CHAPTER 12
Cellular Organelles and Membrane Trafficking part one

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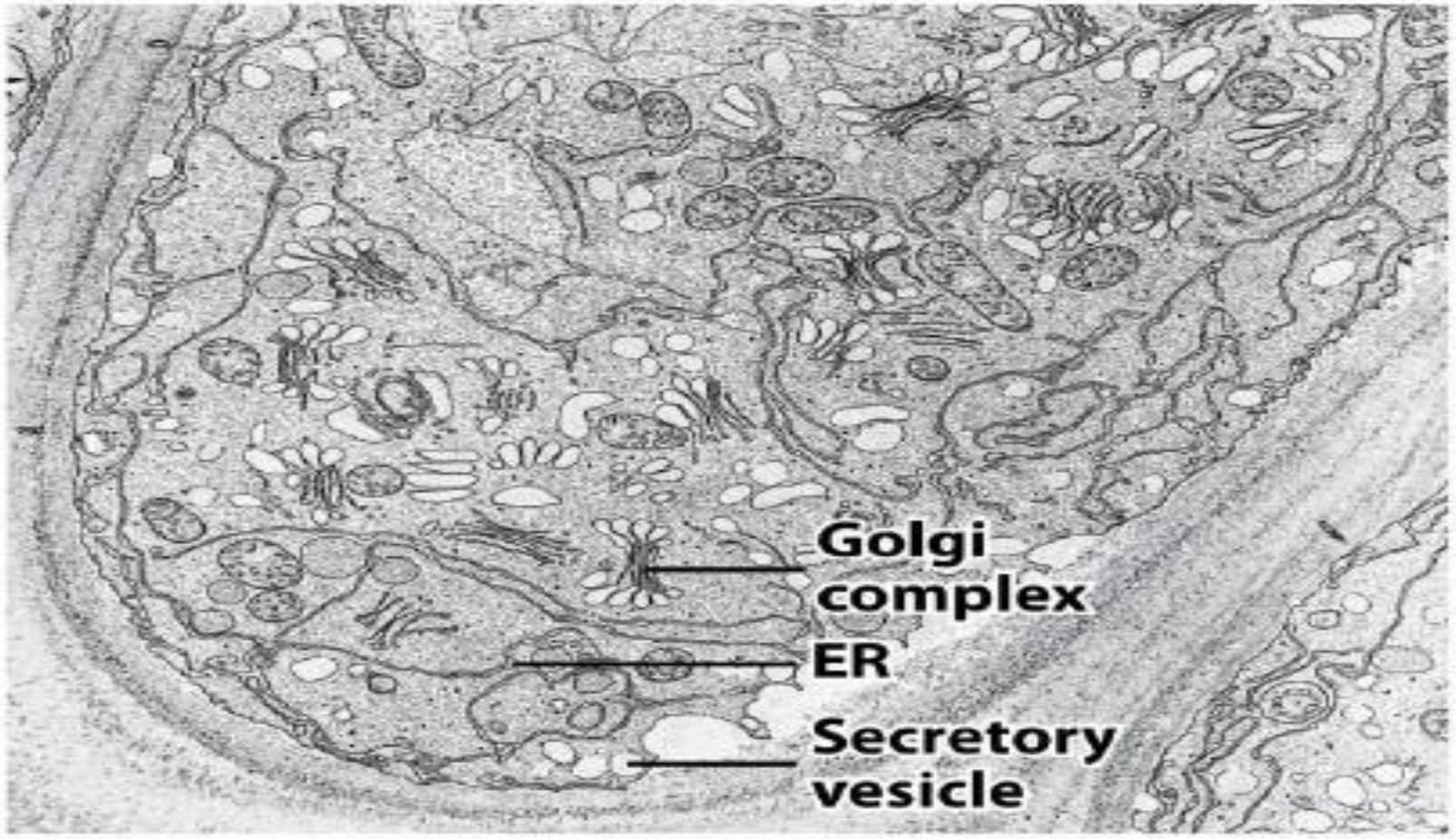
12.1 | An Overview of the Endomembrane System

Eukaryotic cell cytoplasm is subdivided into a variety of distinct compartments bounded by membrane barriers (the internal membrane is responsible for compartmentalization)

Cytoplasmic compartments form different organelles, each containing specialized proteins for particular activities.

Organelles may appear as stable structures, but in fact they are dynamic compartments that are in continual flux (the movement of molecules and materials which enter and exit the organelles and the secretion of proteins).

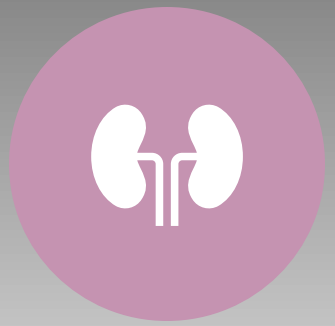
Endomembrane system: act as a coordinated unit & is formed from The ER, Golgi complex, endosomes, lysosomes, and vacuoles.



Courtesy of Hilton H. Mollenhauer

Membrane-bound compartments of the cytoplasm

Organelle boundary membranes probably arise from the ER.



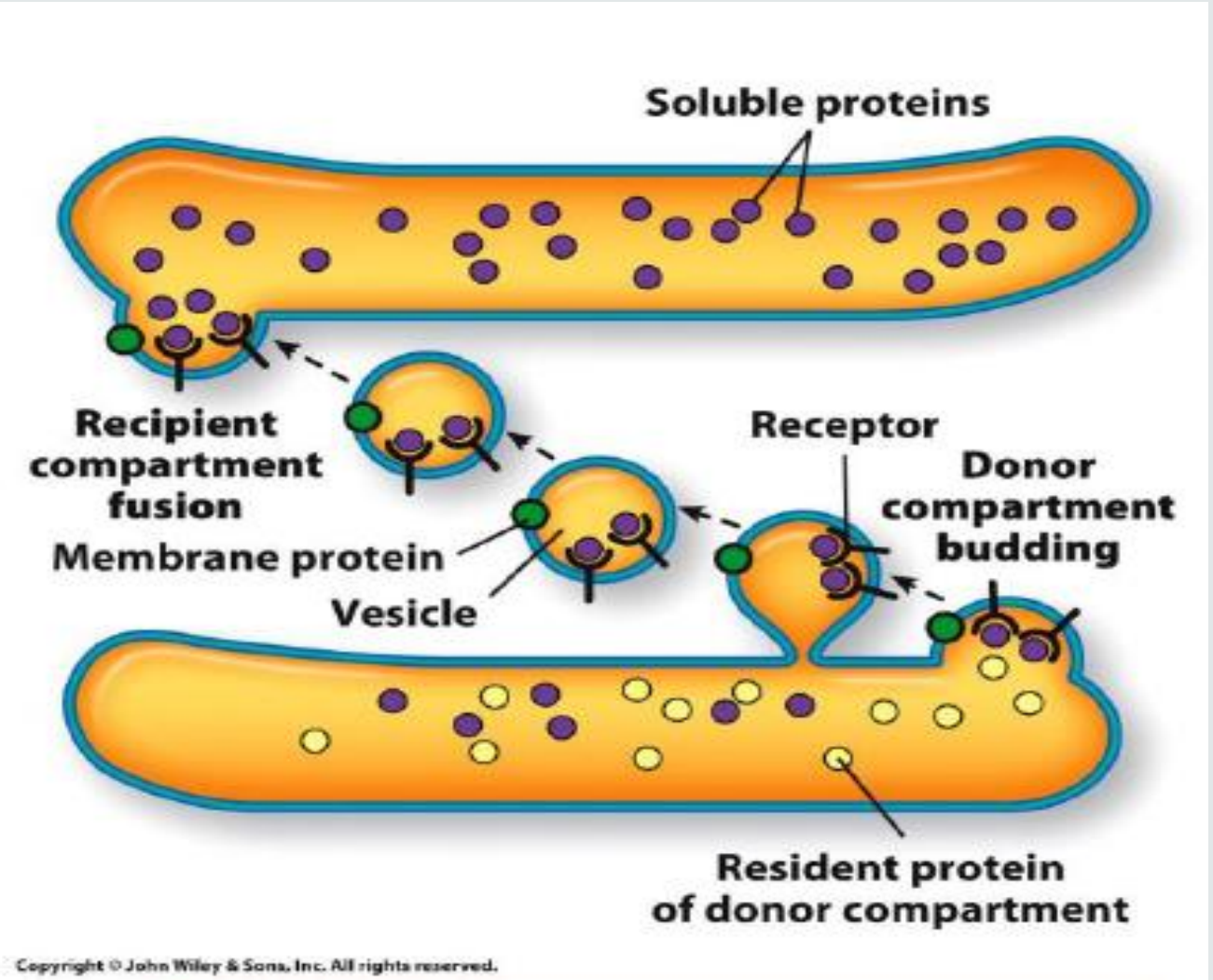
Materials are shuttled between organelles in small, membrane-bounded transport vesicles that bud from a donor membrane compartment.

Transport vesicles move directionally via motor proteins on microtubules and microfilaments of the cytoskeleton.

Vesicles fuse with the membrane of the acceptor compartment, which receives the vesicle's soluble cargo and membranes.

- *The steps by which proteins are exchanged between compartments:*

1. The preparation of proteins (membrane proteins or soluble proteins) and their receptors (to increase the specificity in the surface of vesicle by binding with the proteins and the enzymes from the acceptor) in the donor compartment.
2. The budding from the donor cells.
3. The vesicles carry the cargo and move by motor proteins on the cytoskeleton.
4. The vesicles fuse with the acceptor cell's membrane.



Inside vesicle: orientation remains the same

The ways of transport materials :

- **Biosynthetic pathway**: *Proteins are synthesized in the ER **GENERALLY**, modified at the Golgi complex, and transported to various destinations (e.g. plasma membrane, lysosome, plant vacuole).*

The proteins are synthesized in the ribosomes (don't forget the bound ribosomes which are attached to the ER).

During or after synthesis, the proteins are modified in ER, and further modifications take place in Golgi complex.

- **Secretory pathway**: *Proteins synthesized in the ER are discharged (secreted or exocytosed) from the cell.*

- **Constitutive secretion:** *Materials are transported in secretory vesicles and discharged in a continual manner.*

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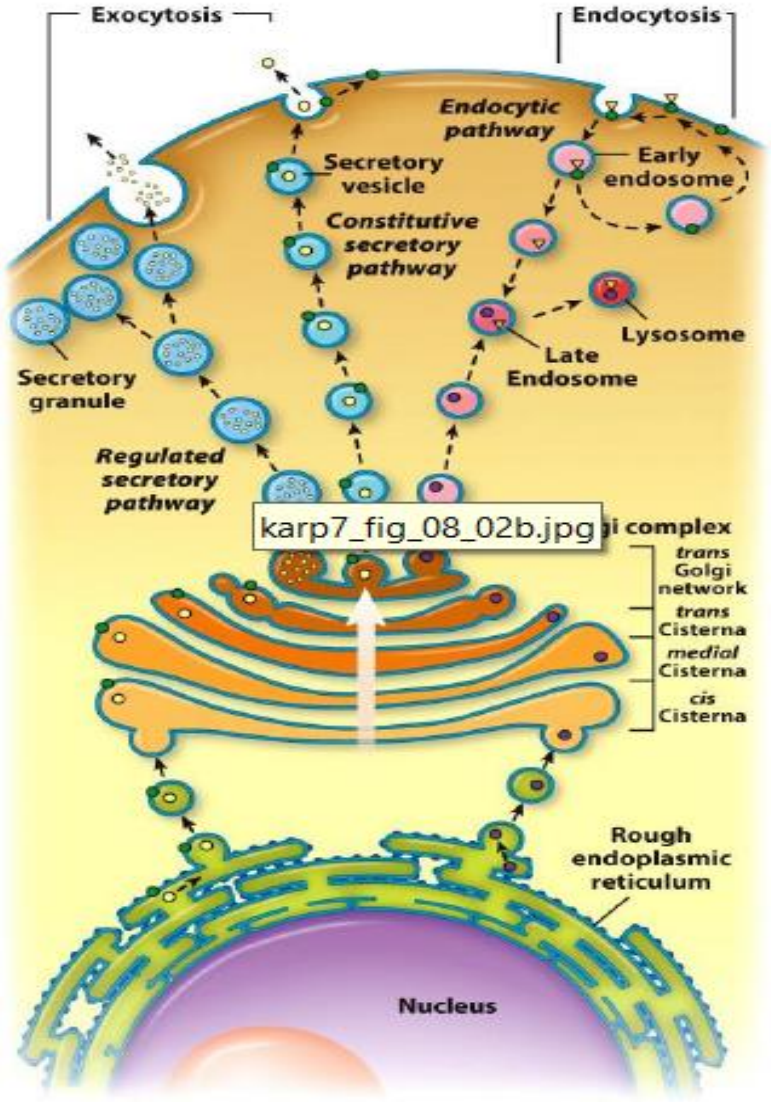
- **Regulated secretion:** *Materials are stored in vesicles and discharged in response to a stimulus.*

e.g. GLUT (glucose transporter which is stored inside the cells –vesicles- and by a response of a stimulus (insulin) it fuses with the cell membrane to attach with glucose.



Endocytic pathways that unite endomembranes into a dynamic, interconnected network.

From the photo

The receptors mediated endocytosis:
the particular material binds with the specific receptors on the surface of the cell, then the cell membrane invagination and buds to the inside and form the early **endosome** which develops to the late **endosome**.
The lysosomes fuse with the vesicle to take advantage from the binding material and by the recycling endosome the receptors are removed and back to the cell surface.

This will be explained in detail later

Regulated secretion occurs in endocrine cells (hormones), pancreatic acinar cells (digestive enzymes), and nerve cells (neurotransmitters).

Secreted materials can be stored in large, densely packed, membrane-bound secretory granules.

- Proteins, lipids, and complex polysaccharides are transported through the cell along the biosynthetic or secretory pathway.

with the endocytic pathway, materials move from the outer surface of the cell to compartments, such as endosomes and lysosomes, located within the cytoplasm.

The various types of cargo (e.g. secreted proteins, lysosomal enzymes, and membrane proteins) are routed to their appropriate cellular destinations by sorting signals (tag) encoded in:

- The amino acid sequence of the proteins which labels the protein

OR

- The attached oligosaccharides.

The sorting signals (tag) are recognized by specific receptors that reside in the membranes or surface coats of budding vesicles, ensuring that the protein is transported to the appropriate destination.

The binding bucket binds with the tag of the protein inside the lumen, the outer side of receptor is recognized by the target cell (membrane).

There are other proteins recognition attached with the surface of vesicle to recognize the target cells

We will talk about them later.

12.3 | The Endoplasmic Reticulum

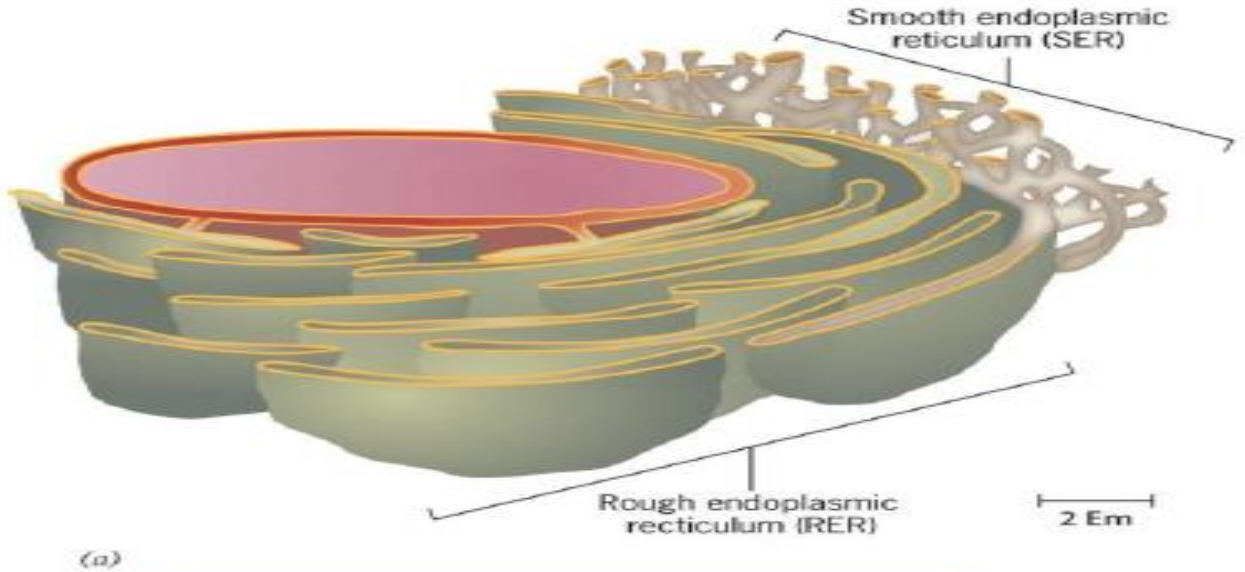
- The ER comprises a network of membranes that penetrates much of the cytoplasm and has a lumen separated from the cytosol by the ER membrane.

- The ER is a highly dynamic structure divided into the rough ER (The RER has ribosomes bound to its cytosolic surface) and smooth ER (SER lacks associated ribosomes).

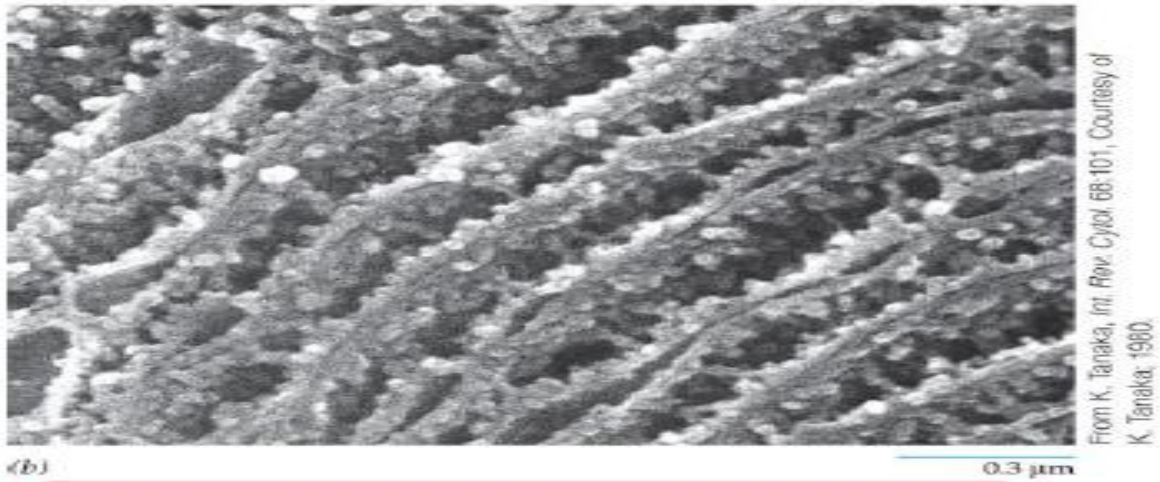
- ***The RER typically:***

1) has flattened sacs (cisternae) connected to neighbors.

2) is continuous with the outer membrane of the nuclear envelope (to exchange materials with the nucleus, it doesn't need vesicles).

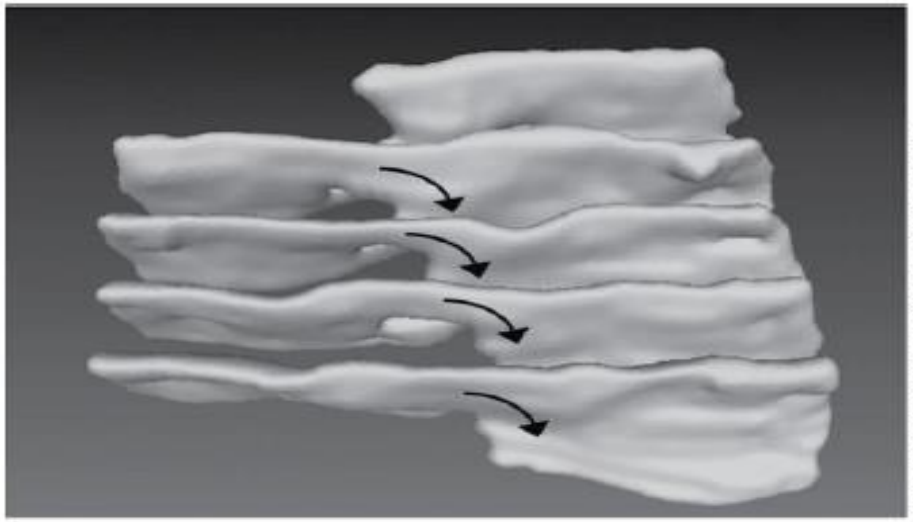


Schematic diagram of the rough ER



SEM of the rough ER

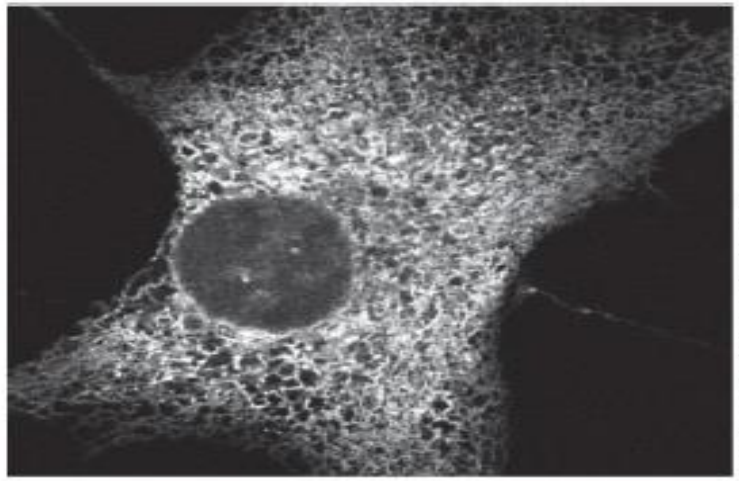
- SER membranes are highly curved and tubular, and continuous with the RER (they exchange materials without vesicles).
- SER and RER share many of the same proteins and common activities (e.g. synthesis of certain lipids and cholesterol).
- Numerous proteins are ER-specific, like the membrane-bending proteins (reticulons) in the SER; RER-specific proteins help move nascent proteins into the ER lumen.
- Different types of cells contain markedly different ratios of the two types of ER, depending on the activities of the cell.



From Terasaki et al., *Cell* 154:285, 2013.

(c)

EM reveals ER sheets connected by helicoidal ramps



From George H. Patterson, Cell Image Library, CIL:721.

(d)

Visualization of ER by GFP fluorescence

The SER is highly developed in skeletal muscle, kidney tubules, and steroid-producing endocrine glands

SER functions include:

1) Steroid hormone synthesis in endocrine cells of the gonad and adrenal cortex.

2) Detoxification of organic compounds (drugs & detox materials) in the liver via oxygenases including the cytochrome P450 family. Hydrophobic compounds are converted into more hydrophilic ones for excretion.

- Organic compounds are hudrophopic materials, cells can remove the hydrophilic materials in the form of sweat or urine,so the body convert these material to hydrophilic ones (aqueuos) this process is called hydroxylation which takes place by adding the hydroxyl group to these hydrophopic compounds to increase the solubility in water.

3) Sequestering Ca2+ within the cytoplasm; its regulated release in skeletal and cardiac muscle cells from the sarcoplasmic reticulum triggers contraction.

Don Fawcett/Photo Researchers, Inc.

Leydig cell: extensive SER where steroid hormones are synthesized

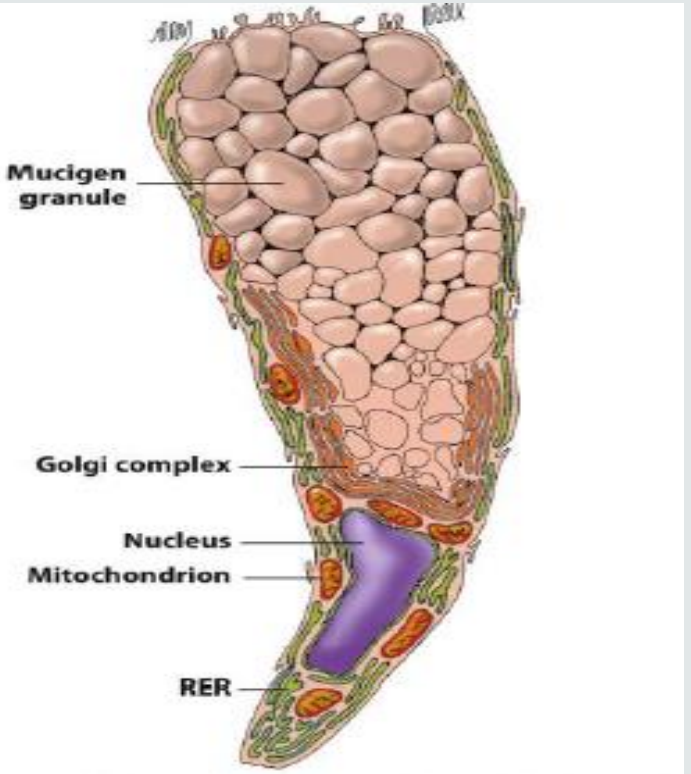
The Rough Endoplasmic Reticulum

- The RER is the starting point of the biosynthetic pathway: synthesized proteins, carbohydrates, and phospholipids then journey through the membranous cell compartments.

- Organelles in epithelial secretory cells are positioned with a distinct polarity, which reflects protein movement.

- The nucleus and RER are near the basal surface, facing the blood supply; the Golgi complex is centrally located; secretory granules are near the apical surface near ducts.

Polarized structure of a secretory cell, a mucus secreting goblet cell.



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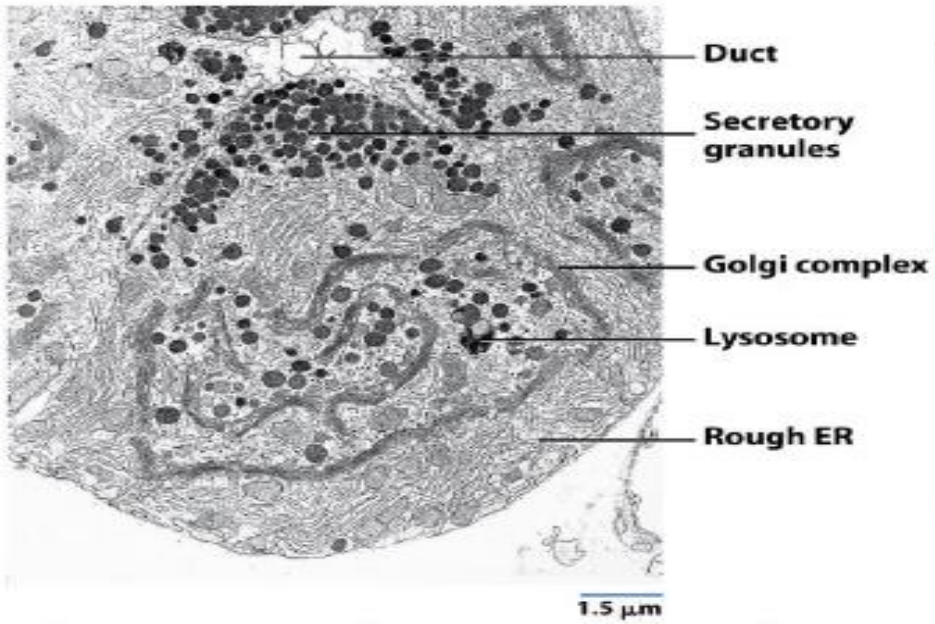


Mucus-secreting cell from mouse small intestine

Synthesis of Proteins on Membrane-Bound versus Free Ribosomes

- Polypeptides are synthesized at two distinct location within the cell.
- Proteins themselves determine the location where they will be synthesized according to their functions and final destination.
- The cells are highly organized they precisely determine the location of synthesis proteins, and so they don't lose any energy.

About one-third of the proteins are synthesized at the RER and released into the ER lumen in a process called co-translational translocation:

(a) secreted proteins

(b) integral membrane proteins

(c) soluble proteins that reside in the ER, Golgi complex, lysosomes, endosomes, vesicles, and plant vacuoles.

co-translational translocation: it is translated and transported to the ER lumen at the same time.

Polypeptides synthesized on “free” ribosomes in the cytosol include:

(a) proteins destined to remain in the cytosol

(b) peripheral proteins of the cytosolic surface of membranes

(c) proteins that are transported to the nucleus and those incorporated into peroxisomes, chloroplasts, and mitochondria.

These are synthesized posttranslationally into the appropriate organelle.

Posttranslationally: that meant that the polypeptides are transported to the destination after they were translated.

Synthesis of Proteins on Membrane-Bound versus Free Ribosomes

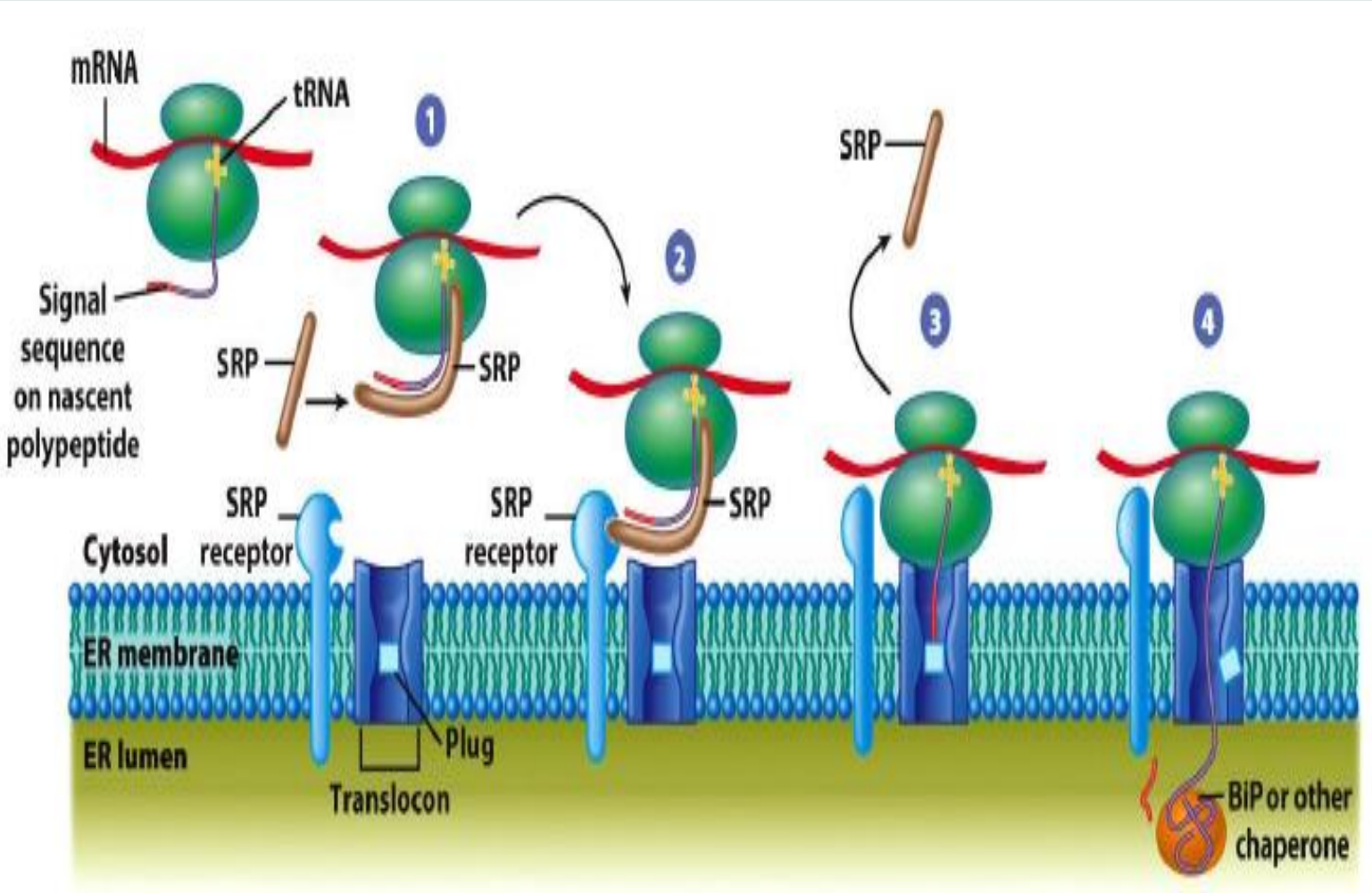
- The site of protein synthesis is determined by the sequence of amino acids in the N-terminal portion (which is first synthesized part) of the polypeptide.
- Proteins functions are determined by the N-terminal and C-terminal.
- All ribosomes in fact are free ribosomes, but the presence of signal sequence on the N-termina potion makes these free ribosomes transport and be bounded ribosomes.
- m-RNA is synthesized in the nucleus and then transported to the cytosol where it attaches with the small subunit of ribosome and then the large subunit is attached with them and all form the initiation translation complex.
- Then the process of synthesis the protein begins, if the protein has the sequence signal that meant that this protein will be transported to the ER lumen, and so this complex binds with the signal recognition particle SRP which makes recruitment on the surface of the ER membrane (as long these SRPs are attached, the translation stops), this membrane has a specific site with specific receptors for these SRP which will be removed.

- Secretory proteins contain a signal sequence at their N-terminus that directs the emerging polypeptide and ribosome to the ER membrane.

- The polypeptide moves into the cisternal space of the ER through a protein-lined, aqueous channel in the ER membrane (translocon), as it is being synthesized (co-translationally).

Proteins contain built-in “address codes” for protein trafficking pathways throughout the cell.

Synthesis of Secretory, Lysosomal, or Plant Vacuolar Proteins



A schematic model of the synthesis of a secretory protein (or a lysosomal enzyme) on a membrane-bound ribosome of the RER

- Co-translational translocation deposits protein into the ER lumen by a ribosome that is attached to the ER membrane.

- These polypeptides contain a signal sequence, a stretch of 6–15 hydrophobic amino acid residues, that targets the nascent polypeptide to the ER membrane.

- The hydrophobic signal sequence is recognized by a signal recognition particle (SRP).

- The SRP binds to both the signal sequence on the nascent polypeptide and the ribosome arresting synthesis.

- This complex is recruited to the ER membrane through an interaction between the SRP and the SRP receptor on the ER membrane.

- The ribosome is then handed off from the SRP to the translocon, a protein channel embedded in the ER membrane. Upon attachment, the signal sequence is recognized, and the polypeptide is inserted into the channel of the translocon.

If you have any question

Contact with me

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GOOD LUCK FOR ALL GREAT DOCTORS