Start video lecture uploaded on youtube on 6:35

Cell Membranes

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Warning: The slides are a bit crowded
The last three slides were not shoot on video because the the first two videos were taken from different sections

Cell and Molecular Biology

Done by Munia Karmi

Organelles

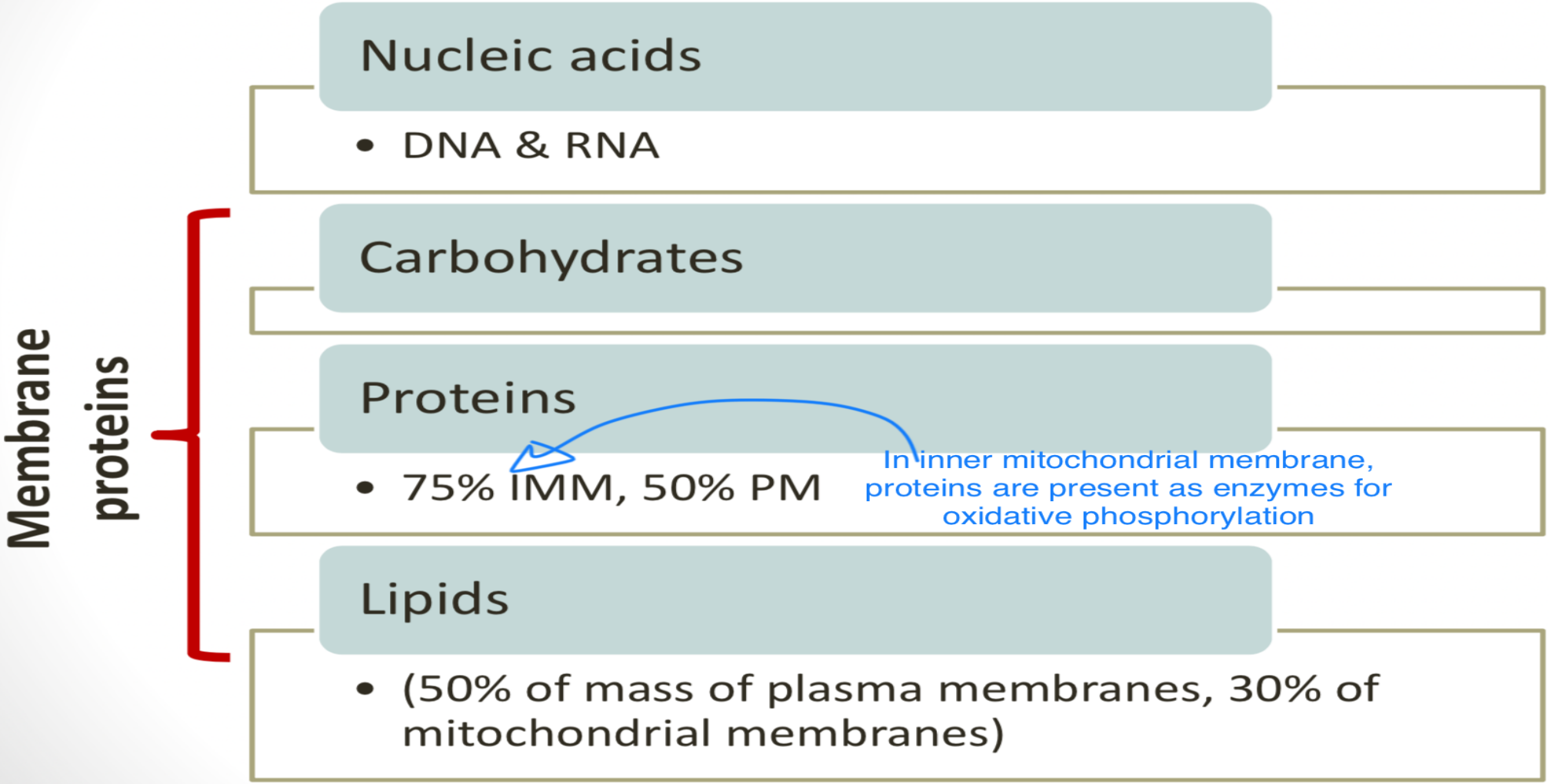
Don't memorize the fxns
We will discuss them in detail later

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 components of cells



Composition of membranes

Myelin sheaths wrap neuron axons to isolate electrical flow along most parts of the axon, they are mainly made up of lipids which are completely non-polar

Table 8.18. Mass % Biochemical Composition of Cell and Organelle Membranes

Type of Membrane Molecule	Liver Cell Plasma Membrane	Red Cell Plasma Membrane	Myelin Sheath	Mitochondrion Inner/Outer Membranes	Endoplasmic Reticulum Membrane	*E.coli* (Bacterial Membrane)
Lipid	--	40%	~81%	~24%/~48%	--	--
Protein	~50%	52%	~19%	~76%/~52%	~50%	~50%
Carbohydrate	--	8%	--	--	--	--
Lipid Class:						
Cholesterol	17%	23%	22%	3%	6%	0%
Phospholipids						
Phosphatidylethanolamine	7%	8%	15%	35%	17%	70%
Phosphatidylserine	4%	7%	9%	2%	5%	trace
Phosphatidylcholine	24%	17%	10%	39%	40%	0%
Sphingomyelin	19%	18%	8%	0%	5%	0%
Glycolipids	7%	3%	28%	trace	trace	0%
Other lipids	22%	13%	8%	21%	27%	30%

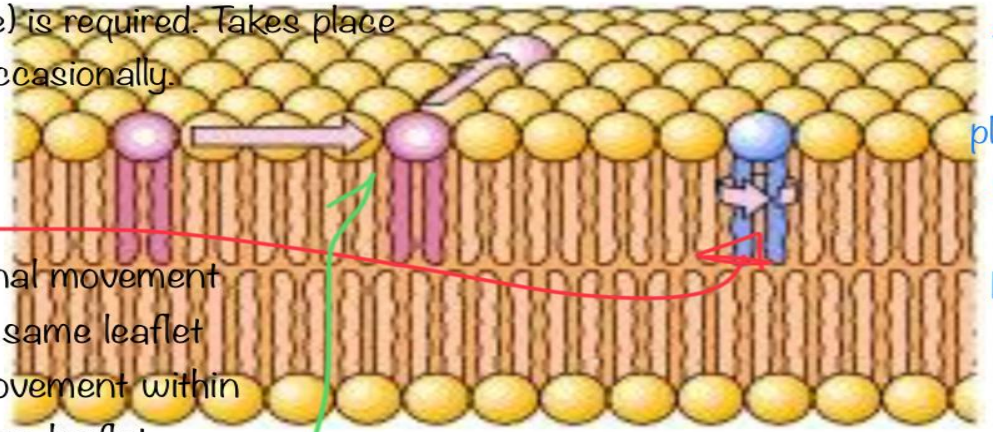
Don't memorize

Made of proteins and lipids in general

Composition and properties of membranes

Movement types

1) flip-flop movement: rare, since the polar head has to cross the non polar area, which is energetically unfavorable so an enzyme(flippase) is required. Takes place occasionally.



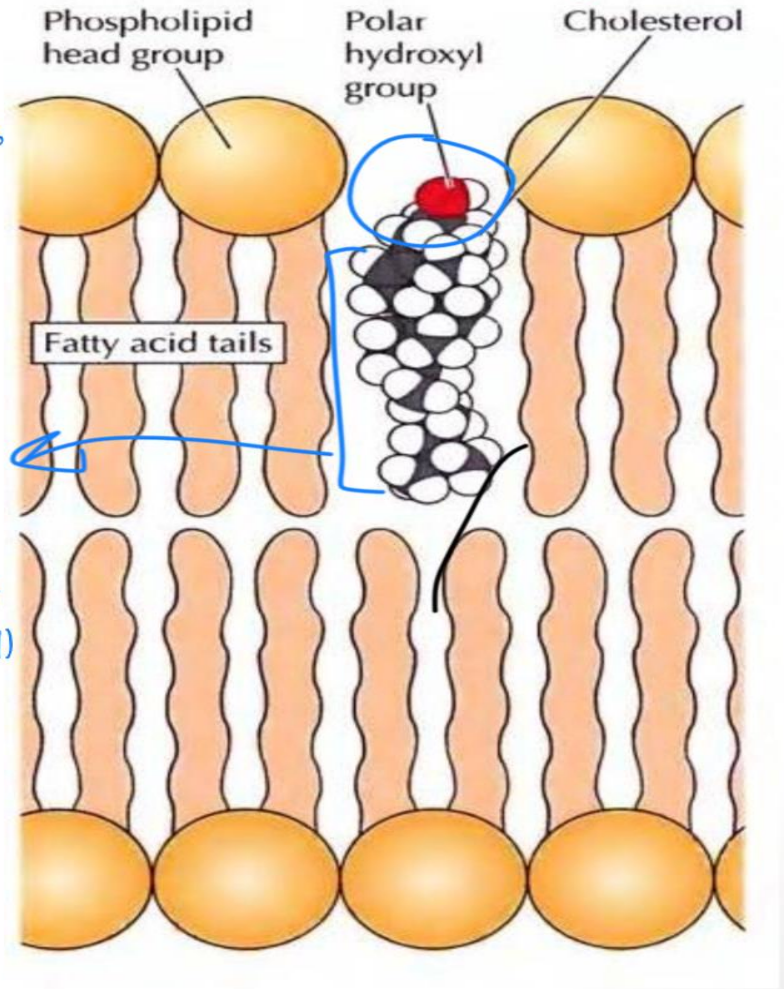
2) Rotational movement within the same leaflet

3) lateral movement within the same leaflet

Phospholipids can rotate and move laterally within a layer

This Nonpolar steroid nucleus is made of four planner fused rings, which make a big number of hydrophobic rxns with adjacent phospholipids, therefore, high concentration of cholesterol in a membrane makes it more rigid (less fluid)

The the phospholipids are dynamic and the best model that describes them is the fluid mosaic model (always moving, different components)

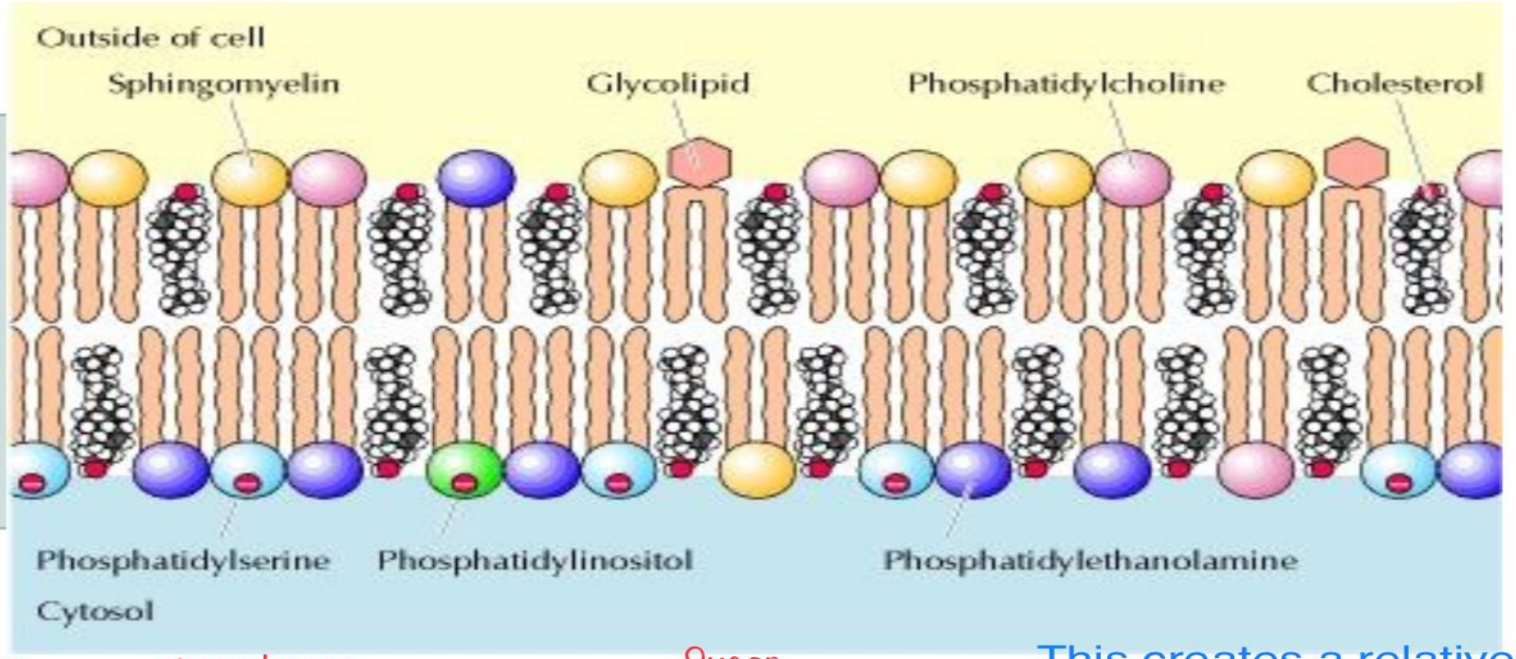


Cholesterol is an essential component of animal plasma membrane.
It is not present in bacteria and plant cells, but the latter cells contain sterols.

Composition and properties of plasma membranes

Not the same lipid on the opposite leaflet

Asymmetric distribution of phospholipids between the two leaflets of the membrane bilayer.



+ve charge +ve charge Sugar

- The outer leaflet: Ⓟcholine, sphingomyelin, glycolipids → This creates a relatively more charge on the outer leaflet an ve charge on the inner leaf
- The inner leaflet: Ⓟethanolamine, Ⓟserine, Ⓟinositol (minor)

+ve charge -ve charge -ve charge

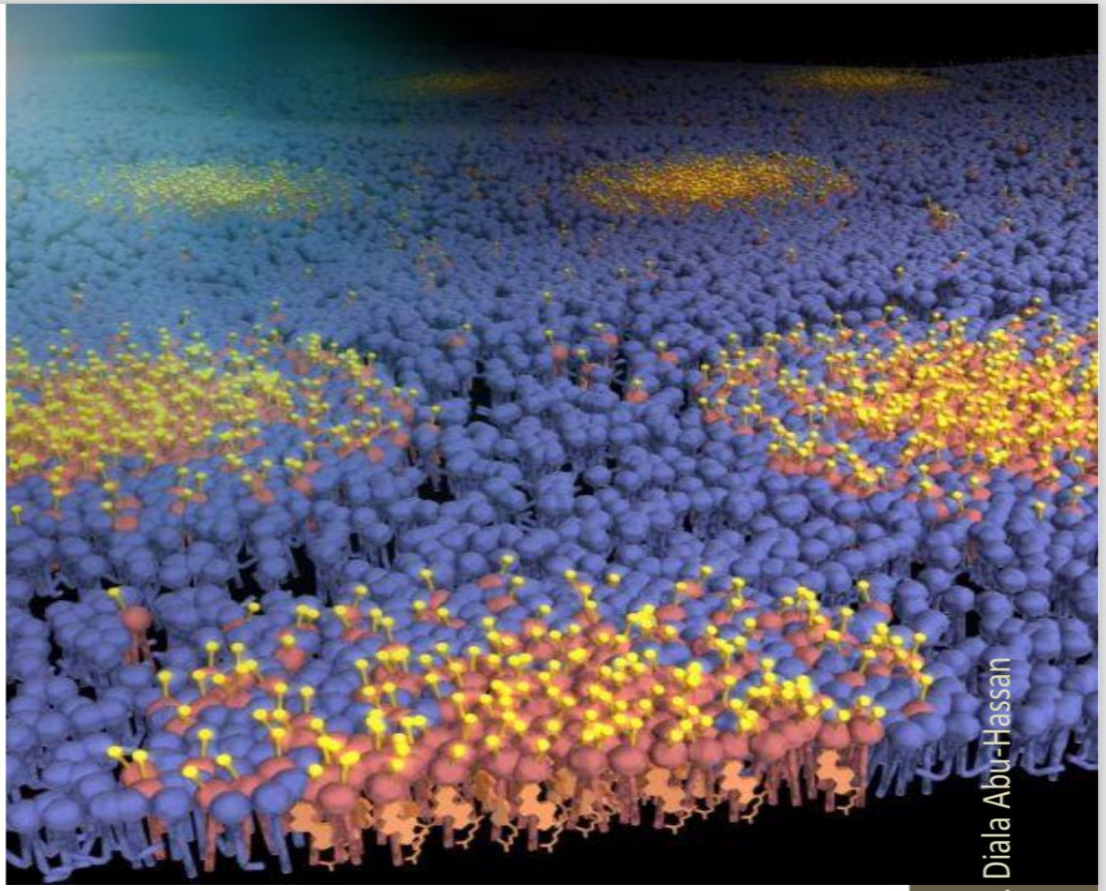
- Ⓟinositol has a role in cell signaling, cell junctions and endocytosis.
- The head groups of both Ⓟserine and Ⓟinositol are negatively charged, thus, the cytosolic face of the plasma membrane has a net negative charge.

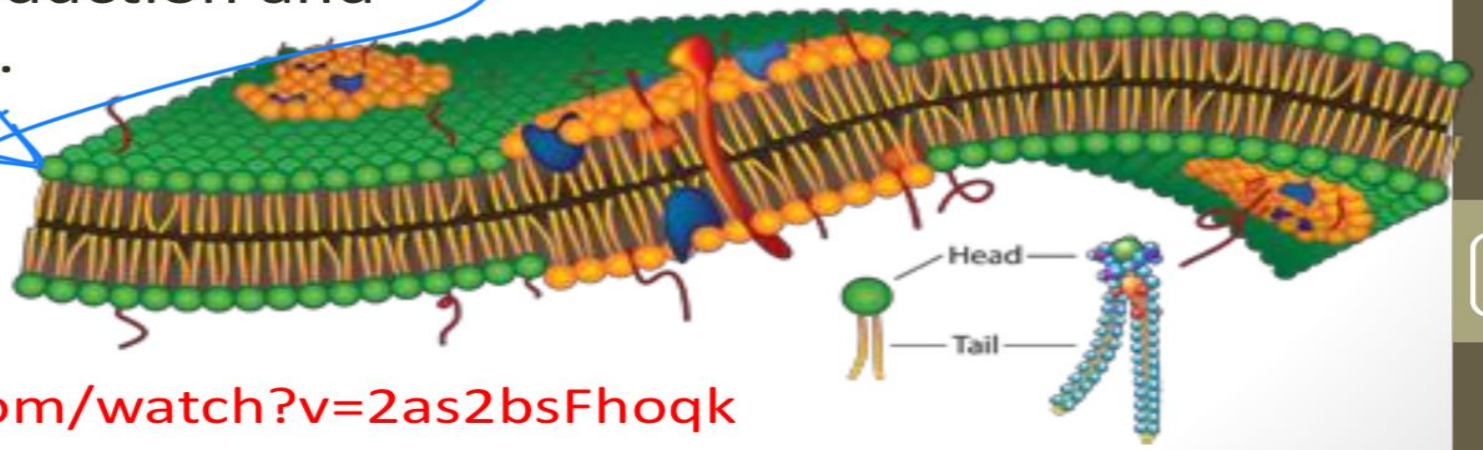
Lipid rafts

Move as a mass faster than other membrane components, and they vary in size

- Semisolid clusters (10-200 nm) of cholesterol and sphingolipids (sphingomyelin and glycolipids).
- Sphingolipids provide a more ordered lipid structure than phospholipids.
- Are enriched in glycosylphosphatidylinositol (GPI)-anchored proteins, and proteins involved in signal transduction and intracellular trafficking.

As well as phosphatidyl inositol and phosphatidyl choline, which are both important in anchoring proteins on the surface





https://www.youtube.com/watch?v=2as2bsFhoqk

Application: Lipid rafts and viral infections

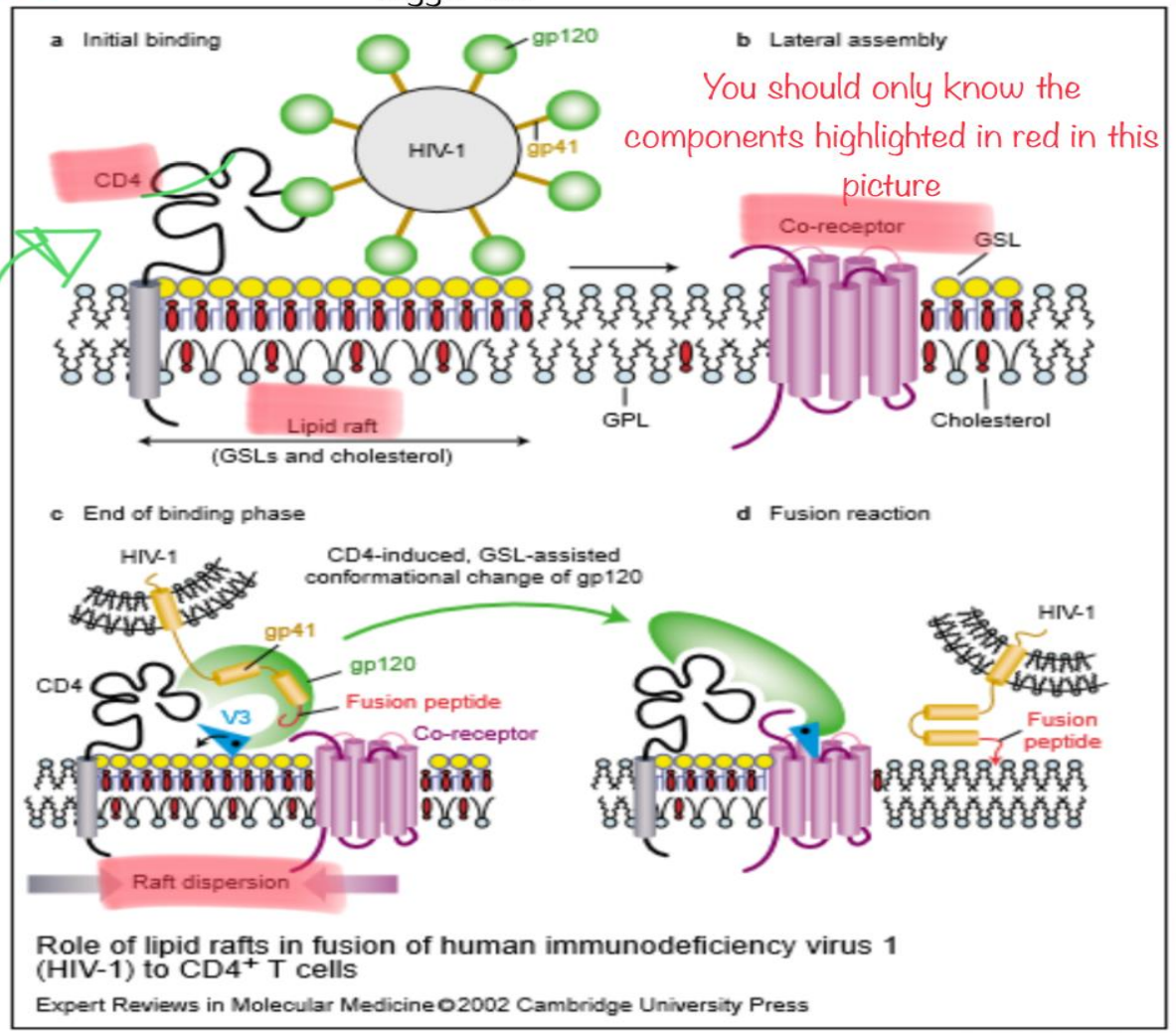
First, we should know that rafts can collide if they meet and form a one bigger raft

1. HIV virus
   - Budding may occur from lipid rafts
   - Viral fusion to $CD4^+$ T cells

The protein HIV recognizes

The target cell

2. Influenza virus
   - Raft-associated glycoproteins in envelope



Role of lipid rafts in fusion of human immunodeficiency virus 1 (HIV-1) to $CD4^+$ T cells

Rafts facilitate viral infections by transporting the necessary proteins (CD4 and co-receptor), due to their fast movement. Once the viral protein is attached o n the same raft that has these proteins, fusion process will happen

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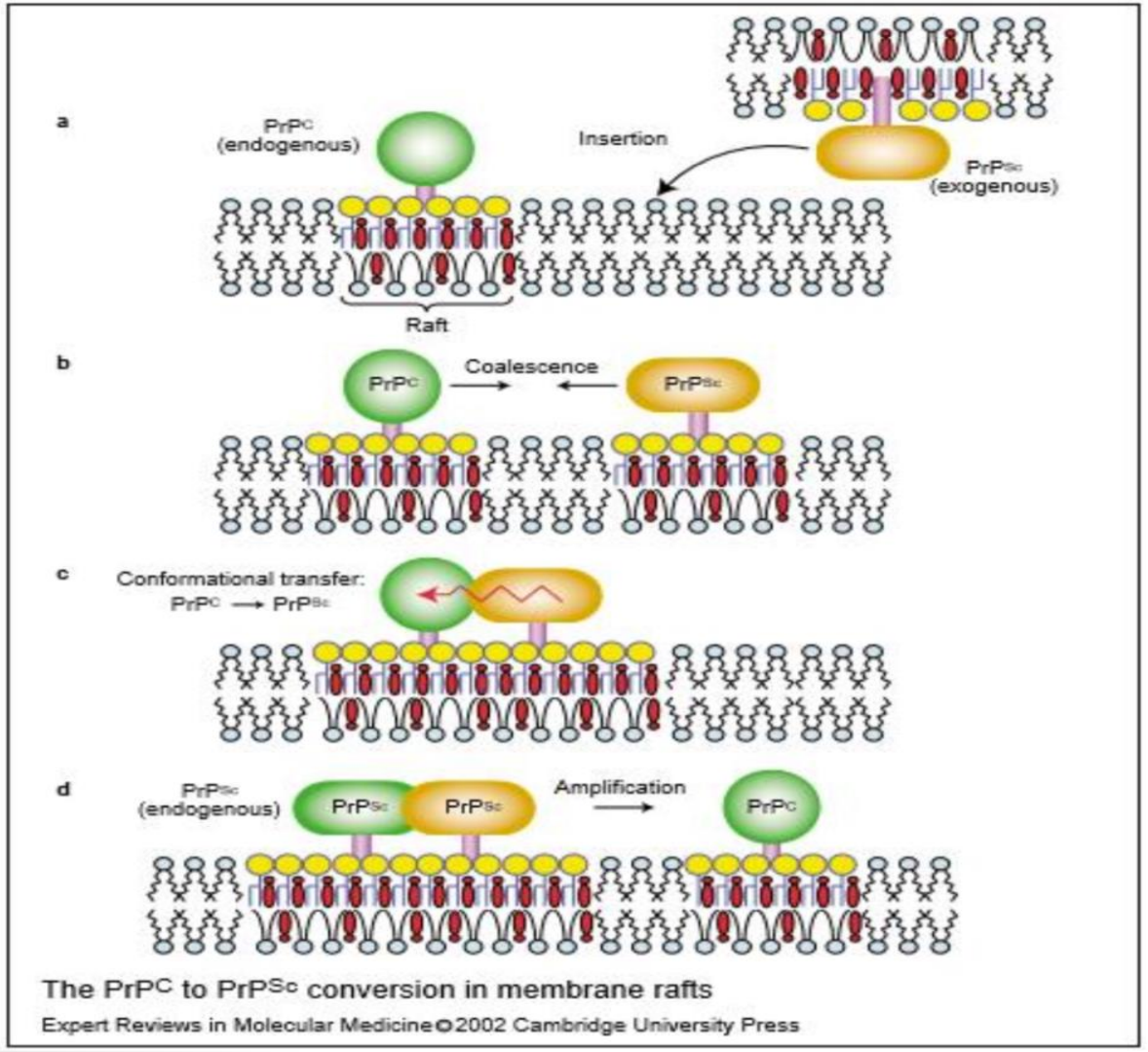
Application: Lipid rafts & diseases



The PrPC to PrPSc conversion in membrane rafts

Expert Reviews in Molecular Medicine ©2002 Cambridge University Press

Stands for proteinious infectious particle

3. Prion disorder Ex: Mad cow disease

- Normal prion protein (PrPc) is converted to abnormal proteins (PrPsc) in lipid rafts . Present in our body normally

The exogenous (disease causing prion) is inserted on a raft that will collide witha another raft that contains our normal prion=> transformed into an abnormal prion

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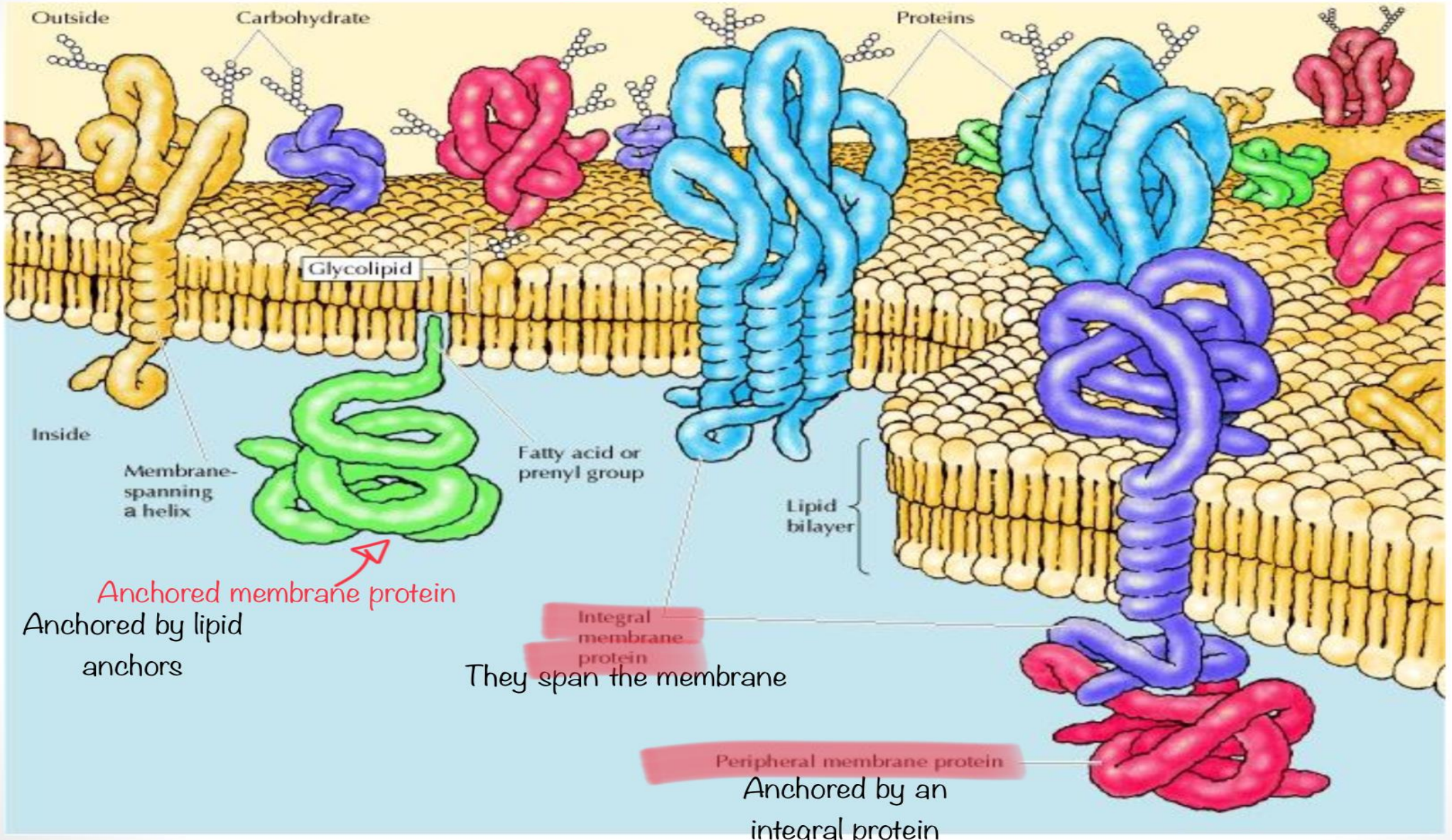
Membrane proteins



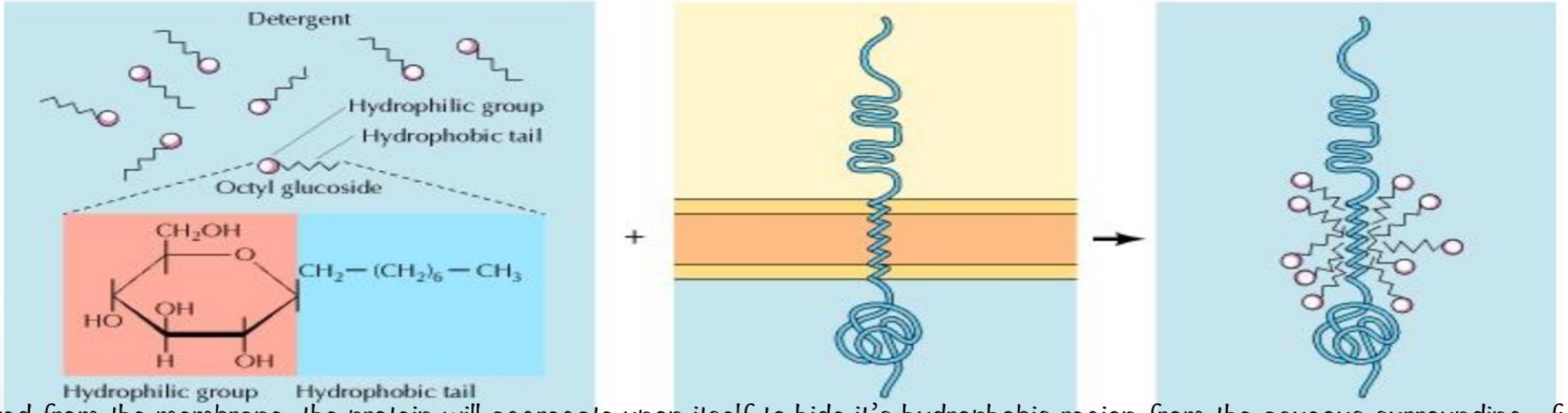
Anchored by lipid anchors

They span the membrane

Anchored by an integral protein

Integral membrane proteins

- Portions of integral membrane proteins are inserted into the lipid bilayer.
- They are dissociated by reagents of small amphipathic molecules.
  - The hydrophobic portions of detergents disrupt hydrophobic interactions.
  - The hydrophilic part makes the detergent-protein complexes soluble in aqueous solutions.



When removed from the membrane, the protein will aggregate upon itself to hide it's hydrophobic region from the aqueous surrounding , fxn will be lost. If we used a detergent (amphipathic compound) to collect these proteins,the hydrophobic regions of the detergent will prevent this misfolding just like in the last picture

α-helices vs. β-sheets

integral proteins

- The membrane-spanning portions of transmembrane proteins are usually α-helices of 20-25 hydrophobic amino acids.
- They are usually glycosylated with the oligosaccharides exposed on the outer surface of the cell.

The Majority are alpha helices

Ex: aqua pores

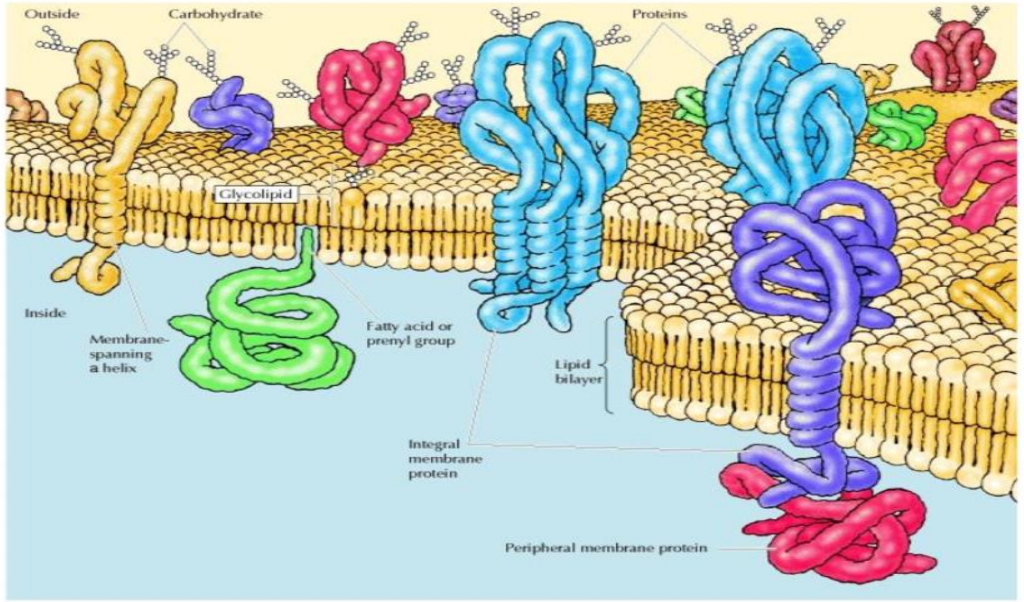
قنوات المياه

Beta-barrel (example: porins)

Peripheral membrane proteins

- Are proteins that dissociate from the membrane following treatments with polar solutions of extreme pH or high salt concentration
- They do not disrupt the phospholipid bilayer.
- Once dissociated, they are soluble in aqueous buffers.
- Are indirectly associated with membranes through protein-protein interactions, mainly ionic bonds.

Non covalent bonds



Lipid-anchored membrane proteins

- Proteins are anchored to the inner or outer leaflets of the membrane.
- Types of anchors:

A &B&C anchor the protein to the cytosolic side of the membrane.

D on the other hand anchors proteins on the extracellular side.

Remember: lipid anchors

a) Myristoylation
   - Myristoyl group is attached the N-terminus

b) Palmitoylation
   - Palmitate is added to –SH group of the side chains of internal cysteine residues.

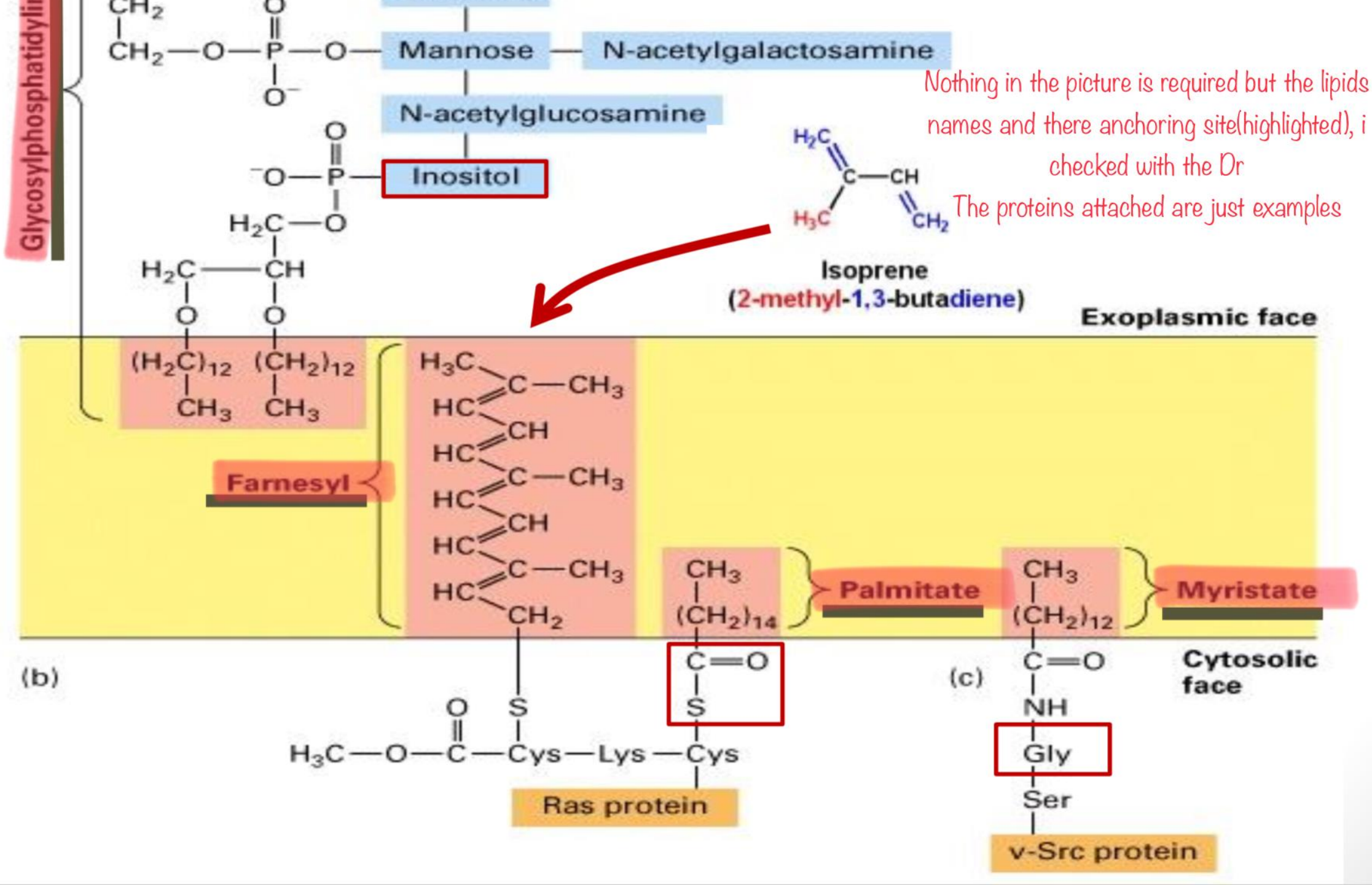
In the middle of the A.A

c) Prenylation
   - It refers to linking of "isoprene"-based groups
   - Prenyl group is attached to –SH group of cysteine near C-terminus of proteins

d) Glycosyl phosphatidylinositol (GPI) anchors on the **outer** surface
   - The carbohydrate bridges the protein with the fatty acid chains of the phospholipid (usually ethanolamine)
   - GPI anchors are added to the C-terminus of a protein in the ER

Sugar group that isn't glucose

NOT A GLYCOLIPID, THE SUGAR IS JAST AN ADDITION TO THE IP



Nothing in the picture is required but the lipids names and there anchoring site(highlighted), i checked with the Dr

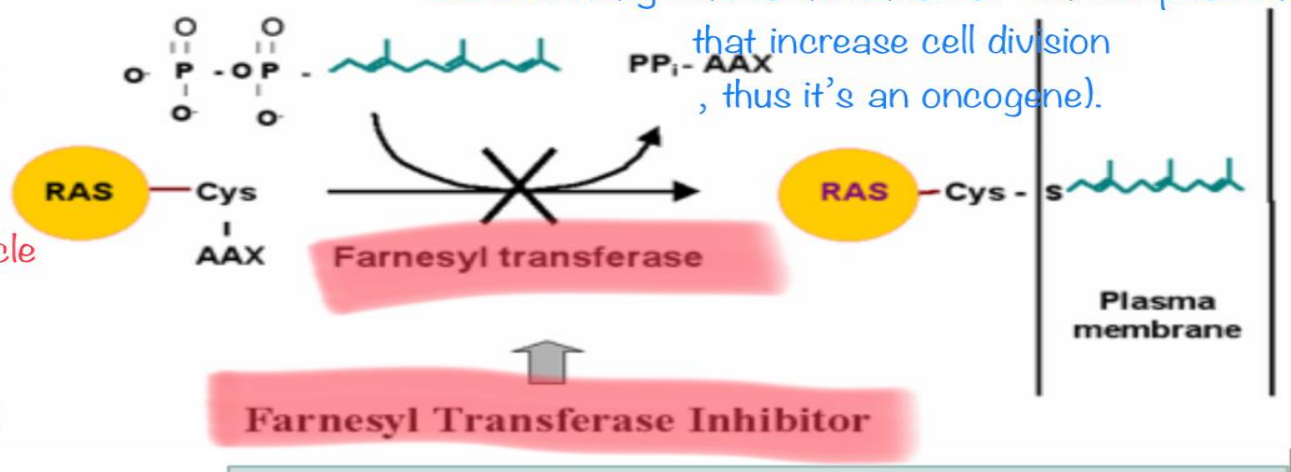
The proteins attached are just examples

Application: farnesylation inhibitors and disease treatment

Anchored membrane protein to the inner leaflet (look at the previous slide), it's also a signaling molecule (a protein kinase activated when a ligand is bound, which will eventually lead to activation of transcription factors that increase cell division , thus it's an oncogene).

- Ras is an oncogene that needs farnesylation for its function and oncogenic activity.
- Farnesyl transferase inhibitors (FITs) have anti-tumor activity in preclinical cell culture and mouse models, but they failed in human clinical trials because:
  - FTIs did not block prenylation of other Ras isoforms (N-Ras and K-Ras) and their tumorigenic activity.
  - Other farnesylated proteins have important roles in cell including growth regulation In normal body cells.

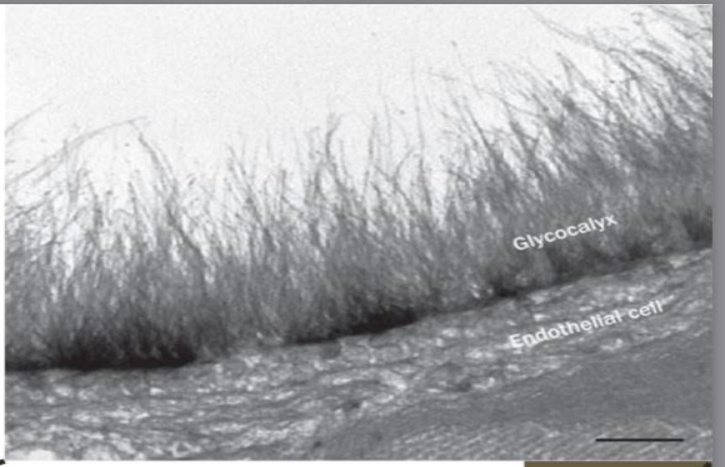
By stopping cell cycle

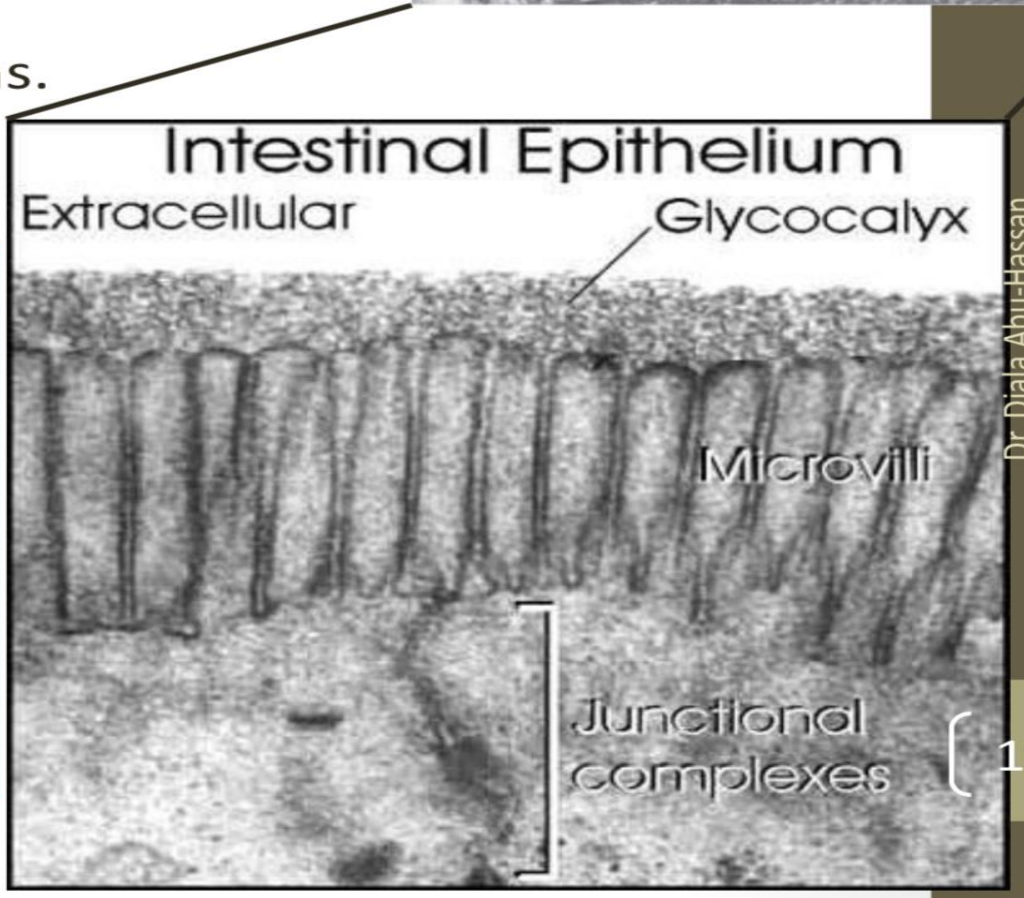


-FTIs are considered for the treatment of other diseases such as Hutchinson-Gilford Progeria Syndrome (AKA progeria), caused by mutated farnesylated lamin A protein.
-FITs can be used in the treatment of malaria.

Glycocalyx

- A carbohydrate coat that covers the surface of the cell.
- Is formed by the oligosaccharides of glycolipids and transmembrane glycoproteins.





Functions:

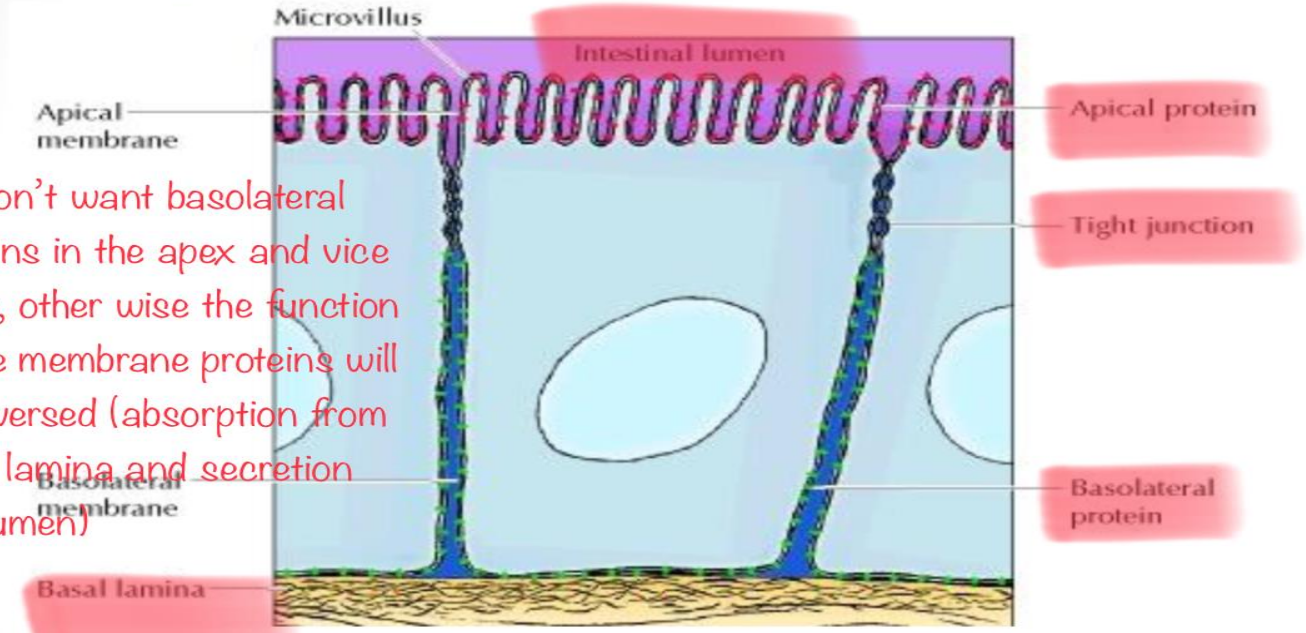
- **Cell-cell interactions (leukocytes)**
- **Protection of cell surface from ionic and mechanical stress**
- **Acts as a barrier for microorganisms**

*Recognition

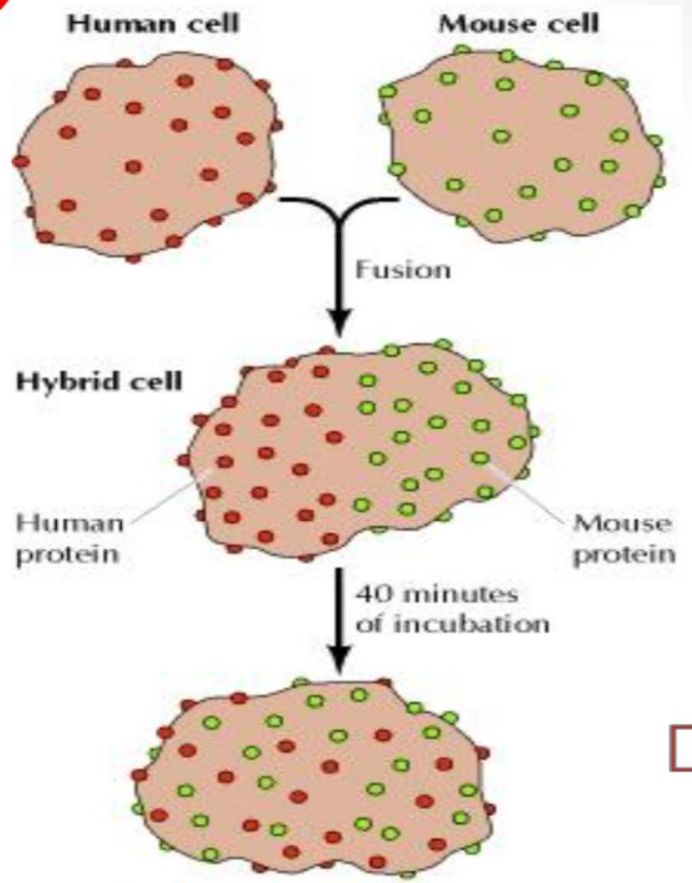
*protection against microorganisms (eg:protection from viral fusion to the PM, viruses overcome this by producing ingesting enzymes) and mechanical or ionic stresses

Protein mobility

Both proteins and lipids diffuse laterally through the membrane.



We don't want basolateral proteins in the apex and vice versa, other wise the function of the membrane proteins will be reversed (absorption from basal lamina and secretion into lumen)



The mobility of membrane proteins is restricted by

- **Association with the cytoskeleton, ECM proteins, proteins on the surface of adjacent cells)**
- **Specific membrane domains such as tight junctions, that maintain the spatial distribution of apical and basolateral proteins**
- **Lipid composition (lipid rafts rich in GPI anchored-proteins) restrict protein mobility.**