



# Lecture 1: Introduction & endoplasmic reticulum

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**School of Medicine**  
**Second year, First semester, 2024-2025**

# Me!



- Prof. Mamoun Ahram
- Office location: first floor, School of Medicine, Main building
- Office hours: By appointment; Tuesday 12-2
- Come in groups

# Course outline (1)



## Focus on diseases

- Introduction and biomembranes
- Endoplasmic reticulum and protein sorting
- Golgi apparatus
- Vesicular network
- Mitochondria and mitochondrial diseases
- Peroxisomes
- The nucleus
- Cytoskeletal networks
- The extracellular network
- Cell signaling, proliferation, differentiation, and death
- Cancer cells

# Course outline (2)



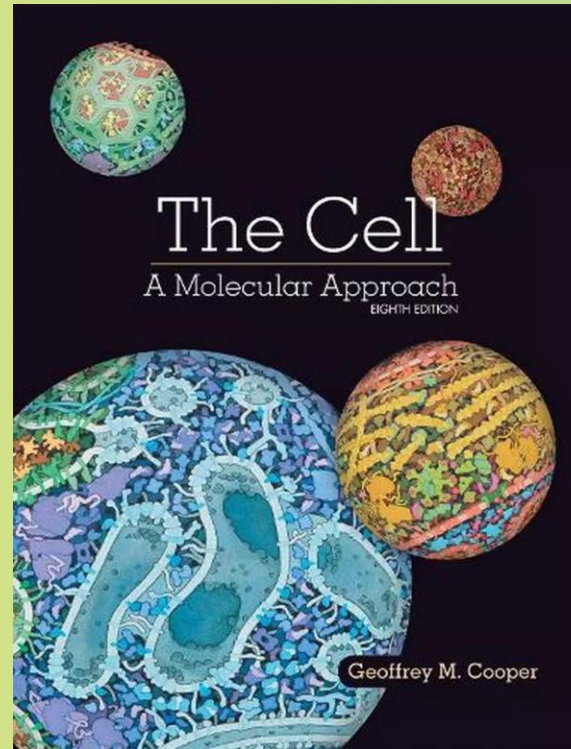
**Focus on  
processes  
and  
techniques**

- Introduction and the central dogma of molecular biology
- Gel electrophoresis, restriction endonucleases, recombinant DNA technology, DNA cloning, and RFLP
- The utilization of denaturation/renaturation concepts
  - Dot blotting and Southern blotting
- DNA replication
- PCR and DNA sequencing
- The human genome
- Transcription, mechanisms of regulation, and epigenetics
  - Coding and non-coding RNAs
- RNA detection, quantification, and detection
- Translation
- Yeast two-hybrid system
- DNA mutations
- DNA repair and CRISPR-Cas9

# The textbook



- **The Cell: A Molecular Approach 8th Edition** by Geoffrey Cooper, Sinauer Associates is an imprint of Oxford University Press.





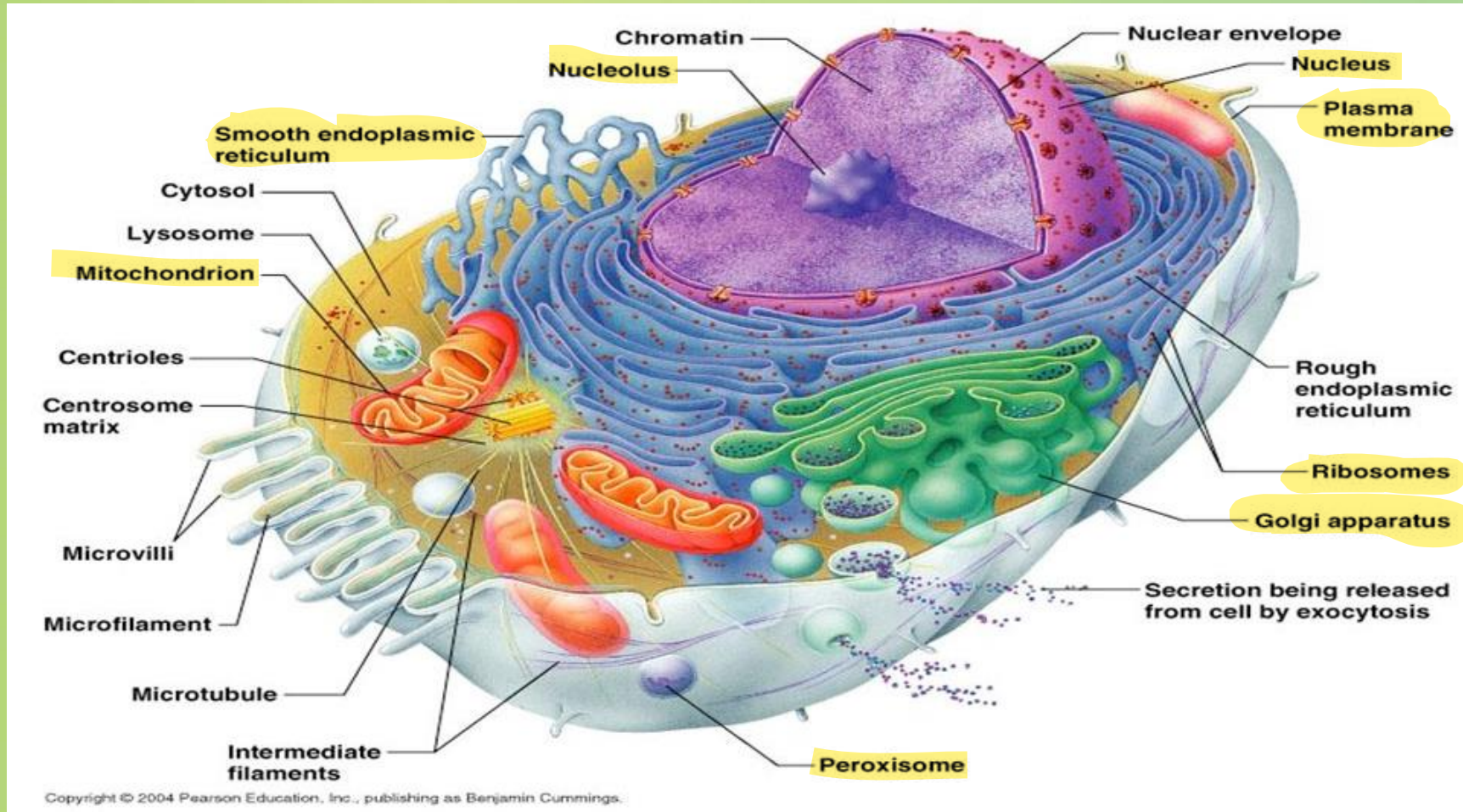
# The cell

Cell is the central unit of life

In eukaryotes: DNA is enclosed by a nucleus, and there are organelles

Prokaryotes: don't contain organelles

All organelles depends on each other, and they are organelles in special places



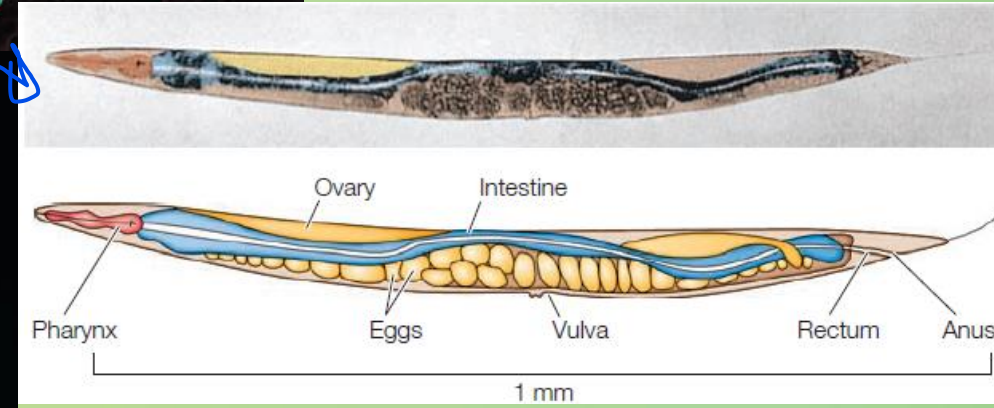
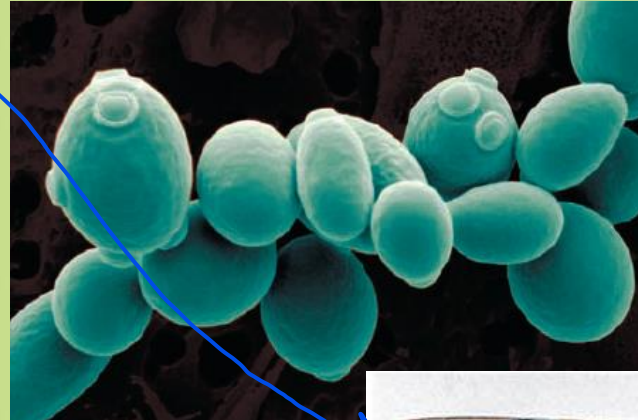
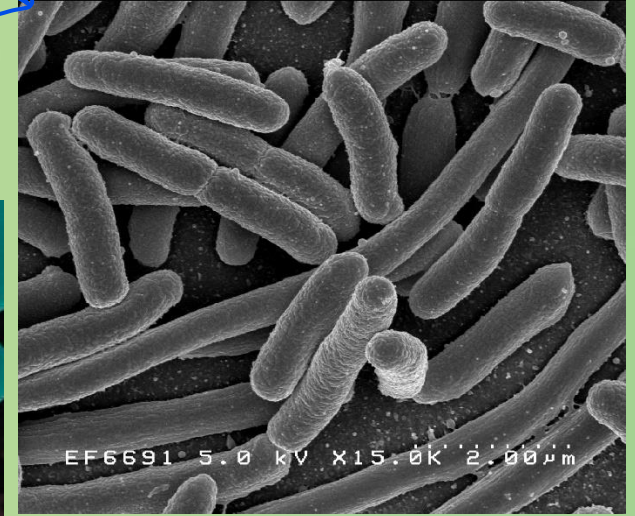


# What organisms do we use to study cells?

(Model systems)

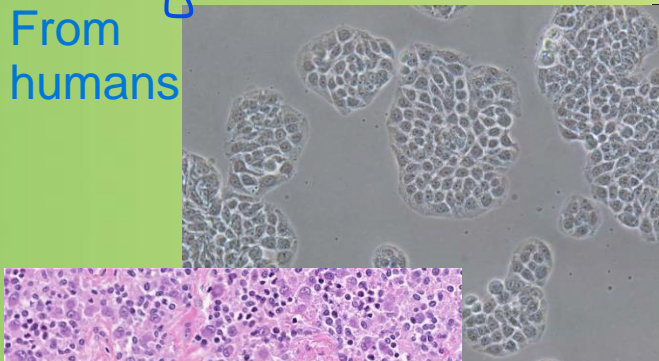
Contain 4000 genes

- Escherichia coli (E. coli) (Bacteria)
- Yeast (Saccharomyces cerevisiae)
- Caenorhabditis elegans (worm)
- Drosophila melanogaster (Fruitfly) (Used to study cell differentiation and genetic mutation)
- Mice (Contain gene number as human)
- Cultured cells and tissues



Used to know cell differentiation and death, immature contains 1059 type of cells, and mature contain 959 type

From humans





## Nucleus

### Nuclear envelope:

membrane enclosing the nucleus. Protein-lined pores allow material to move in and out.

**Chromatin:** DNA plus associated proteins.

### Nucleolus:

condensed region where ribosomes are formed.

## Cytoskeleton

**Microtubules:** form the mitotic spindle and maintain cell shape.

**Centrosome:** microtubule-organizing center.

**Intermediate filaments:** fibrous proteins that hold organelles in place.

### Microfilaments:

fibrous proteins; form the cellular cortex.

**Peroxisome:** metabolizes waste

## Endoplasmic reticulum

**Rough:** associated with ribosomes; makes secretory and membrane proteins.

**Smooth:** makes lipids.

**Plasma membrane**

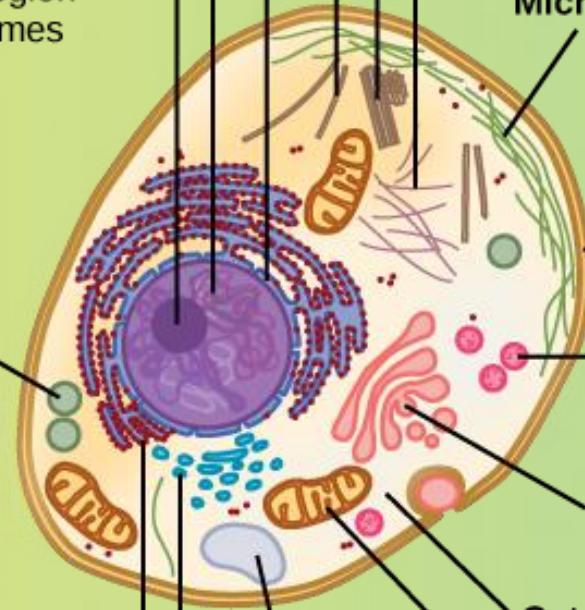
**Lysosome:** digests food and waste materials.

**Golgi apparatus:** modifies proteins.

## Cytoplasm

**Mitochondria:** produce energy.

**Vacuole**



Just take a general idea



# Organelles

Just take a general idea



**TABLE 4-2** *Organelles*

Organelle	Function
Mitochondrion	transfers energy from organic compounds to ATP
Ribosome	organizes the synthesis of proteins
Endoplasmic reticulum (ER)	prepares proteins for export (rough ER); synthesizes steroids, regulates calcium levels, breaks down toxic substances (smooth ER)
Golgi apparatus	processes and packages substances produced by the cell
Lysosome	digests molecules, old organelles, and foreign substances
Microfilaments and microtubules	contribute to the support, movement, and division of cells
Cilia and flagella	propel cells through the environment; move materials over the cell surface
Nucleus	stores hereditary information in DNA; synthesizes RNA and ribosomes
Cell wall*	supports and protects the cell
Vacuole*	stores enzymes and waste products
Plastid*	stores food or pigments; one type (chloroplast) transfers energy from light to organic compounds

\*Cell walls, large vacuoles, and plastids are found in the cells of plants and some other eukaryotes, but not in the cells of animals.

# Major molecular components of cells



Function by noncovalent interactions with other molecules (e.g. receptors and ligands)

- Nucleic acids
- Carbohydrates
- Proteins
- Lipids (50% of mass of plasma membranes, 30% of mitochondrial membranes)
- Molecules function by interacting with each non-covalently.



# How do we study cell components?

## Cell and protein detection

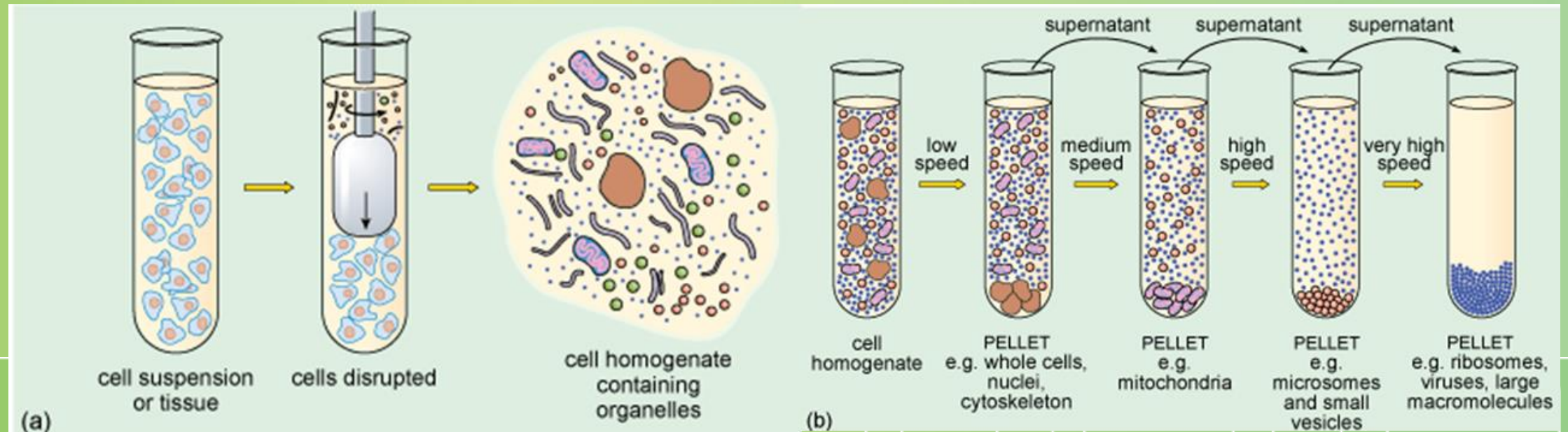
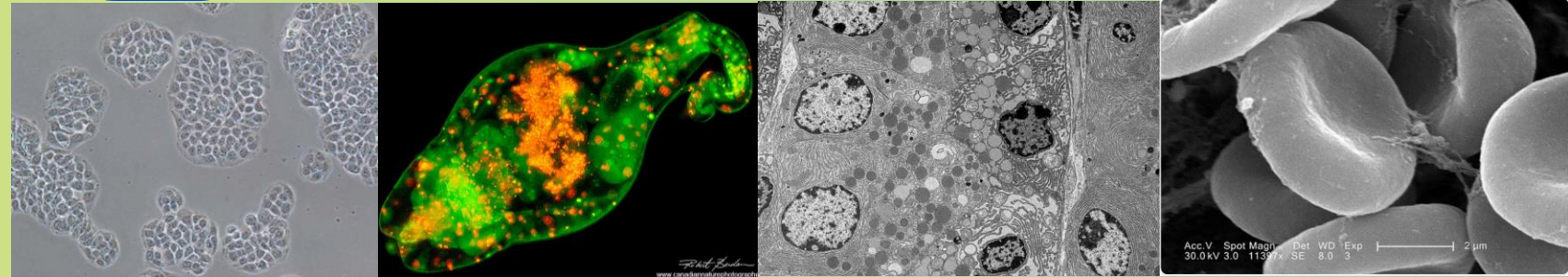
(Use antibodies that carries a fluorescence material that gives color when hit by light)

(Type of fluorescence) Remember immunohistochemistry !

### • Microscopy

- Light, fluorescence (immunofluorescence), electron, scanning electron

### • Cell fractionation



# Biochemical composition of plasma membranes



Question in exam might come as: which of the following contains highest amount of lipids?

Membrane	Protein (%)	Lipid (%)	Carbohydrate (%)	Weight fraction of protein	Ratio of protein to lipid
<b>Plasma membranes</b>					
Myelin	18	<u>79</u>	3	0.18	<u>0.23</u>
Blood platelets	33—42	51—58	7.5	0.4	0.7
Mouse liver cells	46	54	2—4	0.46	0.85
Human erythrocytes	<u>49</u>	43	8	0.49	<u>1.1</u>
Amoeba	54	42	4	0.54	1.3
Rat liver cells	58	42	(5—10)*	0.58	1.4
HeLa cells	60	40	2.4	0.6	1.5
Nuclear envelope of rat liver cells	59	35	2.9	0.59	1.6
Retinal rods, bovine	51	49	4	0.51	1.0
Mitochondrial outer membrane	<u>52</u>	48	(2—4)*	0.52	<u>1.1</u>
Sarcoplasmic reticulum	<u>67</u>	33	—	0.67	2.0
Chloroplast lamellae, spinach	70	30	(6)*	0.7	2.3
Mitochondrial inner membrane	<u>76</u>	24	(1—2)*	0.76	32
Gram-positive bacteria	<u>75</u>	25	(10)*	0.75	3.0
<i>Halobacterium</i> purple membrane	75	25		0.75	3.0



# Lipid composition of organelles



Table 1: Head group composition of the membranes of some mammalian liver cells, erythrocytes , and nerve cells in weight percent. Adapted from Jamieson and Robinson (1977). Abbreviations: PC = phosphatidylcholines, PE = phosphatidylethanolamines, PS = phosphatidylserines, PI = phosphatidylinositols, SM = sphingomyelin, CL = cardiolipin.

Membrane	PC	PE	PS	PI	SM	CL	Glycolipid	Cholesterol	Others
Erythrocyte (human)	20	18	7	3	18	–	3	20	11
Plasma (rat liver)	18	12	7	3	12	–	8	19	21
ER	48	19	4	8	5	–	tr	6	10
Golgi	25	9	3	5	7	–	0	8	43
Lysosome	23	13	–	6	23	≈ 5	–	14	16
Nuclear membrane	44	17	4	6	3	1	tr	10	15
Mitochondria	38	29	0	3	0	14	tr	3	13
Neurons	48	21	5	7	4	–	3	11	1
Myelin	11	17	9	1	8	–	20	28	6

To make it rigid

**Cholesterol is an essential component of animal plasma membranes. It is not present in bacteria and plant cells, but the latter cells contain sterols.**

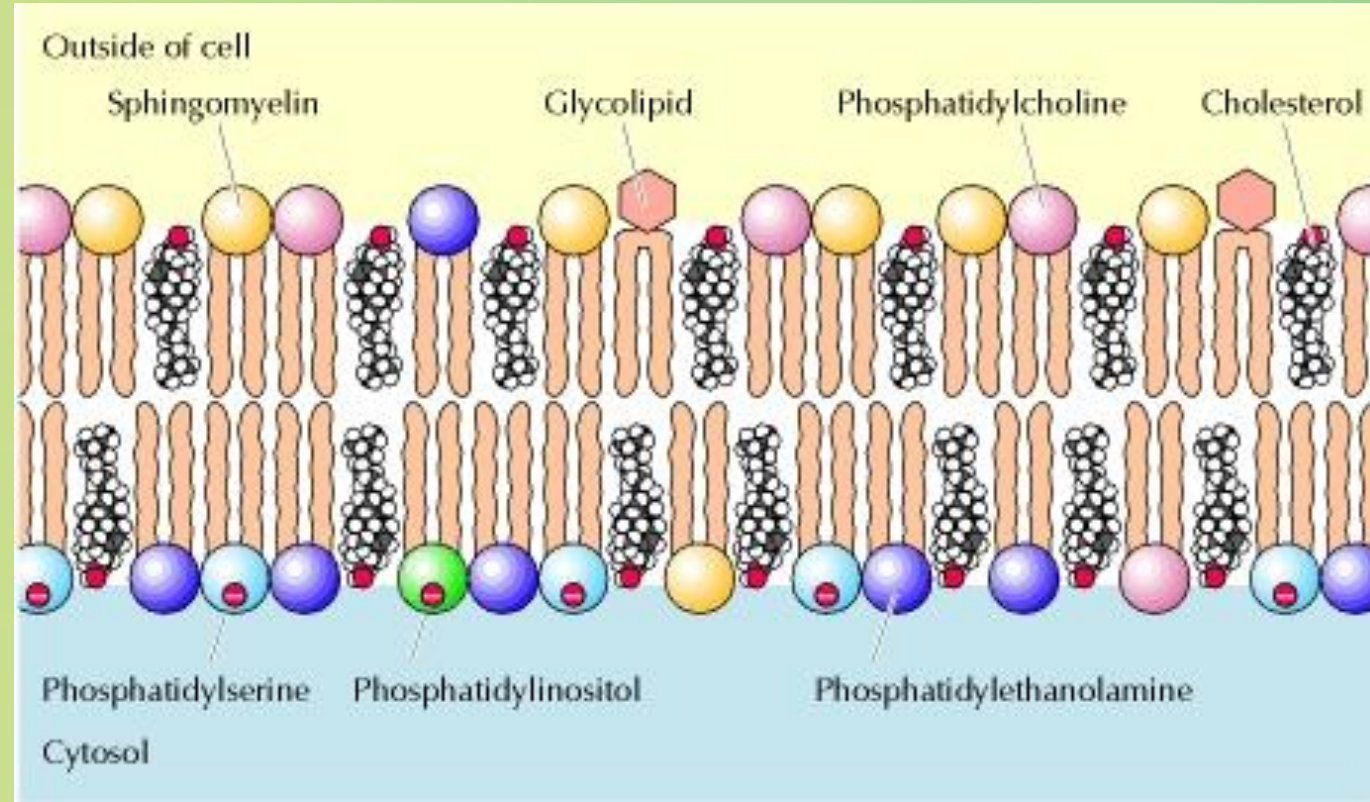
# Composition and properties of plasma membranes



phosphatidyl

- The phospholipids are asymmetrically distributed between the two halves of the membrane bilayer.

- The outer leaflet: Ⓟcholine, **sphingomyelin** found in myelin mainly
- The inner leaflet: Ⓟethanolamine, Ⓟserine, Ⓟinositol (minor)
  - Ⓟinositol has a role in cell signaling.
- Glycolipids are found exclusively on the outer membrane.



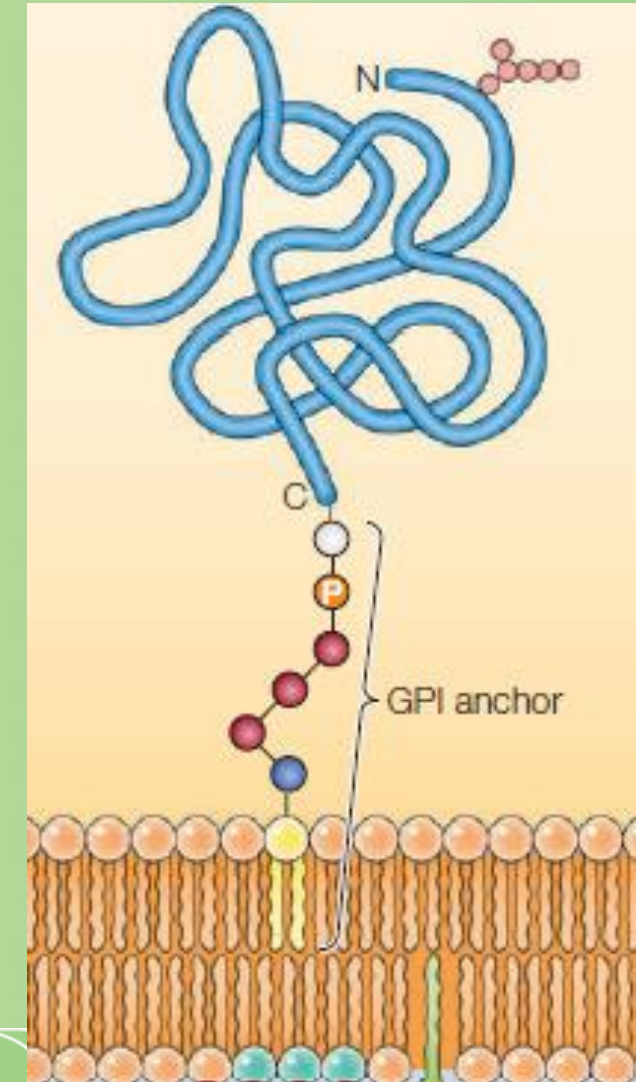
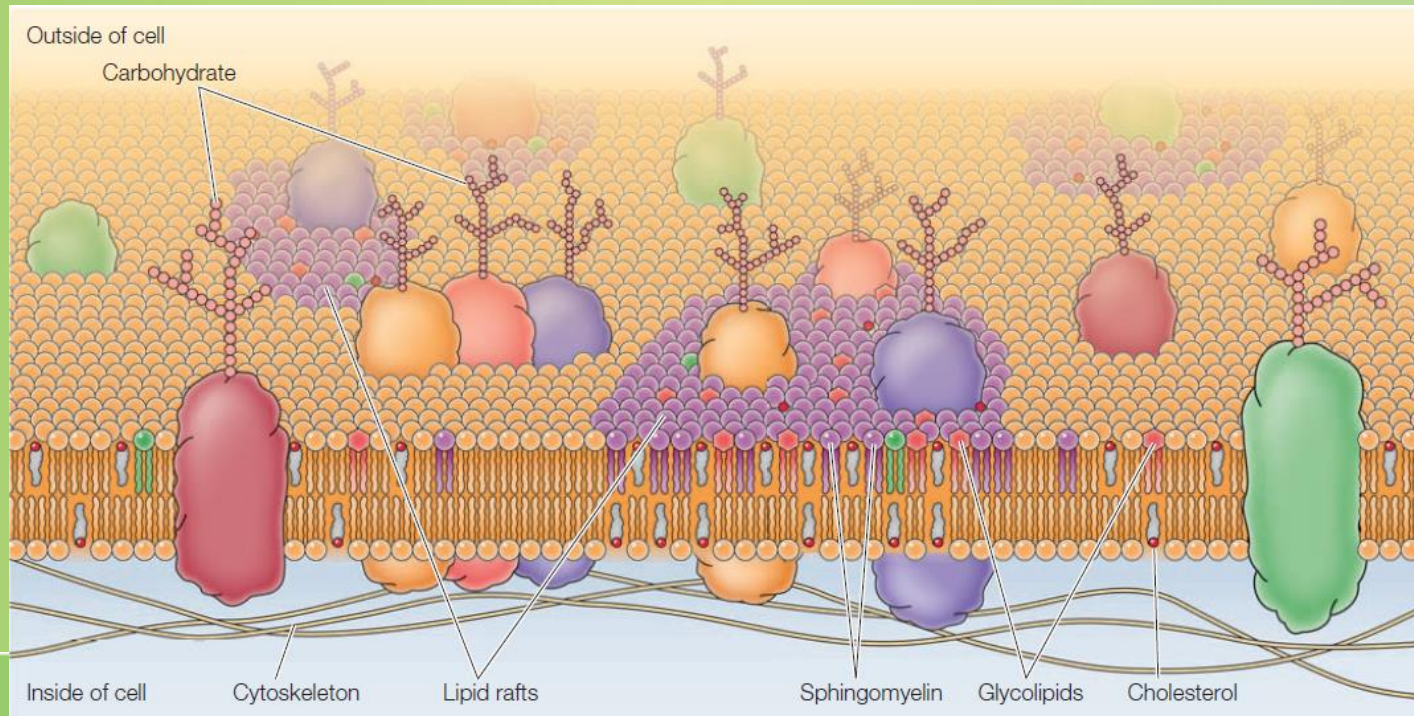


# Lipid rafts

Remember fluid mosaic model !



- Specialized membrane regions with clusters of cholesterol and the sphingolipids (sphingomyelin and glycolipids).
- Rafts are enriched in glycosylphosphatidylinositol (GPI)-anchored proteins, and proteins involved in signal transduction and intracellular vesicular trafficking (transport).



# Caveolae (Latin for “little caves”)

- They are a subset of lipid rafts that require cholesterol for their formation.
- They are formed the membrane protein caveolin, which interacts with cholesterol and the cytoplasmic protein cavin.
- They are important for several cellular activities, including endocytosis, cell signaling, regulation of lipid transport, and protection of the plasma membrane against mechanical stress.

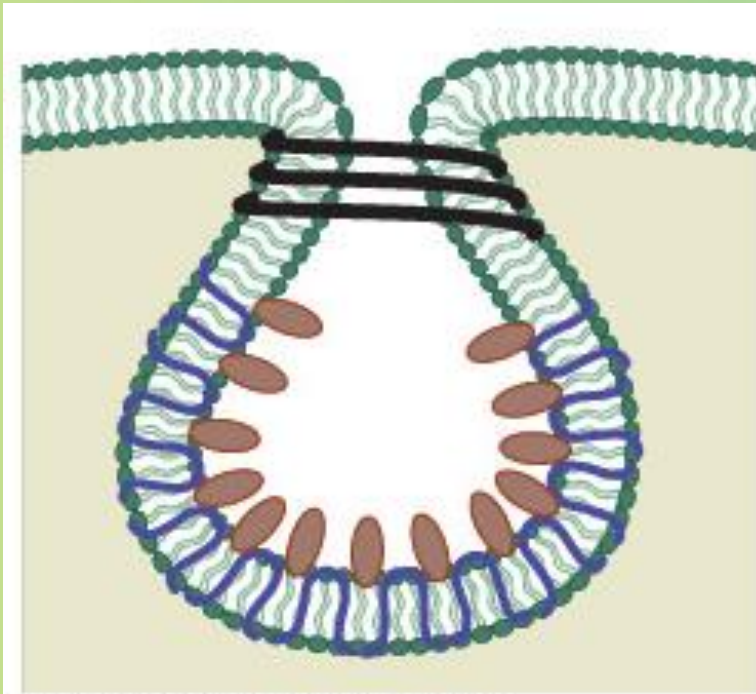
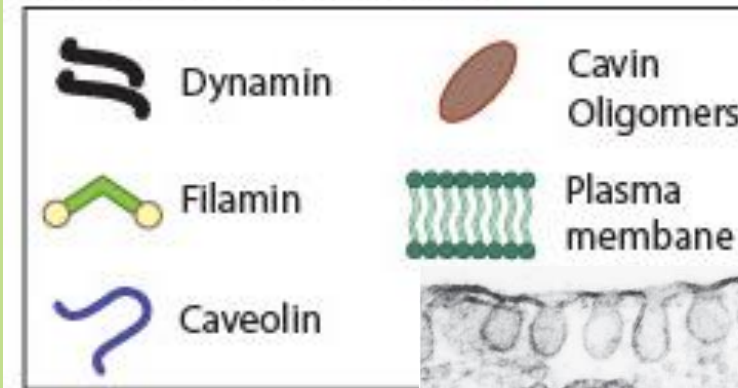


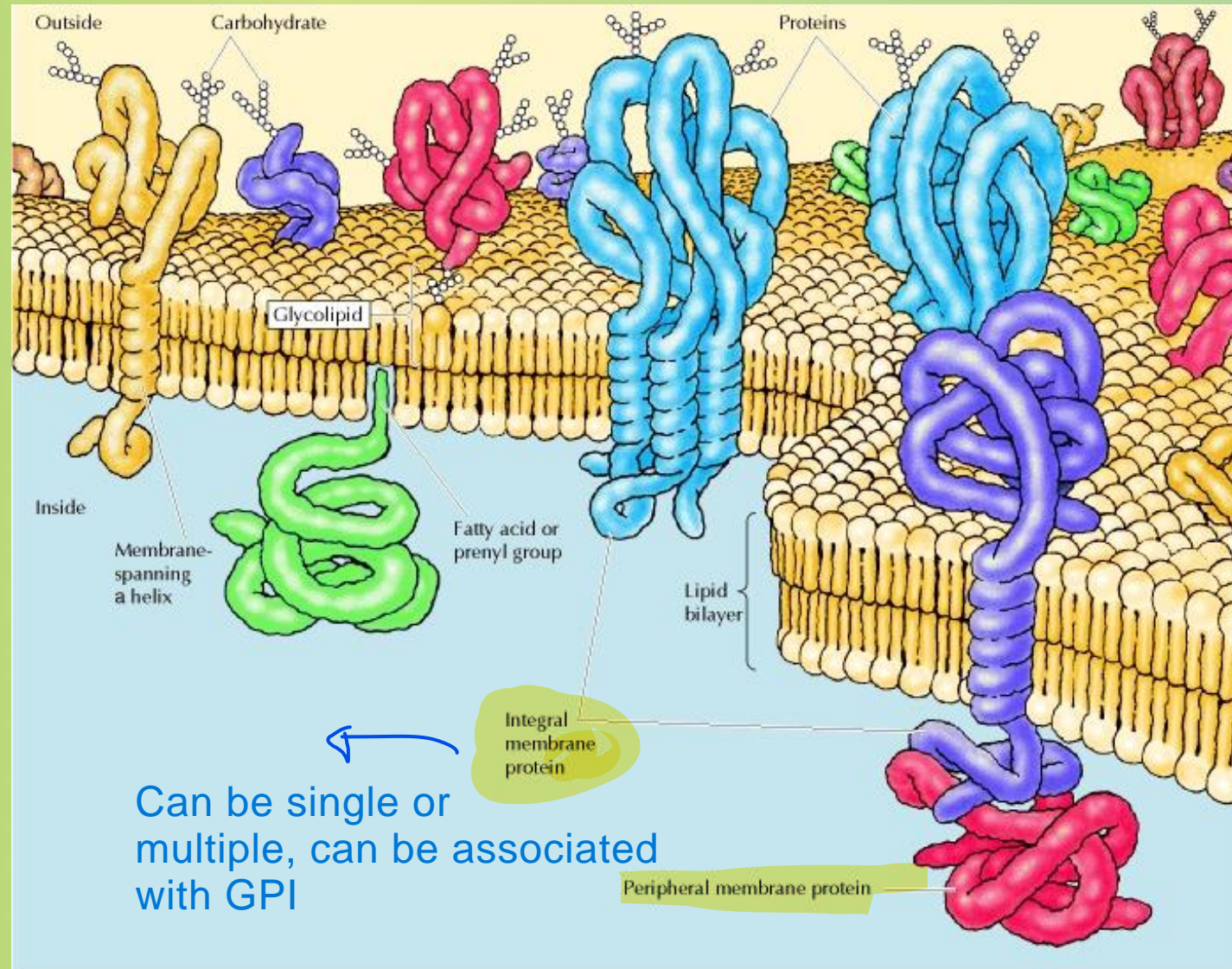
Fig. Simplified model of the Caveolae



Lipids rafts are rich in? (exam question)



# Membrane proteins

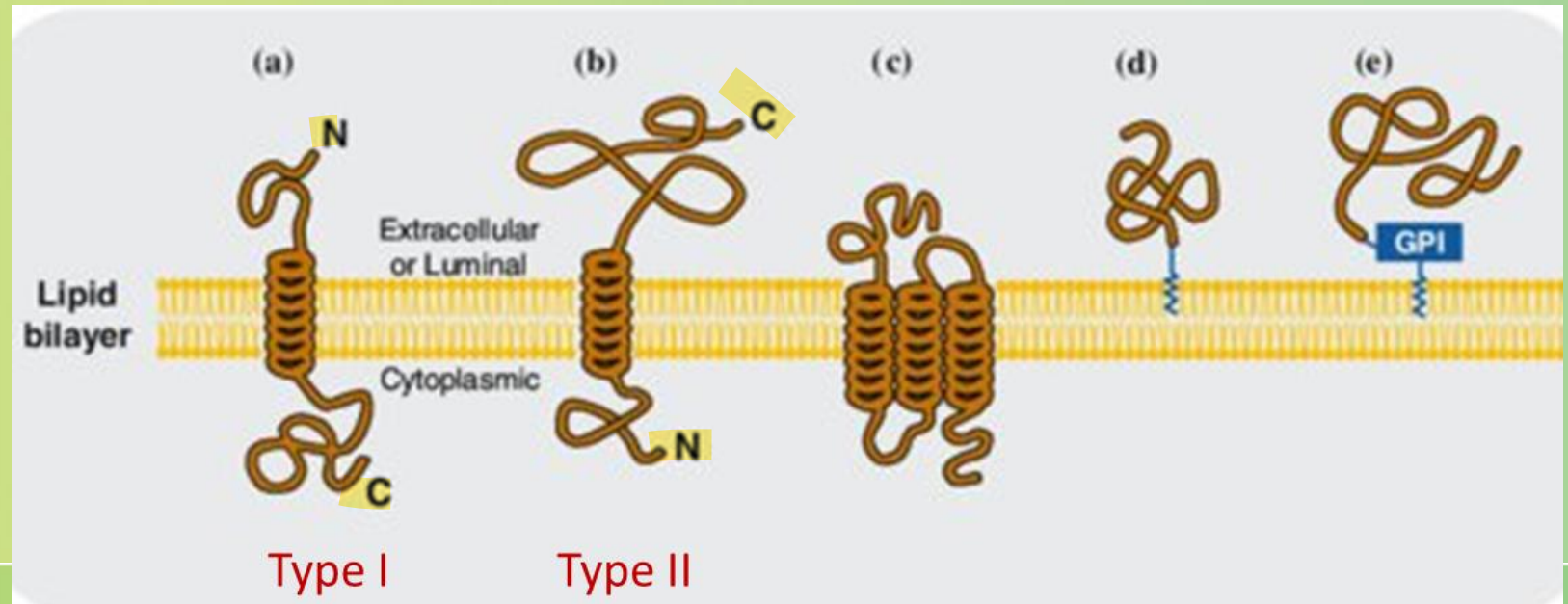


# Types of membrane proteins



Can interact with lipids (hydrophobic interactions) or phosphate (electrostatic)

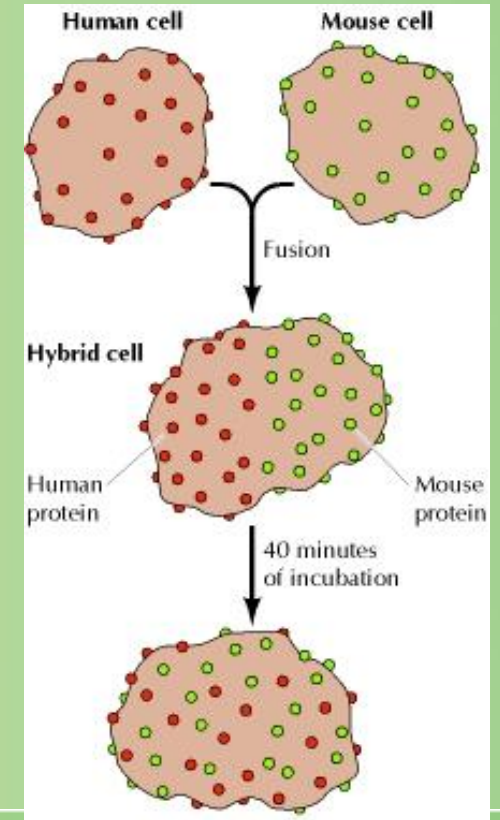
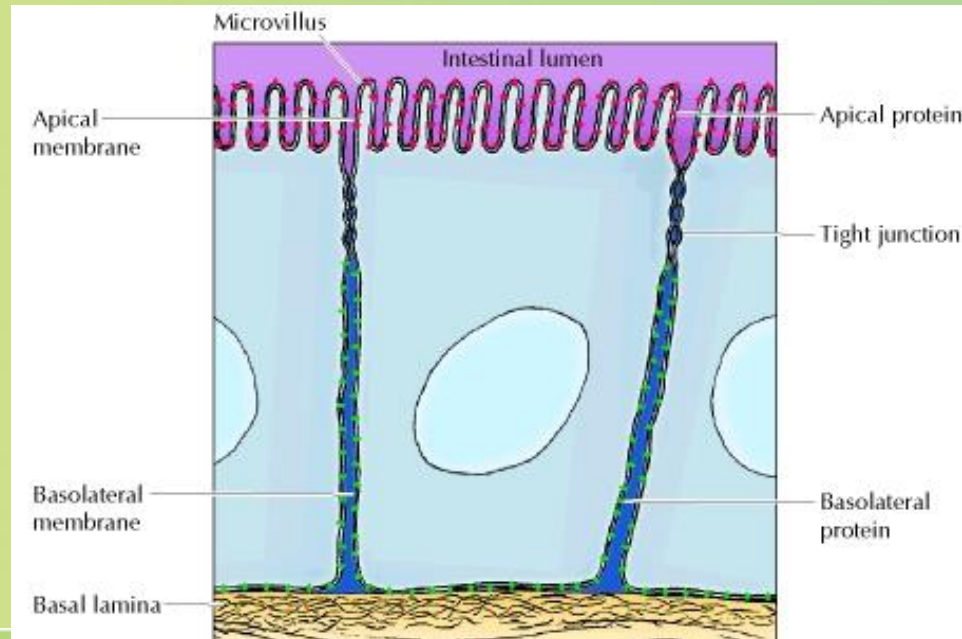
- Peripheral membrane proteins are indirectly and loosely associated with membranes through protein-protein interactions, mainly ionic bonds.
- Integral membrane proteins have some of their **helical** parts inserted into the lipid bilayer.
  - Single-pass (type I or II) or multi-pass proteins.
- Lipid-anchored membrane proteins (myristoylation, palmitoylation, glycosylphosphatidylinositol)





# Protein mobility

- Proteins and lipids are able to diffuse laterally through the membrane.
- The mobility of membrane proteins is restricted by
  - Their association with the cytoskeleton
  - Specific membrane domains, which maintain the specific distribution of apical and basolateral proteins
  - Specific lipid composition (e.g. lipid rafts).



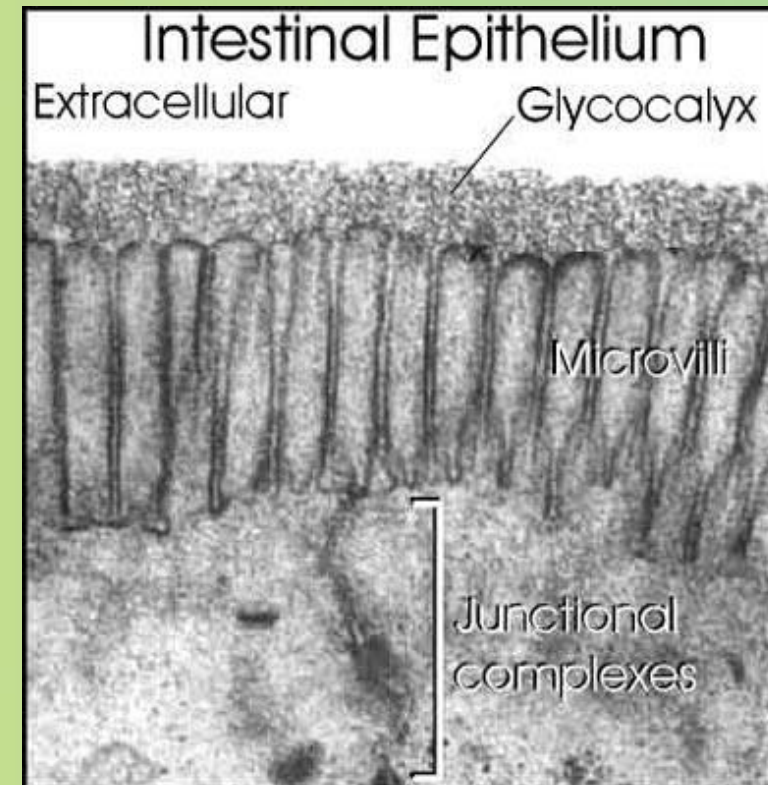
# Glycocalyx



- The surface of the cell is covered by a carbohydrate coat, known as the glycocalyx, formed by the oligosaccharides of glycolipids and glycoproteins.

## Functions:

- Cell-cell interactions such as immune cells
- Protection of cell surface from ionic and mechanical stress
- Formation of a barrier for microorganisms

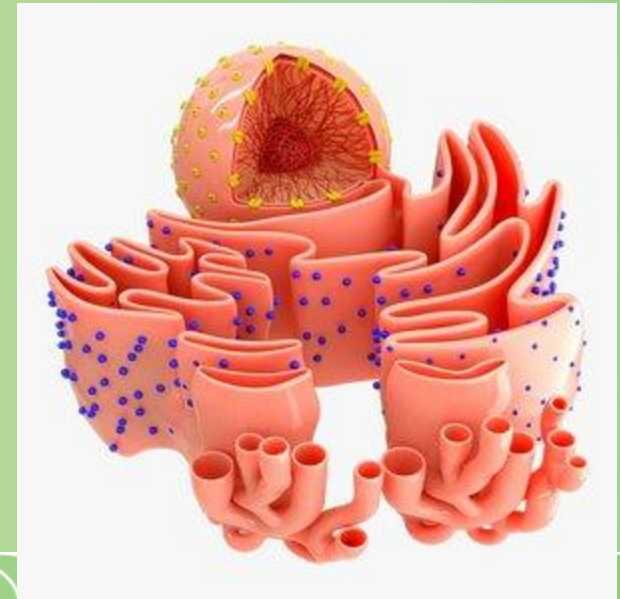
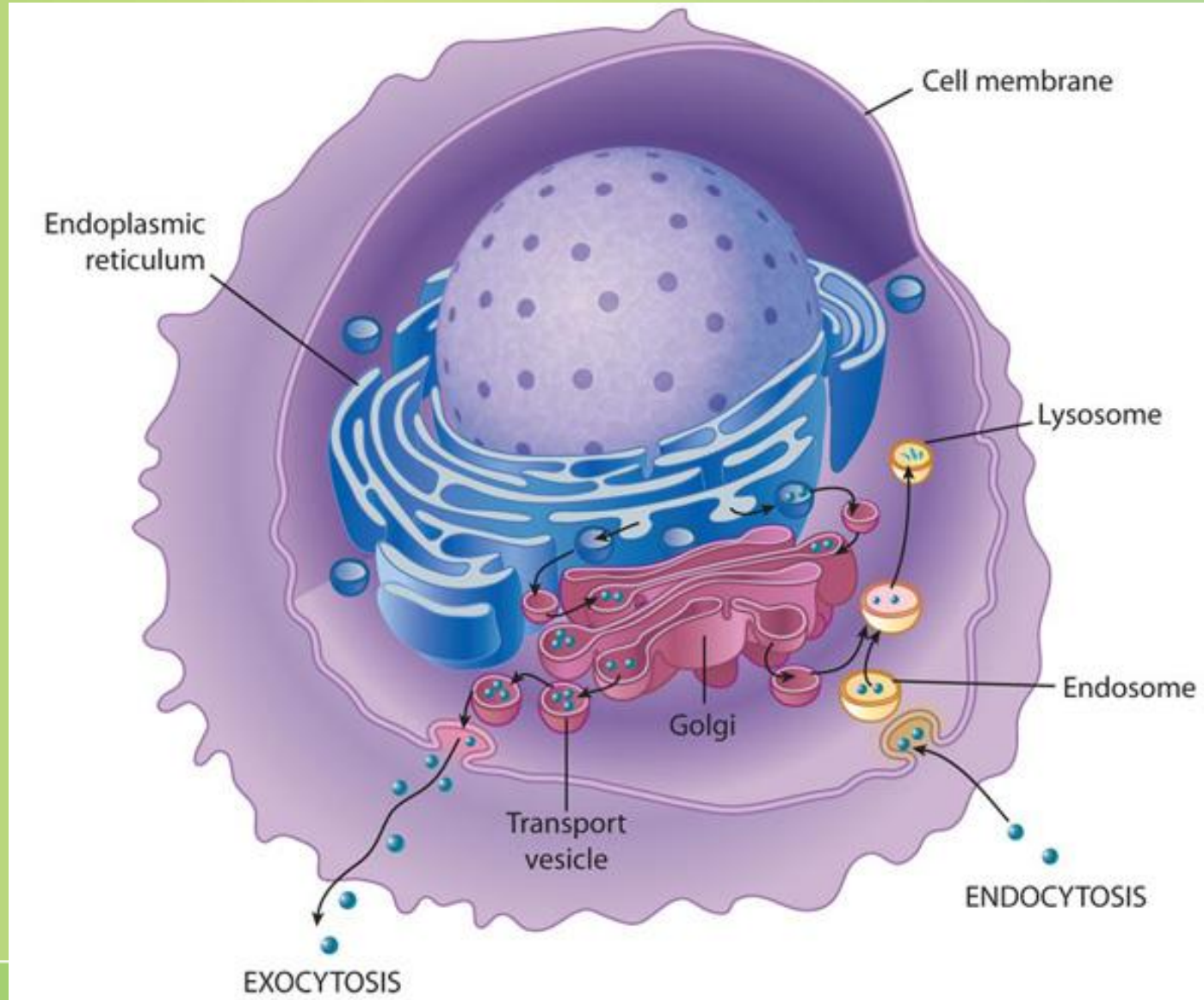






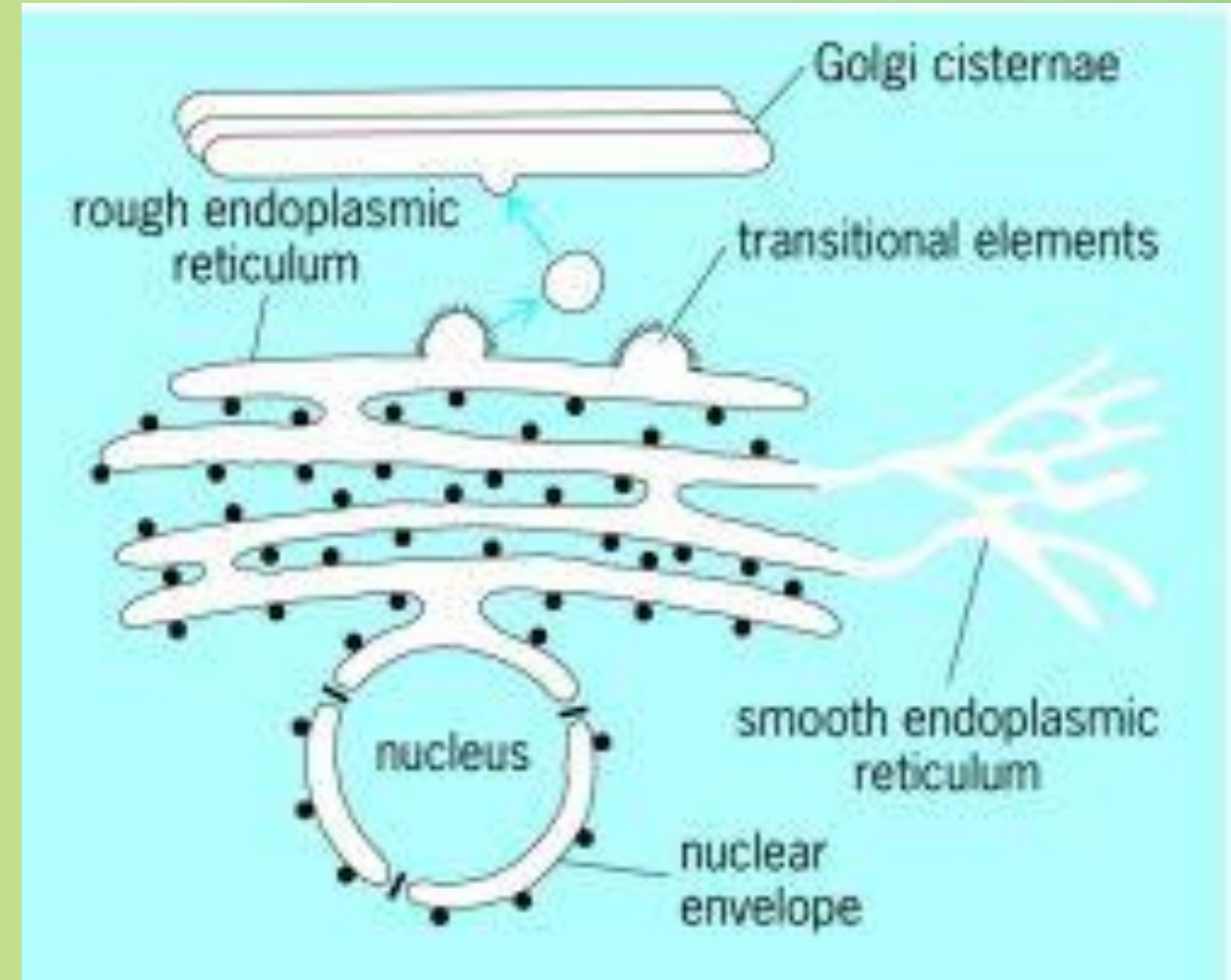
# *Protein sorting (endoplasmic reticulum)*

# An overview



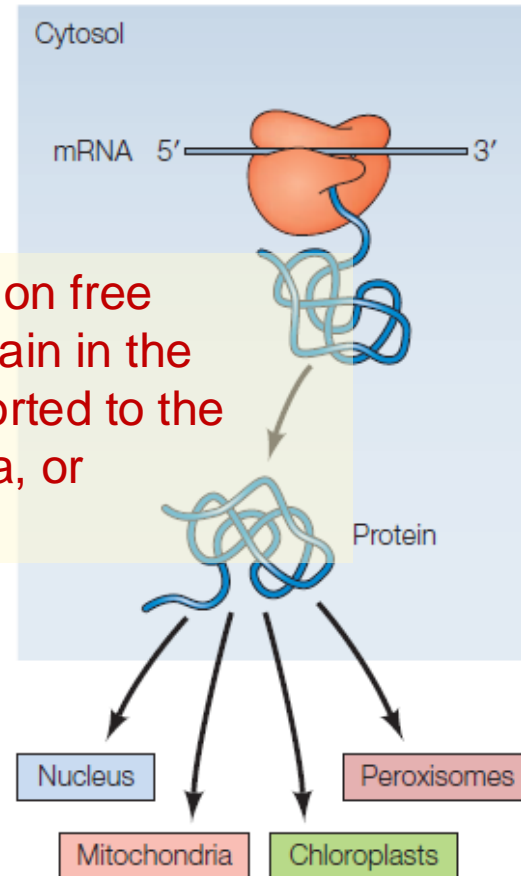
# Endoplasmic reticulum (ER)

- It is a network of membrane-enclosed tubules and sacs (cisternae) that extends from the nuclear membrane throughout the cytoplasm.
- It is the largest organelle of most eukaryotic cells.
- The rough ER: covered by ribosomes on its outer surface and functions in protein processing.
- The smooth ER: lipid metabolism
- Transitional ER: exit of vesicles to Golgi apparatus



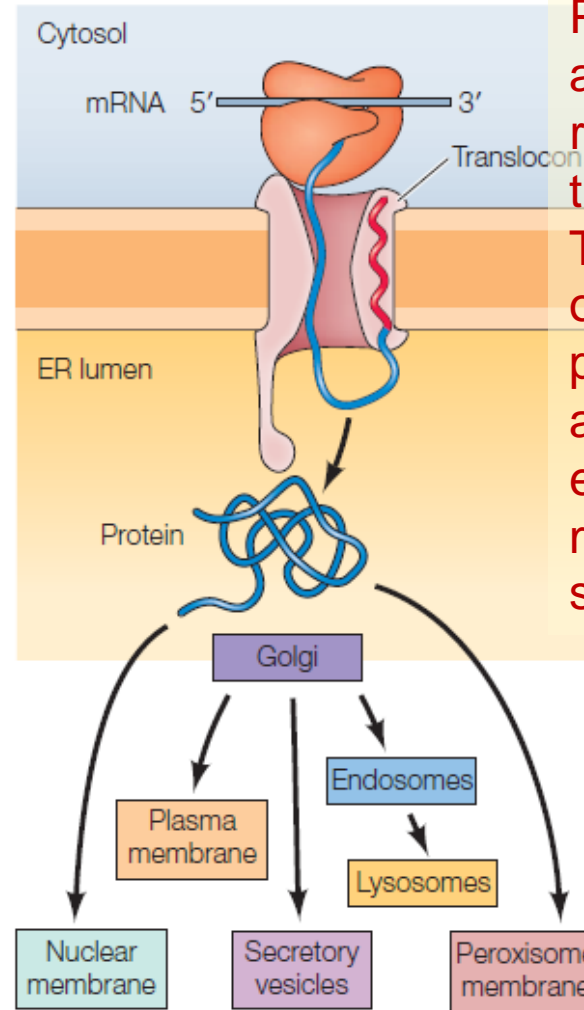
# Protein sorting

Free ribosomes in cytosol



Proteins synthesized on free ribosomes either remain in the cytosol or are transported to the nucleus, mitochondria, or peroxisomes.

Membrane-bound ribosomes



Proteins containing **signal sequences** are synthesized on membrane-bound ribosomes and translocated directly into the ER.

These proteins may stay within the ER or transported to nuclear membranes, peroxisomal membranes, or the Golgi apparatus and, from there, to endosomes, lysosomes, the plasma membrane, or outside the cell via secretory vesicles.

*In cell biology, a lumen is a membrane-defined space that is found inside several organelles, cellular components, or structures*

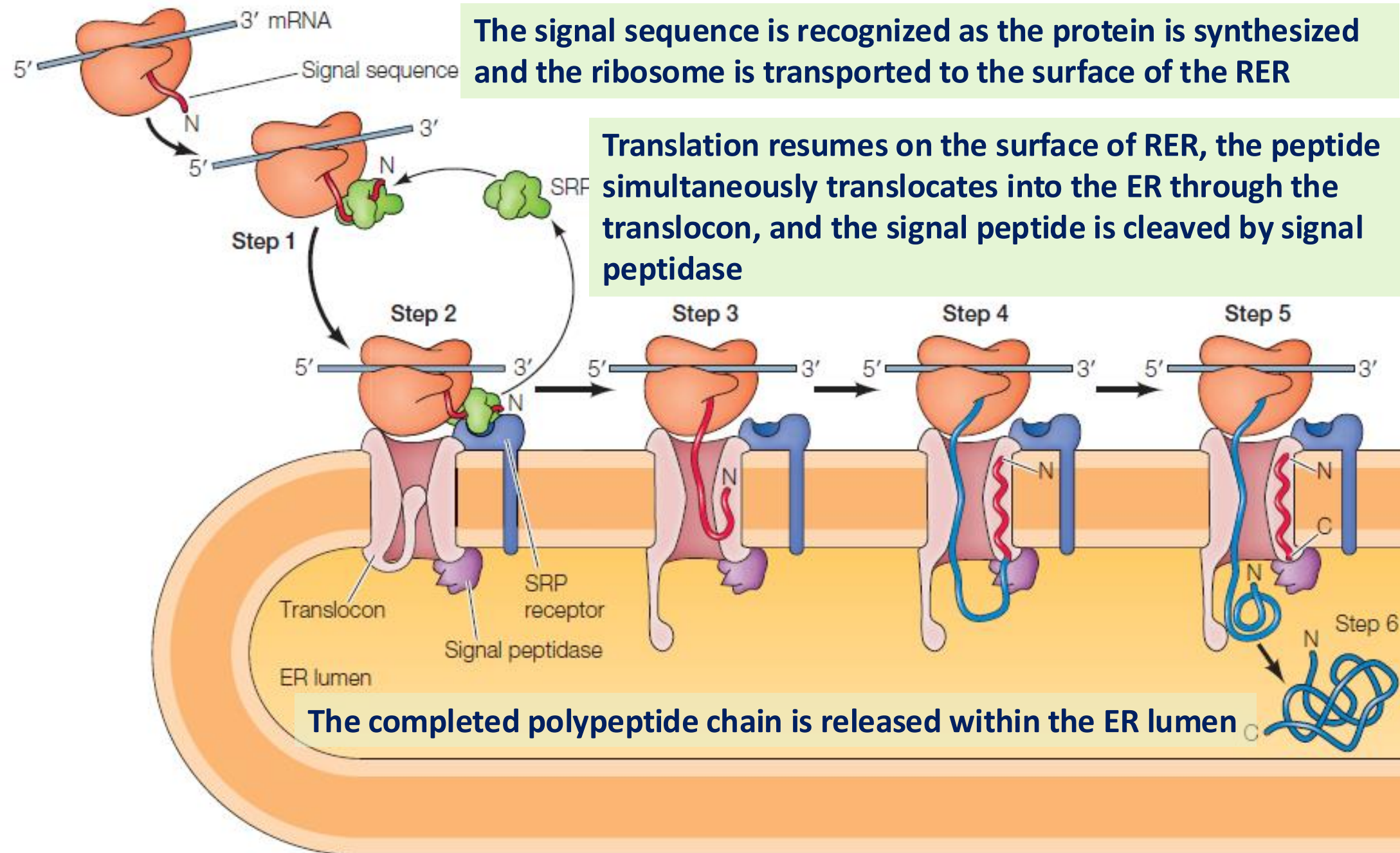


**Signal sequence:** a short sequence of amino acids of the polypeptide at the amino terminus. It is then cleaved from the polypeptide chain during its transfer into the ER lumen.



The signal sequence is recognized as the protein is synthesized and the ribosome is transported to the surface of the RER

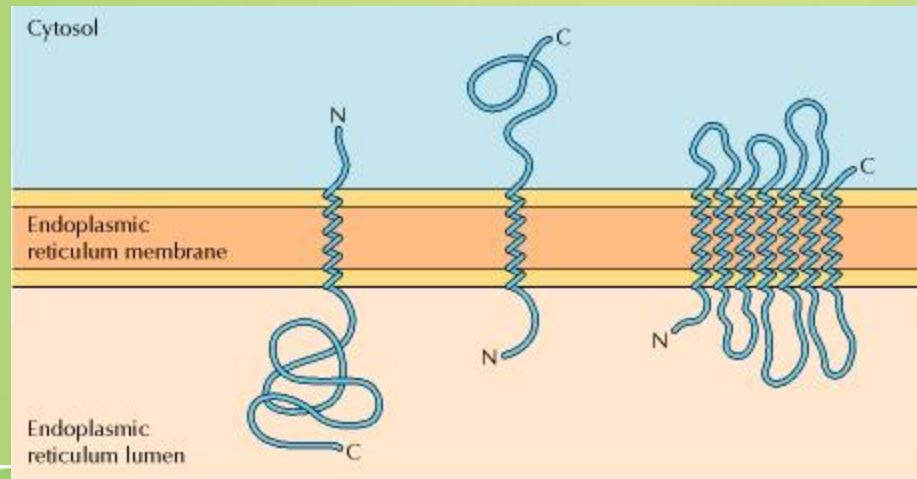
Translation resumes on the surface of RER, the peptide simultaneously translocates into the ER through the translocon, and the signal peptide is cleaved by signal peptidase



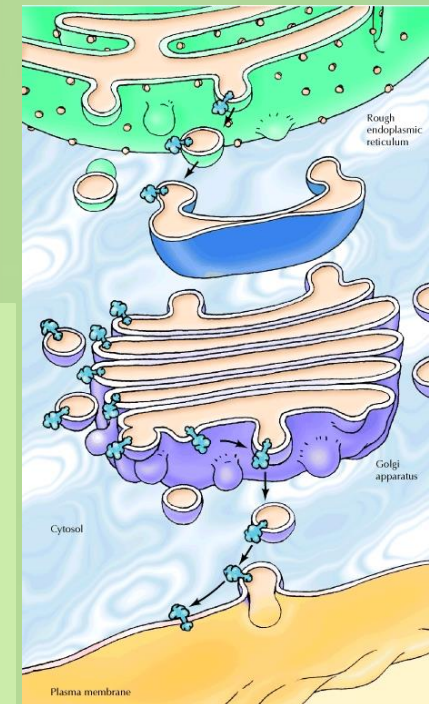
The completed polypeptide chain is released within the ER lumen

# Pathways of protein sorting

- Secretory, ER, Golgi apparatus, and lysosomal proteins are released into the lumen of the ER.
- Membranous proteins are initially inserted into the ER membrane.
- Considerations
  - Single vs. multiple membrane-spanning region
  - Orientation of N- and C-termini

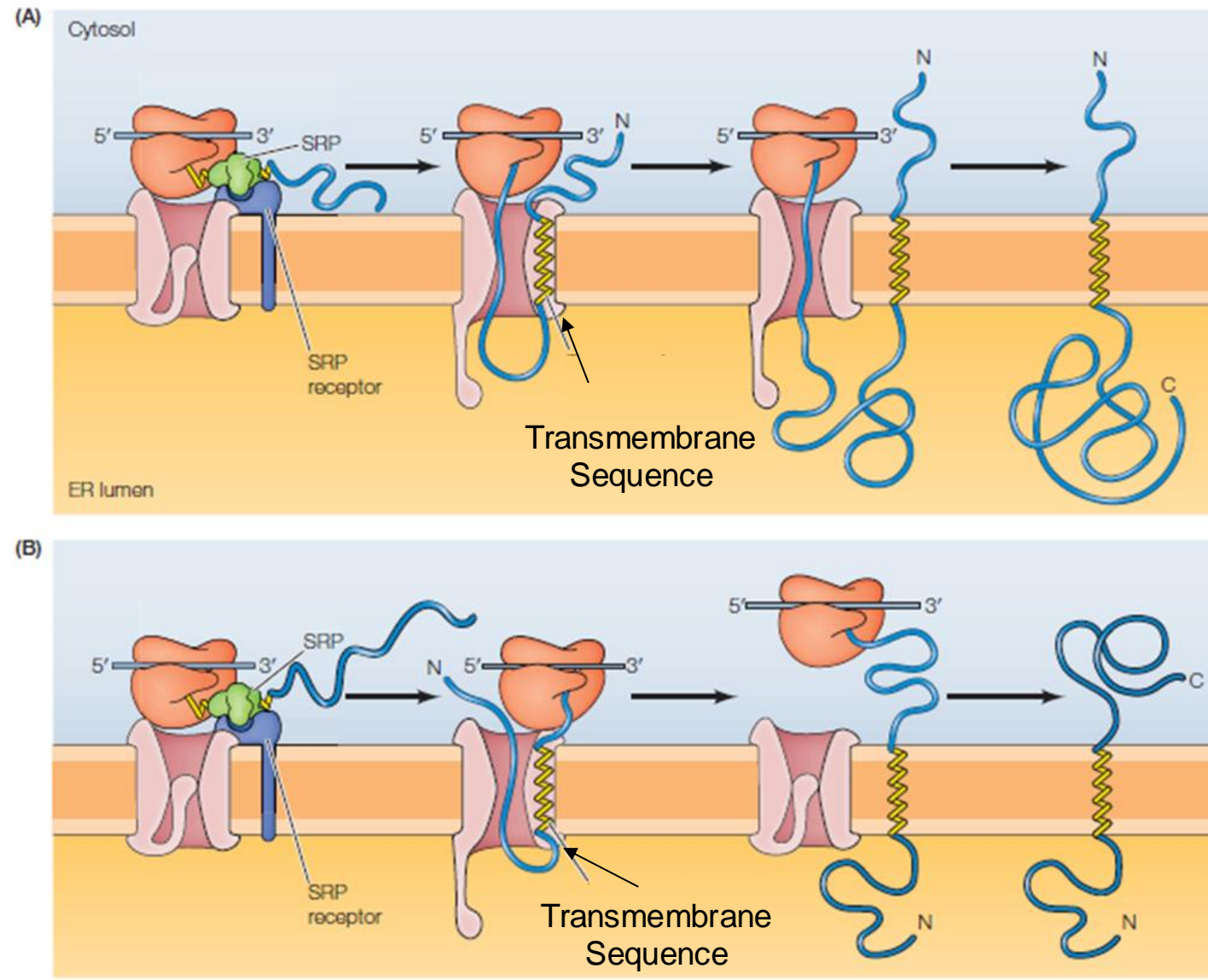


**The lumens of the ER and Golgi apparatus are topologically equivalent to the exterior of the cell.**



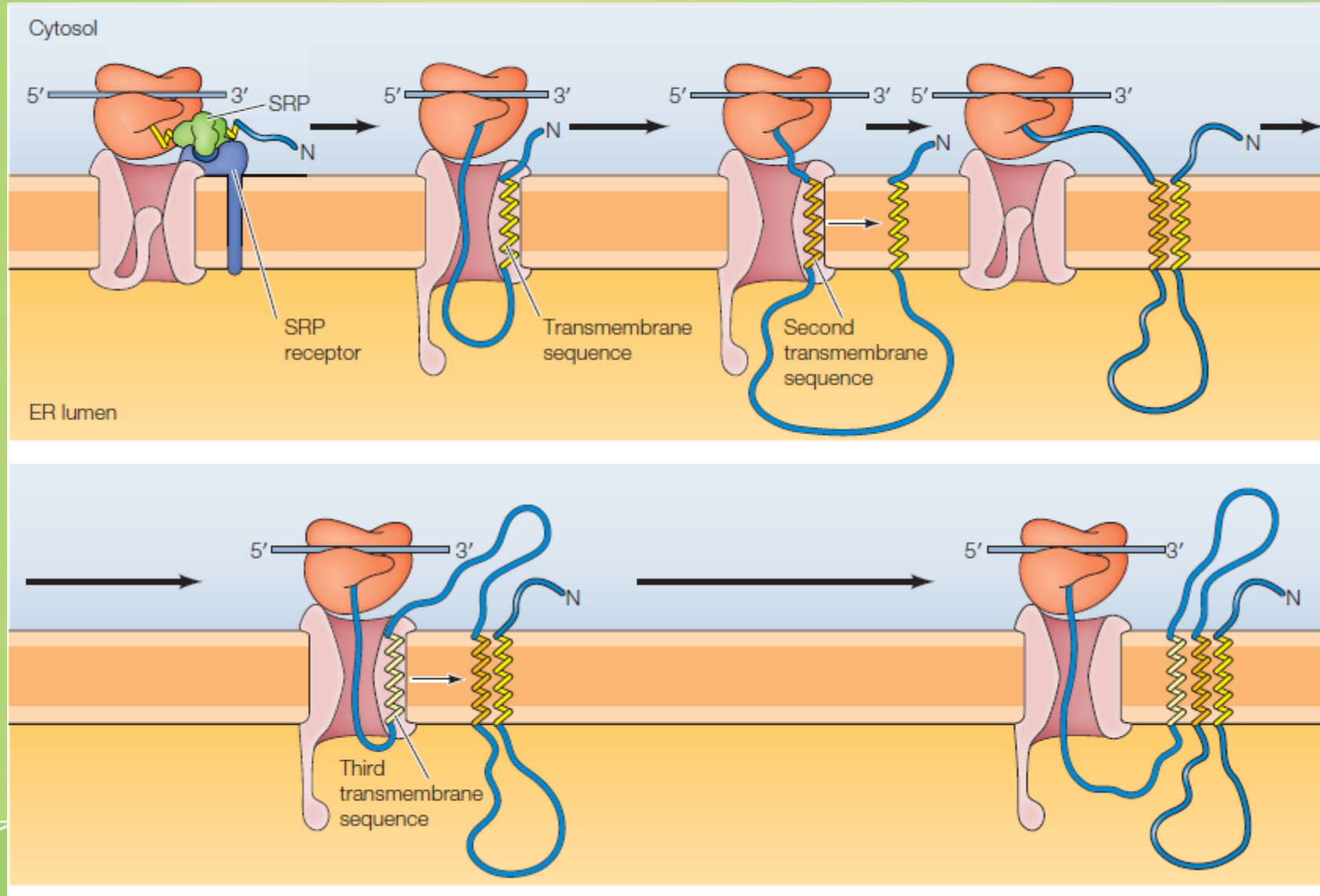
# Insertion of membrane proteins via internal transmembrane sequences

- Translocation of the polypeptide chain stops when the translocon recognizes a transmembrane sequence allowing the protein to become anchored in the ER membrane.
- The direction of the internal transmembrane sequence determines the direction of insertion and orientation of the protein ends.



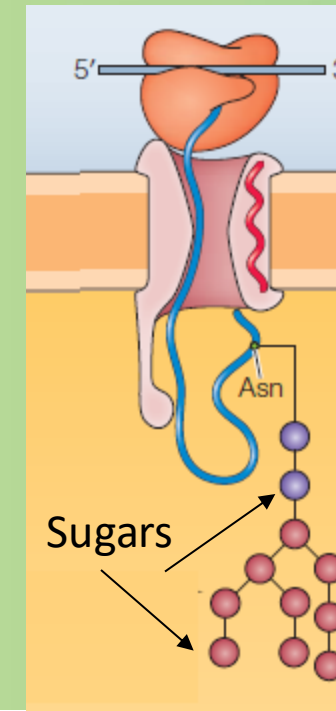
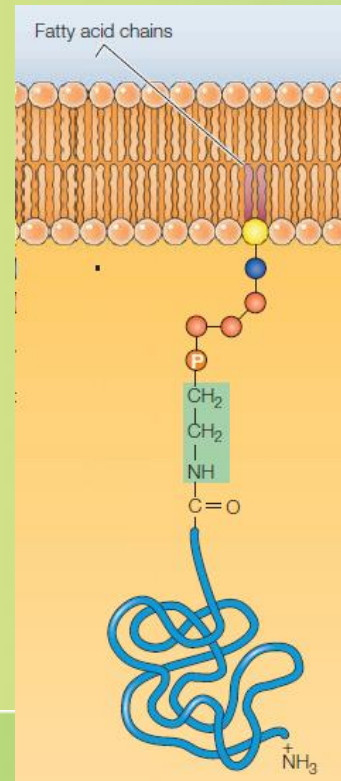
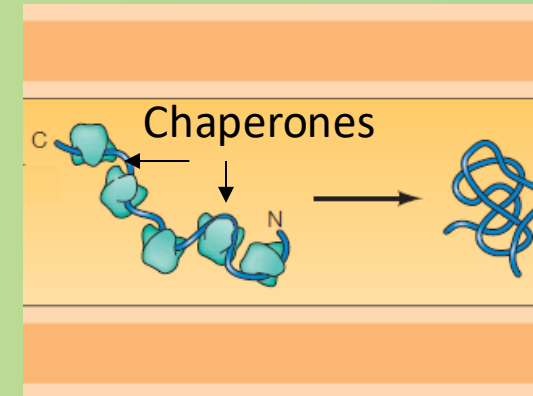


# Multi-transmembrane domain proteins have multiple transmembrane sequences



# Once inside the ER, proteins are

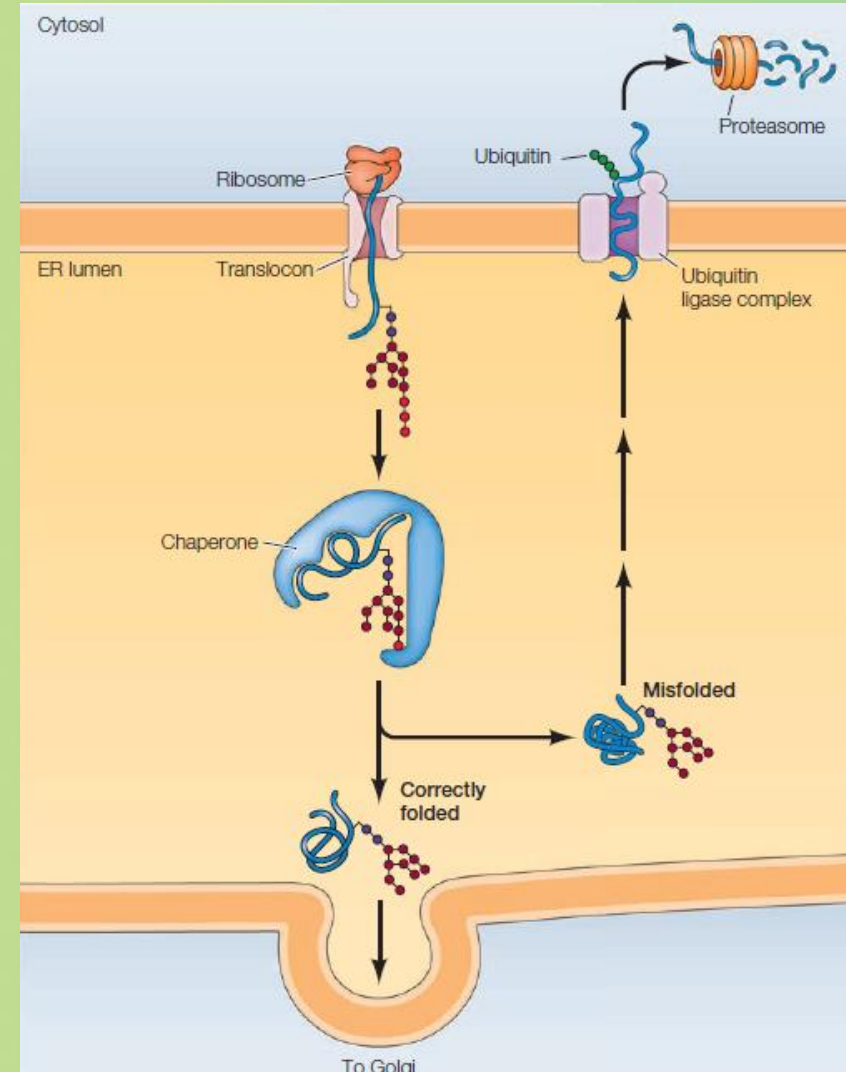
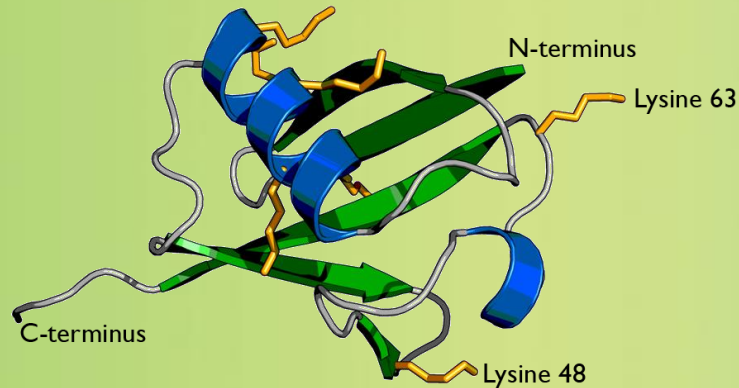
- Folded (with the help of chaperones)
- Complexed (quaternary structure)
  - Disulfide bond formation by protein disulfide isomerase
- Glycosylated
- Anchored by lipids



# Protein folding and ER-associated degradation (ERAD)



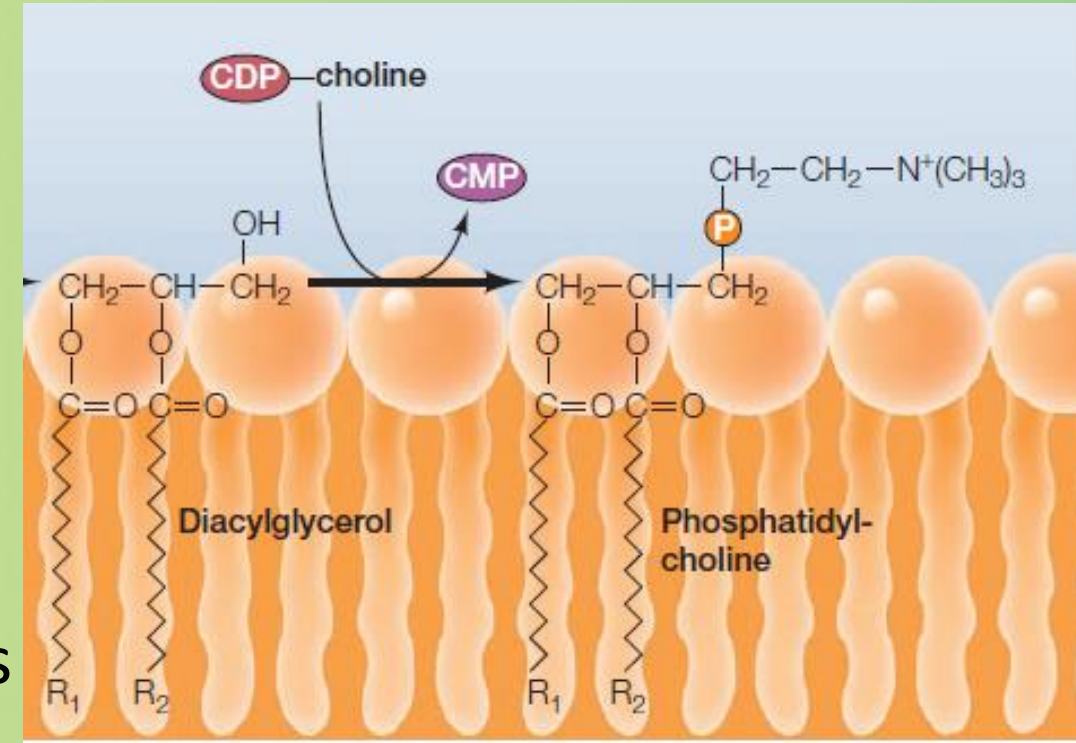
- If correctly folded, proteins move on.
- If misfolded, proteins are sent to the cytosol, ubiquitylated (addition of small proteins called ubiquitins), and degraded in the proteasome.





# Synthesis of phospholipids in ER

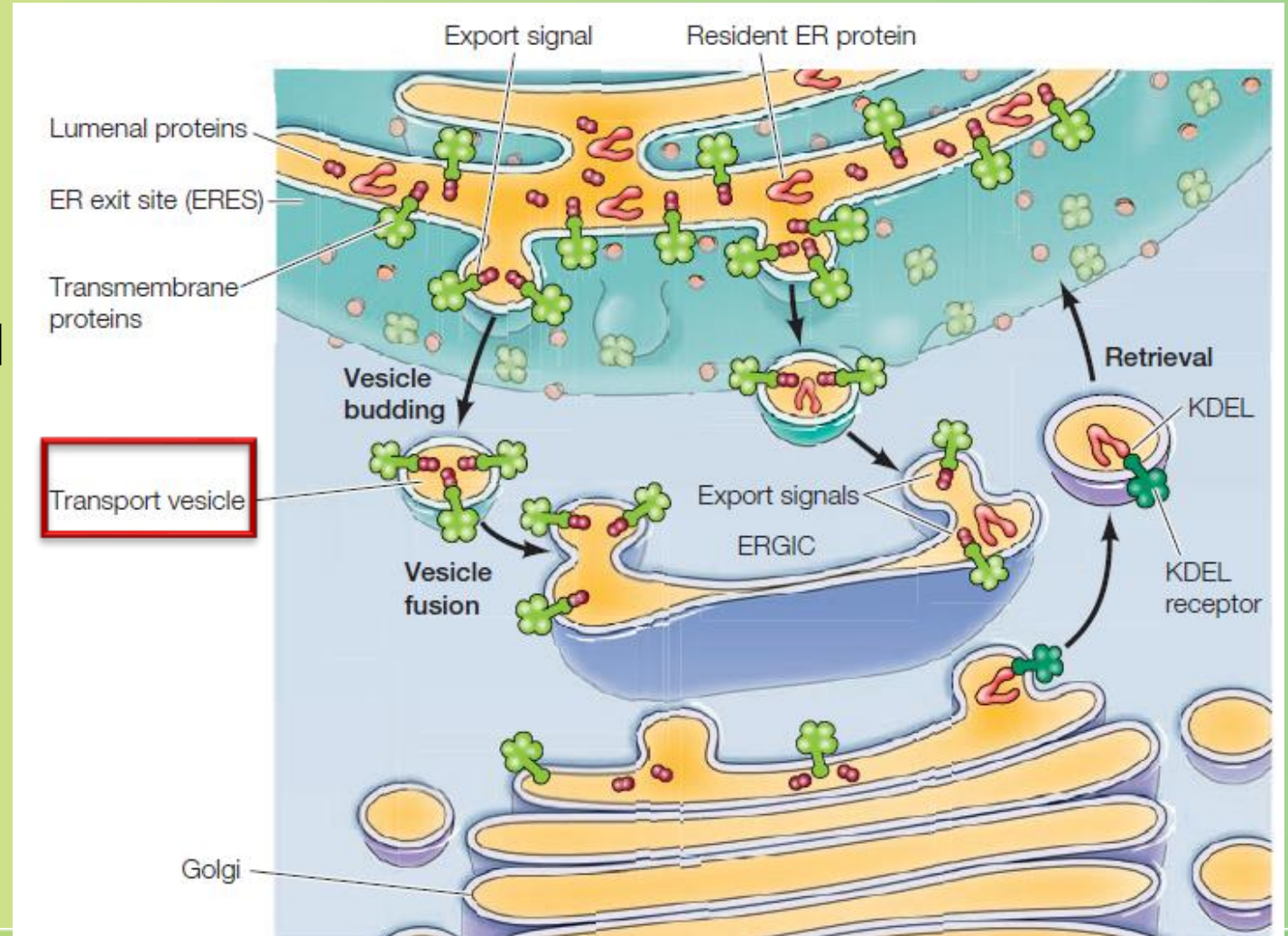
- The smooth ER is the major site of synthesis of:
  - Membrane glycerophospholipids, which are then transported from the SER to other membranes.
  - Sphingophospholipids (like ceramides and glycolipids) and steroids.
    - Large amounts of smooth ER are found in steroid-producing cells, such as those in the testis and ovary.
- SER is abundant in the liver, which contains enzymes that metabolize various lipid-soluble compounds.



# ER-Golgi intermediate compartment (ERGIC)



- Proteins and lipids are carried from the ER to the Golgi in transport vesicles, which fuse with the ER–Golgi intermediate compartment (ERGIC), and are then carried to the Golgi.



# Retention of ER protein

- Many proteins with KDEL sequence (Lys-Asp-Glu-Leu) at C-terminus are retained in the ER lumen.
- If the sequence is deleted, the protein is transported to the Golgi and secreted from the cell.
- Addition of the sequence causes a protein to be retained in the ER.

