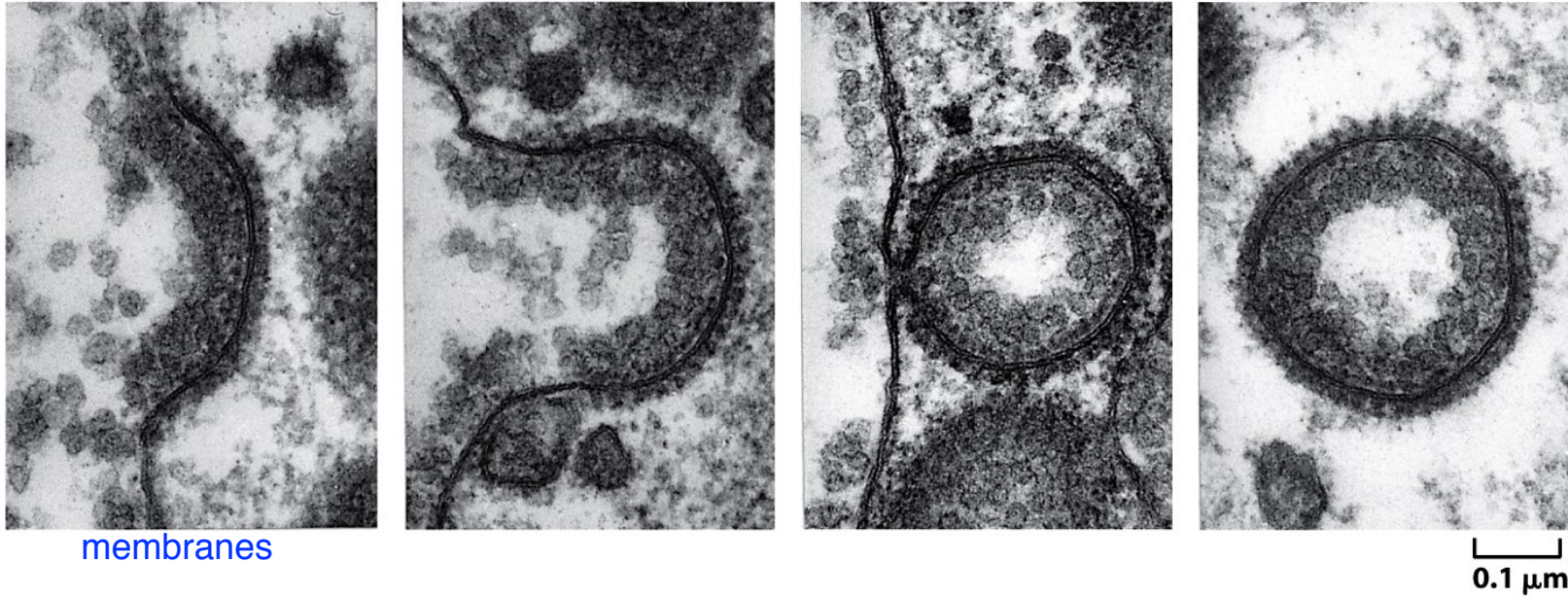


Figure 13-48 Molecular Biology of the Cell 5/e (© Garland Science 2008)

transmembrane proteins usually selected

The endocytosed vesicle joins the early endosome compartment and is then routed to various destinations.

3 diff options for sorting early endosome

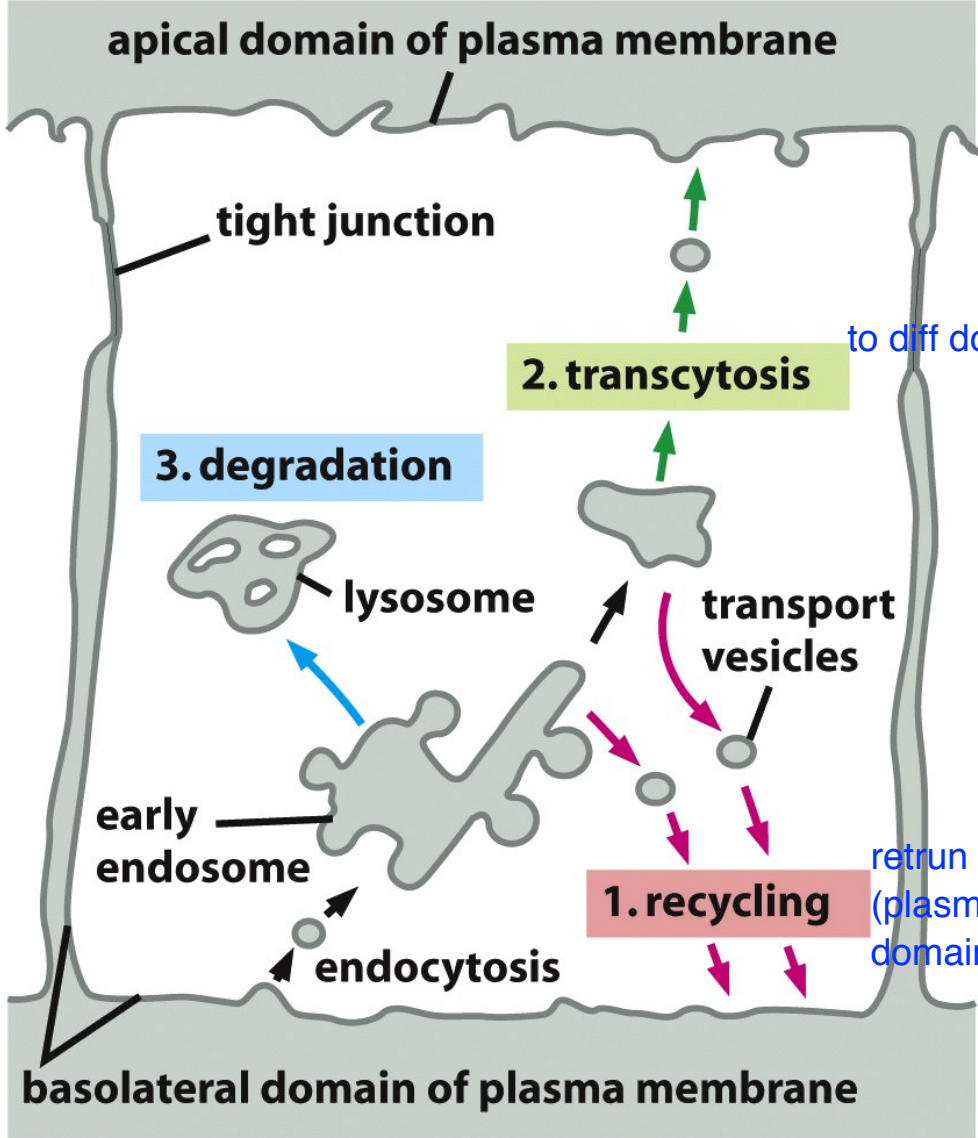


Figure 13-52 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cells collect resources by endocytosis (e.g. cholesterol)

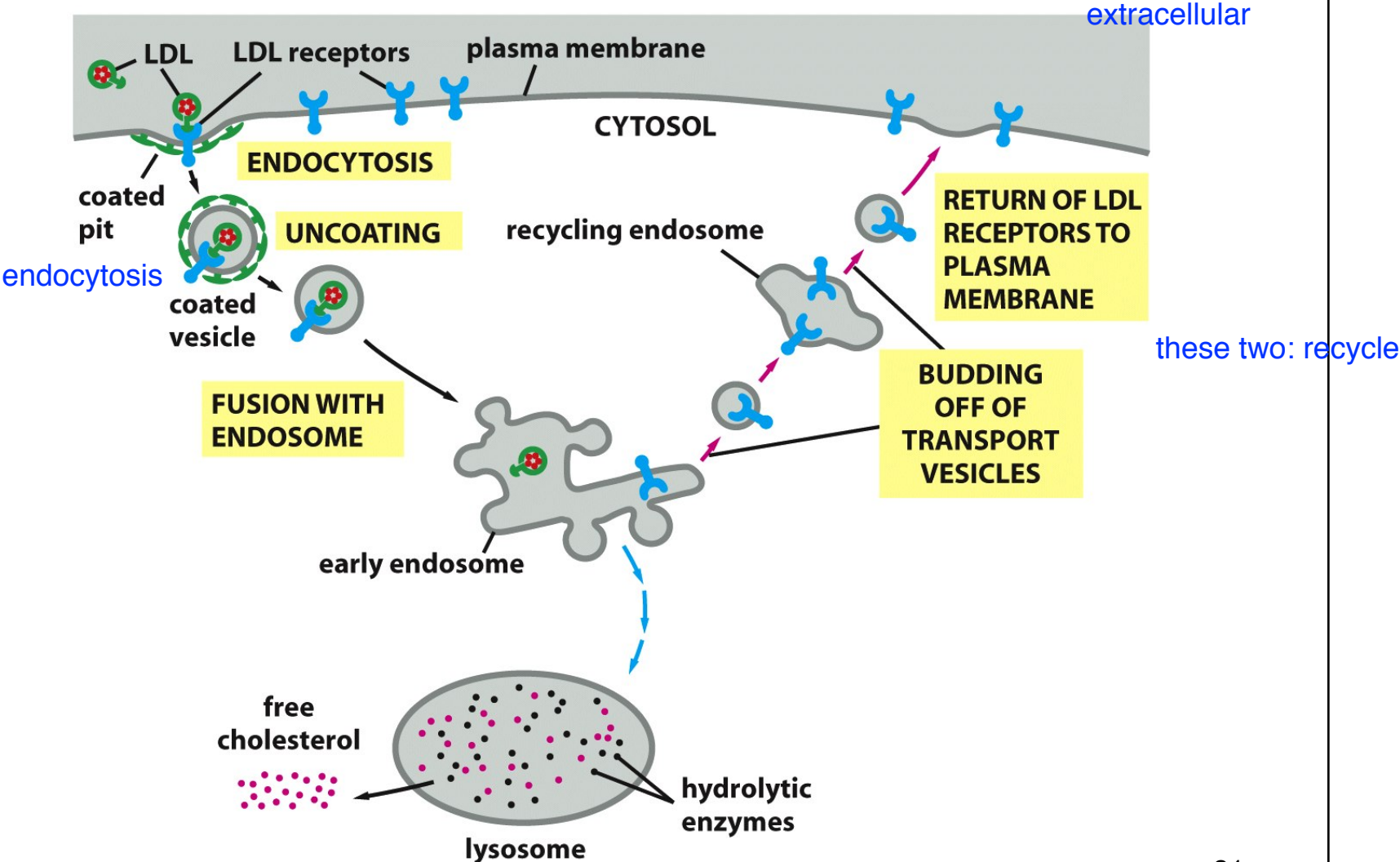
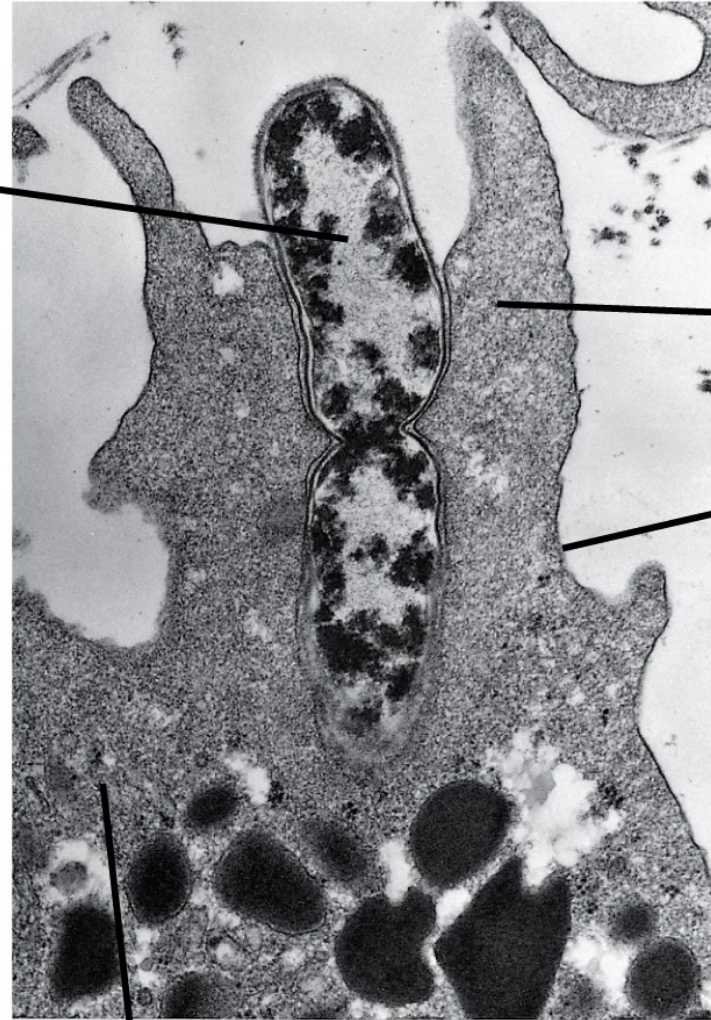


Figure 13-53 Molecular Biology of the Cell 5/e (© Garland Science 2008)

**Cells internalize pathogens
by phagocytosis
(a specialized form of
endocytosis)**

bacterium



pseudopod

extend and engulf

**plasma
membrane**

**phagocytic
white blood cell**

1 μ m

Figure 13-47a Molecular Biology of the Cell 5/e (© Garland Science 2008)

controlling signals

Cells down regulate cell surface signaling by endocytosis

white = cytosol
grey = endosome

multi
for
degrading

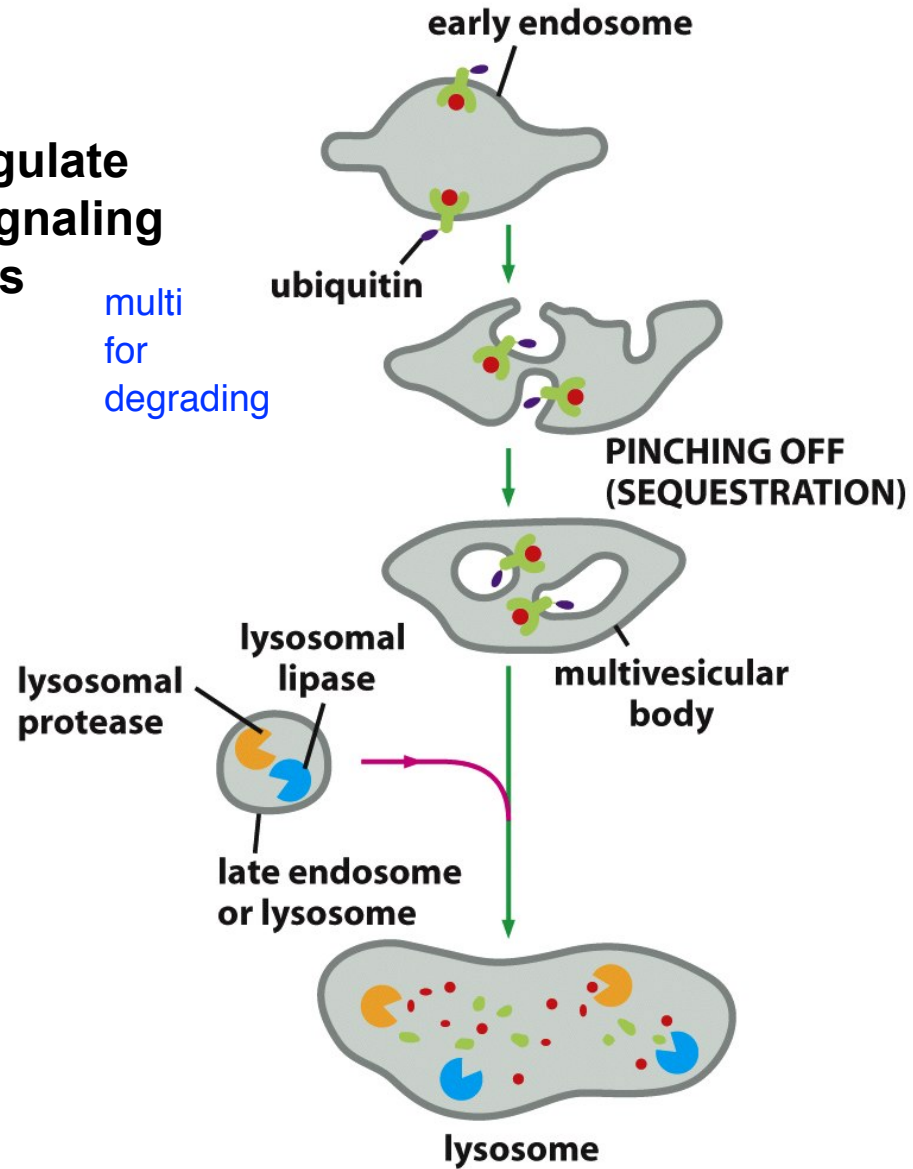


Figure 13-57 Molecular Biology of the Cell 5/e (© Garland Science 2008)

What local membrane changes occur during this trafficking?

consider the two main aq compartments that membranes separate (cytosolic and non cytosolic)

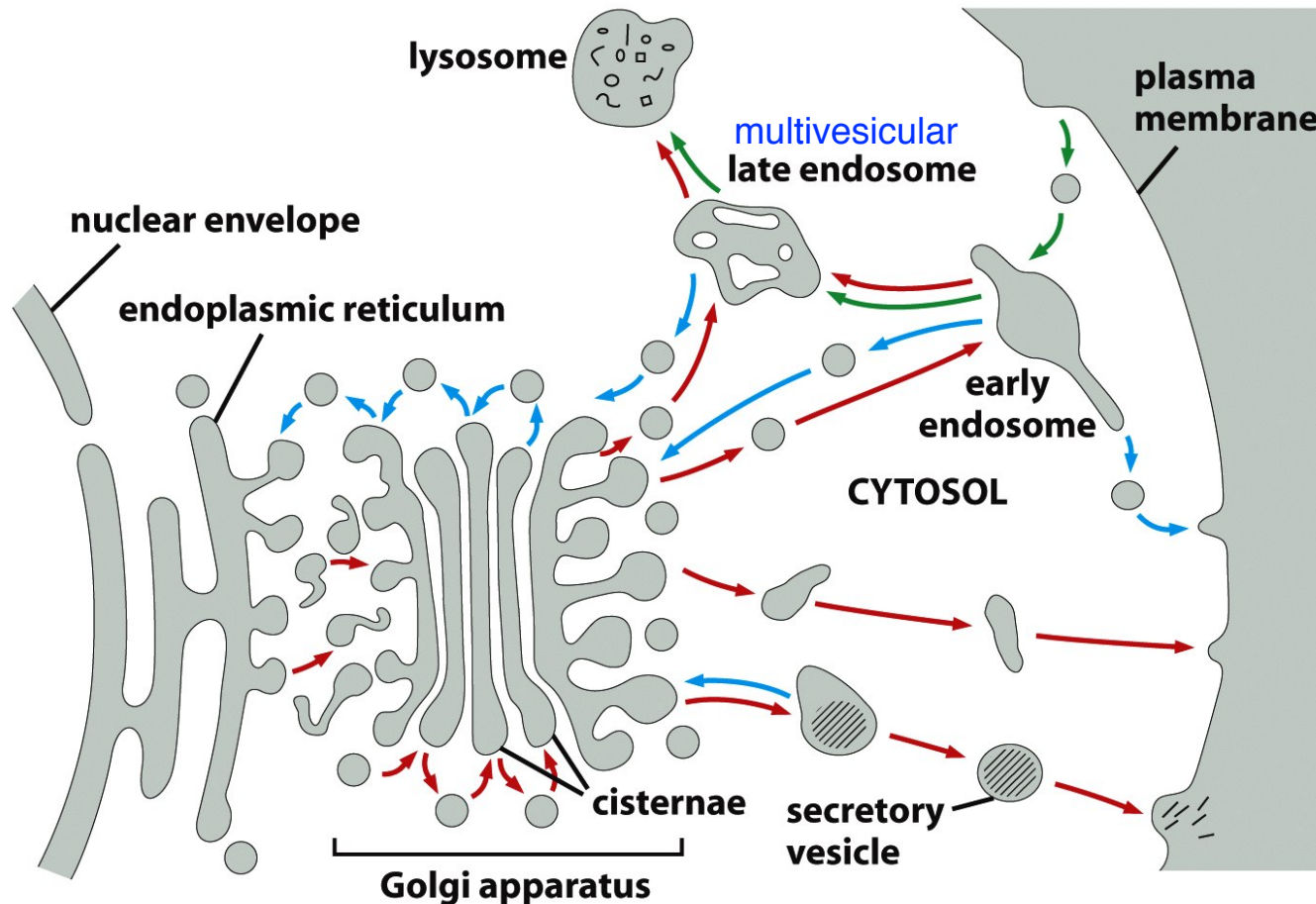


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

What local membrane changes occur during this trafficking?

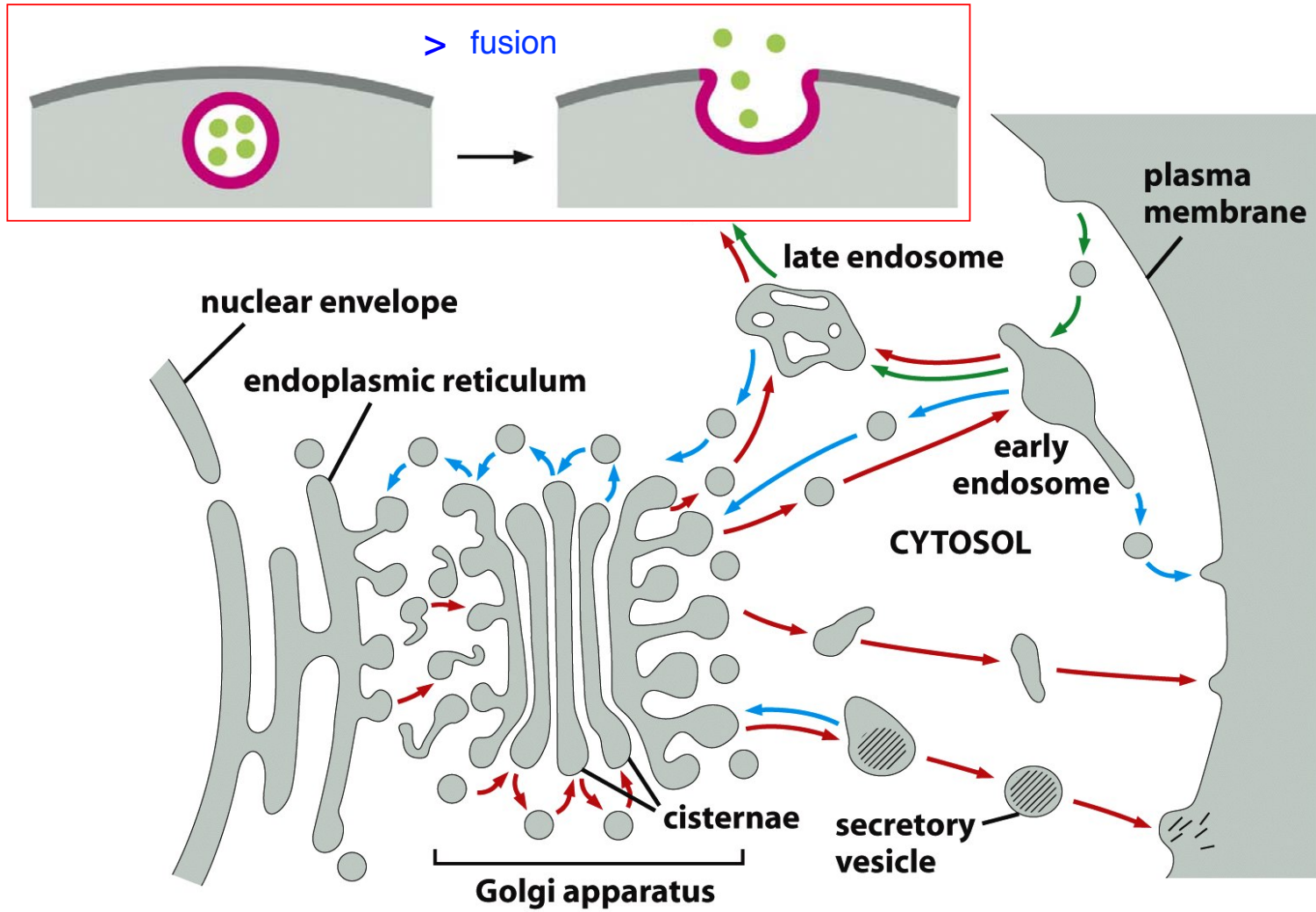


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

What local membrane changes occur during this trafficking?

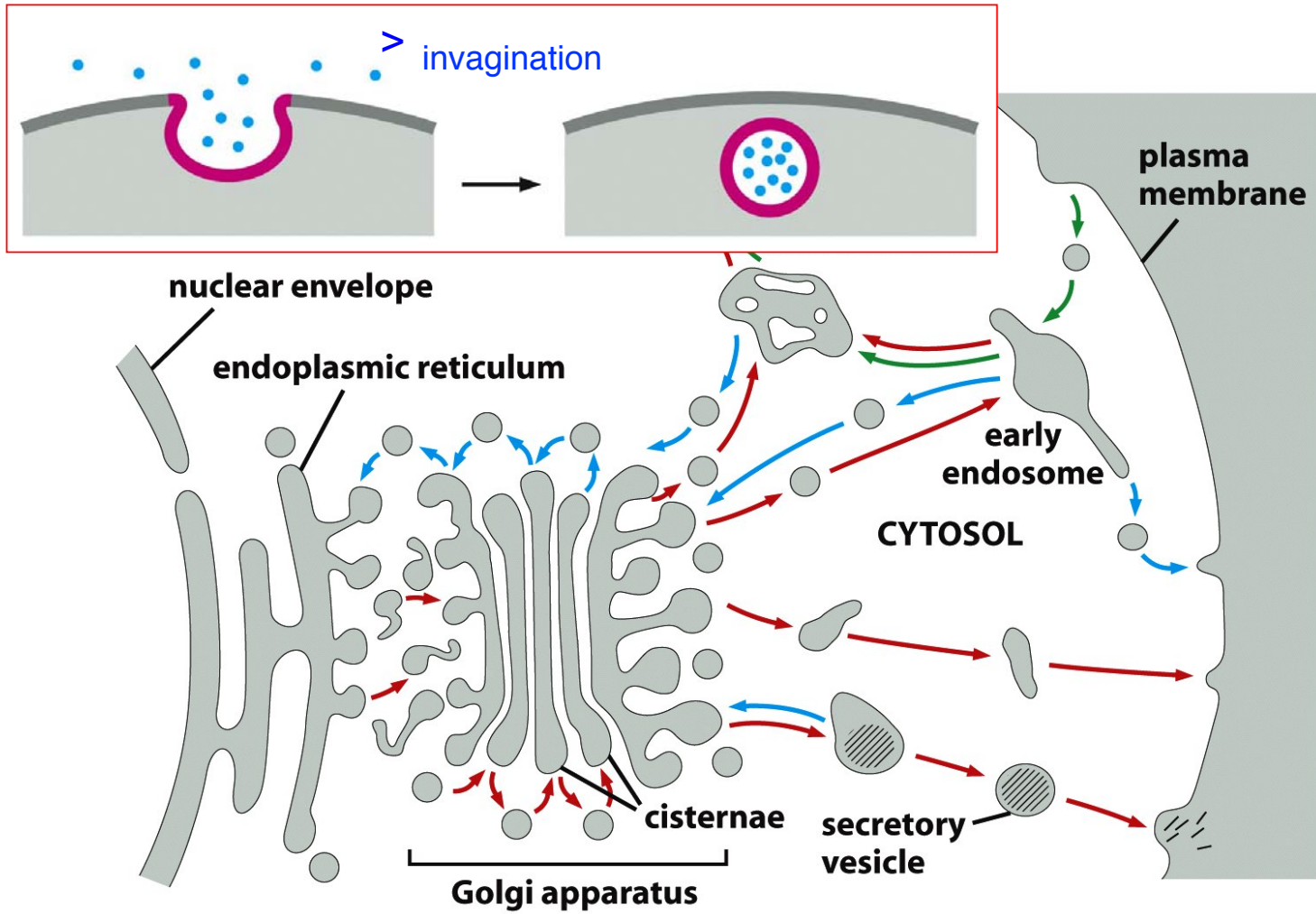


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

What local membrane changes occur during this trafficking?

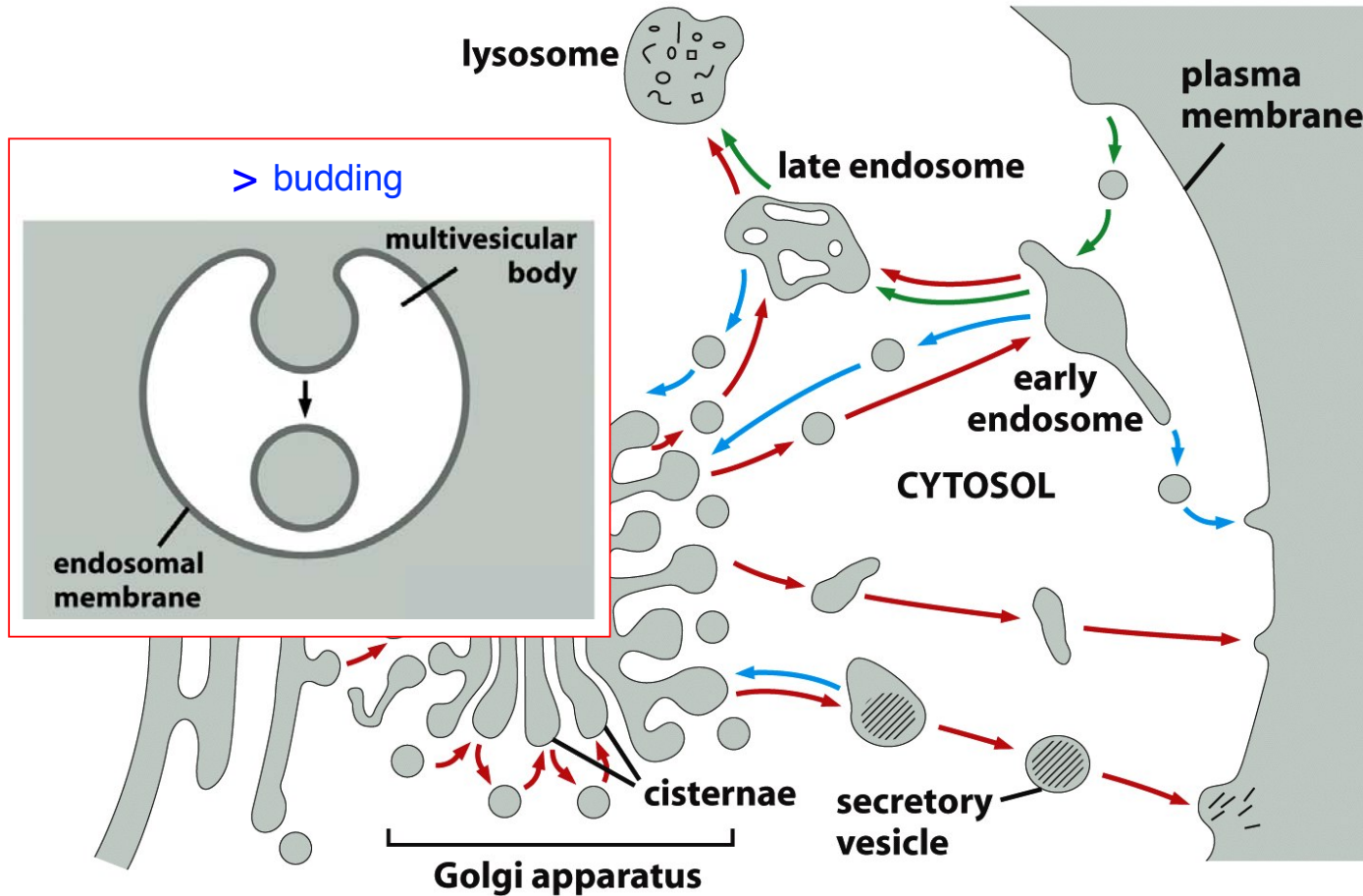


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

What local membrane changes occur during this trafficking?

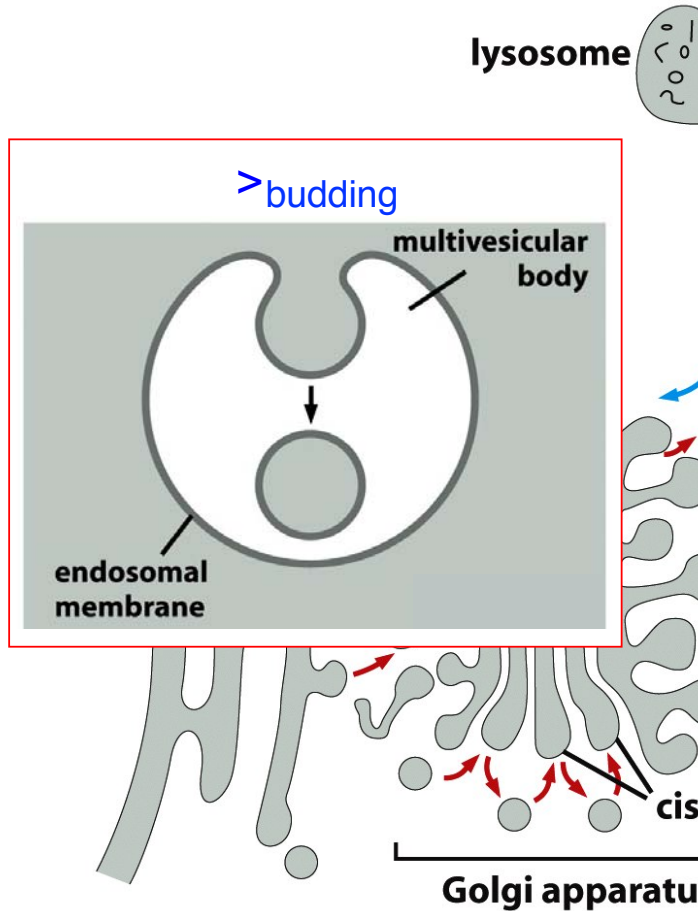


Figure 13-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

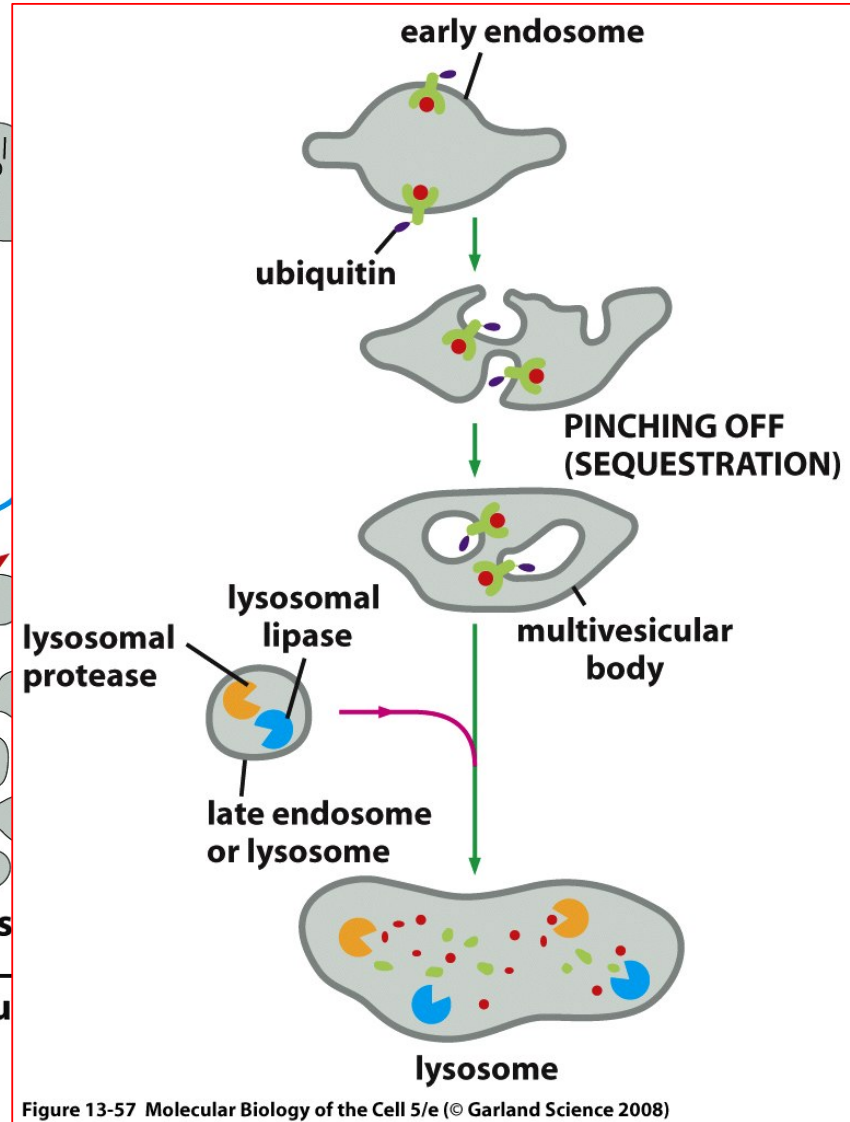


Figure 13-57 Molecular Biology of the Cell 5/e (© Garland Science 2008)

SNARE proteins specify which membranes fuse and conduct the process

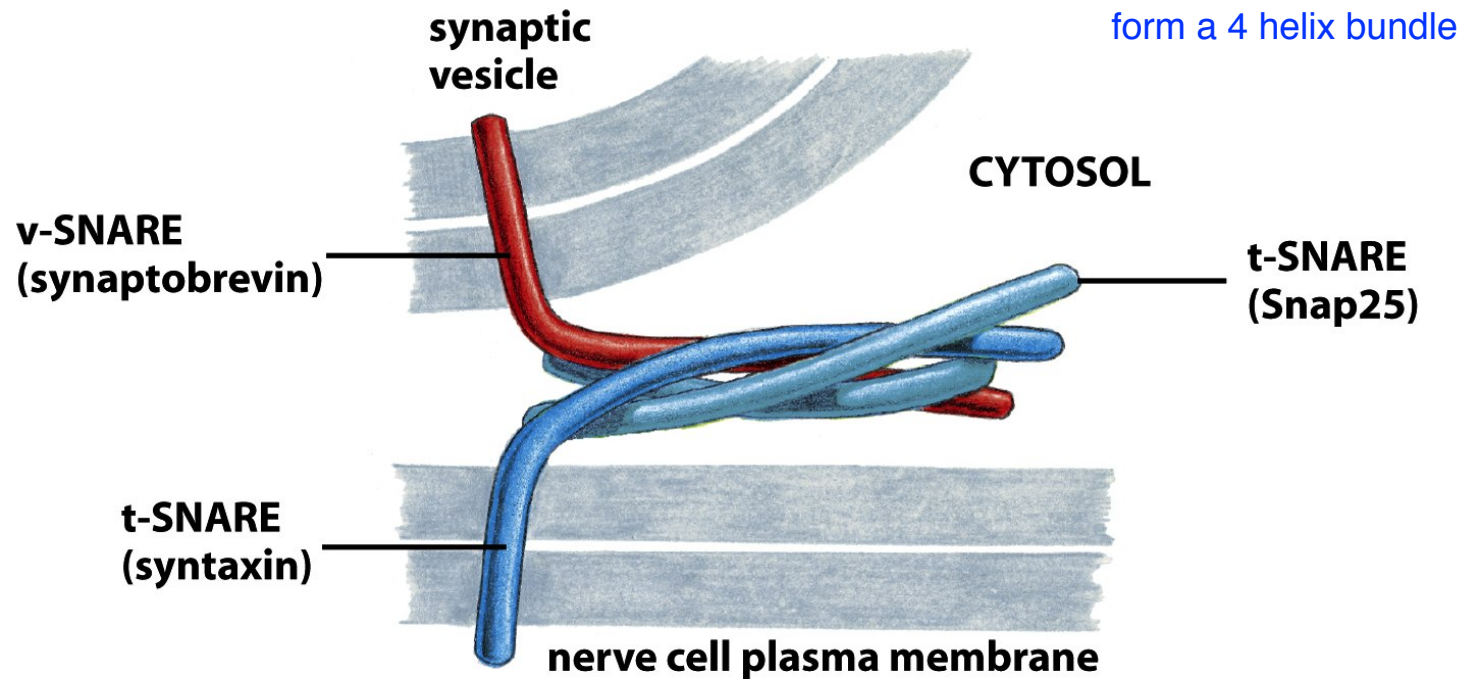
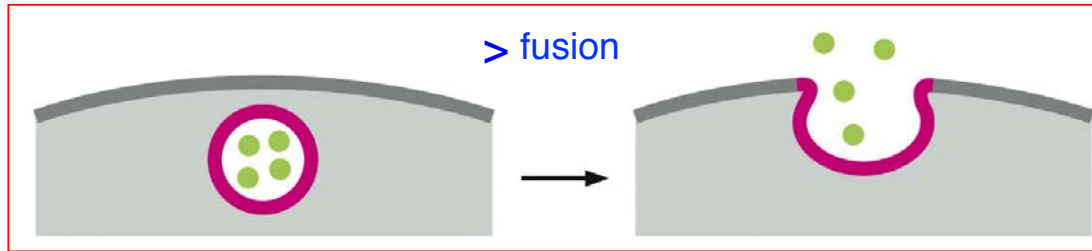


Figure 13-16 Molecular Biology of the Cell 5/e (© Garland Science 2008)

v-SNARES on the vesicle bind specific t-SNARES on the target membrane

SNARE proteins specify which membranes fuse and conduct the process

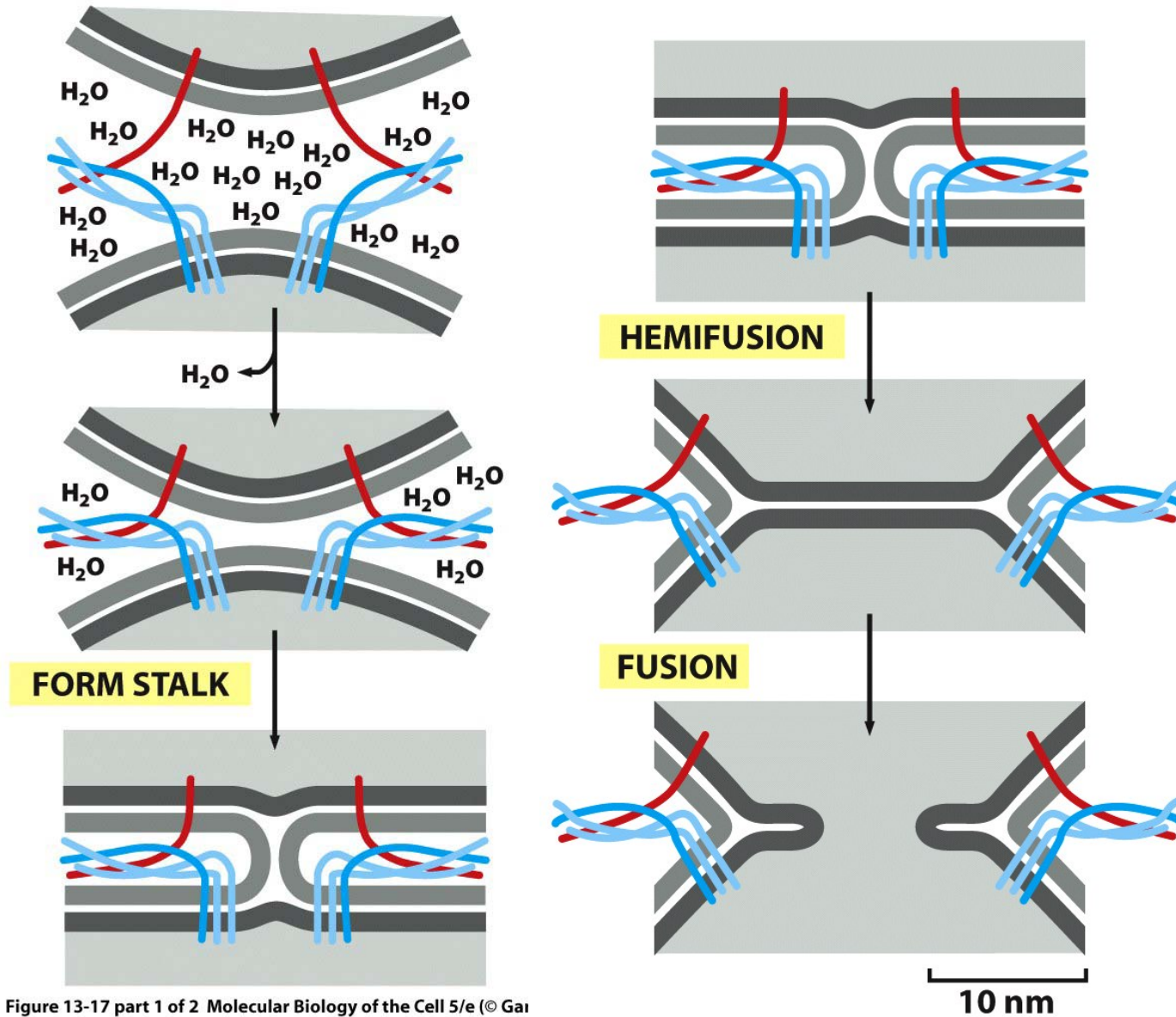
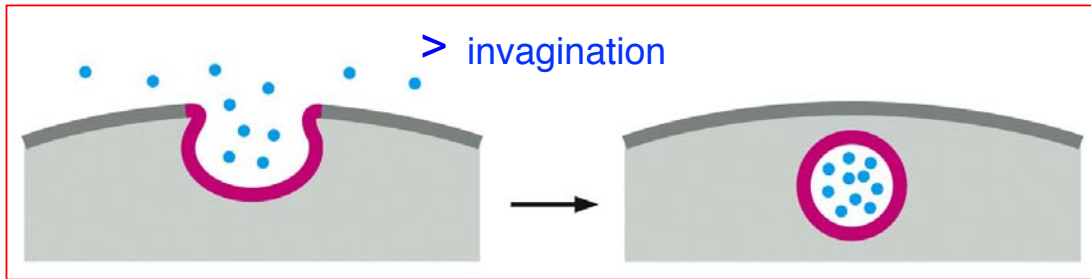


Figure 13-17 part 1 of 2 Molecular Biology of the Cell 5/e © Gar

Clathrin drives vesicle invagination events



protein forms a curved structure which makes it curve inward

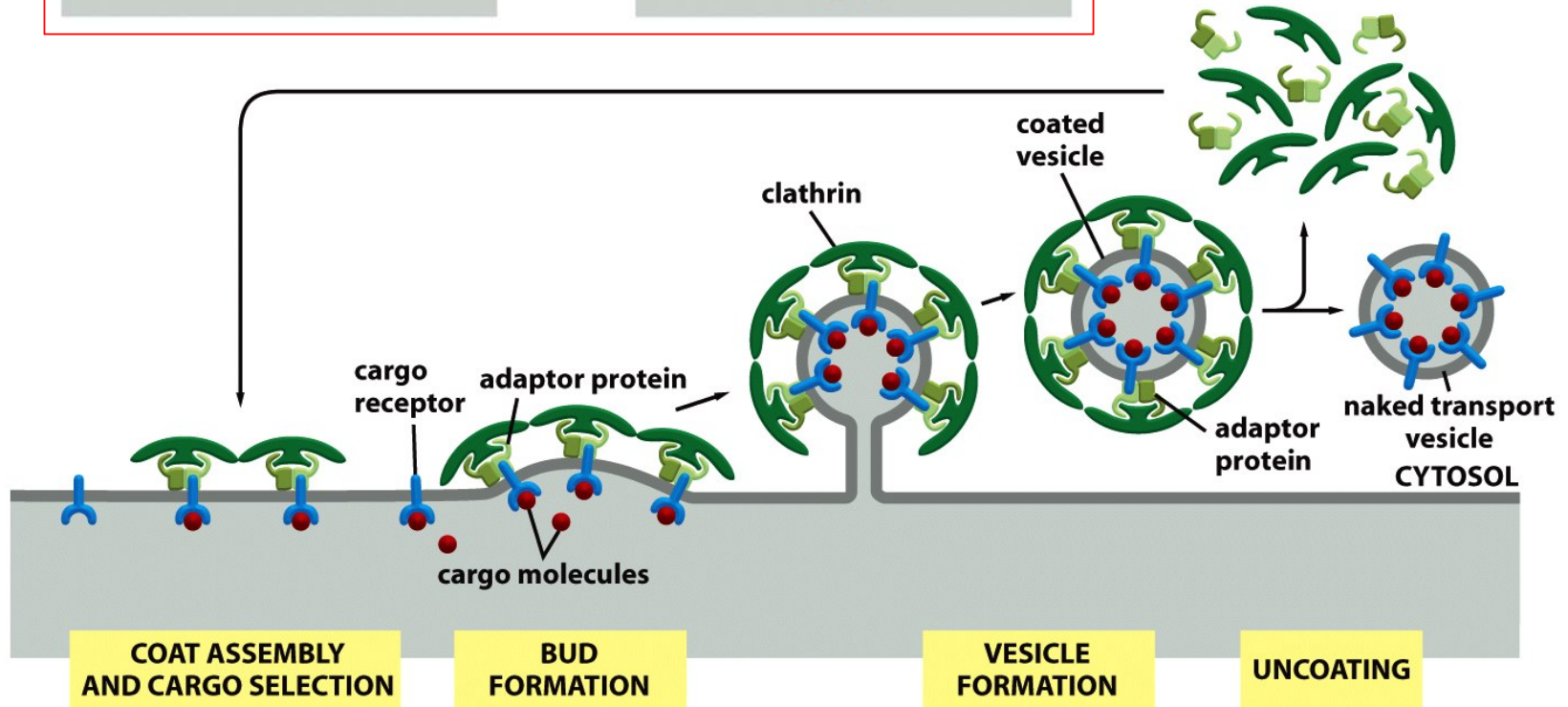
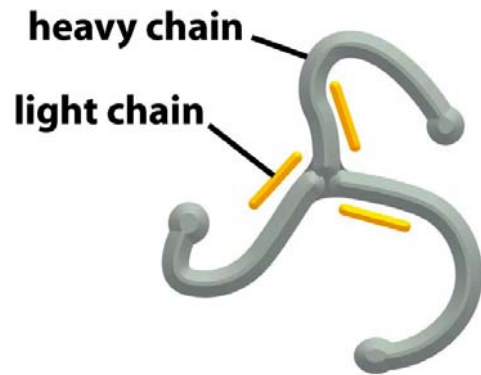


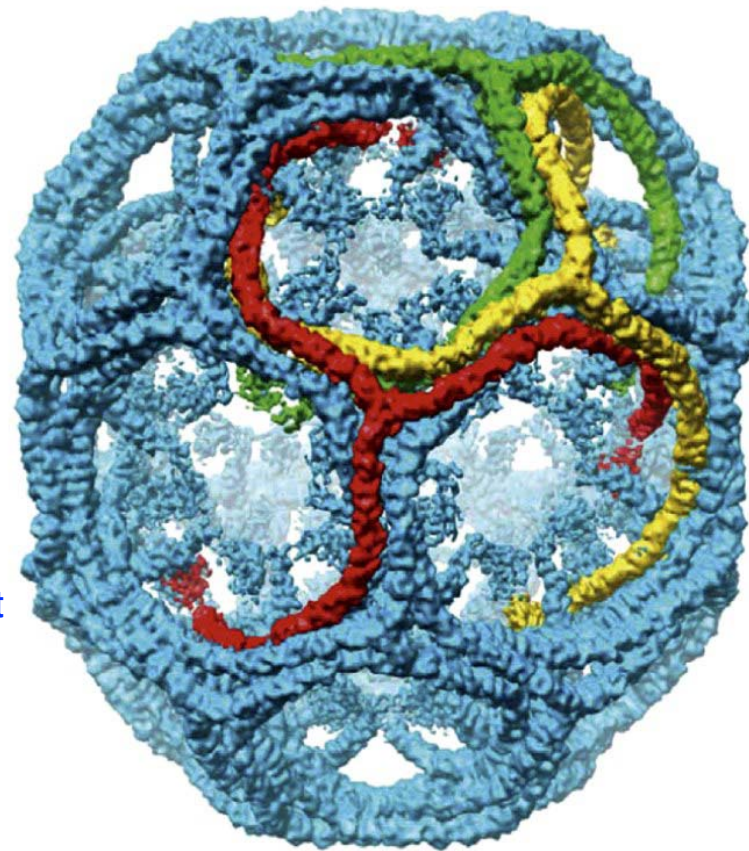
Figure 13-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Clathrin drives vesicle invagination events



A clathrin triskelion

> three heavy chains and three light chains



A cryoelectron micrograph of a clathrin coat
composed of 36 triskelions

Figure 13-7cd Molecular Biology of the Cell 5/e (© Garland Science 2008)

2

COPI and COPII also drive vesicle invagination events

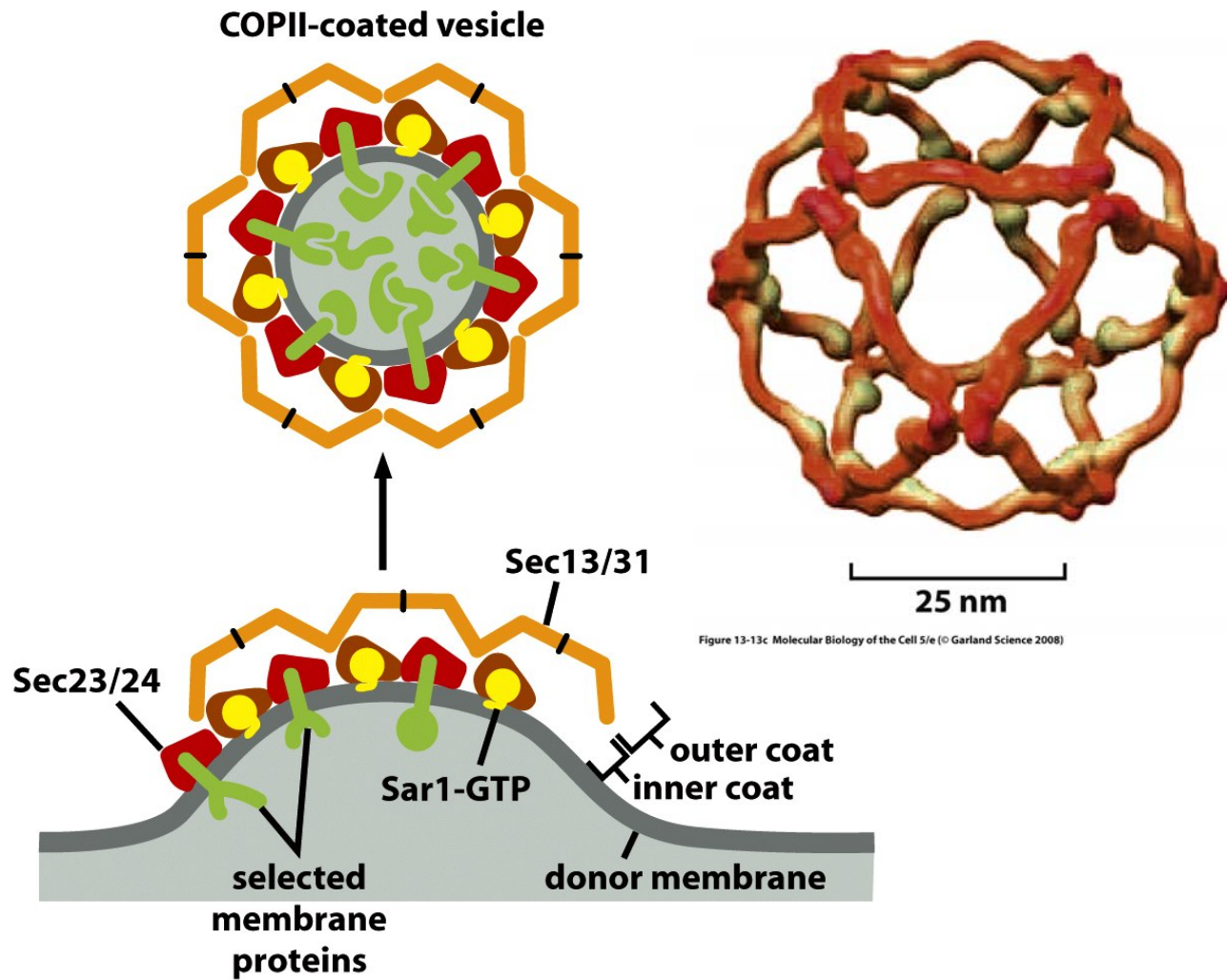


Figure 13-13d Molecular Biology of the Cell 5/e (© Garland Science 2008)

Dynamin drives fission after vesicle invagination events

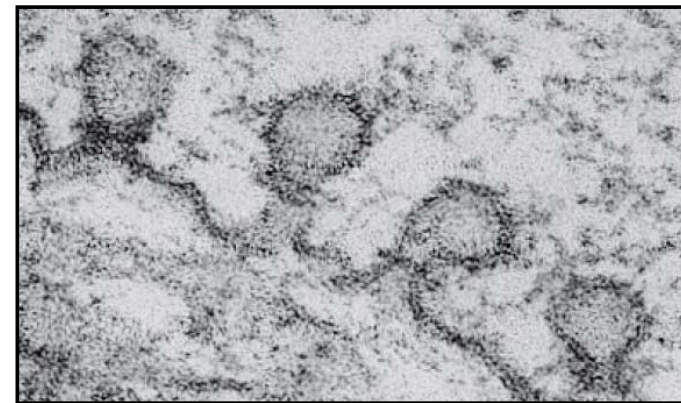
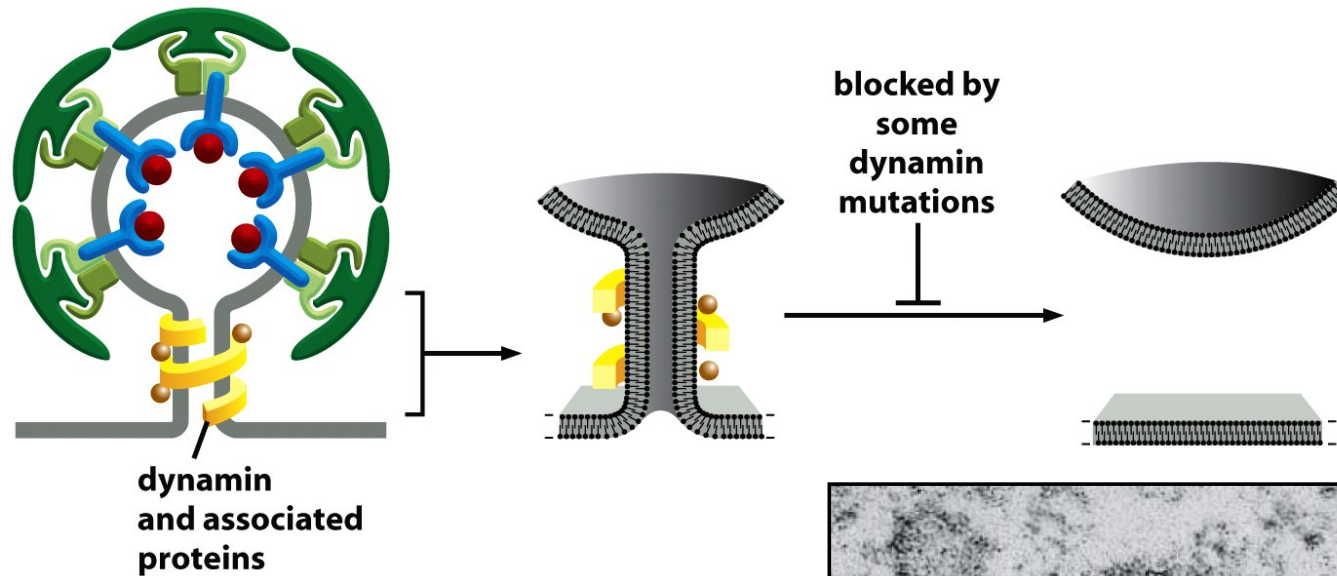
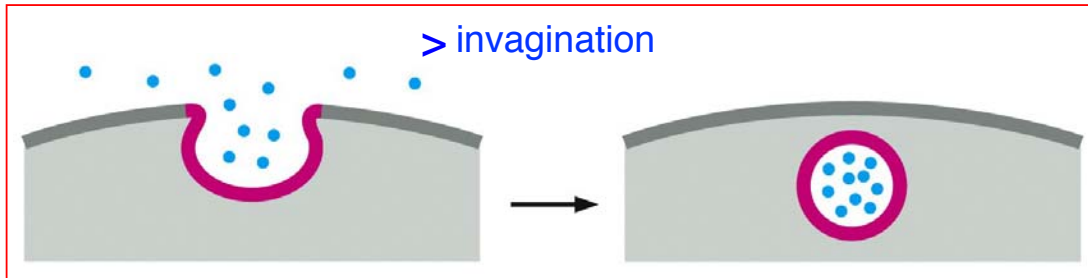
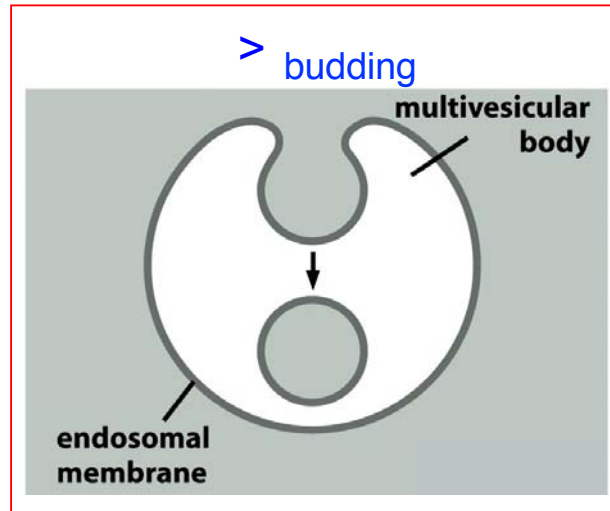


Figure 13-12a Molecular Biology of the Cell 5/e (© Garland Science 2008)

The ESCRT Complex drives budding events



have membrane budding away from the cytosol, depending of which way it is going the machinery will change in that way

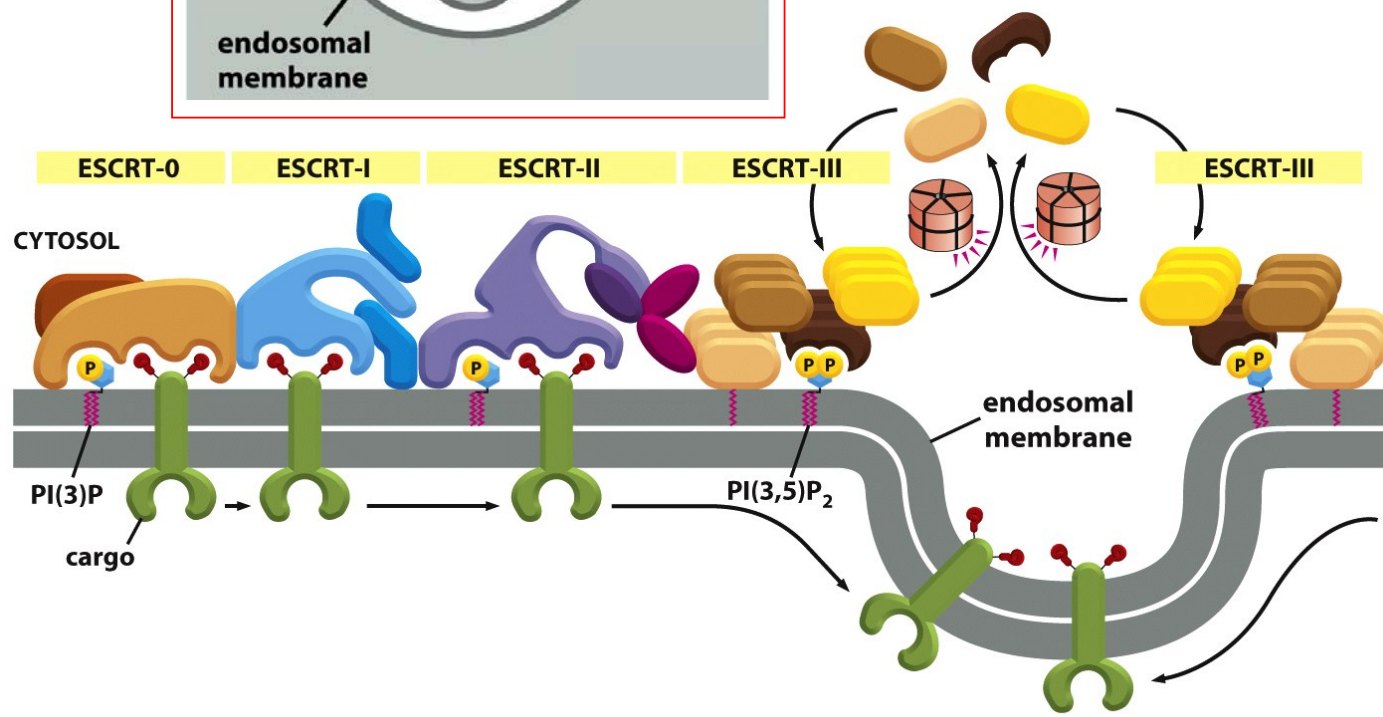
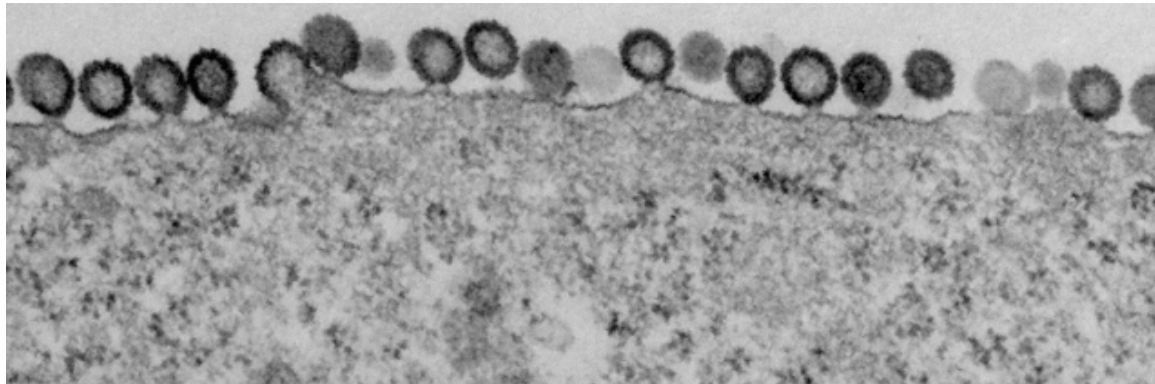


Figure 13-58 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Virus particles found in the cytoplasm would need which of the following machinery to leave the cell?

- a. Clathrin
- b. Dynamin
- c. SNARES
- d. ESCRT complex**
- e. COPI



HIV virus particles budding from an infected cell
(Journal of Virology 85:7419, 2011)

Membrane invagination, fusion and budding events occur at specific sites in the system to control polarized trafficking and retrieval

e.g. invagination events

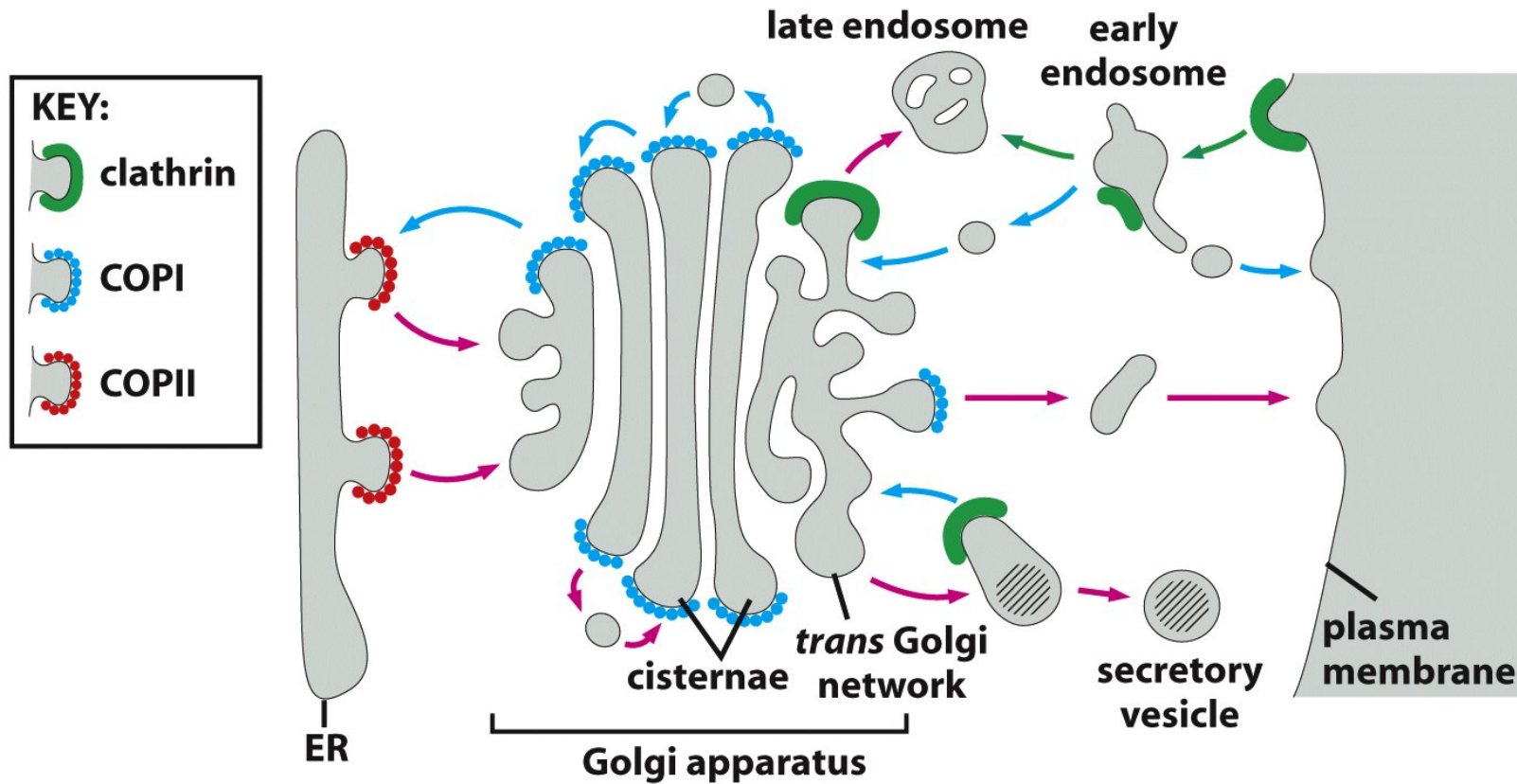


Figure 13-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Membrane invagination, fusion and budding events occur at specific sites in the system to control polarized trafficking and retrieval

Specificity in the system is regulated by:

- SNARES
- Signaling Lipids (PIPs)
- Small GTPases
- Signal sequences/moieties on cargo
- Membrane composition

The inositol sugar head group of inositol phospholipids can be phosphorylated at specific sites

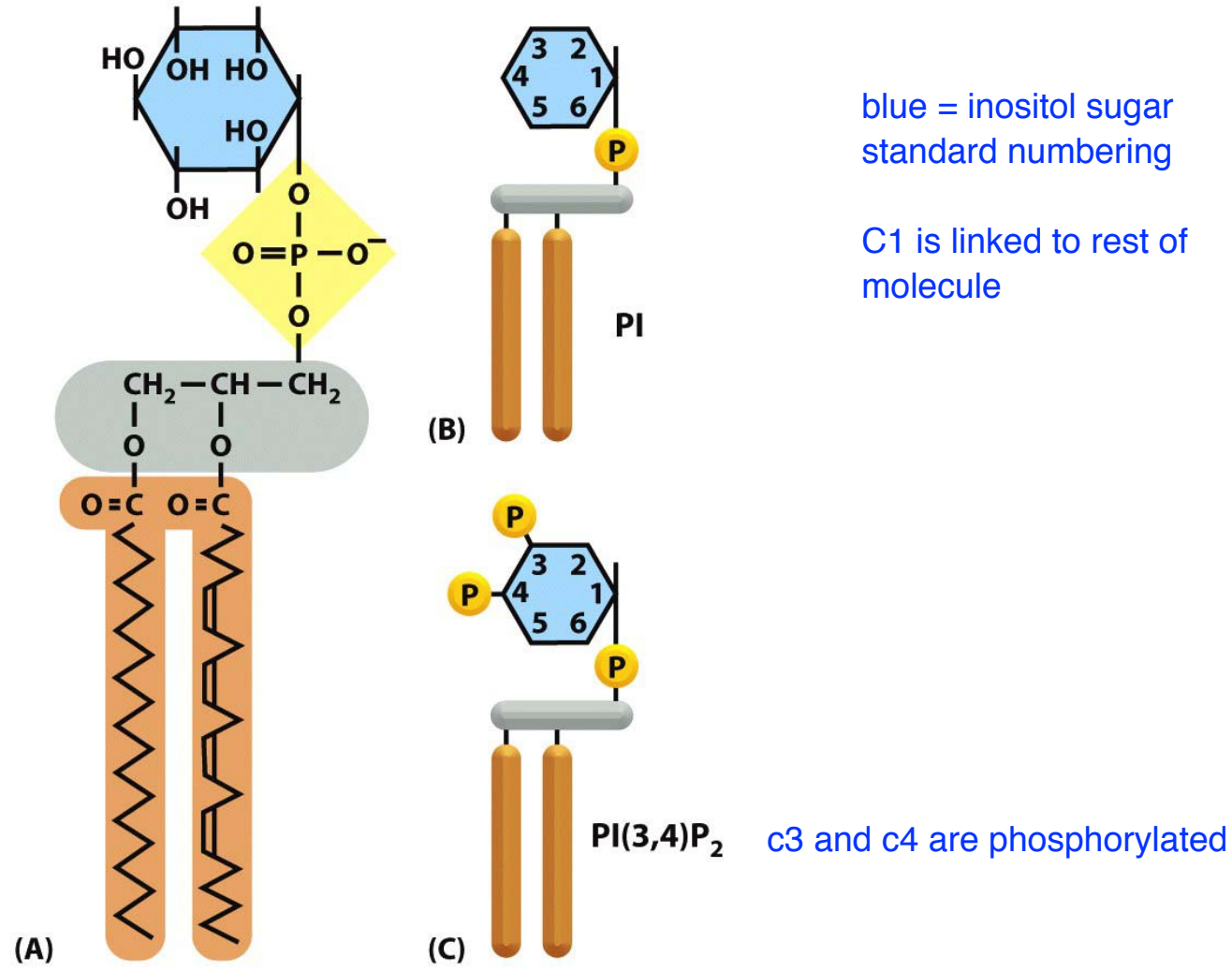


Figure 13-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

rememebr

add

remove

Kinases and **phosphatases** add or remove phosphate groups at different positions of the ring to make a variety of phosphoinositide (PIP) species

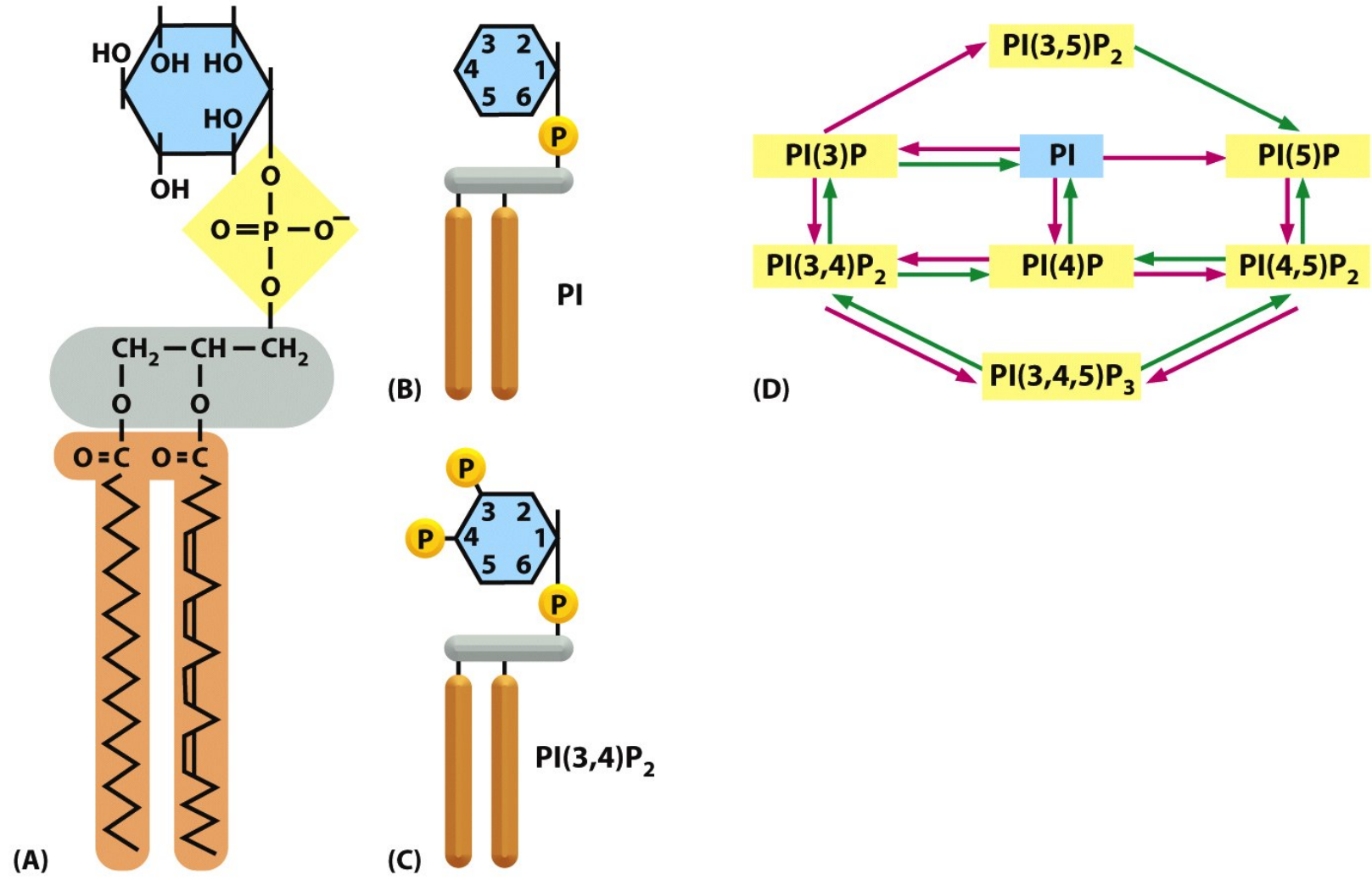
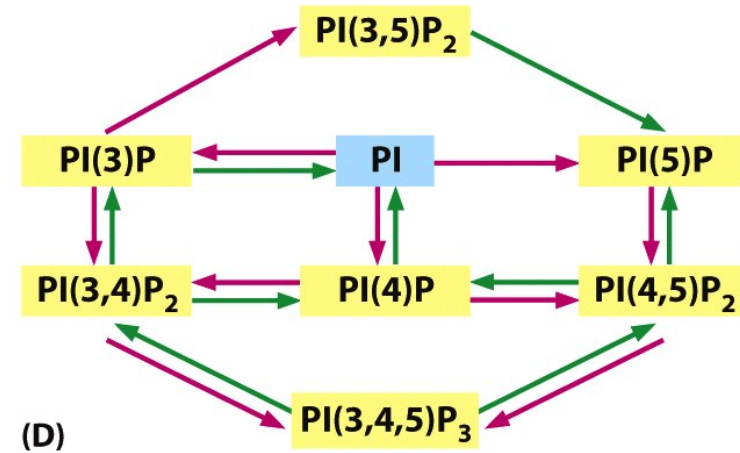


Figure 13-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

remember

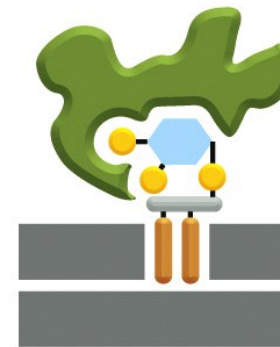
Kinases and **phosphatases** add or remove phosphate groups at different positions of the ring to make a variety of phosphoinositide (PIP) species



Each phosphoinositide (PIP) species binds to specific proteins



(E)



(F)

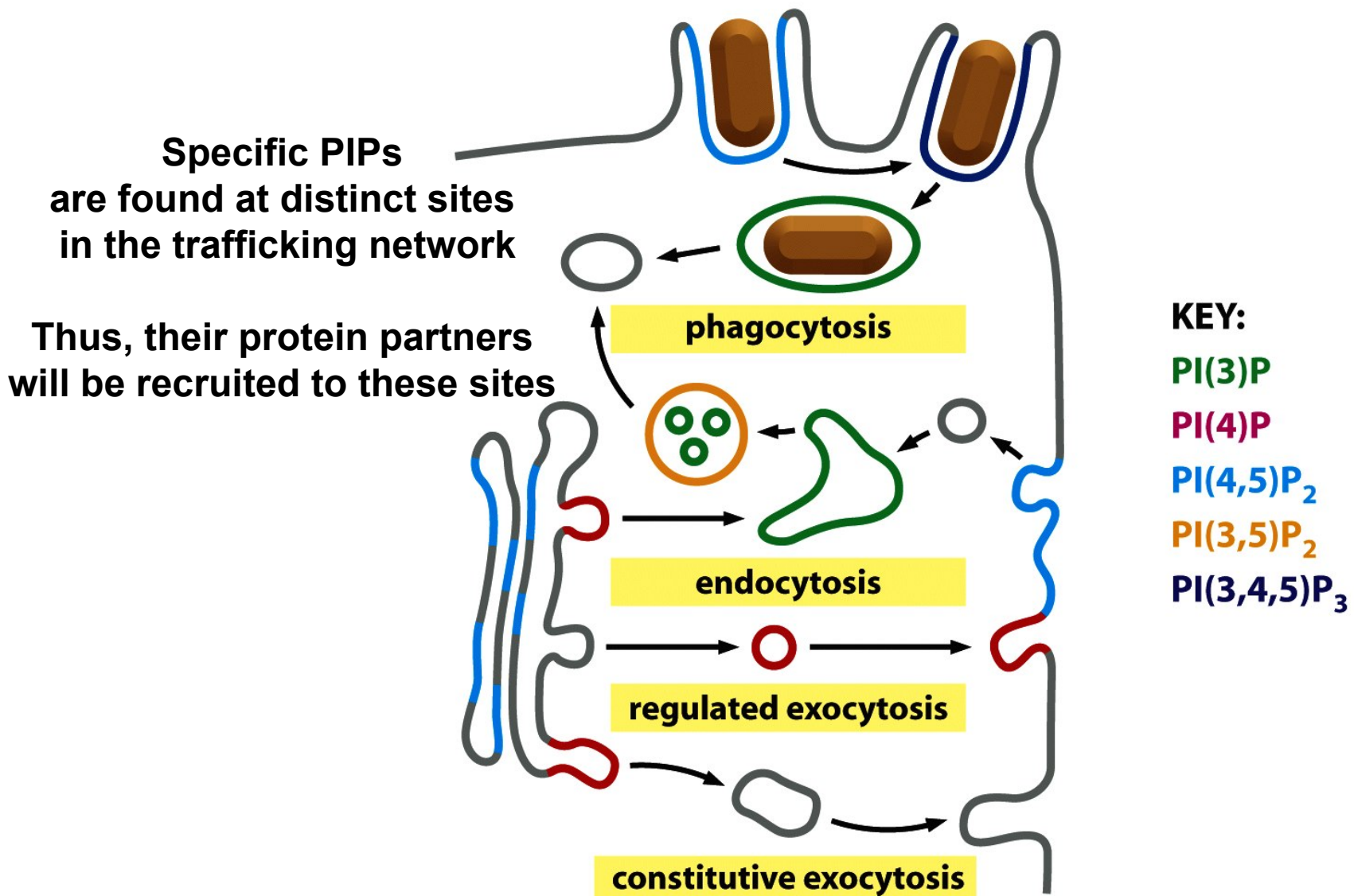
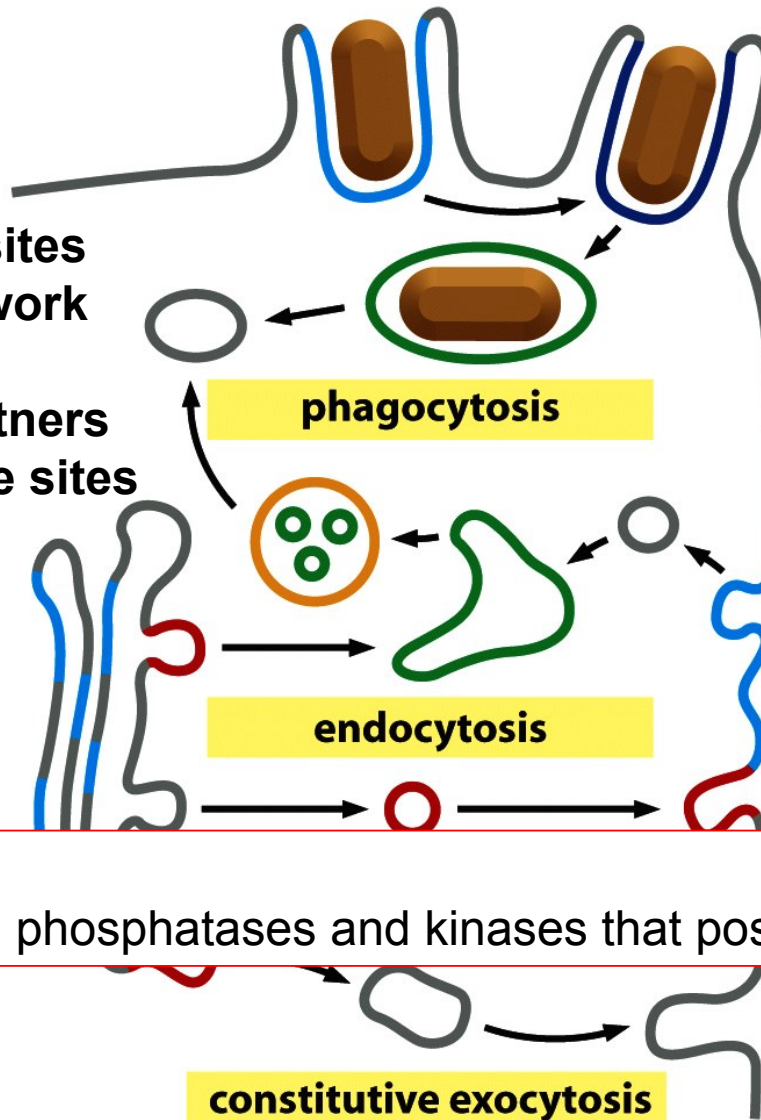


Figure 13-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Focus on the concept—the localization of each species will not be tested

**Specific PIPs
are found at distinct sites
in the trafficking network**

**Thus, their protein partners
will be recruited to these sites**



KEY:

PI(3)P

PI(4)P

PI(4,5)P₂

PI(3,5)P₂

PI(3,4,5)P₃

An open question:

What positions the lipid phosphatases and kinases that position the PIPs?

Figure 13-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Focus on the concept—the localization of each species will not be tested

Small GTPases are active in the GTP-bound state

- they become specifically localized in the cell
- they bind and activate downstream effectors

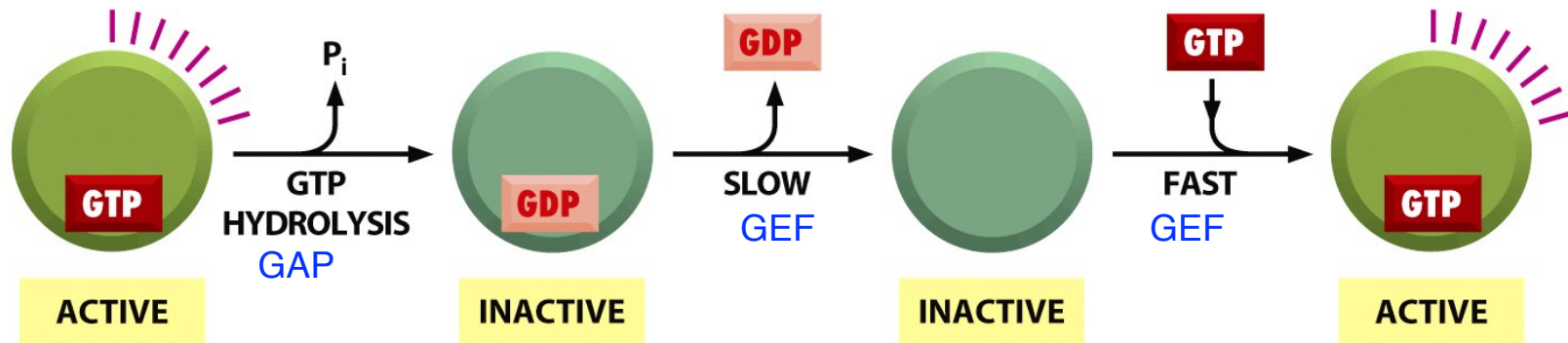


Figure 3-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Guanine-nucleotide-exchange factors (GEFs) promote the exchange of GDP to GTP

GTPase-activating proteins (GAPs) promote the hydrolysis of bound GTP to GDP

Specific Rab small GTPases localize to distinct sites in the trafficking pathway

Table 13-1 Subcellular Locations of Some Rab Proteins

PROTEIN	ORGANELLE
Rab1	ER and Golgi complex
Rab2	<i>cis</i> Golgi network
Rab3A	synaptic vesicles, secretory granules
Rab4/Rab11	recycling endosomes
Rab5A	plasma membrane, clathrin-coated vesicles, early endosomes
Rab5C	early endosomes
Rab6	medial and <i>trans</i> Golgi cisternae
Rab7	late endosomes
Rab8	early endosomes
Rab9	late endosomes, <i>trans</i> Golgi network

Table 13-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Memorize the relationships in red boxes
(these are the ones most commonly discussed)

Rabs are recruited to specific membranes by RabGEFs their activation promotes downstream effects

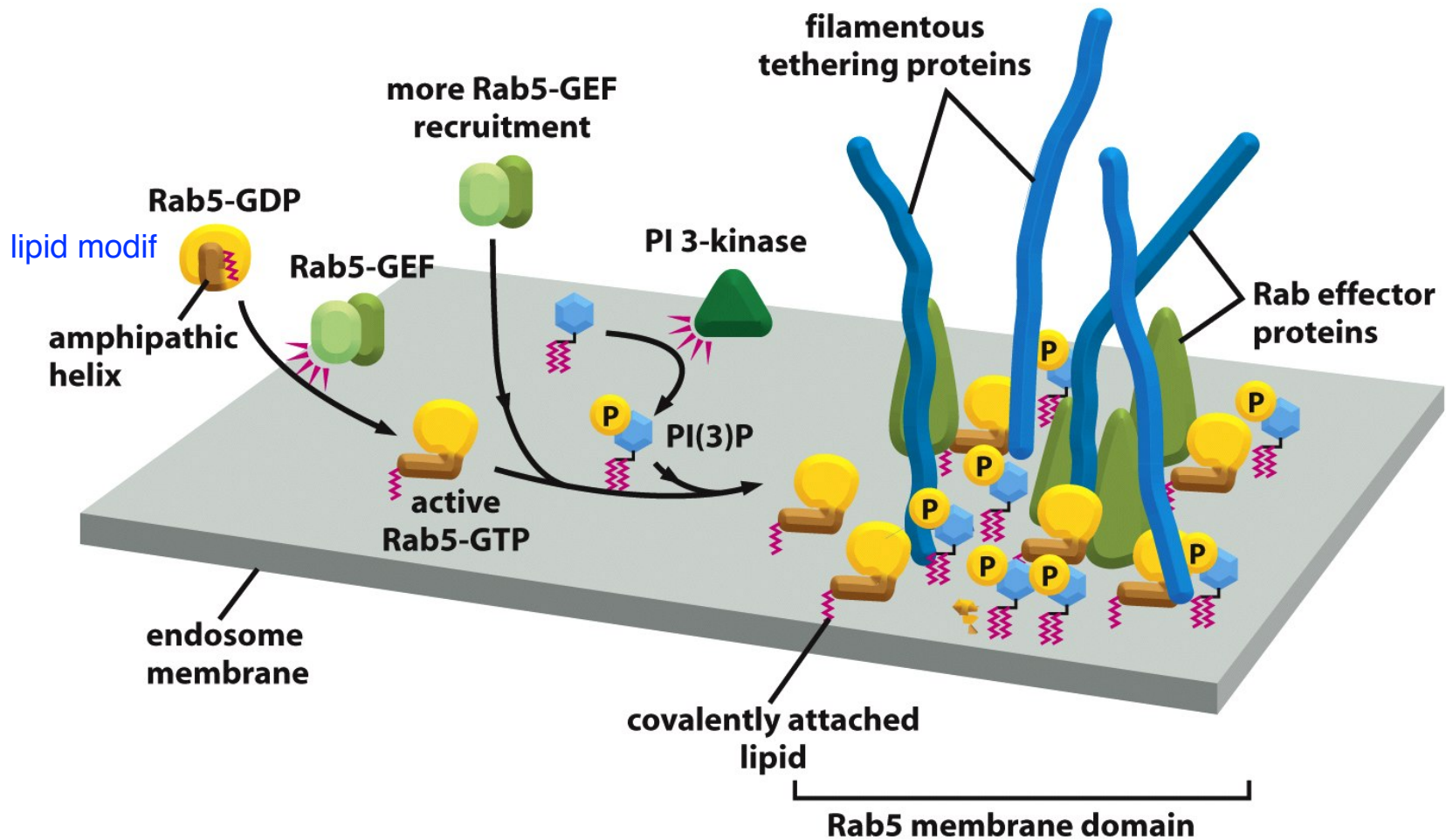


Figure 13-15 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Rabs are recruited to specific membranes by RabGEFs their activation promotes downstream effects

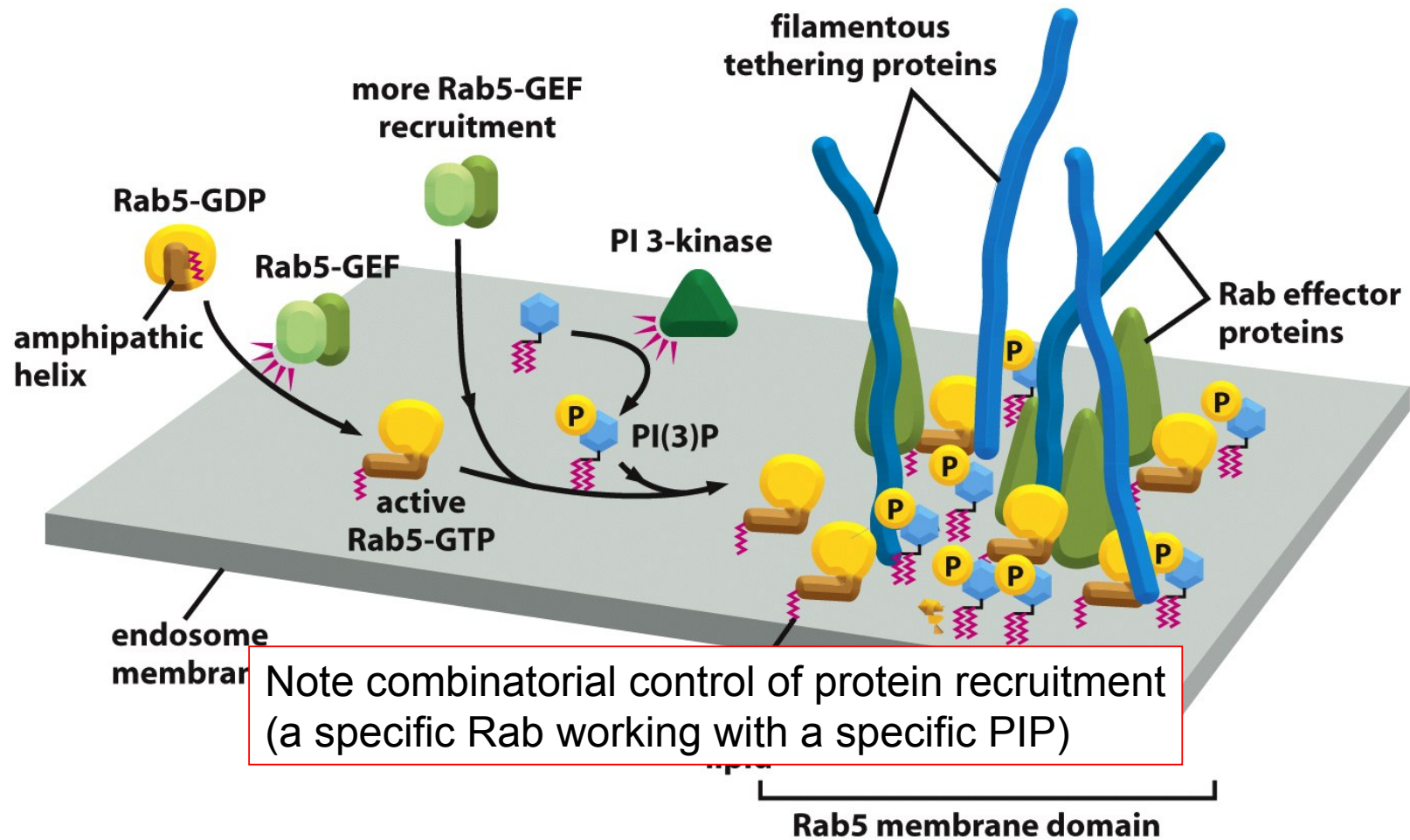


Figure 13-15 Molecular Biology of the Cell 5/e (© Garland Science 2008)

**Rabs are recruited to specific membranes by RabGEFs
their activation promotes downstream effects**

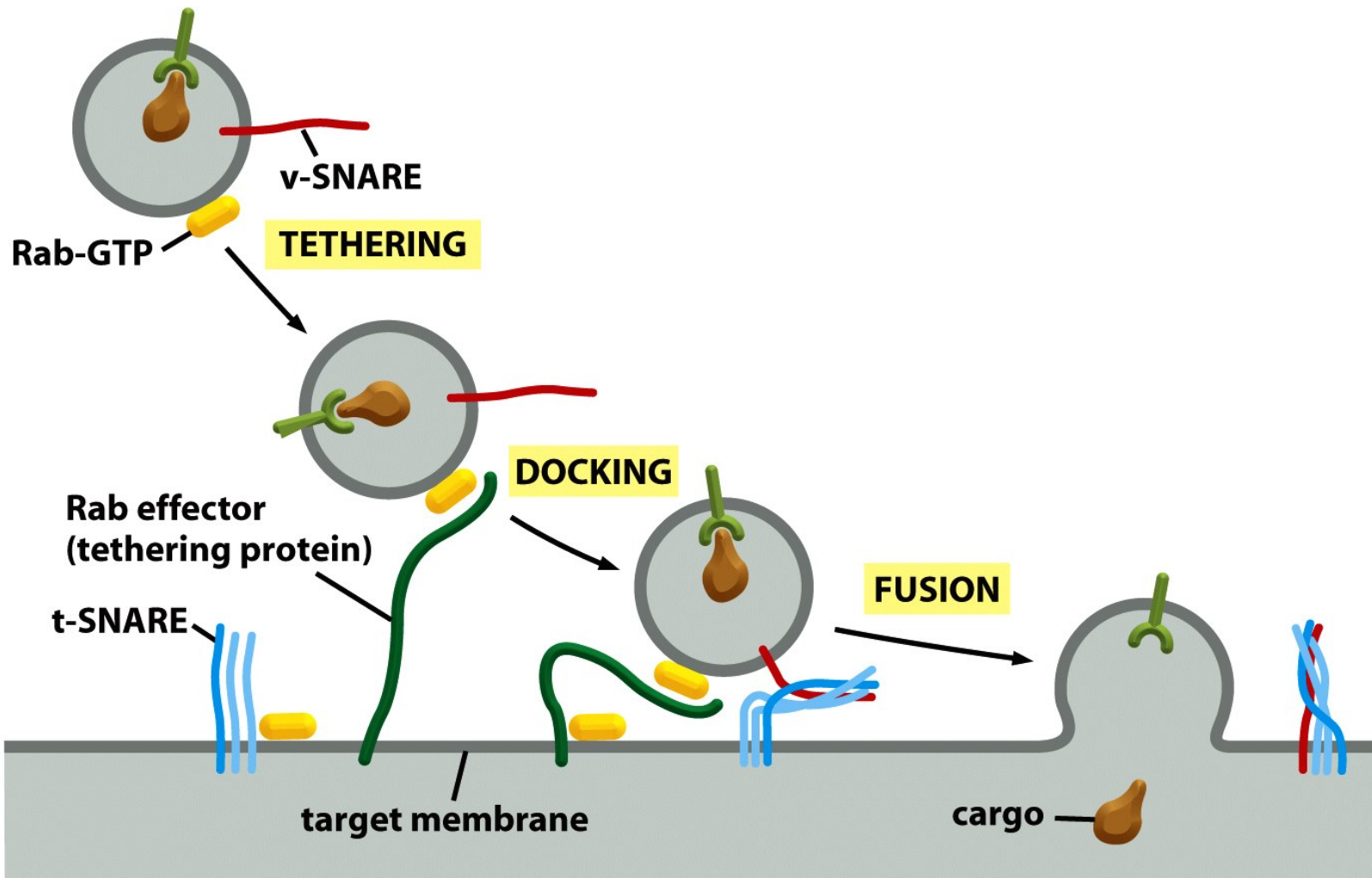


Figure 13-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Rabs are recruited to specific membranes by RabGEFs their activation promotes downstream effects

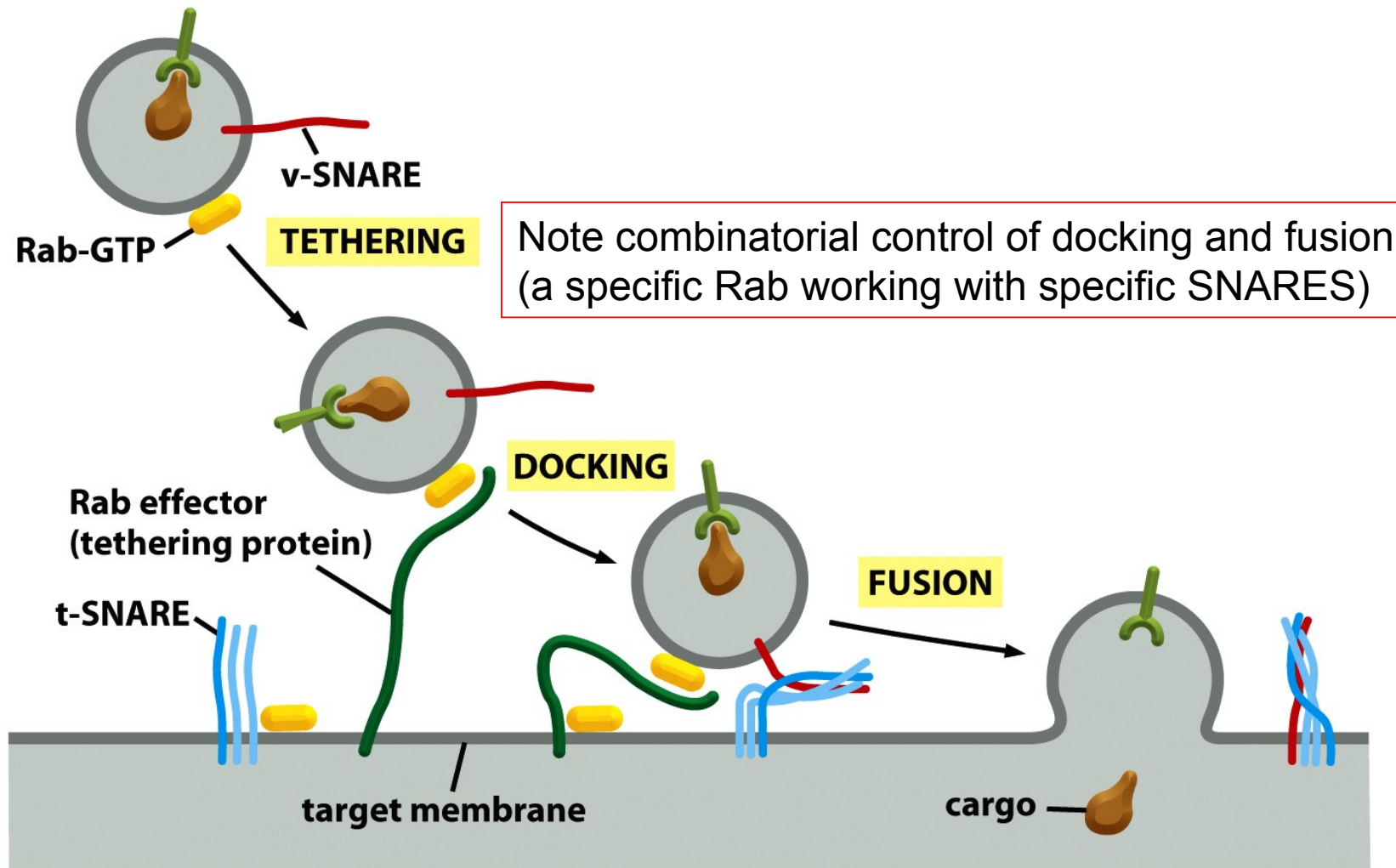


Figure 13-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

**Rabs are recruited to specific membranes by RabGEFs
their activation promotes downstream effects**

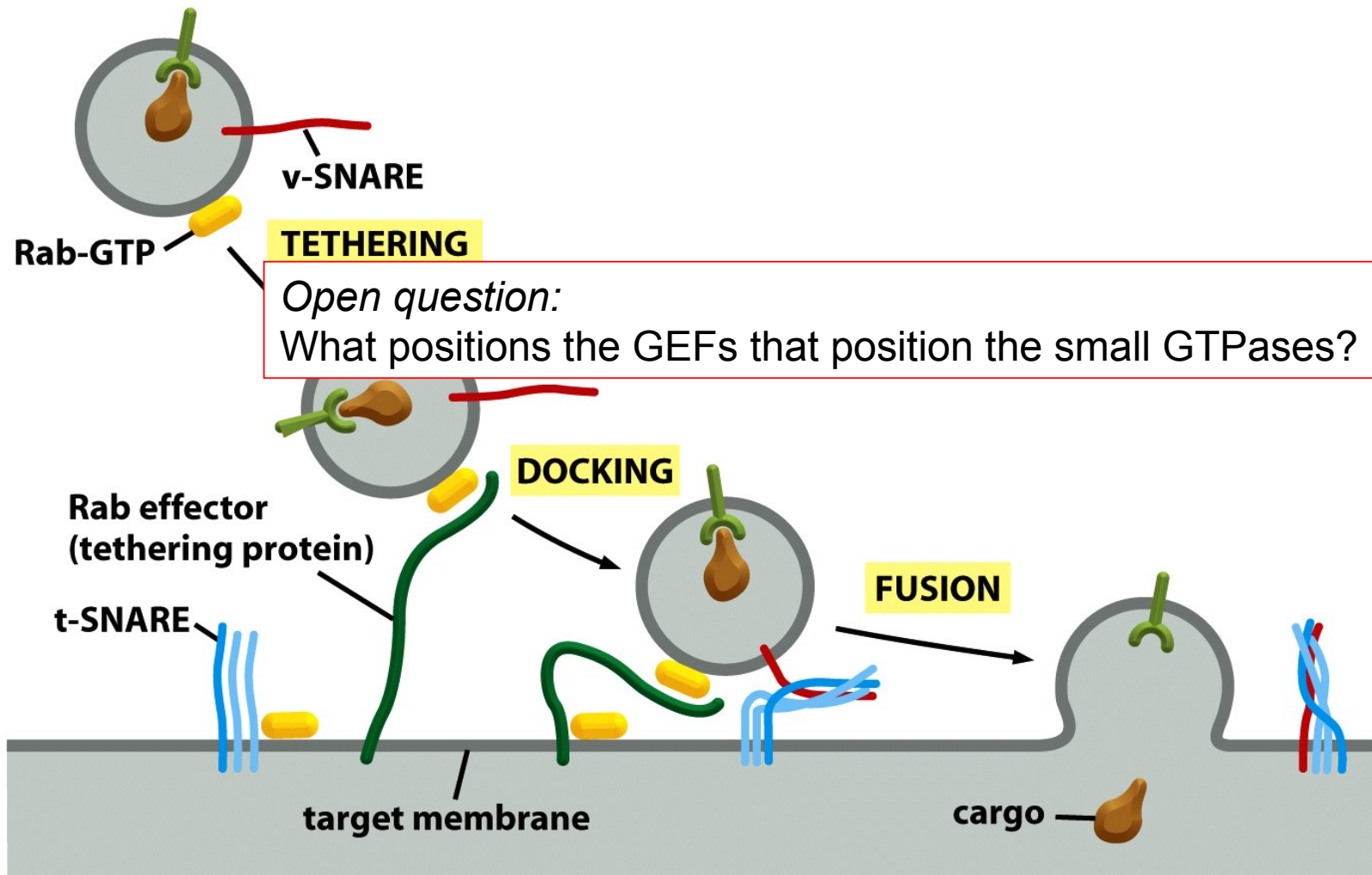


Figure 13-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Spatial organization of individual trafficking events organizes the overall trafficking networks in addition to the plasma membrane

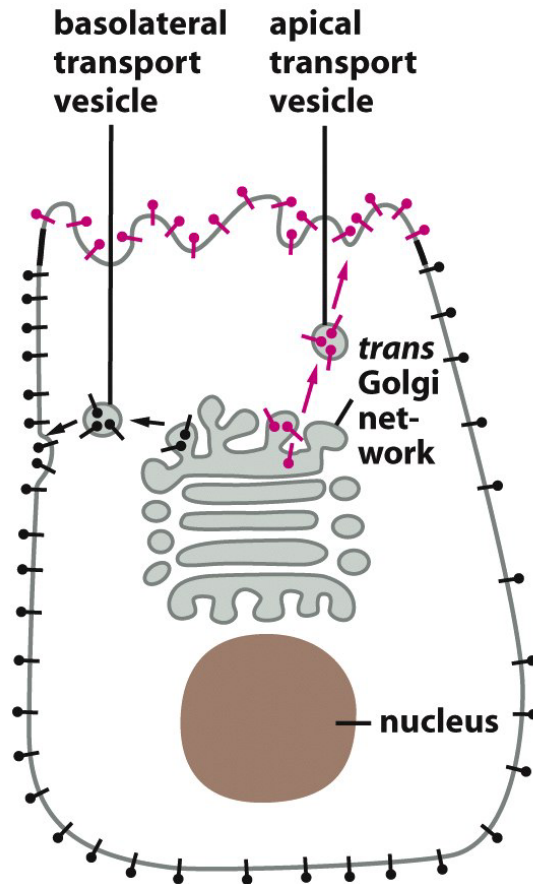


Figure 13-72a Molecular Biology of the Cell 5/e (© Garland Science 2008)

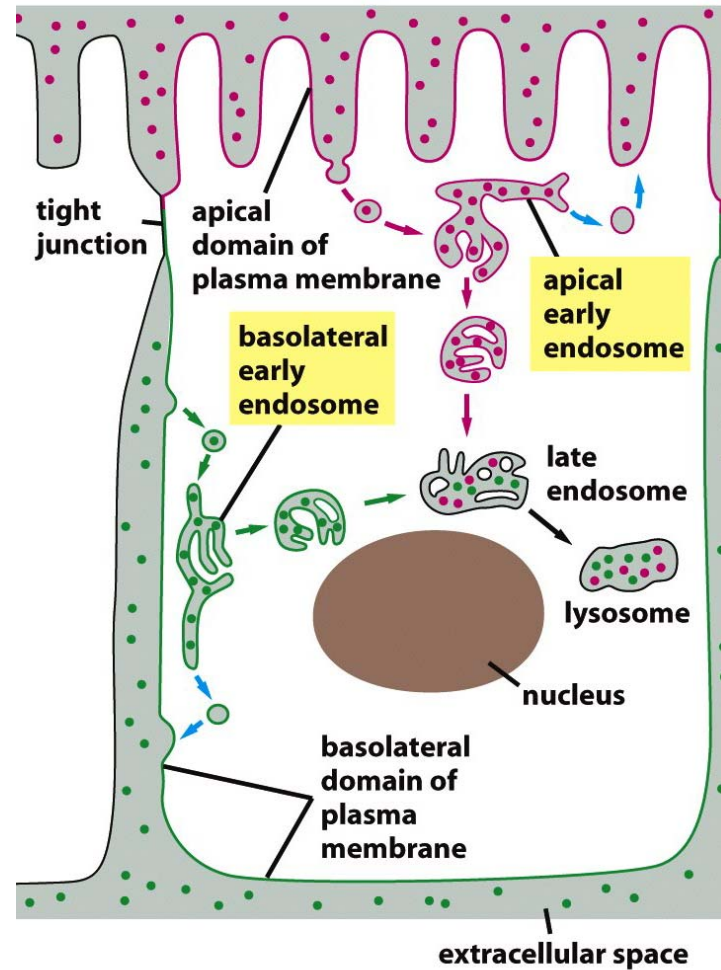


Figure 13-62 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Lecture 1 reading

749-755 (not panel 13-1)

757-758

760-765

787-790

791-797

799-802

803-806 (not figure 13-67)

807-808 (not figure 13-72)