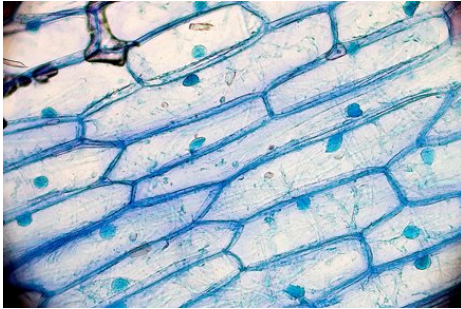
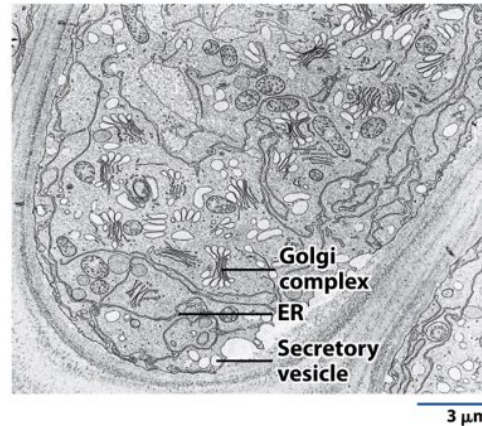


The endomembrane system & the endoplasmic reticulum



Onion cells under a light microscope. With staining you can see nuclei, mitochondria and chloroplasts.



Courtesy of Hilson H. Moellerhauer

TEM image of a maize root cell. Look at all those extra compartments!!

Suggested Readings

Karp 9th ed. Chapter 8

8.1 Overview of the endomembrane system

8.3 Endoplasmic reticulum

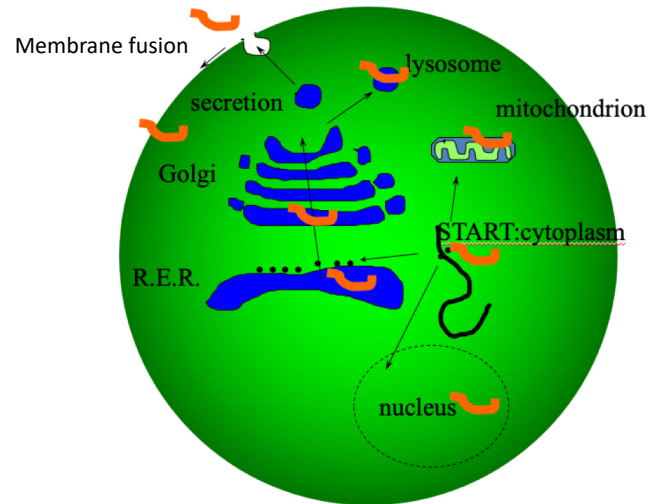
Proteins have a wide range of destinations in the cell

- All proteins are made on ribosomes in the cytoplasm
 - some ribosomes are free in cytoplasm, some become attached to endoplasmic reticulum
 - after translation, all proteins must be sorted to their destinations:

- **Potential destinations;**
- 1. remain in the cytoplasm
- 2. move to cellular compartments via the cytoplasm
- 3. enter the **endomembrane** system, where they are modified and transported through a series of membrane-bound organelles



General pathways of newly (synthesized) proteins



Some proteins are transported in the endomembrane system

1. enter the endoplasmic reticulum
2. move via transport vesicles (budding and fusing "carriers" between other compartments)
3. to Golgi, then to the:
4. trans-Golgi network, then to:
 - lysosomes, or:
 - storage vesicles, or:
 - secretory vesicles and plasma membrane

- NOTE: in addition to the lumen of ER (interior space), the proteins may reside, transfer and function within the membranes of each these compartments

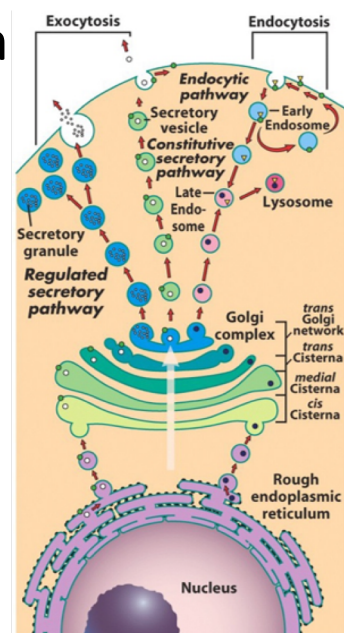
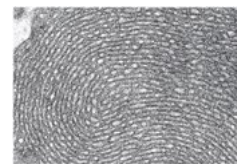
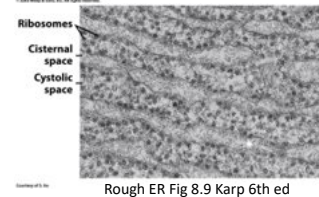
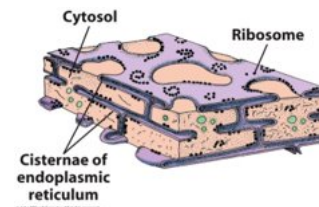


Figure 8-2b Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons, Inc.)

Structure of the endoplasmic reticulum (ER)

- A network of membranous tubules in the cytoplasm of a cell; involved in the production of phospholipids, proteins, and other functions
- Two types: rough and smooth
- Rough ER: studded with ribosomes, continuous with nuclear envelope
- Smooth ER: no ribosomes; site of synthesis of specialized enzymes, functions



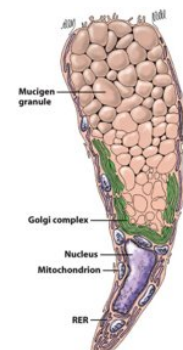
Endoplasmic reticulum- smooth vs rough

Smooth ER concentrated in specialized cells:

- Skeletal muscle, kidney tubules, some endocrine glands, secretory cells
- Synthesis of steroids in gonad and adrenal cortex
- Synthesis of detoxification enzymes in liver
- Enzymes involved in glucose release from liver
- Release of Ca^{2+} ions used in muscle contraction
- **Lipid biosynthesis (membrane biosynthesis)**

Rough ER in most cells:

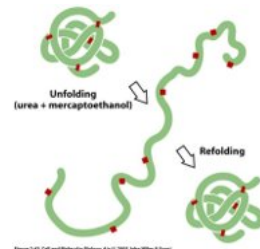
- Synthesis of all proteins to be compartmentalized in lysosomes, secretory vesicles
- Synthesis of integral (membrane bound) proteins
- Membrane biosynthesis (**can assume some SER functions**)
- Glycosylation of many proteins



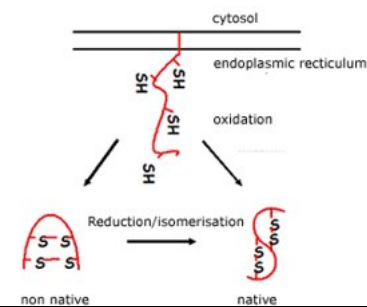
Chemical modifications of proteins in the ER & Golgi

1. disulfide bond formation (cysteines) and folding:

- **Protein folding:** Proteins have a correct or “native” state; the tertiary structure of a protein needs to be correct for it to work properly. It can be misfolded or denatured
- **Molecular Chaperones** are proteins that bind to and alter the folding of newly forming protein
 - **quality control:** proteins that mis-fold cannot bind to chaperones properly and are destroyed
 - With several cysteines, the order in which the disulfide bonds form is important – a **protein disulfide isomerase** in the lumen of ER can help



Formation of disulphide bonds in proteins within the ER



Chemical modifications of proteins in the ER & Golgi

2. Addition of extra chemical groups

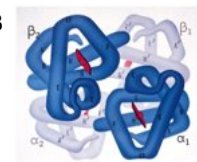
- e.g. methyl, acetyl, formyl, sulfate, hydroxyl, etc.

Methyl -CH₃
Acetyl -COCH₃
Formyl -COH

3. Addition of lipids: lipoproteins are molecules of the cell membranes

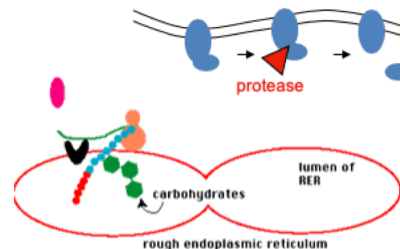
4. Formation of multimeric proteins

- quaternary structure of proteins



Hemoglobin; Fig 2.38 Karp 6th ed

5. Proteolytic cleavage



6. Glycosylation

- Most proteins destined for secretion, the extracellular matrix, the endomembrane system and the plasma membrane are glycoproteins

Rough ER vs cytoplasmic proteins

- RER is the site of synthesis of proteins destined for

- Secretion
- Integral membrane proteins and proteins within lumen of the **endomembrane system**
- Endoplasmic reticulum, Golgi, lysosomes, vesicles, plant vacuoles

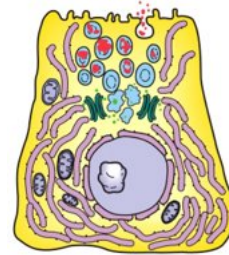


Fig 8.3 Karp 6th ed

- Proteins for the following locations are made within the cytoplasm, **not the RER**.
- Cytosolic proteins
- Peripheral proteins of the cell membrane
- Proteins sent to the nucleus
- Proteins destined for chloroplasts, mitochondria, peroxisomes

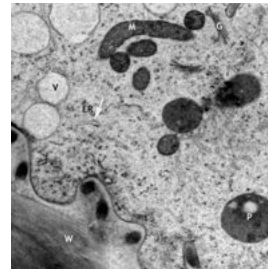
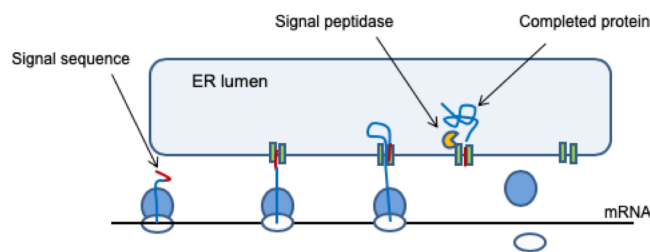


Image acquired from:
<http://www.davidarling.info/images/cytoplasm.jpg>

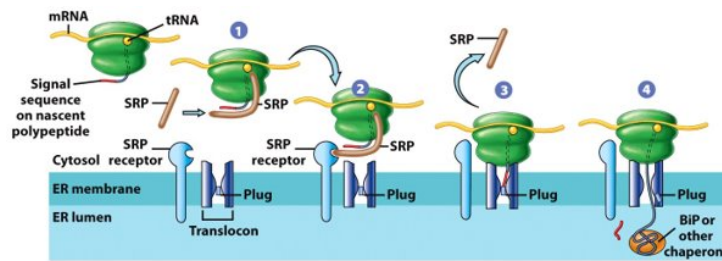
What is different about the protein that is destined for the rough endoplasmic reticulum?

The main difference is that it has a hydrophobic signal sequence.



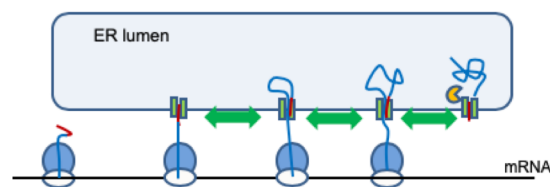
- After the signal sequence is synthesized, protein synthesis temporarily stops until the signal sequence is detected by a protein complex on the rough endoplasmic reticulum.
- The signal peptide enters the ER through a channel and it guides the protein into the lumen of the RER. Protein synthesis resumes and the rest of the protein is inserted in the lumen.
- Note that a signal peptidase near the inner surface of the membrane works to cleave the signal sequence from the growing peptide.

How do proteins get into the Rough ER?



- Proteins are directed to the RER by the **signal sequence (signal peptide)**
 - a sequence of 6 - 15 hydrophobic aa - usually at the N-terminal
- Protein synthesis starts on a cytoplasmic ribosome/mRNA complex
- signal sequence recognized by signal recognition particle (SRP) – binds signal sequence and ribosome
- an RER receptor binds SRP
- translocon (protein channel) binds ribosome
- signal peptide then released from SRP (along with GTP hydrolysis) and binds to interior of translocon
- translated protein enters RER lumen, signal sequence is removed by signal peptidase enzyme

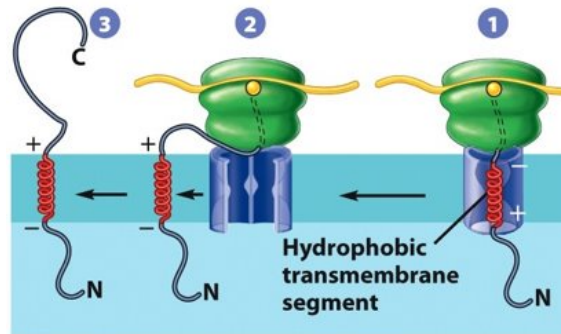
Polyribosomes can be found on the RER



- The fluidity of the membrane allows the ribosome to be docked at its receptor site and also move along the mRNA.
- translocons can move around on the ER membrane, because the membrane has fluidity
- Polyribosomes can form, to speed up translation rate

Integral proteins – proteins embedded in the membrane

- Some proteins get incorporated into the membrane – they do not end up in the ER lumen
- Some proteins have a single transmembrane domain – a stretch of at least 15 hydrophobic amino acids that is embedded in the lipid bilayer
- The translocon can open to allow lateral movement of the hydrophobic segment into the lipid bilayer

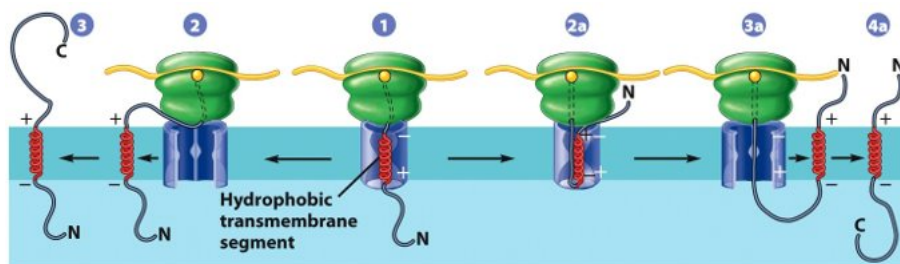


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Translocon opens a side door to let hydrophobic sequence move into a hydrophobic environment

Orientation of the integral protein is dependent on amino acids next to hydrophobic sequence

- The presence of positively-charged amino acids flanking the hydrophobic sequence will determine the orientation of the protein, such that the positive amino acids are pointing toward the cytosolic side (as opposed to the lumen side)
- In figure below, two different proteins have different orientations; one has N-terminal in the lumen, the other has N-terminal in the cytoplasm
- Orientation of protein is adjusted so that the flanking positively-charged amino acids are aligned with negatively charged translocon amino acids

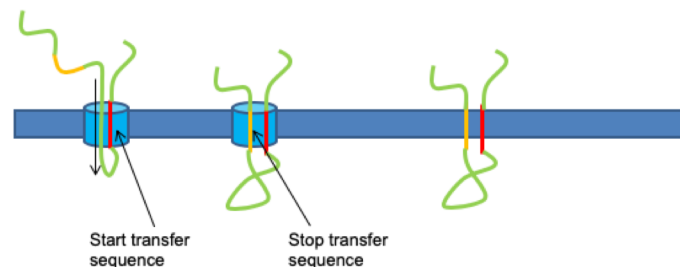


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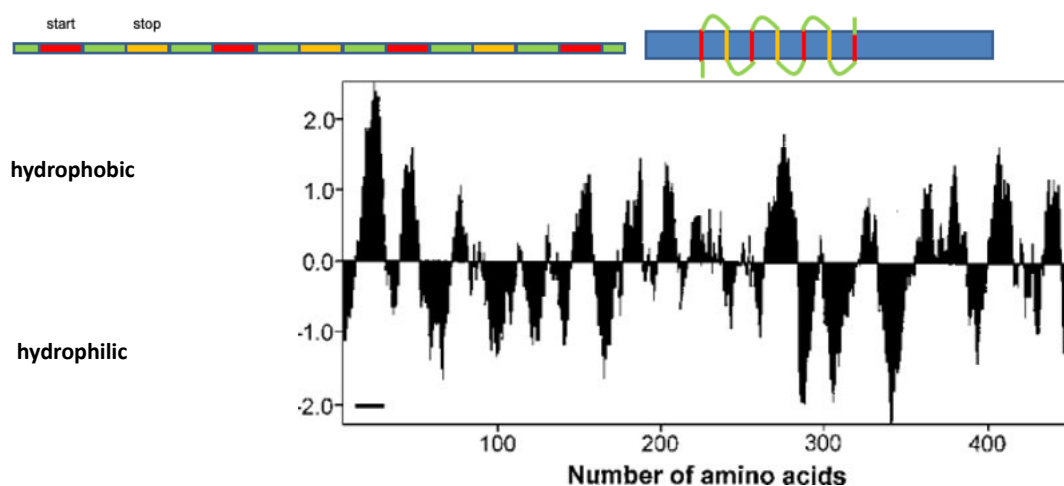
Fig. 8.13 Karp 6th ed

Some integral proteins have multiple transmembrane domains

- Here is the insertion of a double-pass transmembrane protein within the rough endoplasmic reticulum. The red-coloured signal sequence starts the membrane insertion process. This continues until a second hydrophobic signal is reached (orange-coloured). That anchors the second membrane passage.
- These alternating hydrophobic regions are called start-transfer and stop-transfer sequences



Membrane proteins that pass through the membrane multiple times have multiple start and stop signals

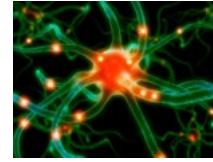


A hydrophobicity plot can predict the number of transmembrane domains a protein can have

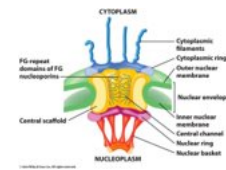
Integral proteins play many key roles

Roles of transmembrane proteins:

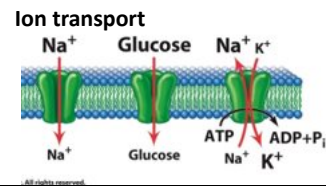
- Communication between cells
- Communication between organelles and cytoplasm
- Ion transport
- Nutrient transport
- Connections for cytoskeleton
- 25% of cell's proteins



Microsoft Clip Art



Nuclear pore

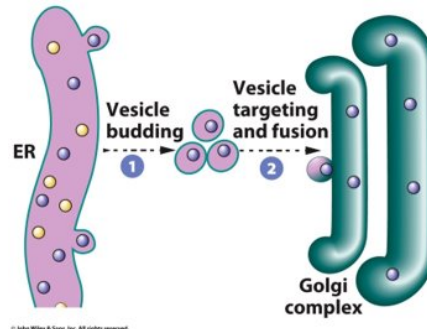


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What you should know after this lecture

- The functions of SER and RER
- Kinds of protein modifications that occur in the endomembrane system
- How a protein enters the endomembrane system (i.e. how a translocon operates)
- How integral proteins form
- Importance of integral proteins

The Golgi Apparatus and Vesicular Traffic



Suggested readings: Karp 9th ed, Chapter 8
Section 8.4 The Golgi Complex
Section 8.5 Types of vesicle transport

Excellent (and long!) video seminar by Randy Schekman:
<https://www.youtube.com/watch?v=U2GoloQVWWE>



got a Nobel for this.

The Golgi apparatus is the cells' 'shipping department'

- The Golgi consists of a stack of membrane-bounded **cisternae** located between the endoplasmic reticulum and the cell surface - resembles a stack of hollow pancakes
- Primary function – to modify and sort proteins for export or other secretory pathway organelles
- Secondary function – make complex carbohydrates to be exported from the cell (especially in plants)

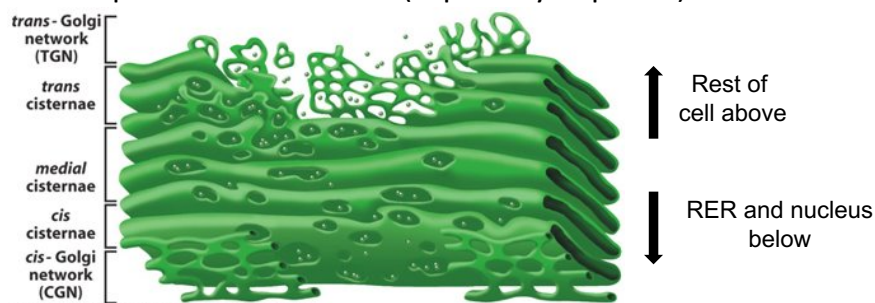


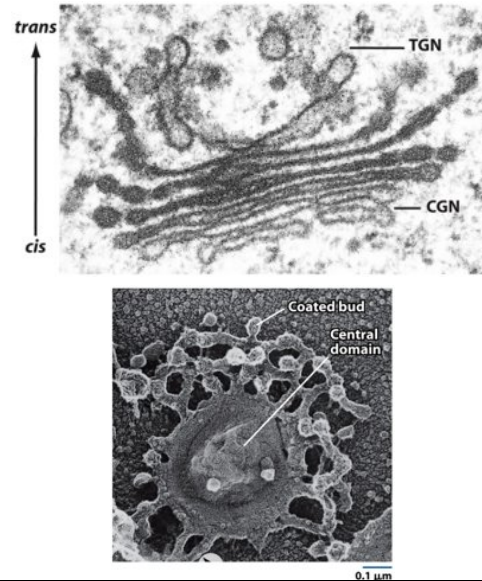
Figure 8.21a Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)



Named after Camillo Golgi (1898)
The Nobel Prize in
Physiology for Medicine 1906

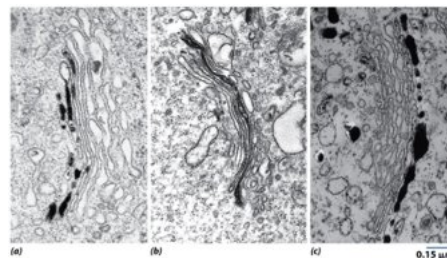
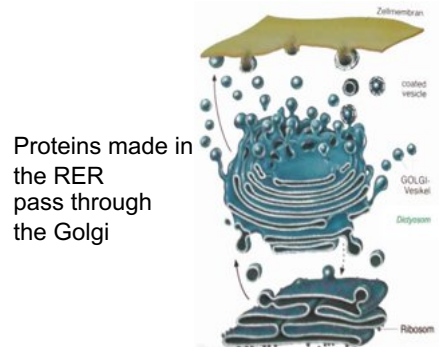
The Golgi apparatus has polarity/directionality

- The ***cis* Golgi network (CGN)** functions to sort proteins for the ER or the next Golgi station.
- The ***trans* Golgi network** functions in sorting proteins either to the membrane or various intracellular destinations.
- The Golgi complex is not uniform in composition; there are differences in composition from the *cis* to the *trans* face.



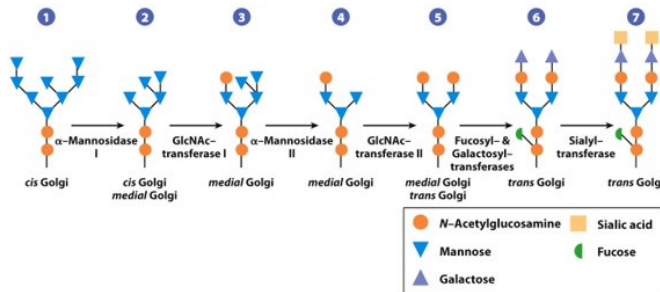
Proteins are modified as they pass through the Golgi

- each compartment (cis, medial, trans) has unique enzymes.
- functional differentiation of the Golgi complex can be studied with the electron microscope with specific techniques that detect different enzymes:
 - a.) cis region is where sugars and proteins are phosphorylated
 - b.) the medial regions add onto the N-linked sugars first made in the RER to make complex glycoproteins
 - c.) the trans region is rich in nucleoside diphosphatase, which is involved in recycling the nucleotide-sugars which are the substrates for glycoprotein glycosylation enzymes in the medial regions



Glycosylation of sugars on glycoproteins continues in the Golgi apparatus

- **N-linked glycoproteins** – sugars attached at the N of an asparagine amino acid
- Processing of N-linked sugars begins in the ER
 - Substrate is a sugar-nucleotide (activated sugar), which is transported into the Golgi from cytoplasm
 - Series of **glycosyltransferases**, which act in a rigidly determined sequence
- **O-linked glycoproteins** - sugars attached to the O of serine or threonine amino acids. This only occurs in Golgi



This figure depicts the removal and addition of sugars in a precise order (you do not need to know the details in this figure)

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Why are proteins glycosylated??

Glycosylation of proteins

- makes proteins more hydrophilic
- Allows them to bind to the extracellular matrix
- reduces their susceptibility to proteases (partly because carbohydrates are more rigid and thereby can provide physical barriers to the core of the protein)
- provides another level of structural complexity to proteins, which can:
- give the protein a new function
- provide more specificity in its interactions with other proteins

Where do we see an abundance of glycosylated proteins?

- On the cell's surface, where cell-to-cell interactions occur

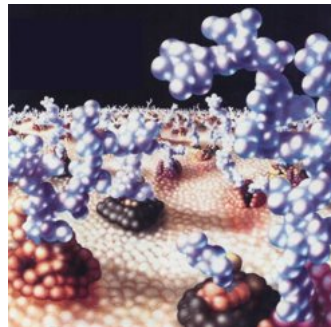
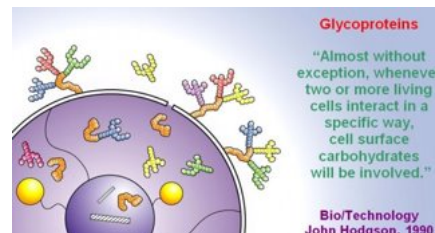
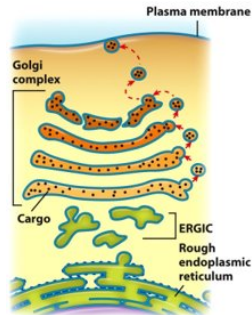


Image from:
<http://restorewellness.com/4/glyconutrients/what-are-glyconutrients-and-glyconutritionals/>



Exactly how proteins are passed through the Golgi is still under debate

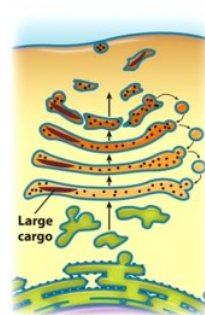


Vesicular transport model

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Cisternae are fixed
All transport is
done forward via
vesicles

Evidence: vesicles were found to move both forward and backward (anterograde and retrograde), so they could maintain enzyme differences.



Cisternal maturation model

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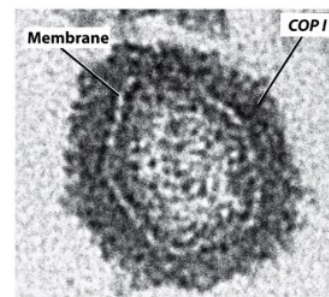
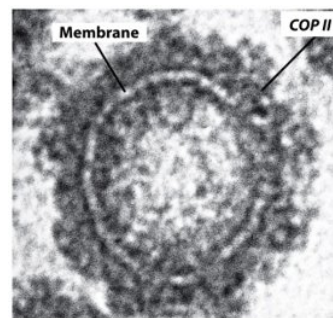
- The cisternae are what moves forward (they 'mature' from one form to the other)
- Vesicles carry cisternae resident enzymes *backwards* to maintain Golgi sidedness

Evidence: there are some materials, including large molecules that are never seen in the vesicles.

<https://www.youtube.com/watch?v=GnlmWUm1Xmk>

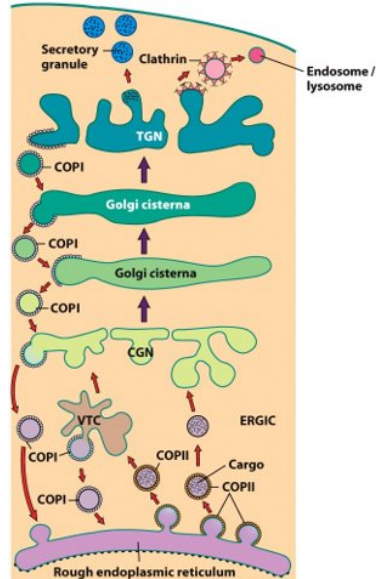
There are three main types of vesicles in the endomembrane system

- Materials are carried between compartment using **coated vesicles**.
- Protein coats have two distinct functions:
 - **Cause the membrane to curve and form a vesicle.**
 - **Select the components to be carried by vesicle.**
- Three different types of coated vesicles:
 - COPI
 - COPII
 - Clathrin-coated



20 nm

These three types operate in different areas of the endomembrane system



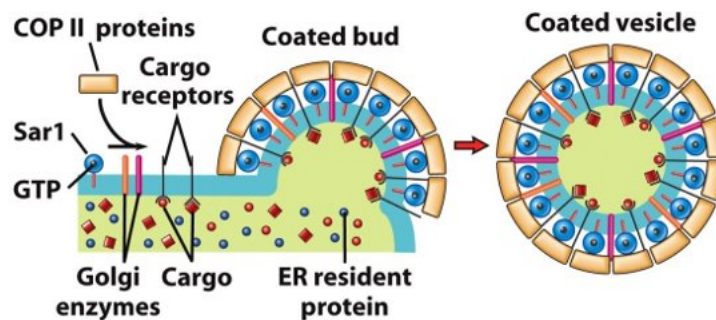
• **COPII-coated vesicles** – move materials from the ER “forward” to the ERGIC and Golgi complex.

• **COPI-coated vesicles** – move materials from ERGIC and Golgi “backward” to ER, or from the *trans* Golgi to the *cis* Golgi cisternae.

• **Clathrin-coated vesicles** move materials from the TGN to endosomes, lysosomes, and plant vacuoles.

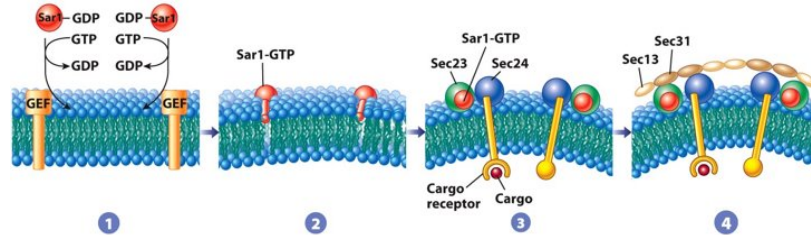
ERGIC = ‘ER Golgi Intermediate Compartment’

COPII coated vesicles transport cargo from the RER to the Golgi complex



- Cargo receptors bind proteins in the ER lumen
- Integral membrane proteins to be recruited are recognized by unique motifs on their cytosolic tail
- A small G protein called *Sar1* plays a regulatory role in vesicle assembly (next slide)

Steps in assembling a COPII vesicle:



Step 1: Sar1 recruited to the ER by GEF (guanine exchange factor) and exchanges GDP for GTP.

Step 2: Sar1 enters the ER bilayer through conformational changes and bends the bilayer.

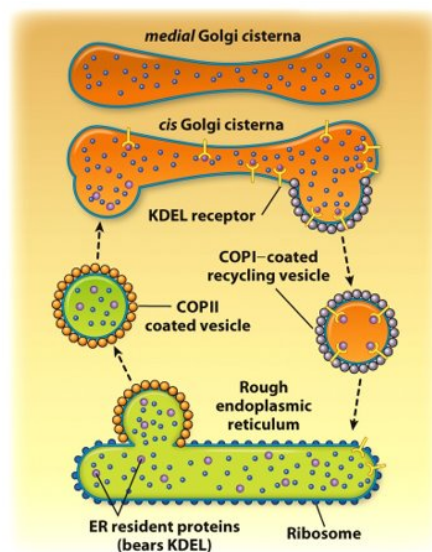
Step 3: Sar1 recruits Sec23 and Sec24 (COPII polypeptides). Cargo accumulates in the vesicle via interactions with Sec24 and cargo receptors.

Step 4: COPII coat recruits Sec13 and 31 and help to support the outer protein coat of the vesicle (protein scaffold).

What causes vesicle to disassemble before fusion with target membrane?

Hydrolysis of GTP on Sar1 disassembles the COPII protein coat.

COPI vesicles transport proteins in a retrograde (backward) direction



- Adenosylation ribose factor 1 (ARF1, a G protein, similar to Sar1), is required for vesicle transfer between cisternae.
- COPI vesicles were first discovered by treating cells with a GTP analog that cannot be hydrolyzed.
- ER resident proteins have a C-terminal KDEL (lys-asn-glu-leu) sequence. If they escape to the Golgi, KDEL receptors recognize them and package them into COPI vesicles to transport back to the RER.
- COPI vesicles also play a role in keeping the proper enzymes in the Golgi cisternae by transporting them backwards as the cisternae mature (see slide 8).

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Clathrin-coated vesicles transport of materials out of the Golgi

The best understood post-Golgi trafficking is how vesicles targeted to the lysosome get made and transported:

Step 1: mannose residues of the lysosomal enzymes are phosphorylated in the Golgi.

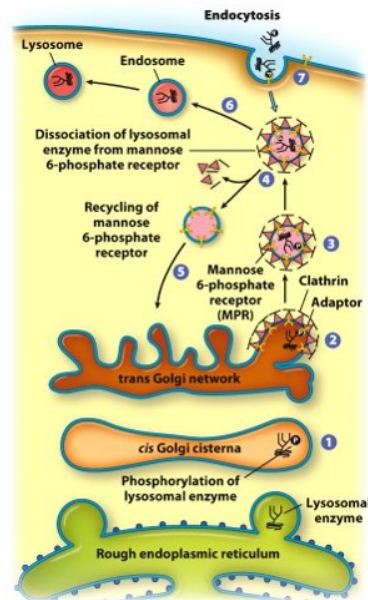
Step 2: selectively incorporated into clathrin-coated vesicles in the TGN by M6P receptors

Step 3: MPRs also interact with adapter proteins (next slide)

Step 4: MPRs separate from enzymes, the enzymes are delivered to the endosome and eventually the lysosome.

Step 5: MPRs are returned to Golgi complex for reuse

Step 6: MPRs are also found in the PM where they capture escaped lysosomal enzymes to return to the lysosome.

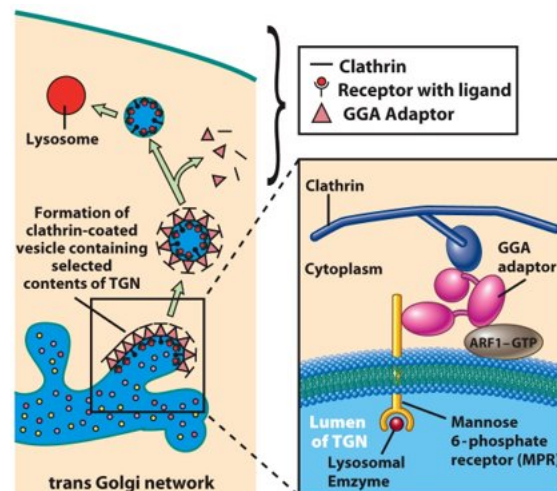


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Transport of materials out of the trans Golgi network is via clathrin-coated vesicles

Clathrin vesicle coats contain:

1. Outer lattice composed of clathrin.
 2. Inner shell composed of protein adaptors called **GGAs**.
- Adaptor protein = binds one or more other proteins in a complex
 - GGAs are involved in vesicle formation and bind to the clathrin molecules.
 - Also binds to ARF1 and MPR
 - Vesicle production requires the activity of ARF1
 - Once the vesicle has budded from the TGN, the clathrin coat molecule



The fusion of a vesicle to the target membrane is regulated by Rabs and SNAREs

1. Vesicles move toward the specific target compartment via the cytoskeleton, pulled by motor proteins.

2. Tethering vesicles to the target compartment is mediated by G proteins called **Rabs** (60 in humans).

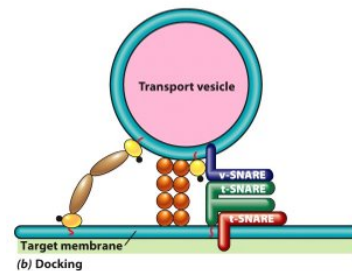
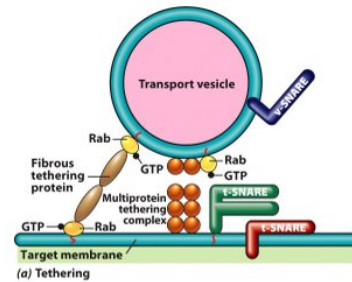
- Different Rabs are on different membrane surfaces!

3. Docking vesicles to the target compartment.

- Protein that engage in these interactions are **SNAREs** (35 in humans).
- SNAREs can be divided into: **v-SNAREs** (incorporated into vesicles) and **t-SNAREs** (located in the target).

4. Fusion between vesicle and target membranes.

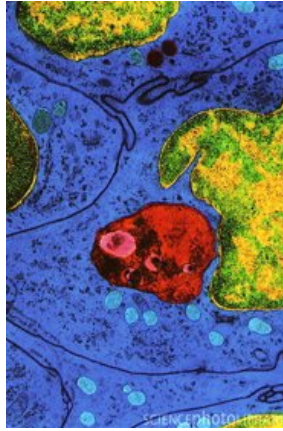
Interactions between t- and v-SNAREs pull the two lipid bilayers together. Not sufficient for fusion!



What you should know from this lecture

- Parts of the Golgi apparatus and their functions
- The differences between O- and N-linked sugars
- Why are proteins glycosylated?
- How do materials move through the Golgi?
- How are vesicles formed?
- How are proteins selectively packaged into vesicles?
- What components are required for COP II vesicles?
- What determines which proteins enter into COP I vesicles?
- How do enzymes targeted to the lysosome get loaded into clathrin-coated vesicles?
- How (in general) do vesicles dock with target membranes?

Lysosomes, Endosomes and Endocytosis



Suggested readings: Karp 9th ed. Chapter 8

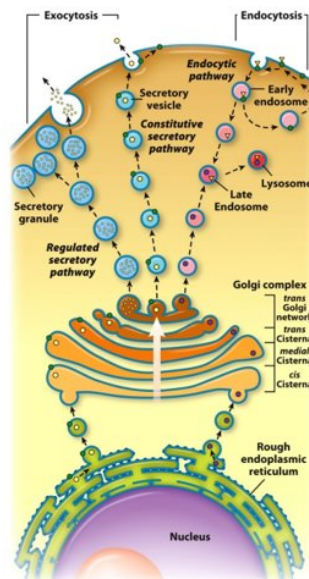
Colour TEM of secondary lysosome
<http://www.sciencephoto.com/media/214856/enlarge>

- 8.5 Types of vesicle transport
- 8.6 Lysosomes
- 8.8 Endocytic pathway

Recall the endomembrane system

So far we've discussed

- How proteins are made in the RER
- How proteins are passed through the Golgi apparatus and modified
- How vesicles are formed on the RER and Golgi to shuttle proteins between the compartments and to lysosomes



Today we're talking about this, the endosome pathway

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Lysosomes are the cells' 'digestive organelle'

- Lysosomes contain ~ 50 different **acid hydrolases** which can digest every type of biological molecule.
- These enzymes are made in the RER, tagged by phosphorylation in the golgi, recognized by M6PR and transported to lysosomes via clathrin-coated vesicles. (which we discussed last class)
- Lysosomes have a low internal pH. These enzymes have a low pH optimum.
- The low pH of the lysosome is maintained by a proton pump (H^+ -ATPase) found in the lysosomal membrane

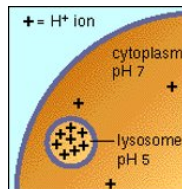


TABLE 8.1 A Sampling of Lysosomal Enzymes

Enzyme	Substrate
Phosphatases	
Acid phosphatase	Phosphomonoesters
Acid phosphodiesterase	Phosphodiester
Nucleases	
Acid ribonuclease	RNA
Acid deoxyribonuclease	DNA
Proteases	
Cathepsin	Proteins
Collagenase	Collagen
GAG-hydrolyzing enzymes	
Iduronate sulfatase	Dermatan sulfate
β -Galactosidase	Keratan sulfate
Heparan <i>N</i> -sulfatase	Heparan sulfate
α -N-Acetylglucosaminidase	Heparan sulfate
Polysaccharidases and oligosaccharidases	
α -Glucosidase	Glycogen
Fucosidase	Fucosyloligosaccharides
α -Mannosidase	Mannosyloligosaccharides
Sialidase	Sialyloligosaccharides
Sphingolipid hydrolyzing enzymes	
Ceramidase	Ceramide
Glucocerebrosidase	Glucosylceramide
β -Hexosaminidase	G_{M2} ganglioside
Arylsulfatase A	Galactosylsulfatide
Lipid hydrolyzing enzymes	
Acid lipase	Triacylglycerols
Phospholipase	Phospholipids

Autophagy requires the lysosome

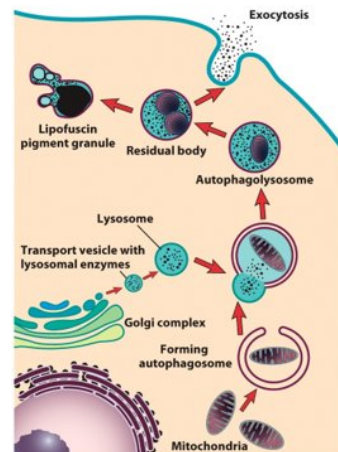
Autophagy ('self eating') is the digestion of intracellular components that have damage or no longer needed

- Autophagosome** = organelle to be digested + surrounding double layer membrane
- Autophagolysosome** = autophagosome fused with a lysosome for breakdown... most components are released and reused

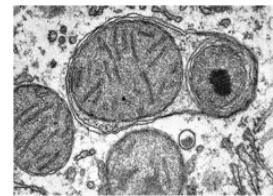
Autophagolysosomes become residual bodies. Unused waste material is either ejected from cell by exocytosis or maintained as a lipofuscin pigment granule.

In a liver cell, 1 mitochondria is degraded every 10 minutes!

Under starvation, autophagy rate increases.



EM of a autophagosome consisting of a mitochondria and a peroxisome surrounded by a membrane.



Examples of lysosome function in development

Autolysis (Cellular self-destruction)

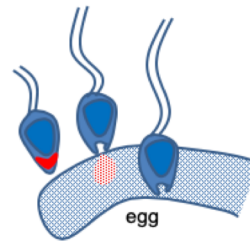
- rupture of lysosome within cytoplasm kills the cell.
- part of programmed cell death during development.
- example is selective removal of cells leads to fingers and toes.



This doesn't occur in 1:2500 of us!

Extracellular digestion

- in rare cases, lysosomes may discharge their enzymes to the outside of cell by exocytosis.
- e.g. in sperm at fertilization



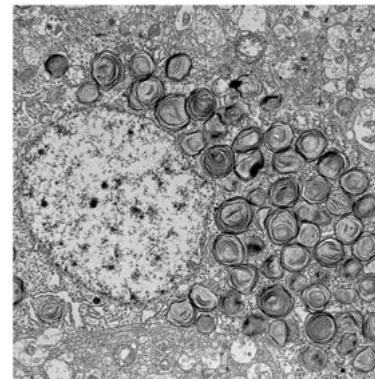
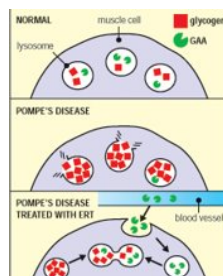
Lysosome malfunction can cause disease

Lysosomes can lack one of the hydrolytic enzymes (due to mutation in the encoding gene)

- these defective lysosomes are the cause of "lysosomal storage diseases"
- ~ 40 different lysosomal storage diseases
- Certain substances can't be broken down, and thus accumulate and cause cellular damage
- e.g. Tay-Sachs disease
 - accumulation of ganglioside (kind of glycolipid) in brains of afflicted children.
 - mental retardation and death by age 3

Enzyme replacement therapy:

Intravenously injected enzyme may be taken up by cells in vesicles, which then can fuse with lysosomes to replace missing enzyme. This won't work in LSDs associated with the brain, because enzymes can't cross the brain blood barrier.

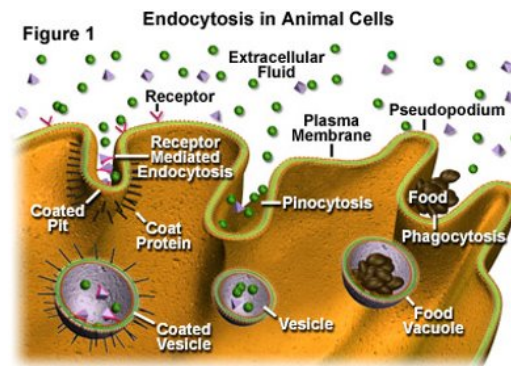


EM of neuron of a person with Tay-Sachs. Note the large number of lysosomes with undigested glycolipid.

Endocytosis is the cellular uptake of particles and macromolecules

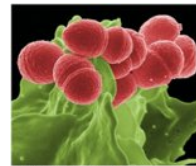
1. **Phagocytosis** - uptake of particulate matter
2. **Pinocytosis** - nonspecific uptake of extracellular fluids and material (aka bulk phase endocytosis). Often a continuous process.
3. **Receptor mediated endocytosis** – uptake of specific molecules following their binding to receptors

Note that plasma membrane lipids get taken up into the cell by all types of endocytosis!



Phagocytosis is the uptake of large material

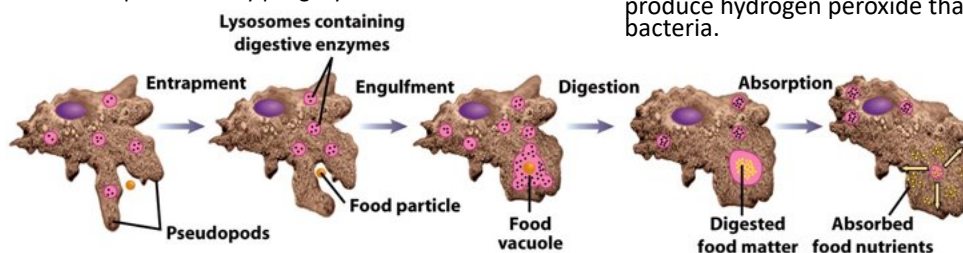
- The plasma membrane takes up a particle and pinches off to form a *phagosome*.
- The phagosome fuses with a lysosome and the material is digested within the phagolysosome.



Macrophages and neutrophils are 'professional phagocytes' and have lysosomal mechanisms for killing ingested microorganisms:

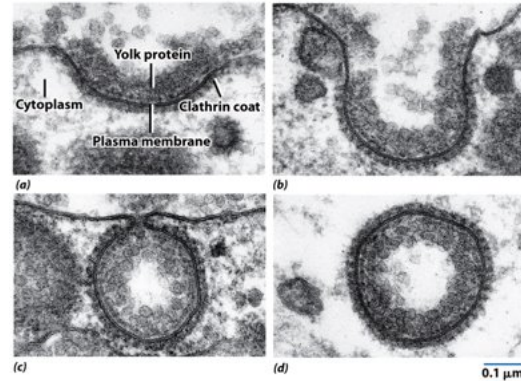
- 1. contain lysozyme, an enzyme that degrades bacterial cell walls.
- 2. acidic pH kills some bacteria.
- 3. oxidases on inner surface of phagosome produce hydrogen peroxide that kills some bacteria.

Amoebas uptake food by phagocytosis...



Receptor mediated endocytosis (RME)

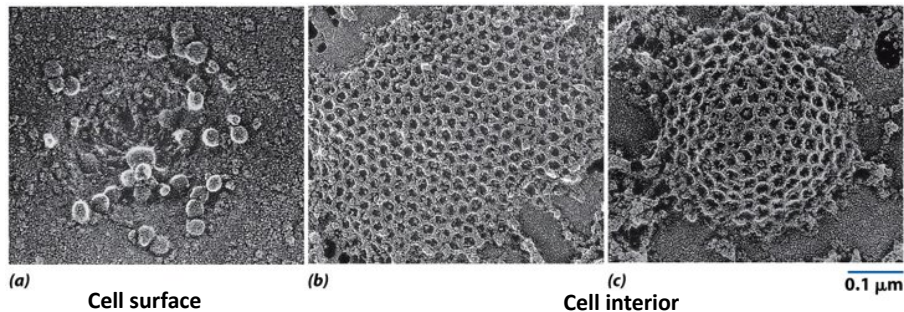
- Selective and efficient uptake of substances like hormones, growth factors, enzymes and nutrients.
- Substances that enter the cell through RME become bound to receptors that are concentrated in *coated pits* on the plasma membrane.
- Clathrin-coated regions invaginate into the cytoplasm and then pinch free of the plasma membrane to create a vesicle.



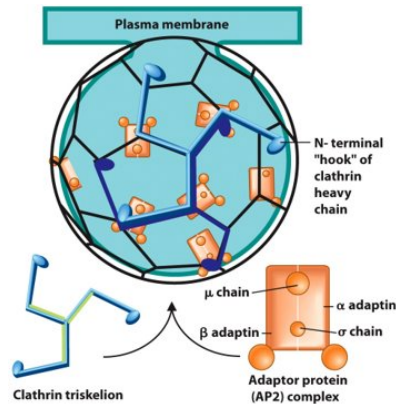
Uptake of yolk lipoprotein by chicken oocyte.
Cargo is located on the extracellular surface of the cell.

Coated pits are visible by EM

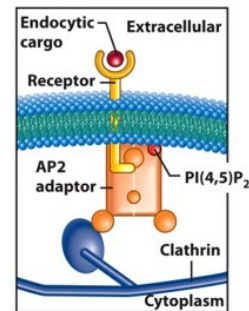
- Fibroblasts were treated with LDL cholesterol (a) – outside cell membrane
- When viewed from the cytoplasm, coated pits appear as polygons resembling a honeycomb (b,c)
- Geometric design is derived from structure of clathrin blocks.



Molecular organization of the coated vesicle

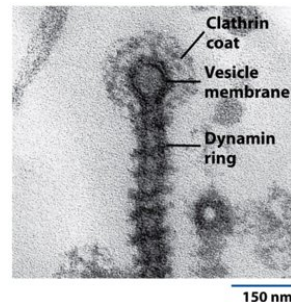
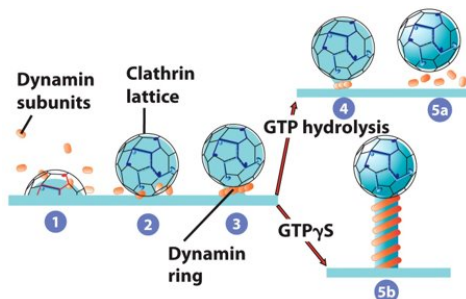


- AP2 adaptor buds from PM and incorporates into the vesicle.
- Contains multiple subunits.



- μ engages the cytoplasmic tails of PM receptors.
- β adaptin binds and recruits the clathrin molecules of the lattice.
- PI(4,5)P₂ (a modified phospholipid) facilitates the recruitment of AP2 adaptors to the PM.

Endocytic vesicles are pinched off by dynamin

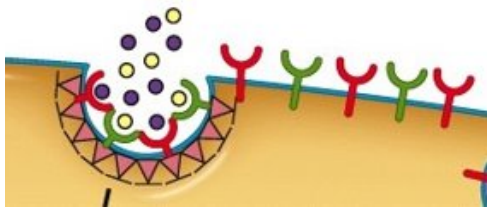


- Step 1: clathrin lattice of pit begins to form around the protruding vesicle.
- Step 2: the vesicle becomes attached to the PM by a stalk.
- Step 3: dynamin subunits polymerize to form a ring (dynamin ring).
- Step 4: hydrolysis of GTP leads to conformation changes in the ring structure.
- Step 5a: fission of the coated vesicle from the PM and hydrolysis of the ring.
- Step 5b: vesicle budding + GTP γ S (a non-hydrolysable GTP analog) induces a long dynamin collar (not normal!!).

Note that both dynamin and G-proteins are GTPases, but dynamin is not a G protein!

http://www.endocytosis.org/Dynamin/Dynamin_pinchase.swf

Two different types of receptors are internalized via endocytosis



Red = housekeeping receptors
Green = signaling receptors

Housekeeping receptors:

- Bind materials that are to be taken up and used by the cell e.g. cholesterol
- These receptors are recycled back to the PM

Signalling receptors:

- Receptors in the plasma membrane that the cell uses to respond to external stimuli (e.g. hormones, growth factors)
- After stimulation, the cell often attenuates the signal by internalizing the receptors via endocytosis
- Signalling receptors to be internalized are tagged with a single ubiquitin
- Receptors are ultimately destroyed in the lysosome

Internalized vesicles enter the endocytic pathway

1. They first are delivered to an early endosome called the **sorting compartment**.

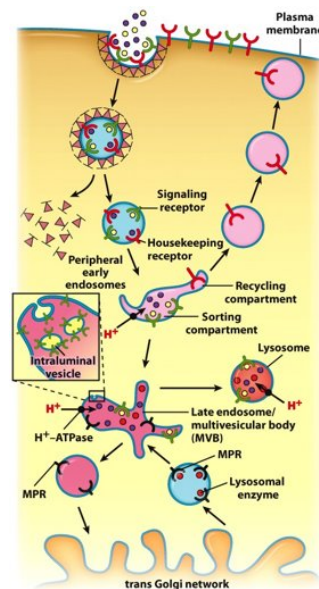
- Lower pH in these compartments make the house keeping receptors release their cargo
- The receptors are recycled back to the plasma membrane.

2. Early endosomes mature into late endosomes, pH keeps increasing

3. Signaling receptors get incorporated into *internal* vesicles in the late endosome, forming **multivesicular bodies**

4. Material is transported from the MVB to the lysosome for degradation.

- Some hypothesize that lysosomes can fuse with MBVs



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What you should know from this lecture

- The contents and internal pH of lysosomes
- How lysosomal enzymes are transferred to the lysosomes (i.e. role of MPRs and clathrin)
- Functions of lysosomes – heterophagy, autophagy, autolysis, extracellular digestion
- How lysosomes can fail to perform their functions
- Types of endocytosis
- Endosomes – early and late – how they arise
- How endosomes can handle receptors and their ligands