



Lecture 2: Golgi apparatus and vesicular transport

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Functions of the Golgi apparatus

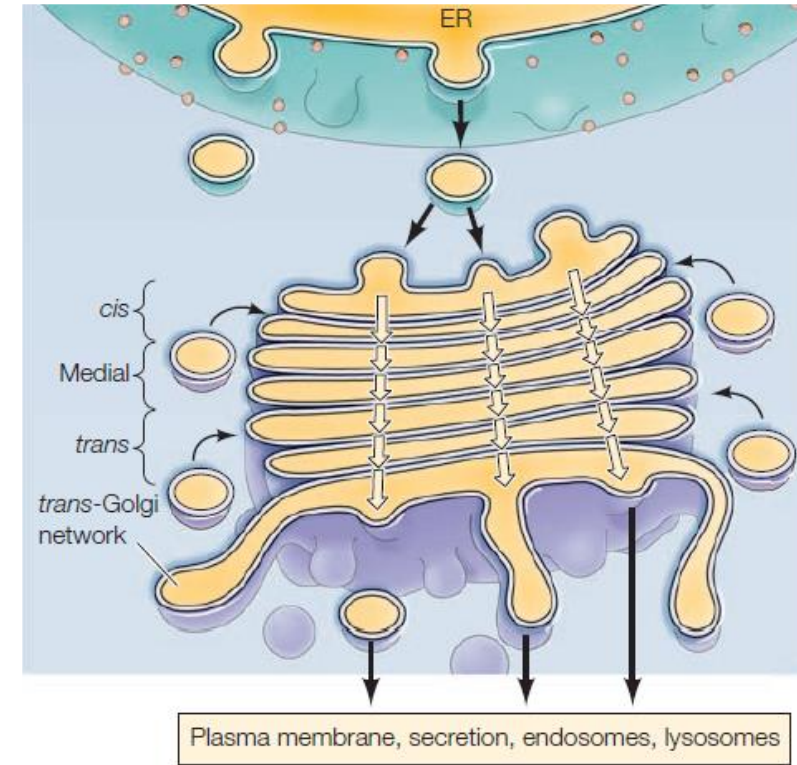
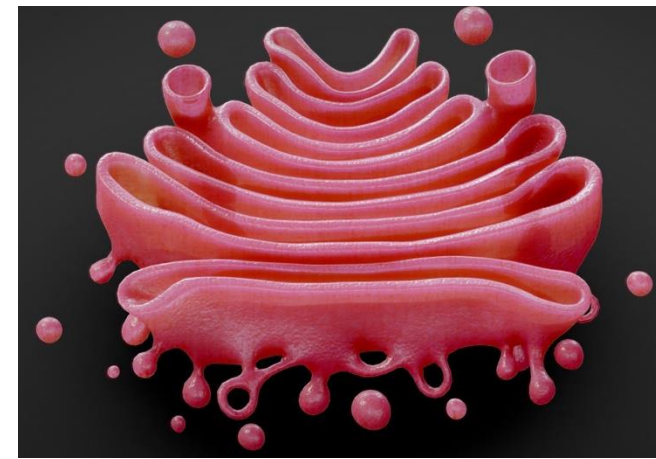


- Further protein processing and modification
- Synthesis of glycolipids and sphingomyelin
- Protein sorting

Structure of the Golgi

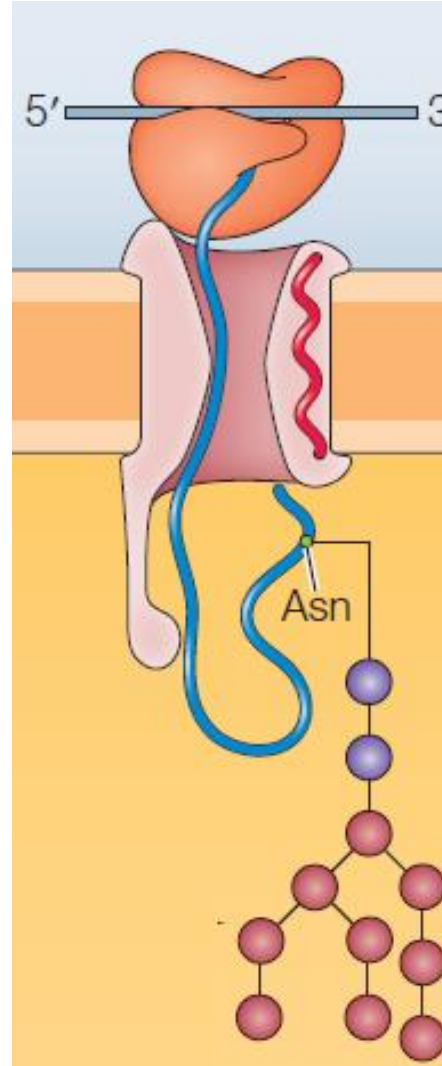


- The Golgi apparatus consists of a stack of flattened sacs (cisternae) of four regions: *cis*, medial, and *trans* compartments and the *trans*-Golgi network.
- Proteins are carried through the Golgi apparatus in the *cis-to-trans* direction.
- Transport vesicles carry the Golgi proteins back to earlier compartments for reuse.

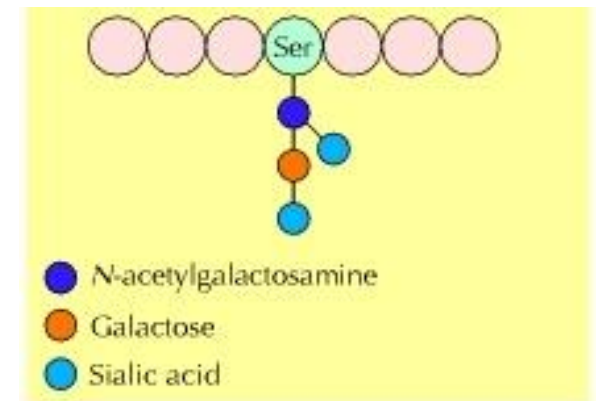


Processing of N-linked oligosaccharides in Golgi

The *N*-linked oligosaccharides, which are added to asparagine residues of glycoproteins in the ER and transported from the ER, are further modified enzymatically in the Golgi.



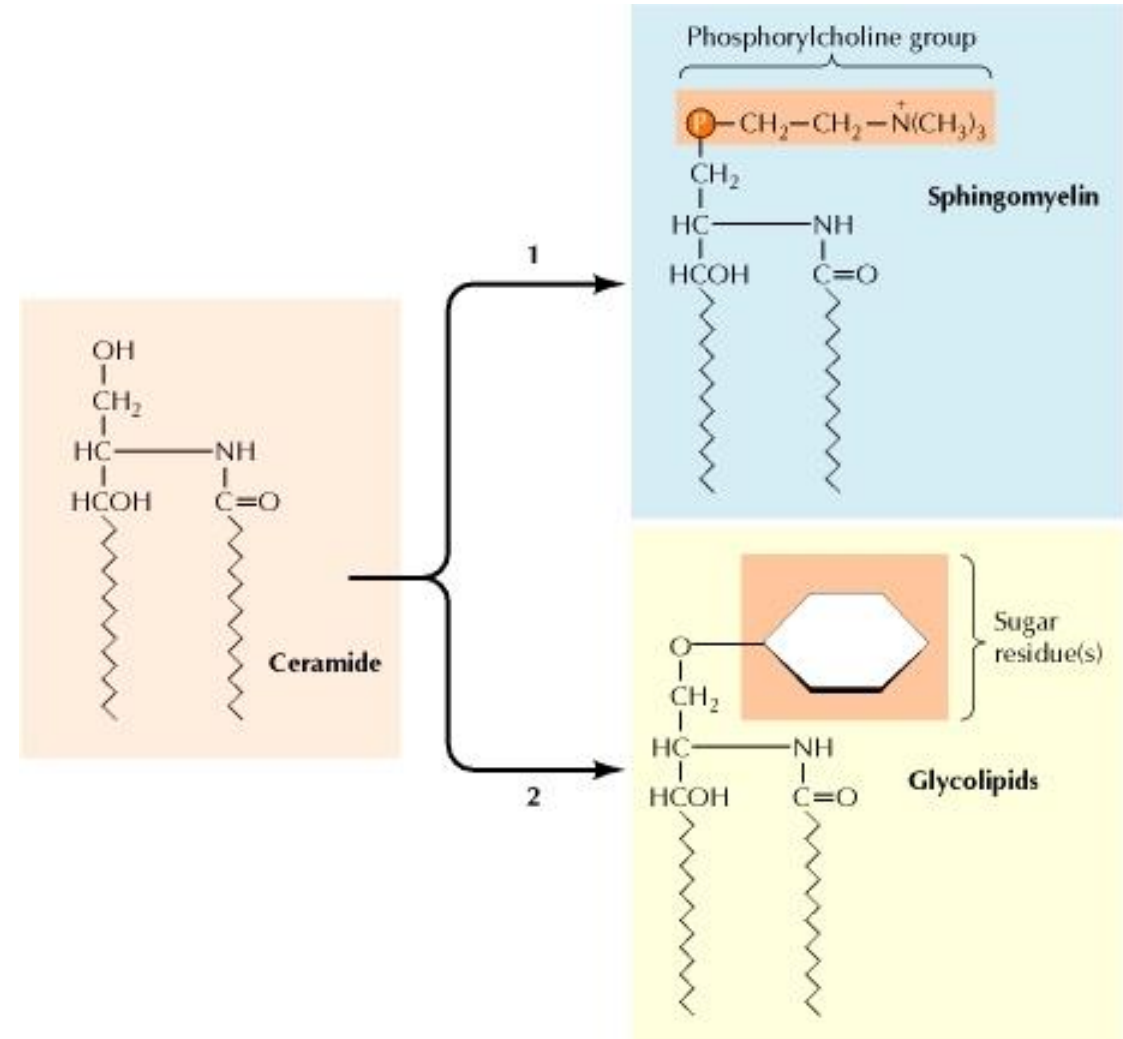
Proteins can also be modified by the addition of carbohydrates to the hydroxyl side chains of serine and threonine residues, hence called O-linked sugars.



Lipid and Polysaccharide Metabolism in the Golgi



- The glycerol phospholipids, cholesterol, and ceramide are synthesized in the ER.
- Ceramide is then converted either to sphingomyelin (a phospholipid) or to glycolipids in the Golgi apparatus.

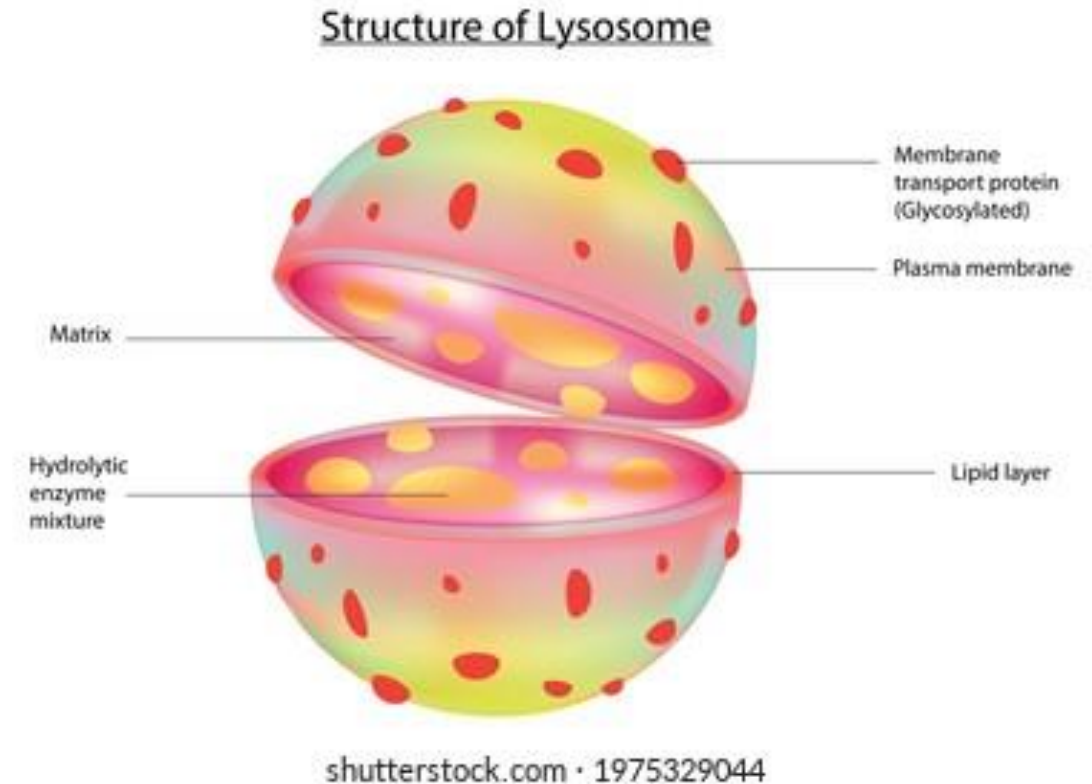


Lysosomes

Structure

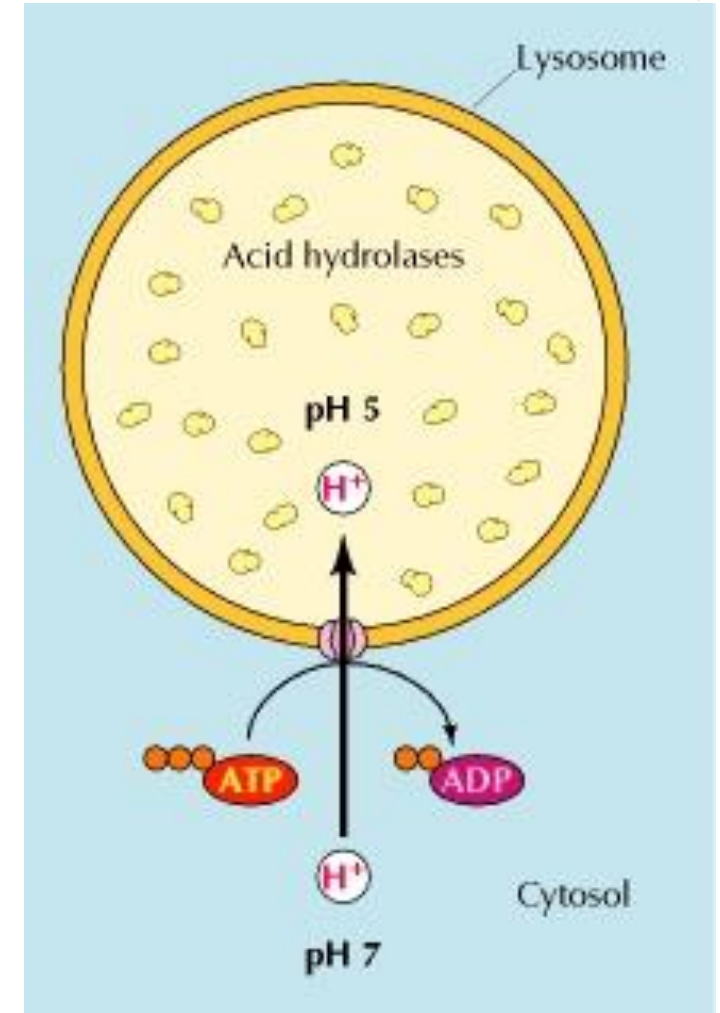


- Lysosomes are membrane-enclosed organelles that contain various hydrolase enzymes that break down all types of biological macromolecules.
- Lysosomes degrade material taken up from outside and inside the cell.

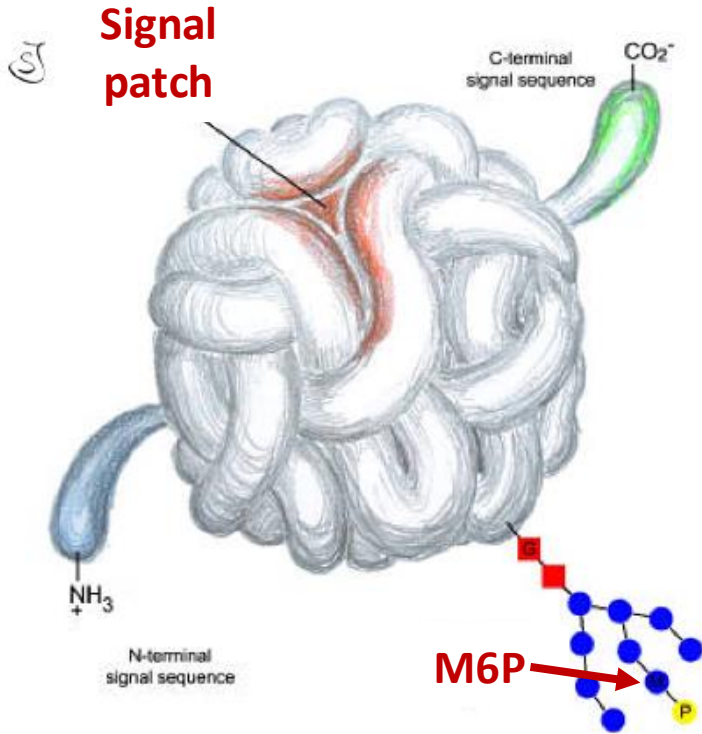


Lysosomal enzymes

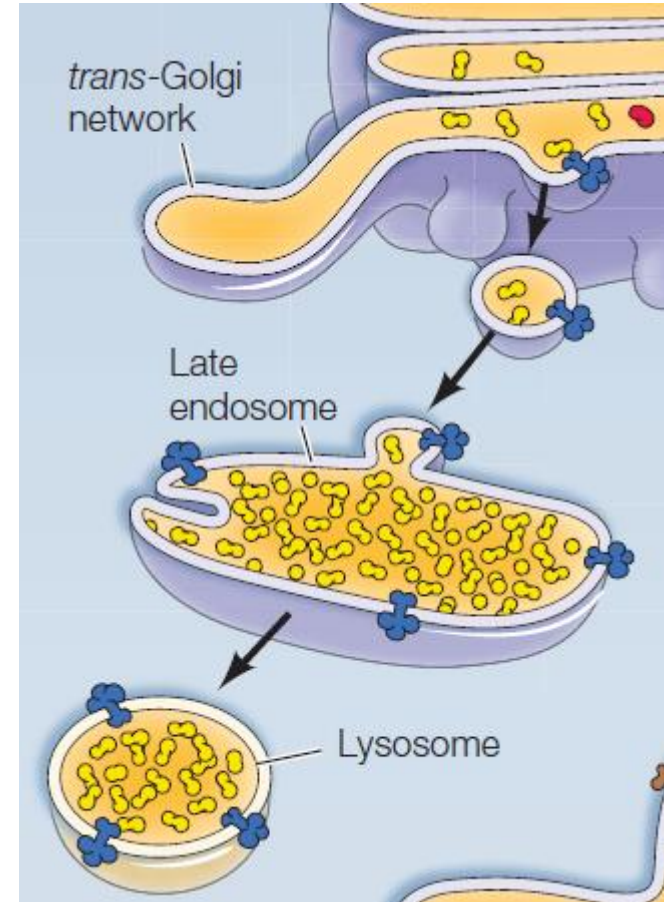
- Lysosomes contain ~60 different acid hydrolases.
- The enzymes are active at the acidic pH (about 5) that is maintained within lysosomes.
- Levels of cell protection from these hydrolases:
 - Containment
 - Inactive if released
- An ATP-dependent proton pump maintains the lysosomal pH.



Targeting of lysosomal proteins to the lysosomes



Proteins destined to lysosomes have a signal patch (a three-dimensional structural determinant), which is recognized by modifying enzymes that add mannose-6-phosphate to the proteins.

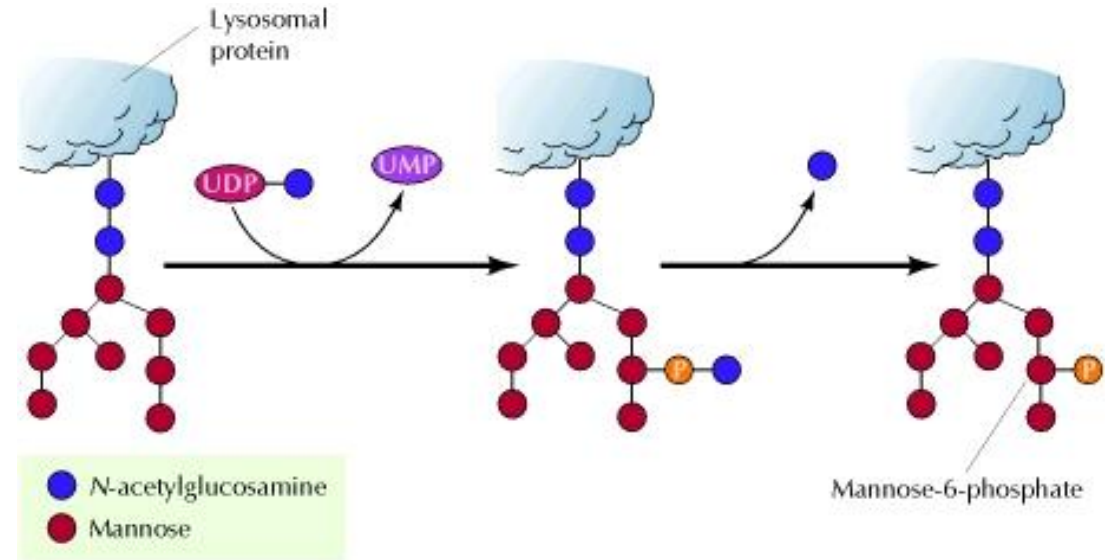


Luminal lysosomal proteins bind to a mannose-6-phosphate receptor in the Golgi and are transported to vesicles known as the late endosome, which mature into lysosomes.

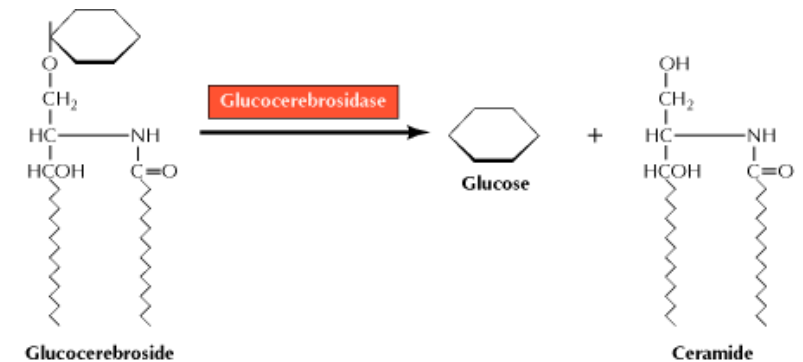
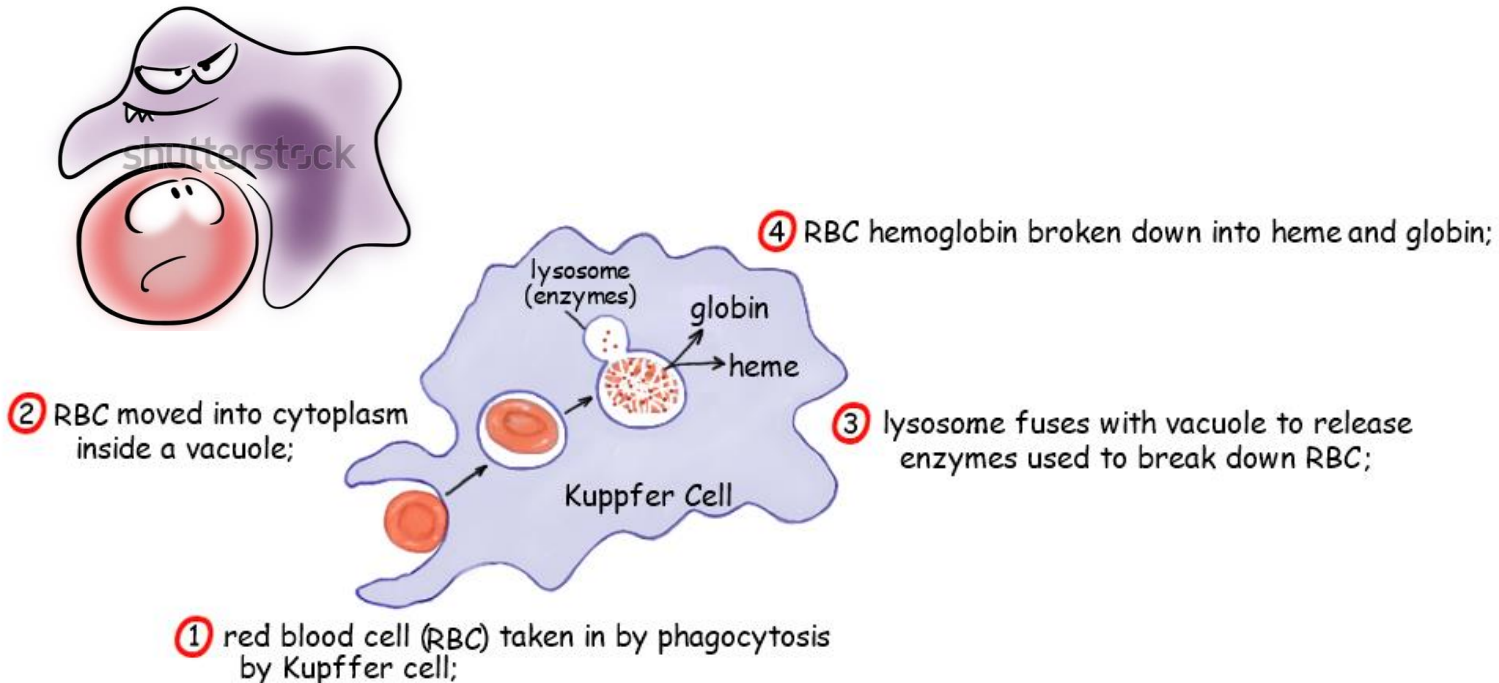
I-cell disease

also called mucopolidosis IIA, or mucopolidosis II alpha/beta: ML-II α / β

- Defective targeting of lysosomal enzymes from Golgi to the lysosomes
- A deficiency in the tagging enzyme that phosphorylates mannose.
- Features: severe psychomotor retardation that rapidly progresses leading to death between 5 and 8 years of age.



- Glucocerebroside is a glycosphingolipid (a monosaccharide attached directly to a ceramide unit (a lipid))
- It is a byproduct of the normal recycling of red blood cells, which are phagocytosed (eaten up) by macrophages, degraded, and their contents recycled to make new cells.





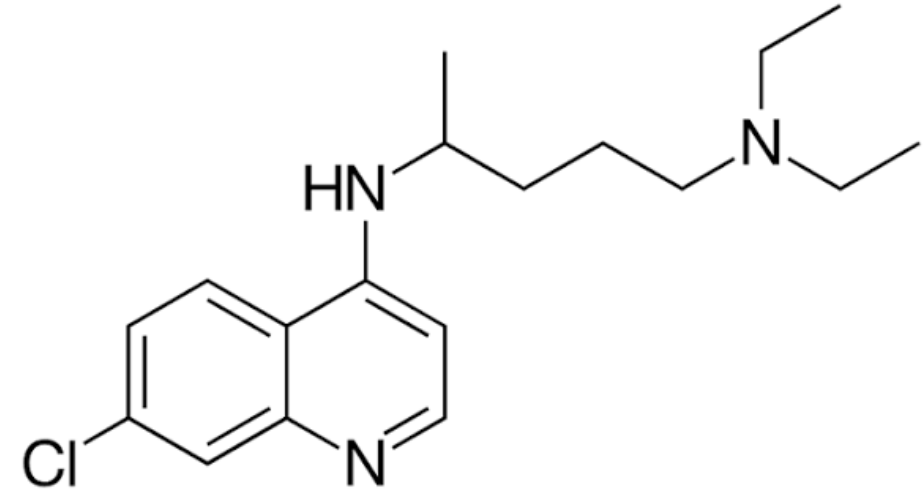
Lysosomal storage diseases

- Gaucher disease (glucocerebrosidase deficiency)
- Glycolipidoses (sphingolipidoses)
- Oligosaccharidoses
- Mucopolysaccharidoses: deficiencies in lysosomal hydrolases of glycosaminoglycans (heparan, keratan and dermatan sulfates, chondroitin sulfates.
 - They are chronic, progressively debilitating disorders that lead to severe psychomotor retardation and premature death.

Targeting malarial lysosomes



- Antimalarial drugs like chloroquine and pyronaridine act as weak bases that raise the acidic pH of the malaria parasite's digestive vacuoles.
- The pH elevation prevents the proper neutralization of the toxic free heme produced during hemoglobin breakdown and the parasite is effectively poisoned and killed by its own accumulated metabolic waste products.



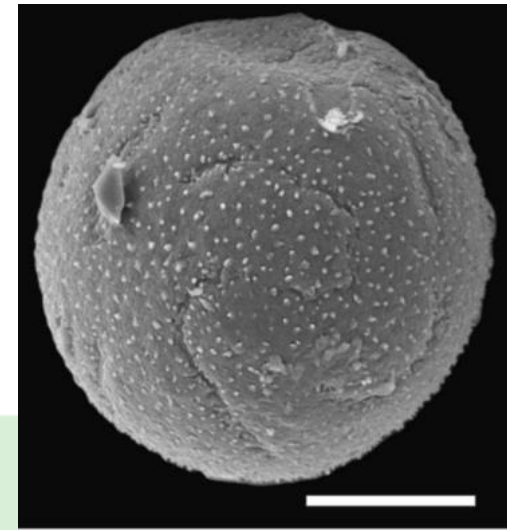
The general mechanism of vesicular transport



What are transport vesicles?



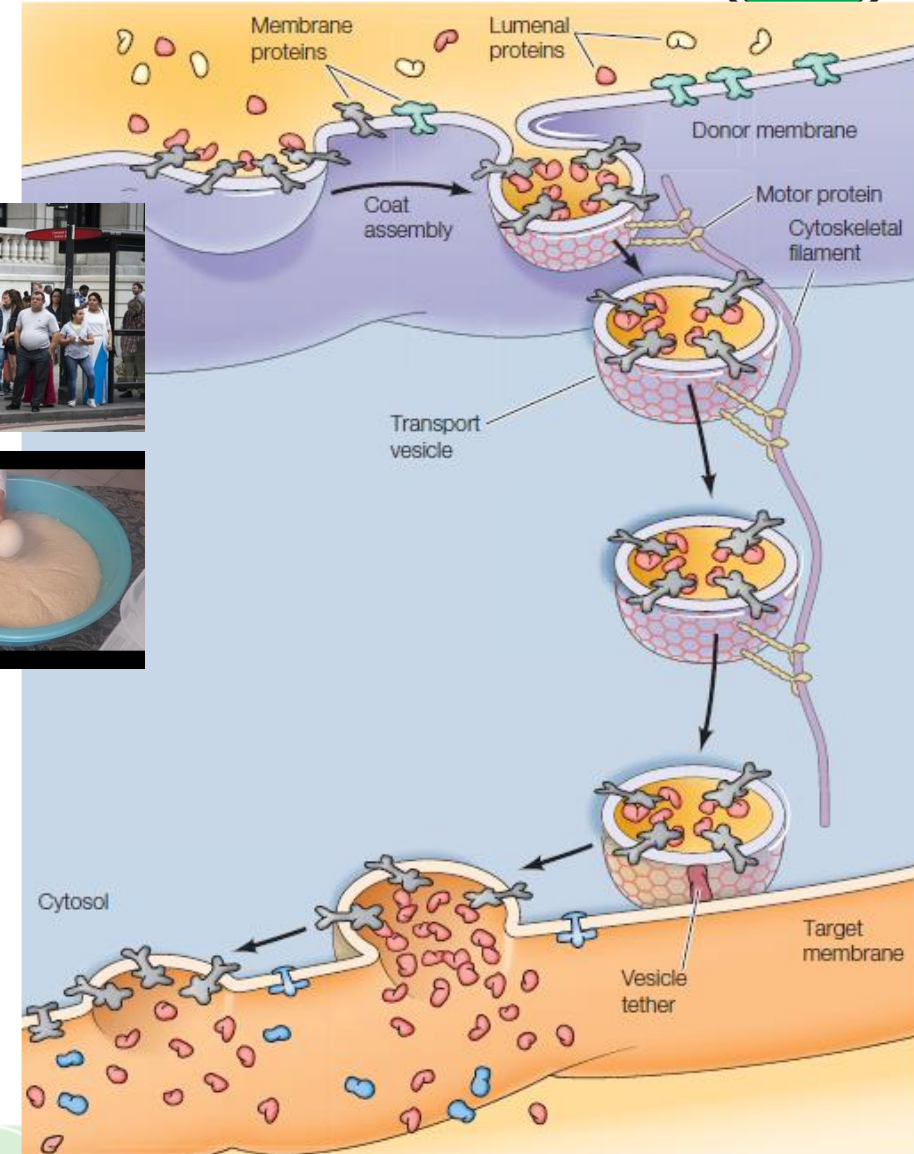
- Vesicular transport is the movement of molecules in bags (or sacs) called transport vesicles in and out of cells or within cells.
 - Examples: (1) the transport of materials taken up from outside the cells at the cell surface into them, or (2) the transport of lysosomal enzymes from the Golgi apparatus to the lysosomes.
- Vesicular transport is selective in terms of destination and packaging.



The general steps of vesicular transport



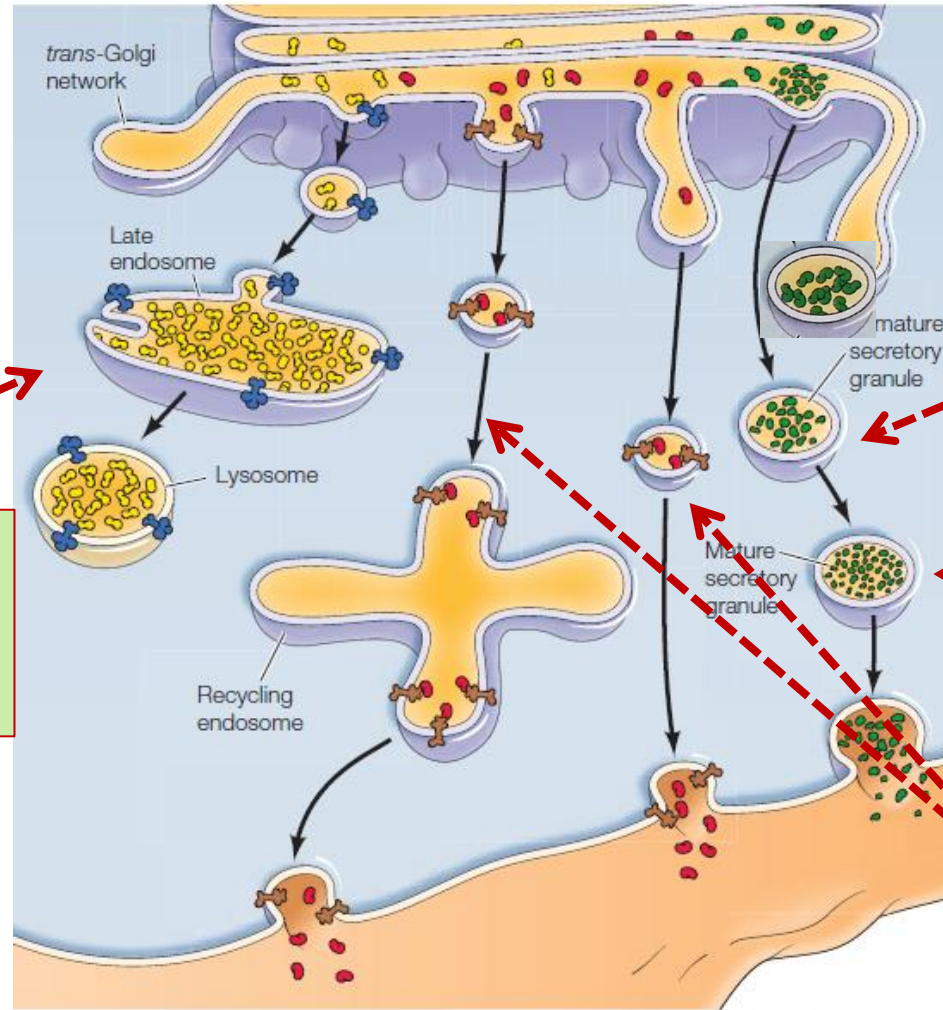
1. The molecules to be transported are aligned along or clustered in the membrane of the donor compartment.
2. A vesicle buds from the donor membrane.
3. The bud grows and ultimately pinches off the donor membrane, yielding a transport vesicle.
4. The vesicle is transported along cytoskeletal filaments to a target membrane.
5. The vesicle fuses with the target membrane, whereupon the transmembrane proteins are incorporated into that membrane and the soluble proteins are released.



The processes of vesicular transport



The secretory pathway (exocytosis)



Cytosis: a cellular process of moving material across membranes

Protein processing in Immature secretory vesicles

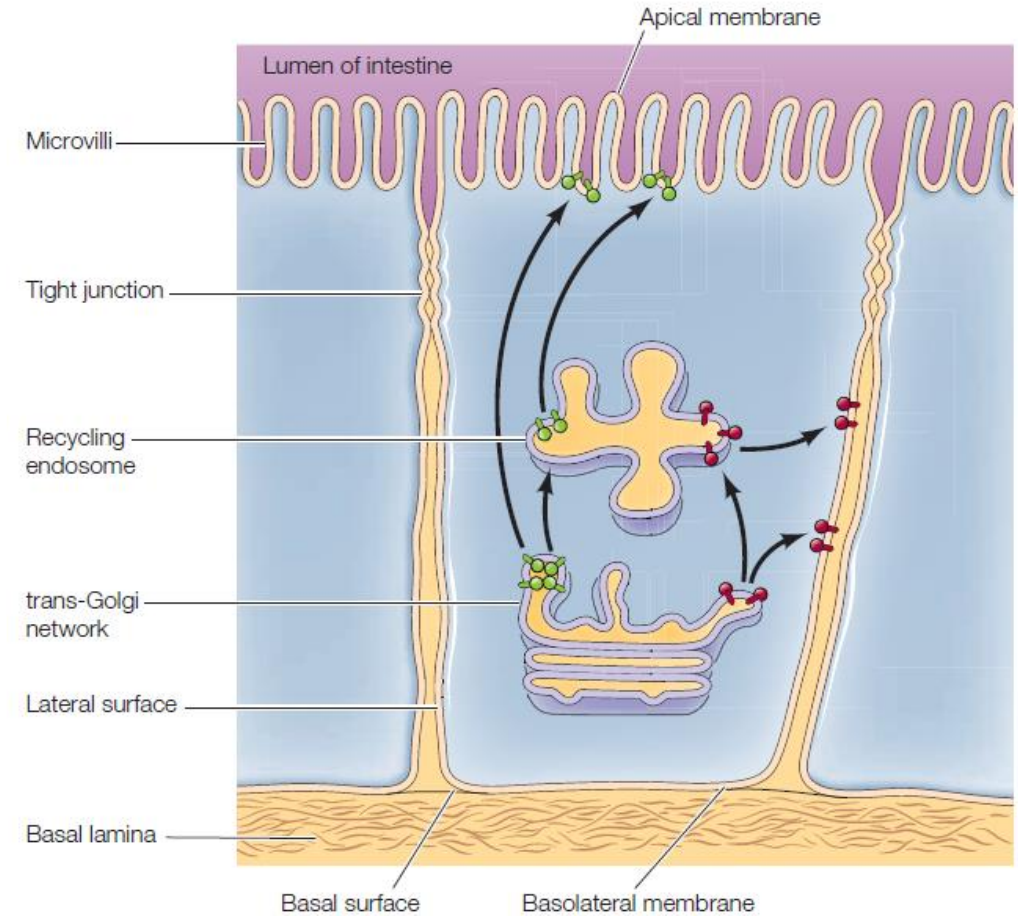
Already discussed: Proteins can be targeted to late endosomes, which develop into lysosomes

2. Regulated, signal-stimulated secretion of processed proteins from specialized vesicles (e.g., neurotransmitters and digestive enzymes)

1. Continuous, unregulated secretion directly or via recycling endosomes, which also act to recycle endocytosed proteins to the plasma membrane

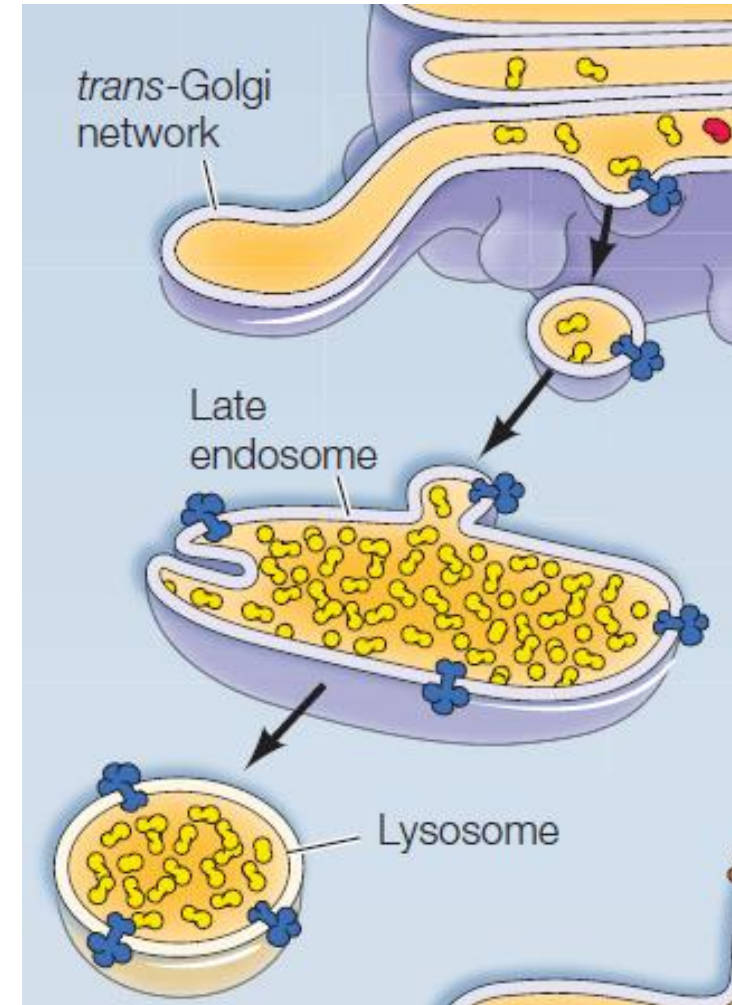
Transport to the plasma membrane of polarized epithelial cells

- Proteins are selectively packaged into transport vesicles from the trans-Golgi or recycling endosomes.
- Targeting is determined by special sequences (basolateral) or GPI sugar modification (apical).



From the Golgi to the lysosomes

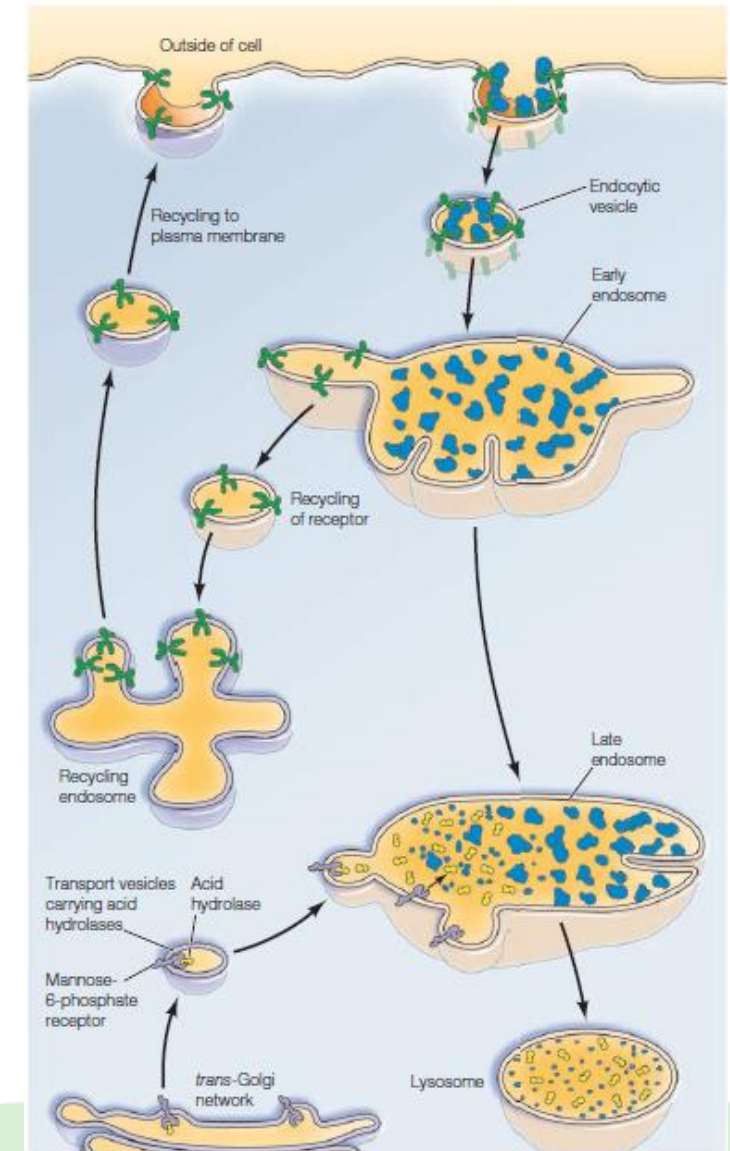
- Transport vesicles carrying acid hydrolases from the trans-Golgi network fuse with late endosomes, which mature into lysosomes.
- Remember the role of mannose-6-phosphate receptor



Endocytosis (from outside the cells to inside)



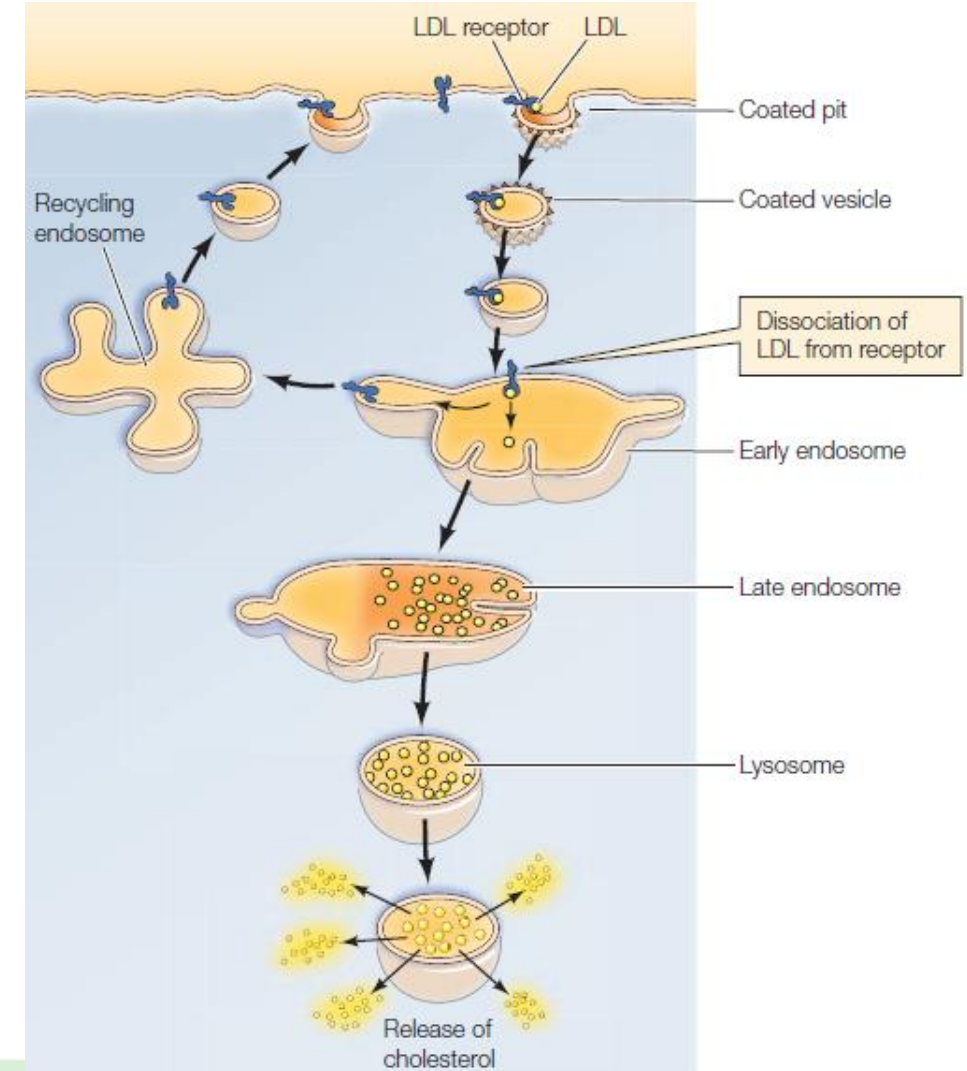
- Molecules are taken up from outside the cell in endocytic vesicles, which fuse with early endosomes.
- Early endosomes mature into late endosomes.
- Transport vesicles carrying acid hydrolases from the Golgi fuse with late endosomes, which mature into lysosomes.
- *Note: early endosomes have a pH of around 6.5, late endosomes around 5.5, and lysosomes a very acidic pH of about 5.0.*



Clathrin-dependent endocytosis

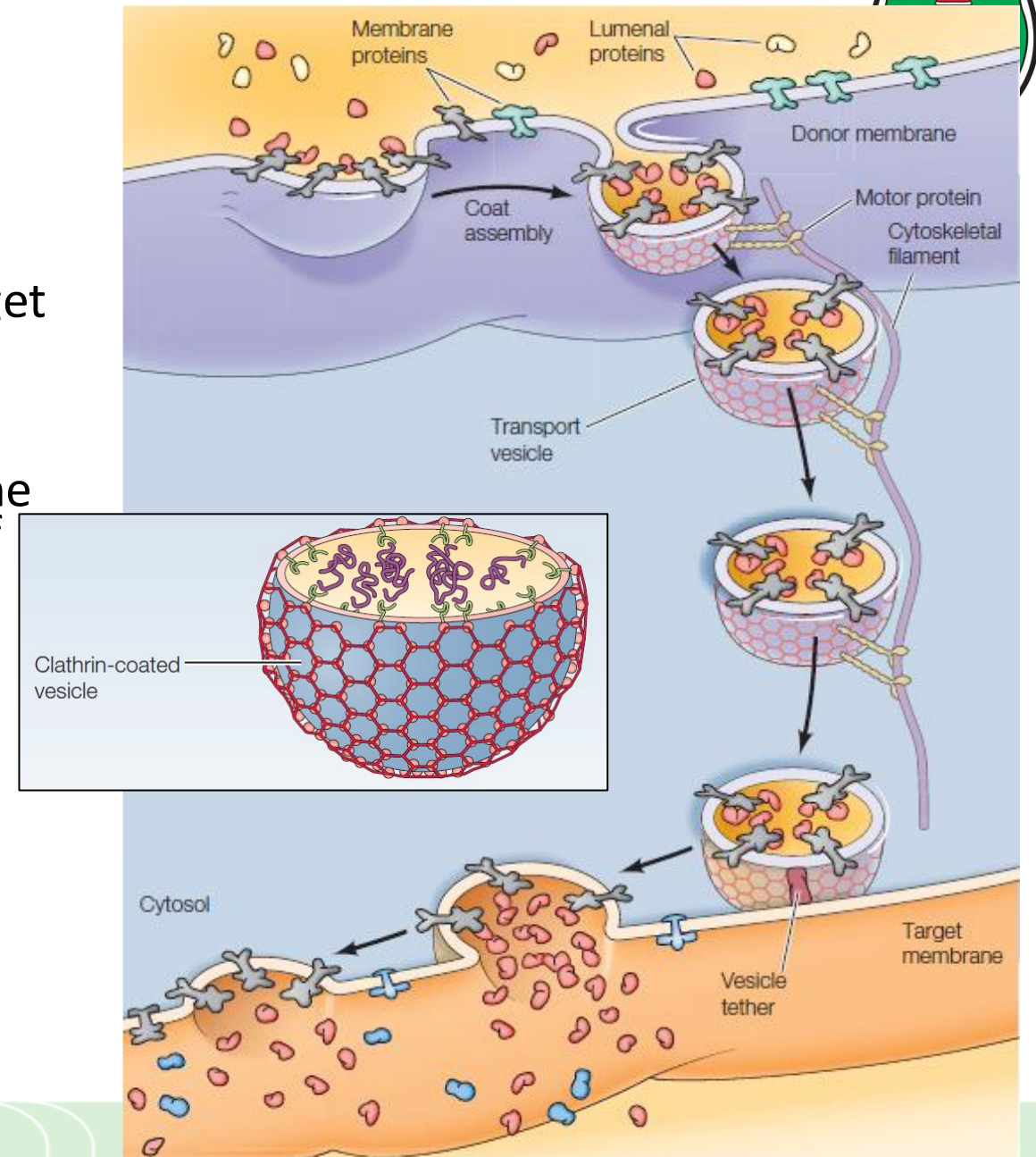
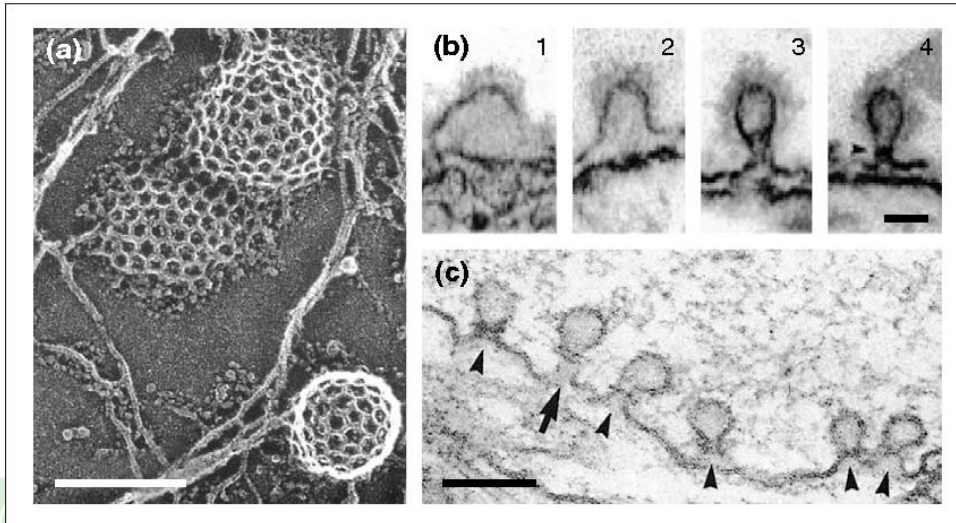
Receptor-mediated endocytosis

- Ligands bind to their receptors stimulating endocytosis, hence it is called receptor-mediated endocytosis.
- In early endosomes, the acidic pH causes the release of ligands from their receptors.
- **Membrane receptors are recycled via recycling endosomes and early endosomes mature into late endosomes.**
- Example: removal of plasma cholesterol by low-density lipoprotein (LDL) receptor



What is clathrin?

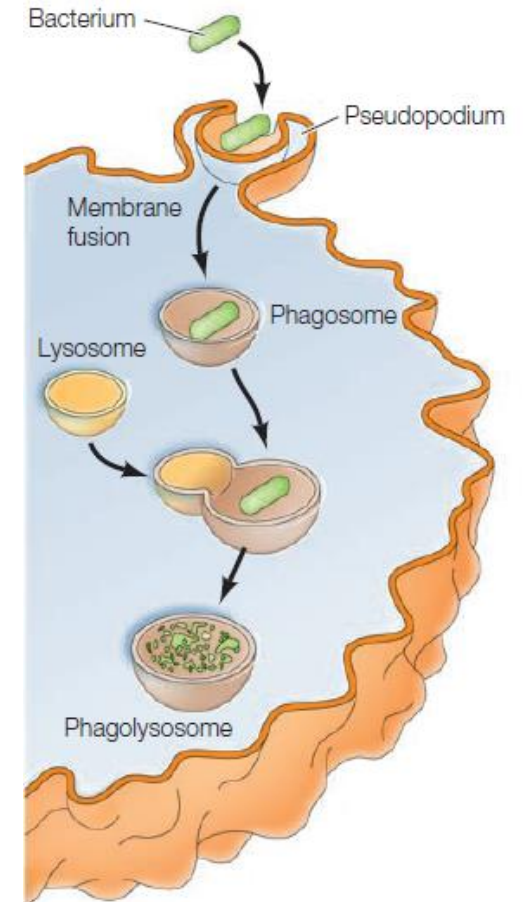
- Before budding of a transport vesicle, they get coated by a protein called clathrin.
- When the clathrin-coated vesicle docks at its target membrane, it gets uncoated, and fuses with the membrane.
- Why clathrin? It shapes the budding vesicle, selectively sorts cargo for packaging, facilitates the budding process, and regulates the movement of vesicles between the membranes.



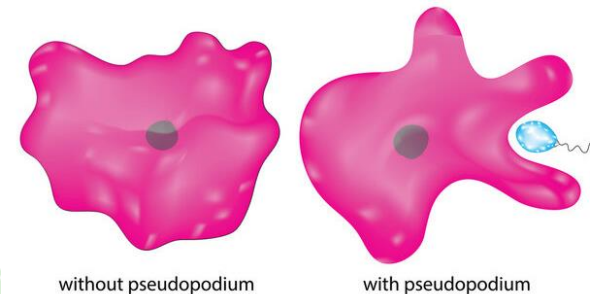
Phagocytosis

(Clathrin-independent)

- The binding of a bacterium to the cell surface stimulates the extension of a pseudopodium (extending arms from the membrane), which eventually engulfs the bacterium.
- Fusion of the pseudopodium membranes then results in the formation of a large intracellular vesicle (a phagosome).
- The phagosome fuses with lysosomes to form a phagolysosome within which the ingested bacterium is digested.
- *Macropinocytosis (also clathrin-independent) is cell drinking via the formation of small vesicles.*



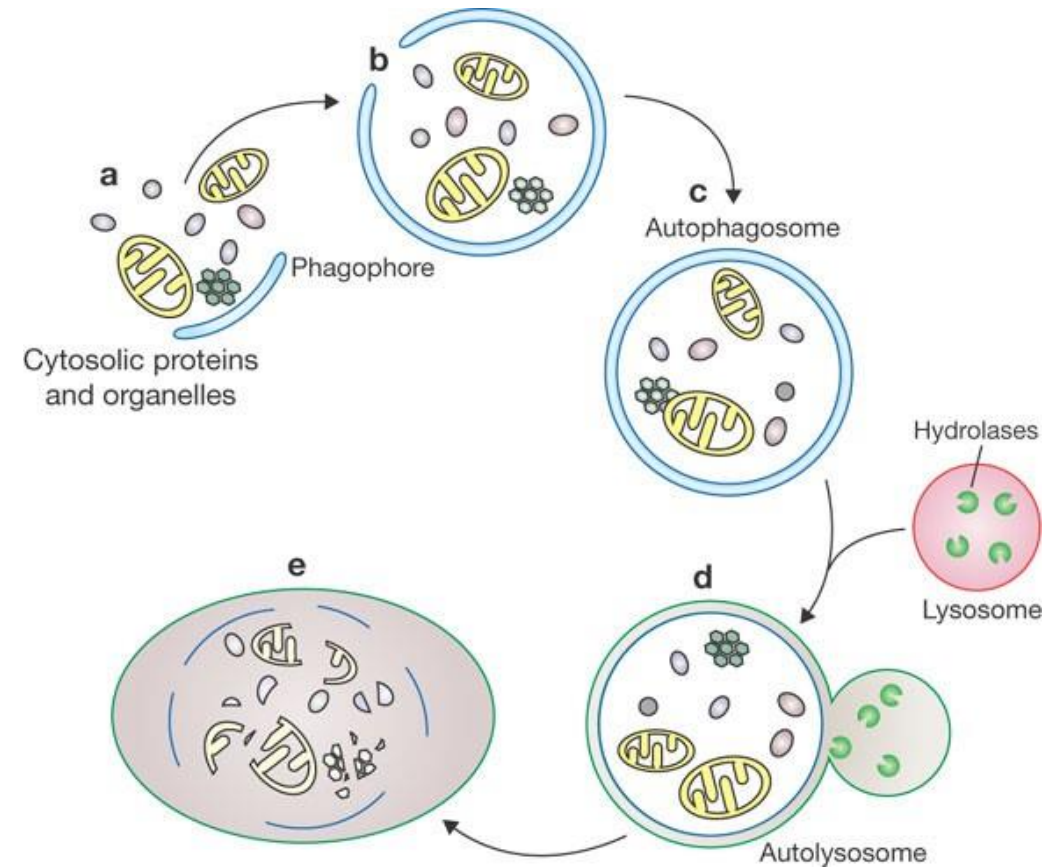
A pseudopodium is a temporary arm-like projection of a eukaryotic cell membrane



Autophagy (self-eating)



- Autophagy involves the formation of a large vesicle called **autophagosome** at the surface of ER with the help of a protein called **Atg9**.
- The formation of autophagosome is concomitant with the encapsulation of dysfunctional and harmful substances and proteins, as well as damaged organelles (such as mitochondria).
- Autophagosomes fuse with lysosomes to form large **phagolysosomes** in which their contents are digested.



Autophagy in health and disease



The good

- Removing dysfunctional and harmful substances and proteins, as well as damaged organelles (such as mitochondria).
- Allowing survival during starvation to eliminate nonessential macromolecules and replenish ATP.
- Remodeling tissues during development.
- Preventing cancer

The bad and the ugly

- Autophagy can help cancer cells survive and proliferate under suboptimal conditions.
- Autophagy is also implicated in several neurodegenerative diseases.
 - Genes responsible for the autophagic degradation of dysfunctional mitochondria in degenerating cells are found to be mutated in early-onset Parkinson's disease.



Reason Behind Fasting !

When the human body is hungry, it eats itself and goes through a cleansing process that eliminates all diseased cells, cancer, ageing cells, and Alzheimer's.



The facts that Never Lie

Fasting triggers a **biological mechanism** called **autophagy**, which breaks down old cells and literally **regenerates the immune system**

"For the greatest benefit to mankind"
Alfred Nobel

The Nobel Assembly at Karolinska Institutet has today decided to award the

2016 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE



Yoshinori Ohsumi

"for his discoveries of mechanisms for autophagy"

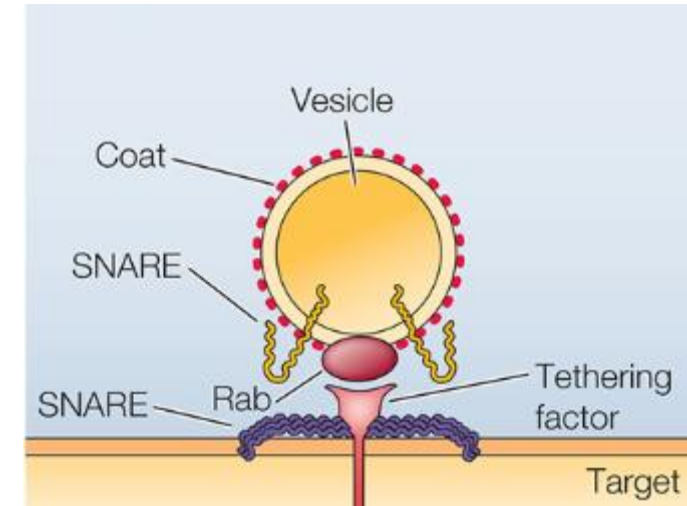
Nobelprize.org



The mechanism of vesicular transport

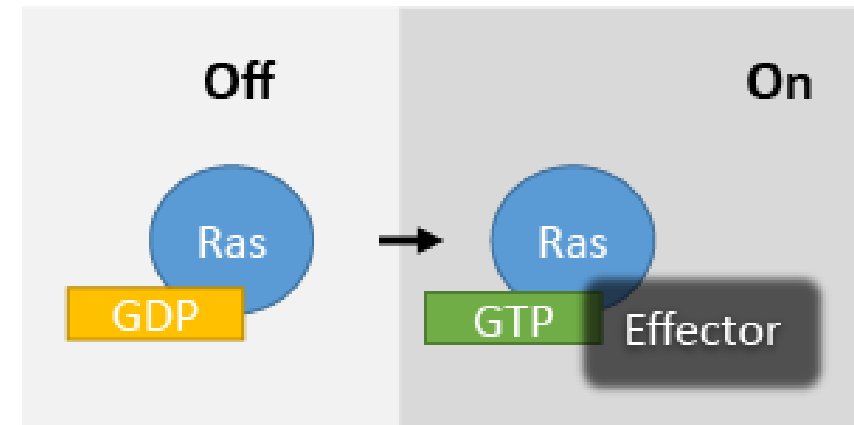
Delivery of vesicles: targeting and fusion

- Vesicular small G proteins called Rab determine the membrane targets of vesicles.
 - There are over 60 Rab proteins that mark different transport vesicles and determine their destinations.
- v-SNAREs-t-SNAREs proteins are responsible for vesicular fusion with the target membranes.

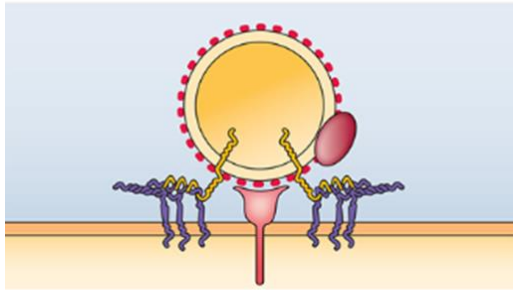
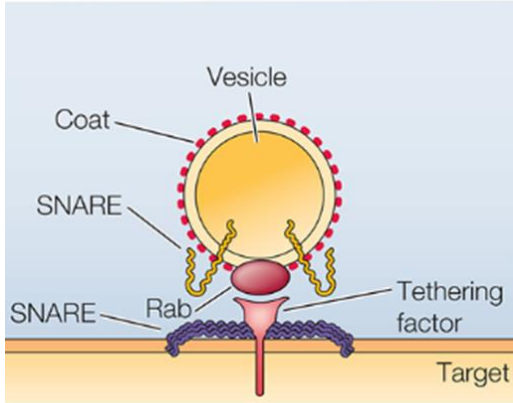


Rab GTPase	Site(s) of action ^a
Rab1	ER to Golgi, intra-Golgi
Rab4	EE to PM
Rab5	PM to EE
Rab6	Golgi to ER, intra-Golgi, EE to TGN
Rab7	EE to LE, LE to lysosome
Rab9	LE to TGN
Rab10	Golgi-associated
Rab11	RE to PM, EE to TGN, TGN to PM

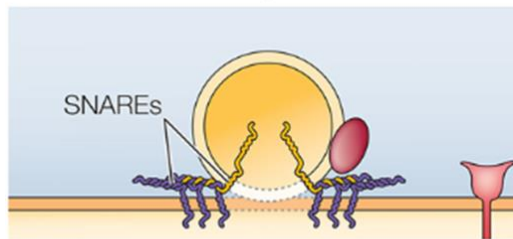
^a Abbreviations: EE, early endosome; PM, plasma membrane; LE, late endosome; RE, recycling endosome.



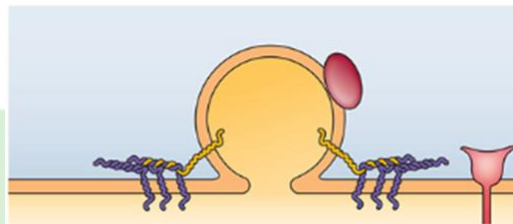
The mechanism of fusion



Removal of coat



Membrane fusion



1. A Rab protein binds to a tethering factor associated with the target membrane.
2. SNAREs on the vesicle and target membranes complex together.
3. The SNAREs zip together, bringing the vesicle and target membranes into close proximity
4. The membranes fuse.

Griscelli syndrome (GS)

- A rare genetic condition
- Mutations in MYO5A (a motor protein), RAB27A, and MLPH (a Rab effector protein) genes that function as a protein complex in melanosome transport and fusion during the transfer of melanin-containing melanosomes from melanocytes to keratinocytes..
- Pigmentary dilution of the skin, silver-grey hair, melanin clumps within hair shafts

