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Cytology

Doctor 2019 | Medicine | JU

◉ Sheet ○ Slides

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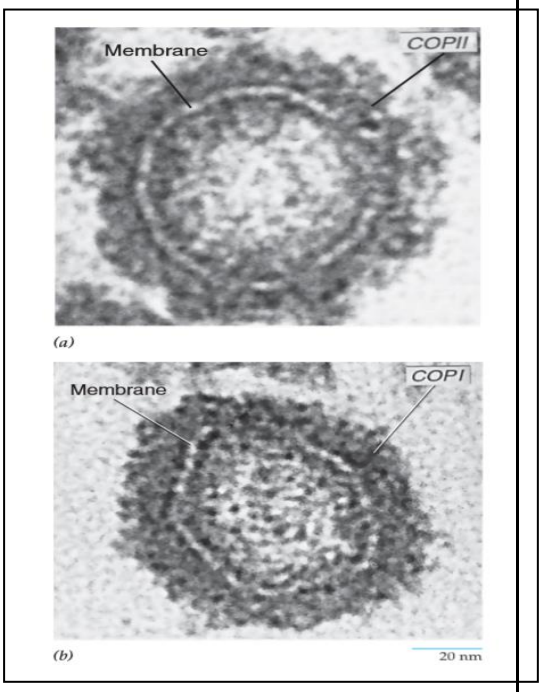
12.10 Types of vesicle transport and their functions:

- Vesicles carry materials between cellular compartments

- Vesicles bud from donor membranes to acceptor membrane.



-These vesicles are coated with proteins, which function as:

a) A mechanical device that causes the membrane to curve and form a budding vesicle

b) They provide a mechanism for selecting the components to be carried by the vesicle. What components?

i) Cargo consisting of secretory, lysosomal, and membrane proteins to be transported

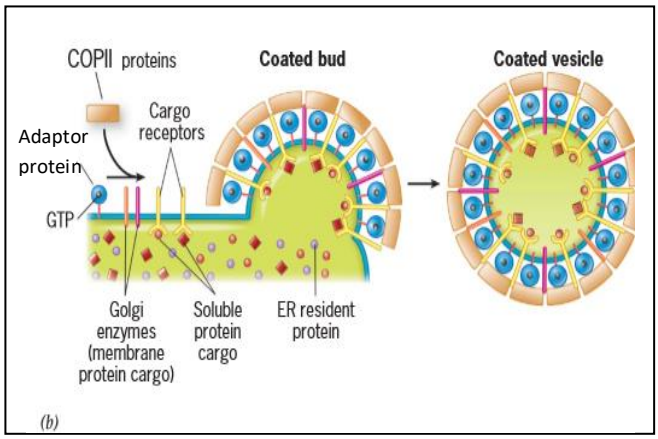
ii) The machinery required to target and dock the vesicle to the correct acceptor membrane

The vesicle coat is composed of:

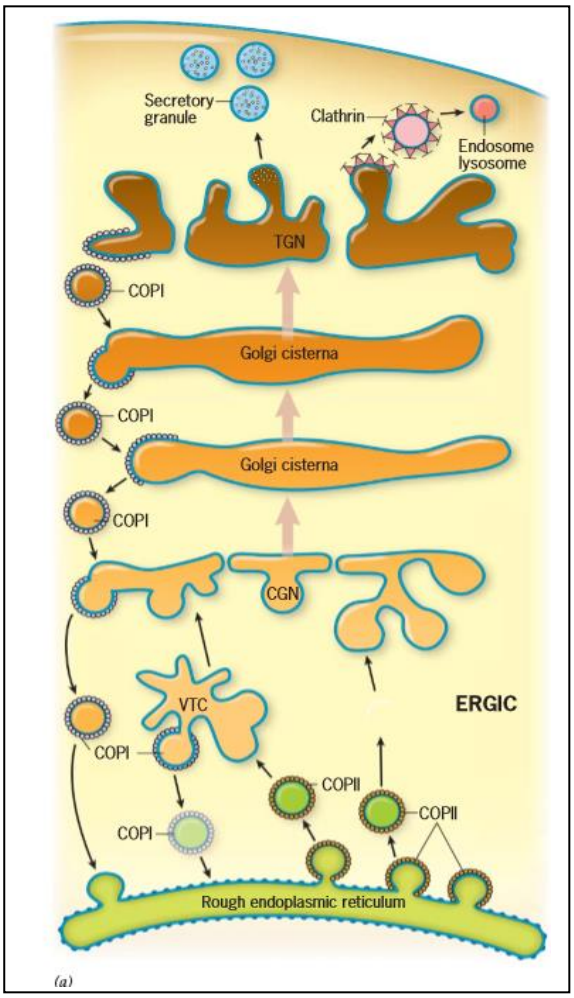
a) An outer cage or scaffolding that forms the framework for the coat

b) An inner layer of adaptors that binds both to the outer surface of the lipid bilayer and the membrane's cargo. Adaptor proteins have different types which are able to select specific cargo molecules. Adaptor proteins are G proteins (Bind to GTP for activation). ** the term adaptor proteins describes a molecule that physically links 2 or more components.

Vesicles are distinguished according to the proteins that make up their coat, their appearance in the electron microscope, and their role in cell trafficking.



1) **COPII coated vesicles**: move materials from the ER "forward"(anterograde) to the ERGIC (the intermediate compartment situated between the ER and Golgi complex) and Golgi complex.



2) **COPI coated vesicles**: move materials in a retrograde(backwards) direction (1) from the ERGIC and Golgi stack "backward" toward the ER and (2) from trans Golgi cisternae "backward" to cis Golgi cisterna

3) **Clathrin-coated vesicles**:

i) Move materials from the TGN to endosomes, lysosomes, and plant vacuoles

ii) Move materials from the plasma membrane to cytoplasmic compartments along the endocytic pathway

iii) They have been implicated in trafficking from endosomes and lysosomes

Before the coated vesicle can fuse with a target membrane, the protein coat must be disassembled and its components released into the cytosol. Disassembly is triggered by hydrolysis of the bound GTP.

How to select ER resident proteins?

-ER resident proteins have specific amino acid sequence at their C-terminus, called retrieval signal.

- If they accidentally carried forward to the ERGIC or Golgi complex, they are captured by specific receptors in Golgi cis network and sent back to the ER in COPI coated vesicles.

- Soluble ER resident proteins have KDEL retrieval signal (each letter indicates an amino acid). In Golgi cis network, there are KDEL receptors, which recognize the escaped proteins and send them back to ER. The most common retrieval sequences for ER

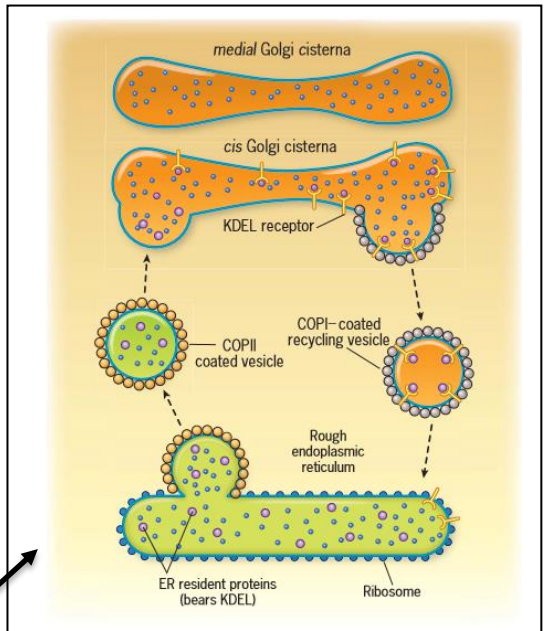


FIGURE 8.28 Retrieving ER proteins. Resident proteins of the ER contain amino acid sequences that lead to their retrieval from the Golgi complex if they are accidentally incorporated into a Golgi-bound transport vesicle. Soluble ER proteins bear the retrieval signal KDEL. Retrieval is accomplished as soluble ER proteins bind to KDEL receptors residing in th membranous wall of *cis* Golgi compartments. The KDEL receptors, in turn, bind to proteins of the COPI coat, which allows the entire complex to be recycled back to the ER.

membrane proteins involve two closely linked basic residues, most commonly KKXX (where K is lysine and X is any residue). (ER soluble -> KDEL. ER membrane->KKXX)

- Each membrane compartment in the biosynthetic pathway may have its own retrieval signals, which helps explain how each compartment can maintain its unique complement of proteins despite the constant movement of vesicles in and out of that compartment.

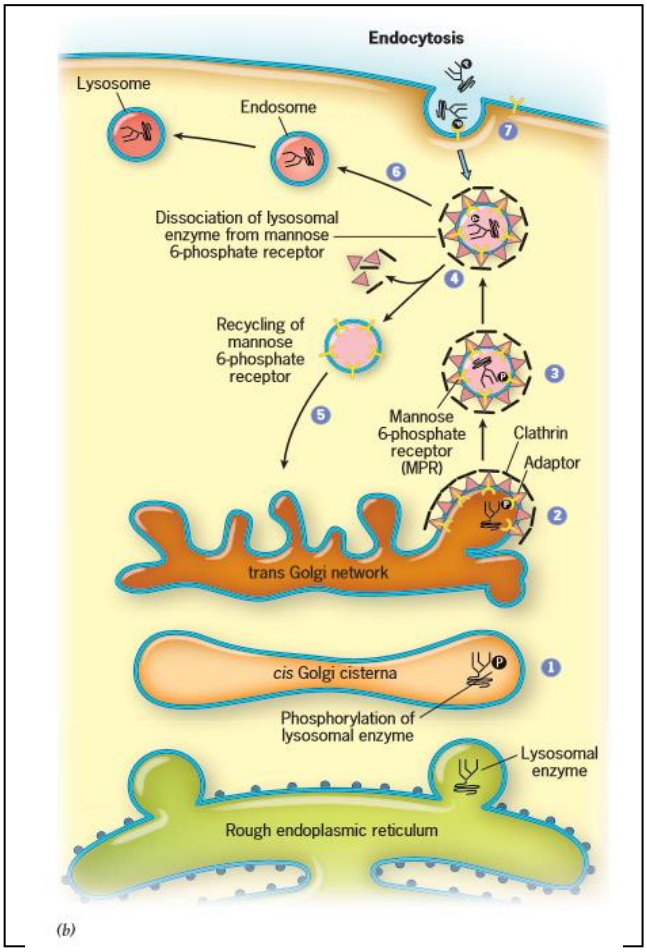
12.11 Beyond the Golgi complex: sorting proteins at the TGN

- The trans Golgi network (TGN), which is the last stop in the Golgi complex, functions as a major sorting station, directing proteins to various destinations.

Sorting and transport of lysosomal enzymes:

- Lysosomal enzymes possess phosphorylated mannose residues, which act as sorting signals.

- Lysosomal enzymes are transported from the TGN in clathrin coated vesicles.



1) The mannose residues of the lysosomal enzyme are phosphorylated in the Golgi cisternae

2) The mannose residues are incorporated into a clathrin coated vesicle at the TGN

3) The mannose 6-phosphate receptors

4) The mannose 6-phosphate receptors separate from the enzymes

5) The mannose-6-phosphate receptors returned to the Golgi complex

6) The lysosomal enzymes are delivered to an endosome

7) Mannose 6-phosphate receptors are also present in the plasma membrane, where they capture lysosomal enzymes that are secreted into the extracellular space and return the enzymes to a pathway that directs them to a lysosome.

Sorting and transport of nonlysosomal proteins:

-Plasma membrane proteins and secretory materials are transported from TGN.

- Proteins that are discharged from the cell by a process of regulated secretion, such as digestive enzymes and hormones, are thought to form selective aggregates that eventually become contained in large, densely packed secretory granules

- The mature granules are stored in the cytoplasm until their contents are released following stimulation of the cell by a hormone or nerve impulse

- The targeted delivery of integral proteins to the plasma membrane appears to be based largely on sorting signals in the cytoplasmic domains of the membrane proteins. In polarized cells, membrane proteins destined to reside in the apical portion of the plasma membrane contain different sorting signals from those destined for the lateral or basal portion. Plasma membrane proteins of nonpolarized cells, such as fibroblasts and white blood cells, may not require special sorting signals.

12.12 Targeting vesicles to a particular compartment

- It is thought that a vesicle contains specific proteins associated with its membrane that govern the movements and fusion potential of that vesicle

** The stages of vesicle budding and vesicle fusion:

1) Movement of the vesicle toward the specific target compartment; these types of movement are mediated largely by microtubules and their associated motor proteins.

2) Tethering vesicles to the target compartment: mediated by diverse collection of "tethering proteins", which have 2 groups:

i) Rod-shaped, fibrous proteins that are capable of forming a molecular bridge between the two membranes over a considerable distance

ii) Large multiprotein complexes that appear to hold the two membranes in closer proximity

**Much of the specificity between vesicle and target may be conferred by a family of small G proteins called Rabs, which cycle between an active GTP-bound state and an inactive GDP-bound state

3) Docking vesicles to the target compartment: the membranes of the vesicle and target compartment come into close contact with one another as the result of an interaction between the cytosolic regions of integral proteins of the two membranes.

**The key proteins in this interaction are called SNAREs, there are more than 35 membrane proteins of this family

-SNARE motif: a segment in SNARE proteins cytosolic side, make them able of forming a complex with another SNARE motif.

-SNAREs are divided functionally into 2 categories:

i) v-SNARE: which become incorporated into the membranes of transport vesicles during budding

ii) t-SNARE: which are located in the membranes of target compartments

4) Fusion between vesicle and target membrane: the interactions between t- and v-SNAREs are capable of pulling two lipid bilayers together with sufficient force to cause them to fuse

- The ability of a particular vesicle and target membrane to fuse is determined by the specific combination of interacting proteins, including tethering proteins, Rabs, and SNAREs that can be assembled at that site in the cell

12.13 Exocytosis

Exocytosis: The fusion of a secretory vesicle or secretory granule with the plasma membrane and subsequent discharge of its contents

- An example to study is the release of neurotransmitters into the synaptic cleft; membrane fusion produces an opening through which the contents of the vesicle or granule are released into the extracellular space

- Exocytosis is generally triggered by release of Ca^{+2} from cytoplasmic stores.

- Fusion pore: a small, protein-lined formed because of the contact between the vesicle and plasma membranes.

- The luminal surface of the vesicle membrane becomes part of the outer surface of the plasma membrane, whereas the cytosolic surface of the vesicle membrane becomes part of the inner (cytosolic) surface of the plasma membrane.