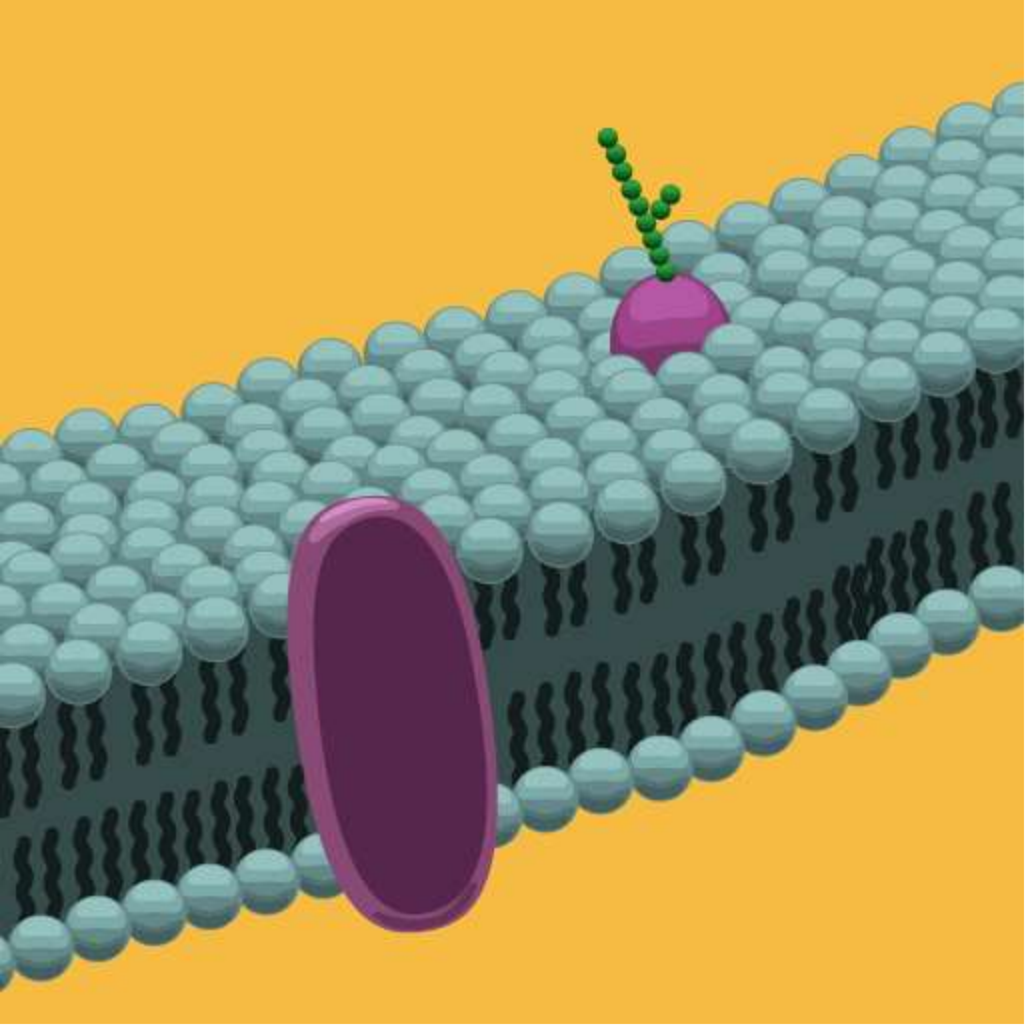
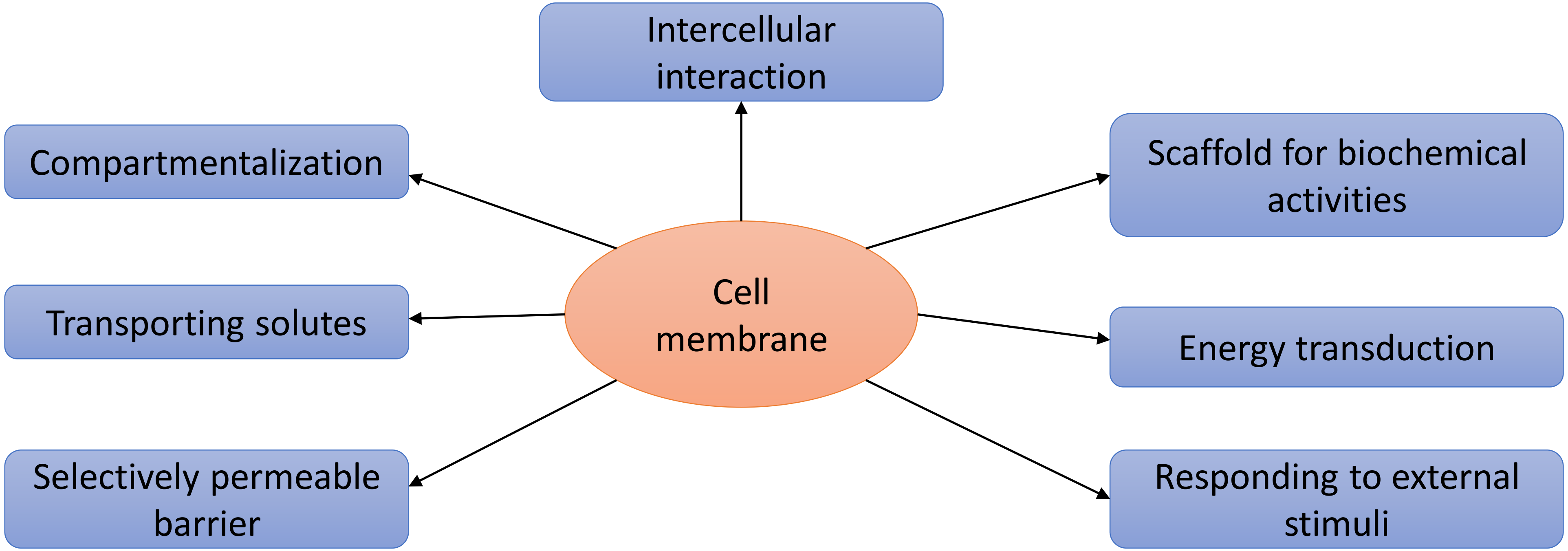
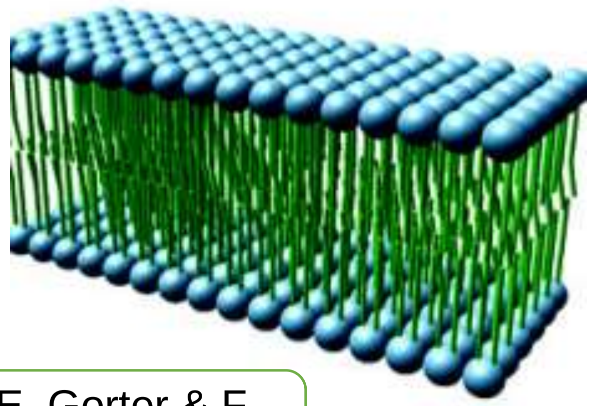


Plasma Membrane

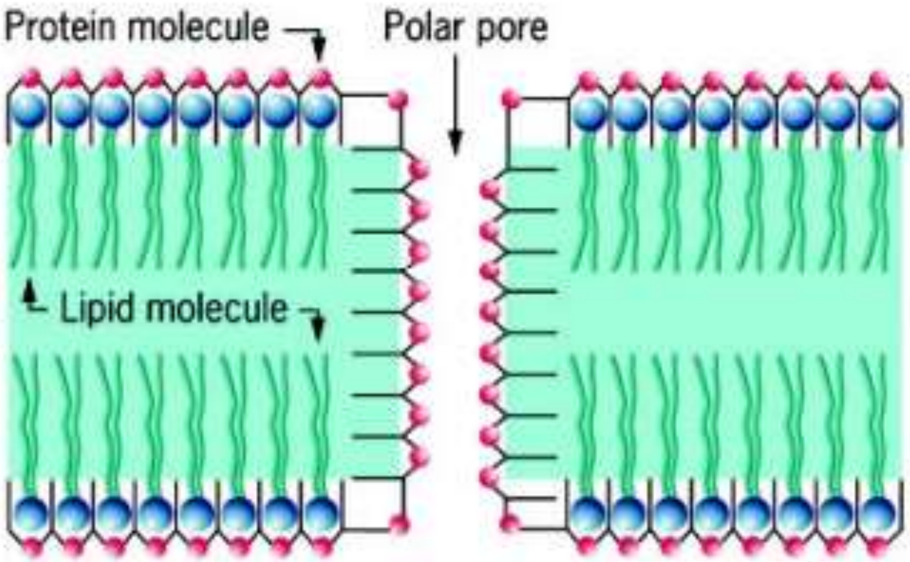
Overview of Membrane Functions



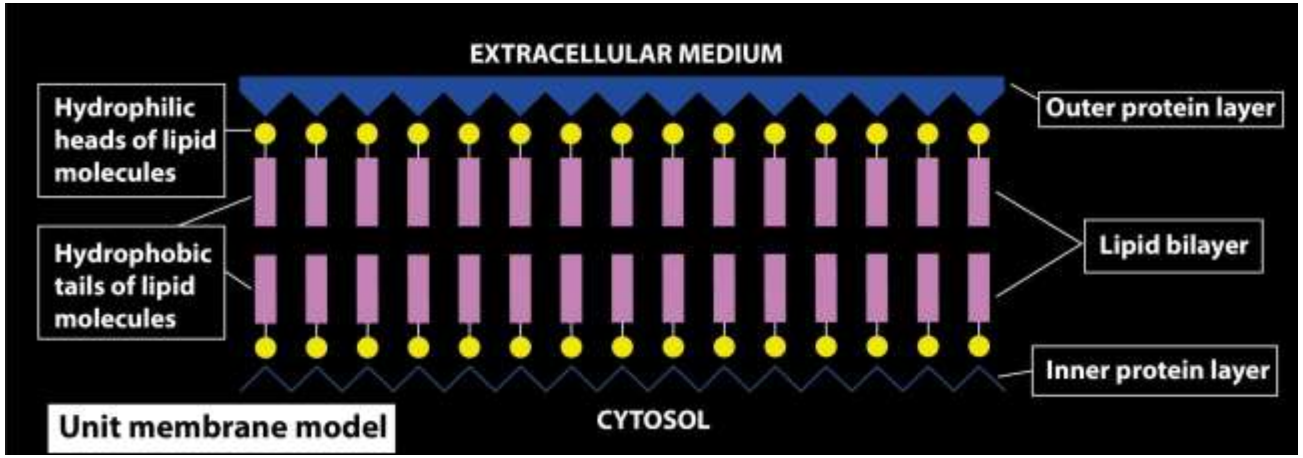
History of studies on Plasma membrane



E. Gorter & F. Grendel (1925)

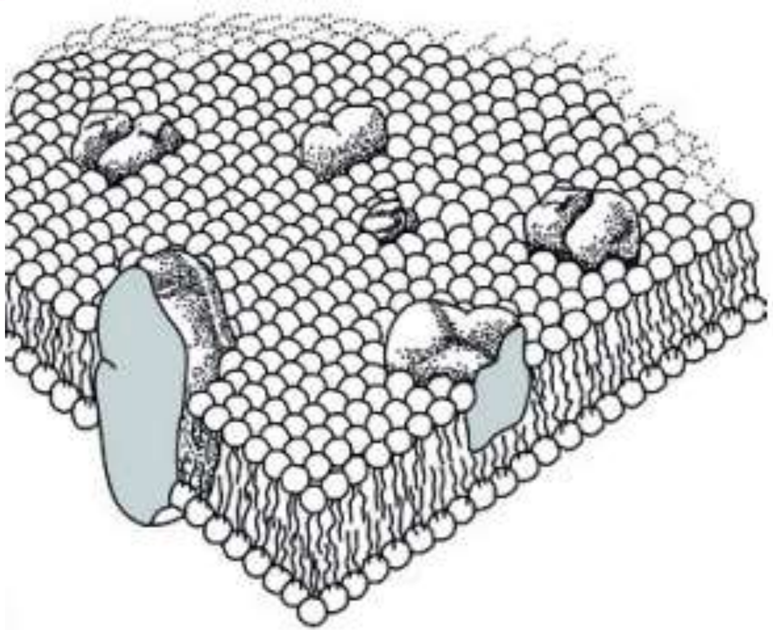


Hugh Davson & James Danielli (1935, Revised 1954)

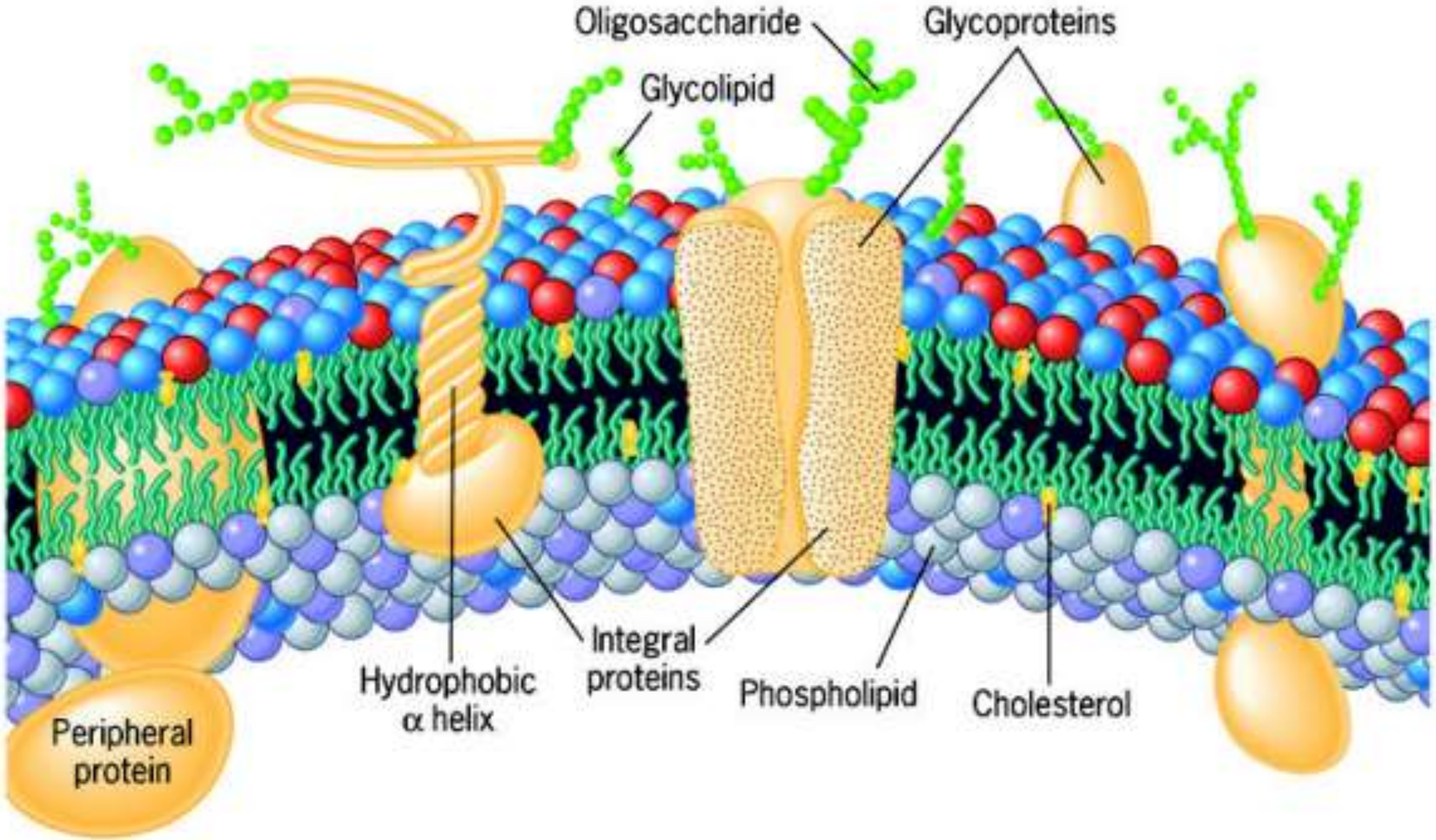


Robertson (1959)

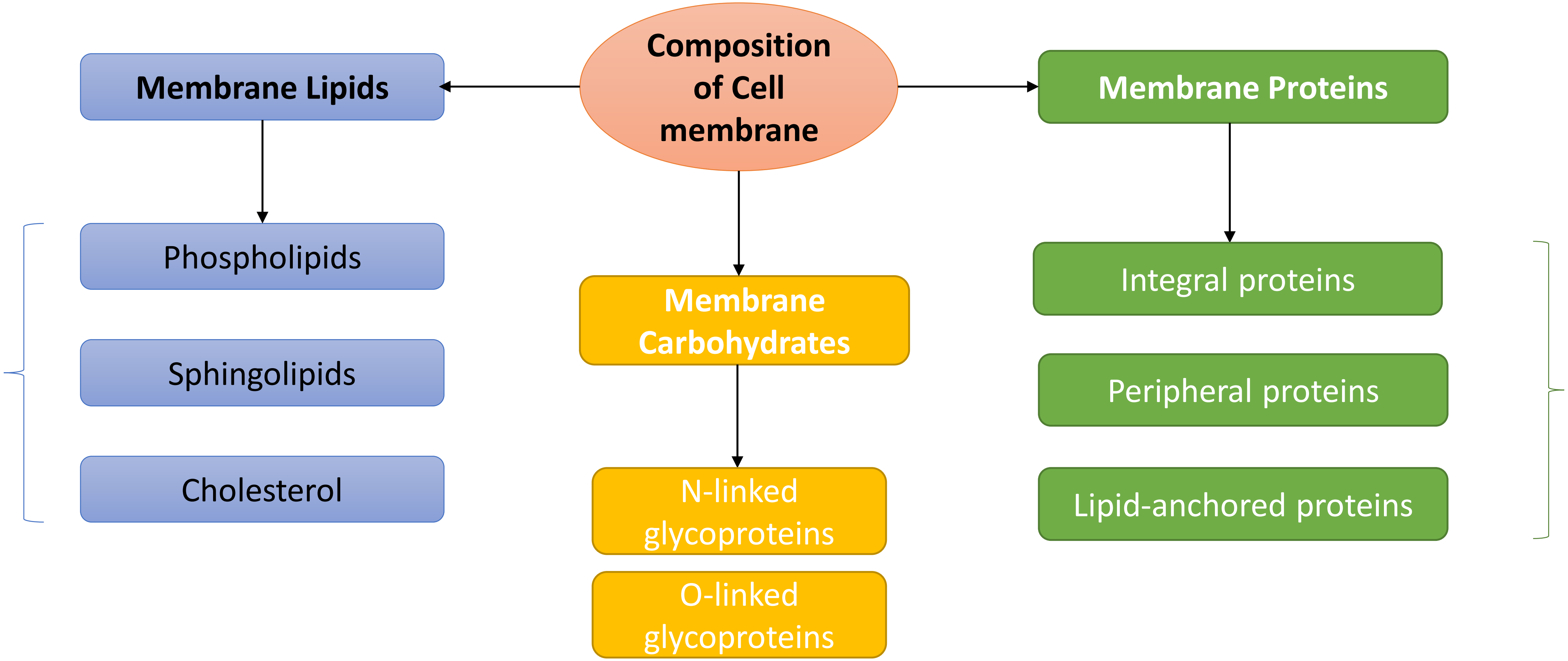
S. Jonathan Singer & Garth Nicolson (1972)



Chemical Composition of Membranes



Chemical Composition of Membranes



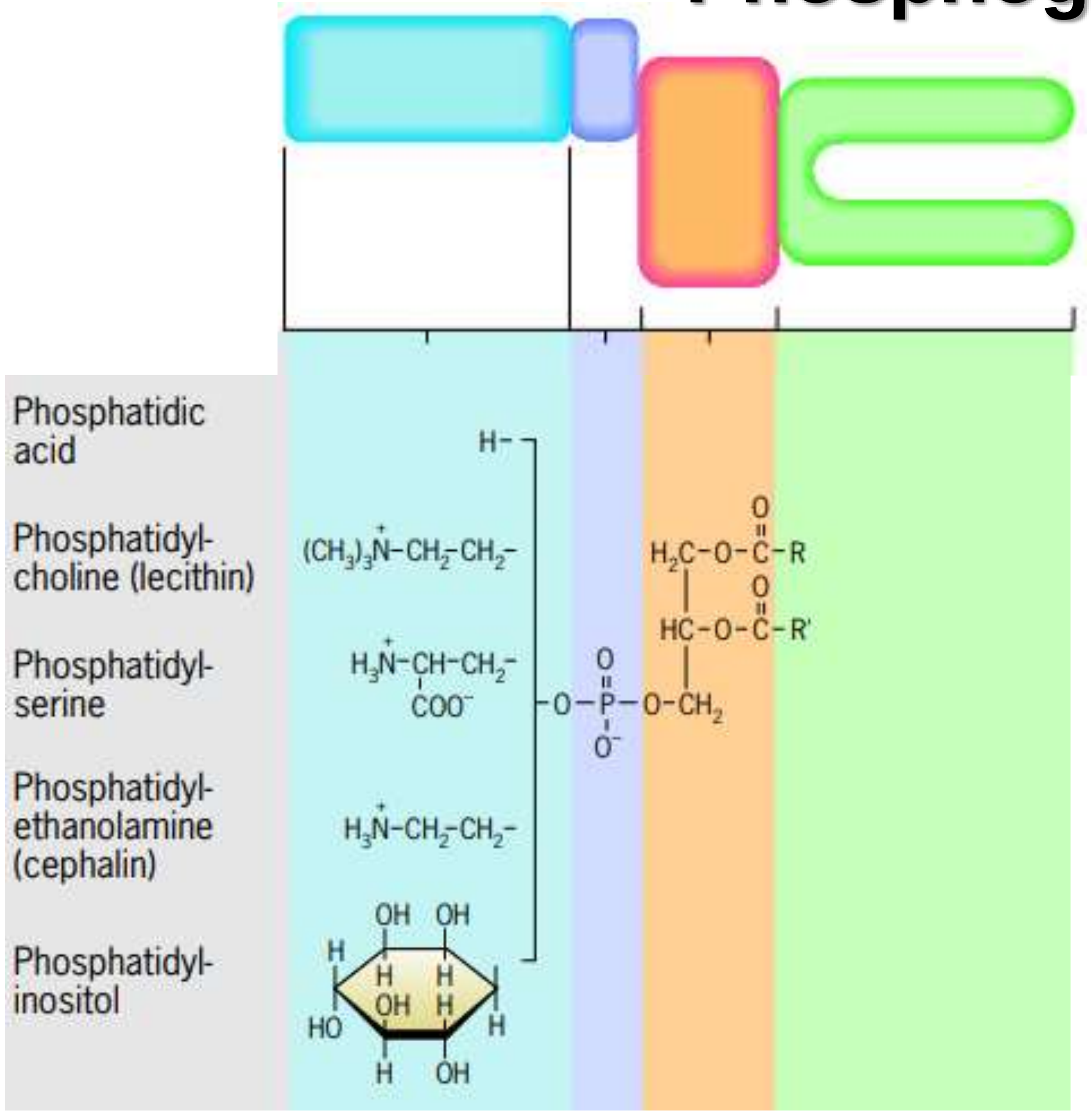
Membrane Lipids: Phosphoglycerides

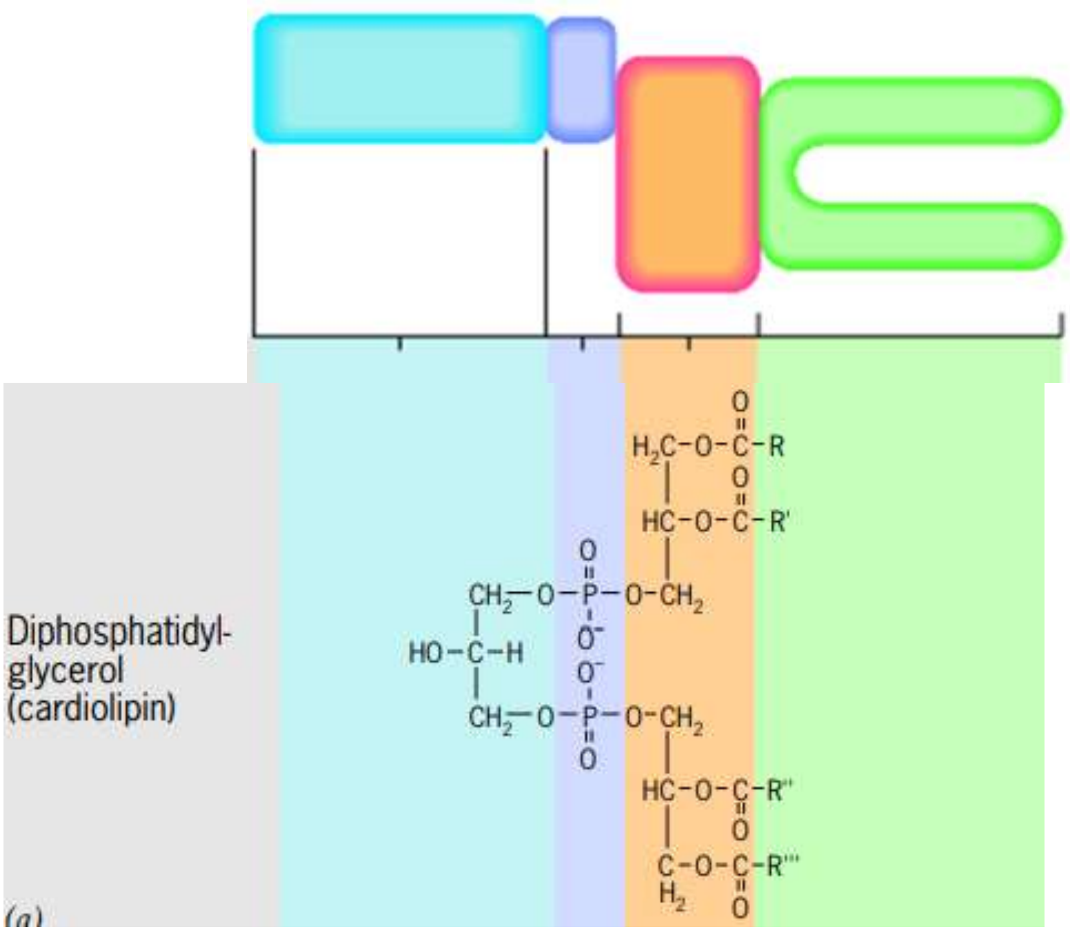
- There are three main types of membrane lipids: phosphoglycerides, sphingolipids, and cholesterol
- **Phosphoglycerides:**
- Phosphatidic acid (Glycerol + 2 FAs + Phosphate group)
- Phosphatidylcholine (Glycerol + 2 FAs + Phosphate group + Choline)
- Phosphatidylethanolamine (Glycerol + 2 FAs + Phosphate group + Ethanolamine)
- Phosphatidylserine (Glycerol + 2 FAs + Phosphate group + Serine)
- Phosphatidylinositol (Glycerol + 2 FAs + Phosphate group + Inositol)

Membrane Lipids: Phosphoglycerides

- Phosphate group + additional group = head group (small, hydrophilic)
- At physiologic pH, the head groups of PS and PI have an overall negative charge, whereas those of PC and PE are neutral
- Fatty acyl chains→ hydrophobic, saturated/unsaturated (16-22 carbons in length)
- Phosphoglycerides often contain one unsaturated and one saturated fatty acyl chain
- Most common phospholipid is PC

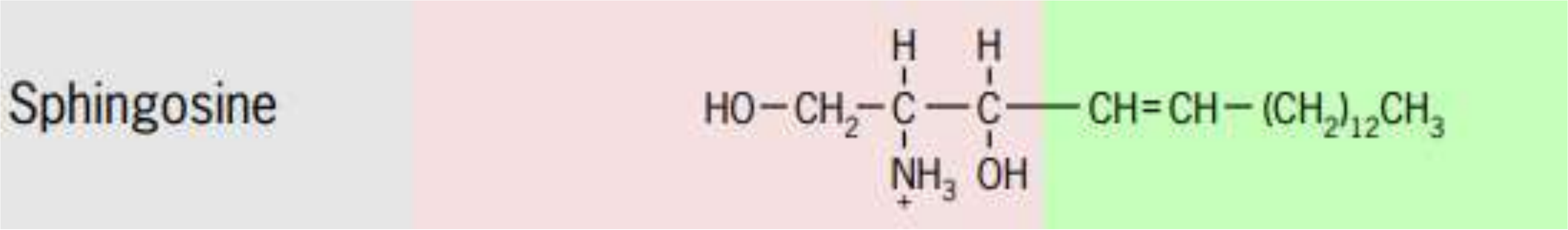
Phosphoglycerides/Phospholipids





Membrane Lipids: Sphingolipids

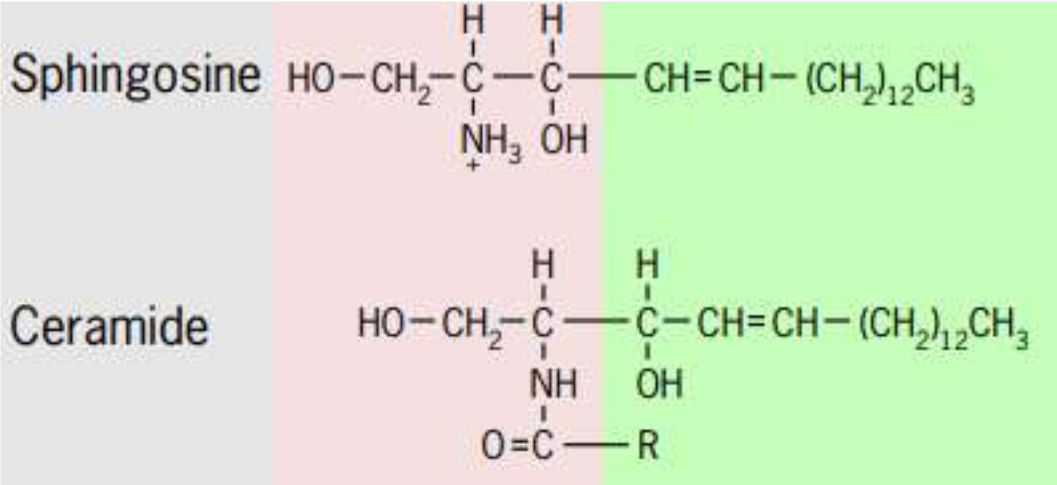
- Sphingolipids→ less abundant class of membrane lipids
- Derivatives of sphingosine, an amino alcohol that contains a long hydrocarbon chain

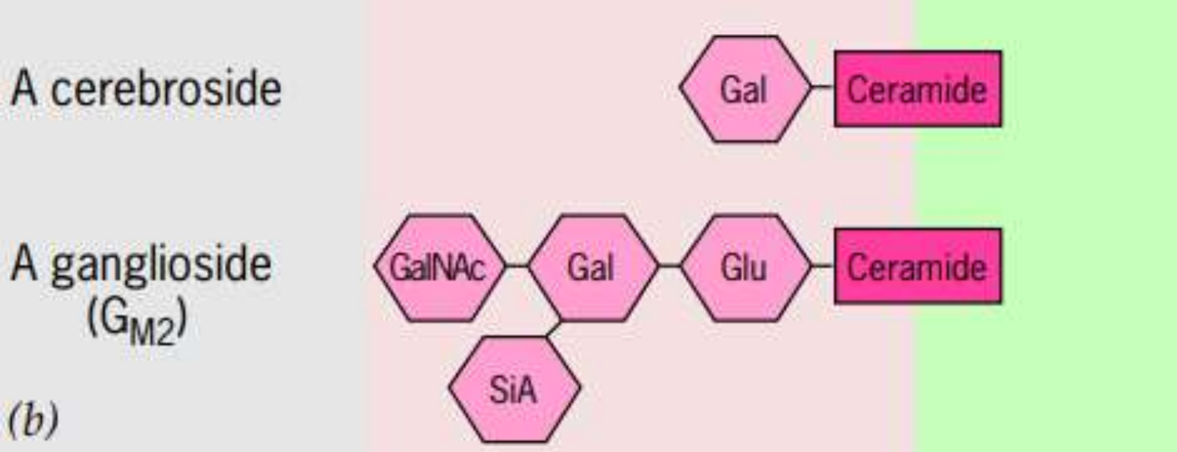


- The fatty acyl chains of sphingolipids, tend to be longer and more highly saturated than those of phosphoglycerides.

Membrane Lipids: Sphingolipids

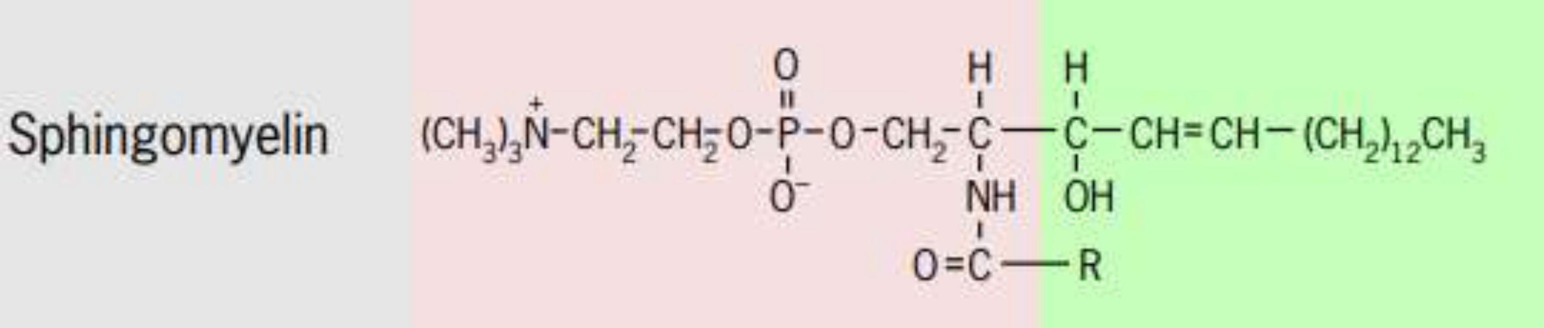
- Ceramide (Sphingosine + FA)
- Cerebrosides (Ceramide + Simple sugar)
- Gangliosides (Ceramide + Cluster of small sugars)





- Sphingomyelin

(Ceramide + phosphorylcholine)

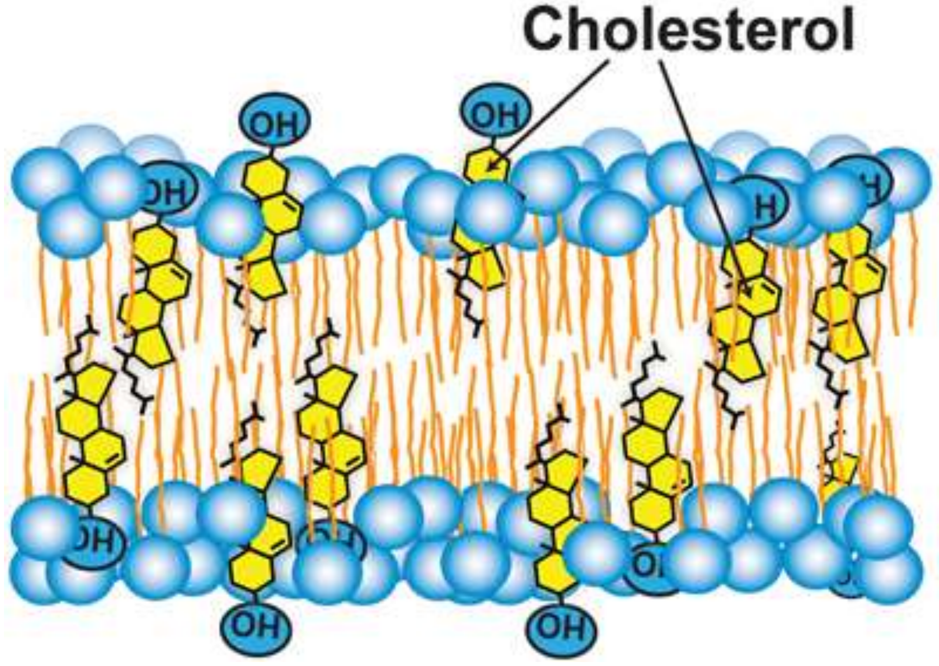


Membrane Lipids: Sphingolipids

- Sphingomyelin is a phospholipid; cerebrosides and gangliosides are glycolipids
- Sphingomyelin, which is the only phospholipid of the membrane that is not built with a glycerol backbone
- Myelin sheath→ high galactocerebroside
- No ganglioside (GM3)→ serious neurological disease
- Cholera and botulism toxins→ binds to cell surface gangliosides, as does the influenza virus.

Membrane Lipids: Cholesterol

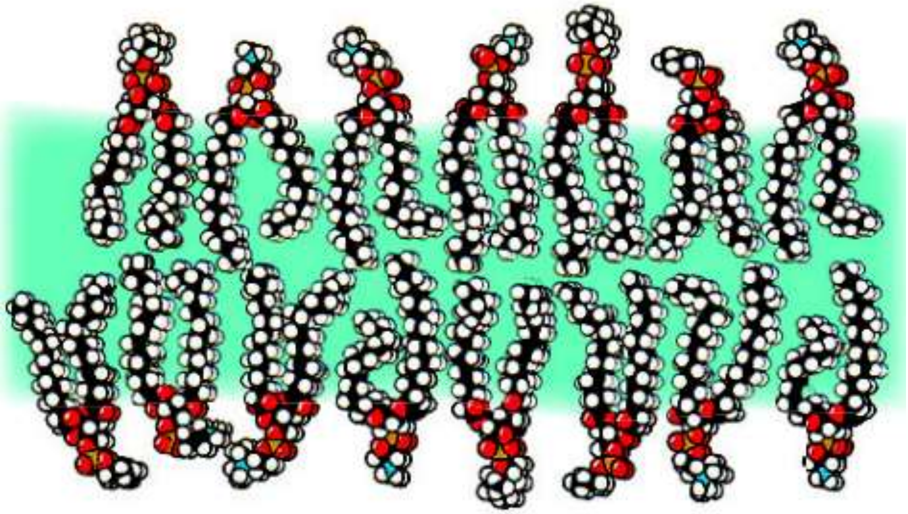
- Cholesterol molecules are oriented with their small hydrophilic hydroxyl group toward the membrane surface and the remainder of the molecule embedded in the lipid bilayer
- The hydrophobic rings of a cholesterol molecule are flat and rigid, and they interfere with the flexibility of the lipid hydrocarbon chains, which tends to stiffen the bilayer while maintaining its overall fluidity
- Unlike other lipids of the membrane, cholesterol is often rather evenly distributed between the two layers (leaflets)



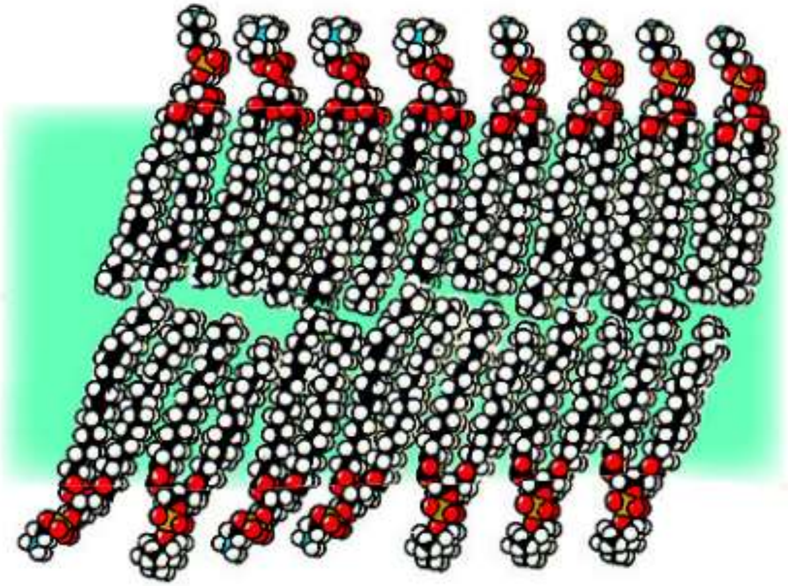
Membrane Lipids & Membrane Fluidity

- The physical state of the lipid of a membrane is described by its fluidity

- Liquid crystal→ at relatively warm temperature
- Above the transition temperature

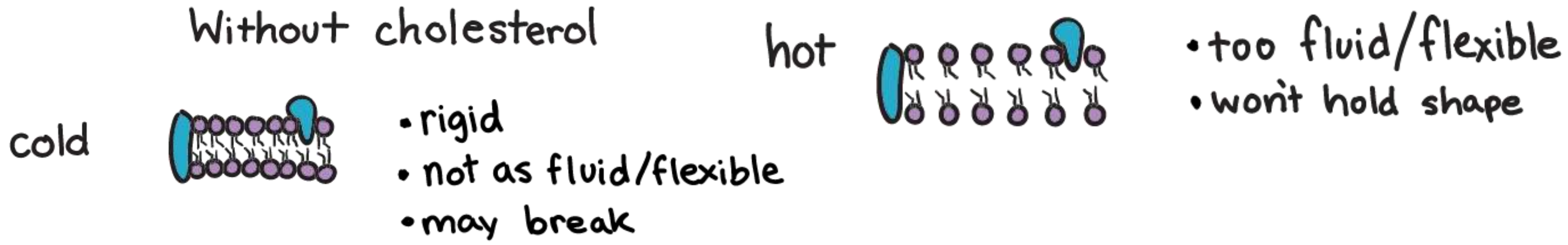


- Frozen crystalline gel→ at low temperature
- Below the transition temperature



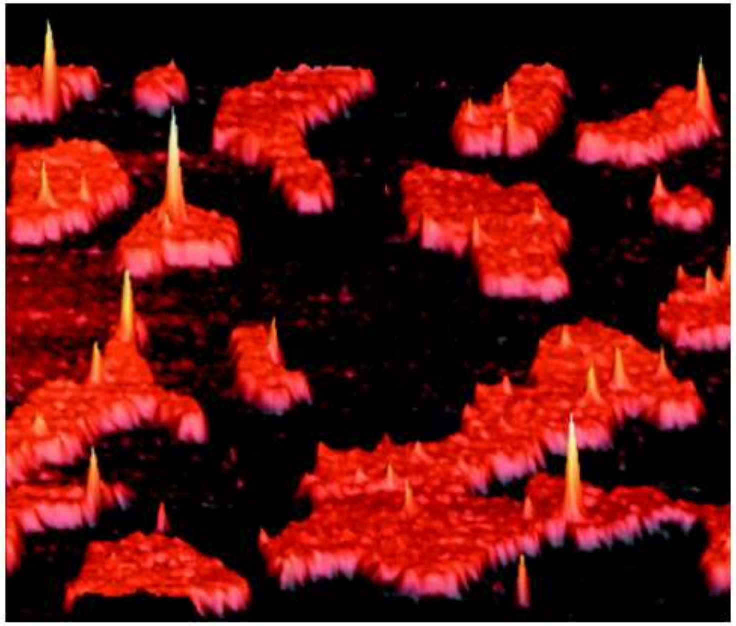
Membrane Lipids & Membrane Fluidity

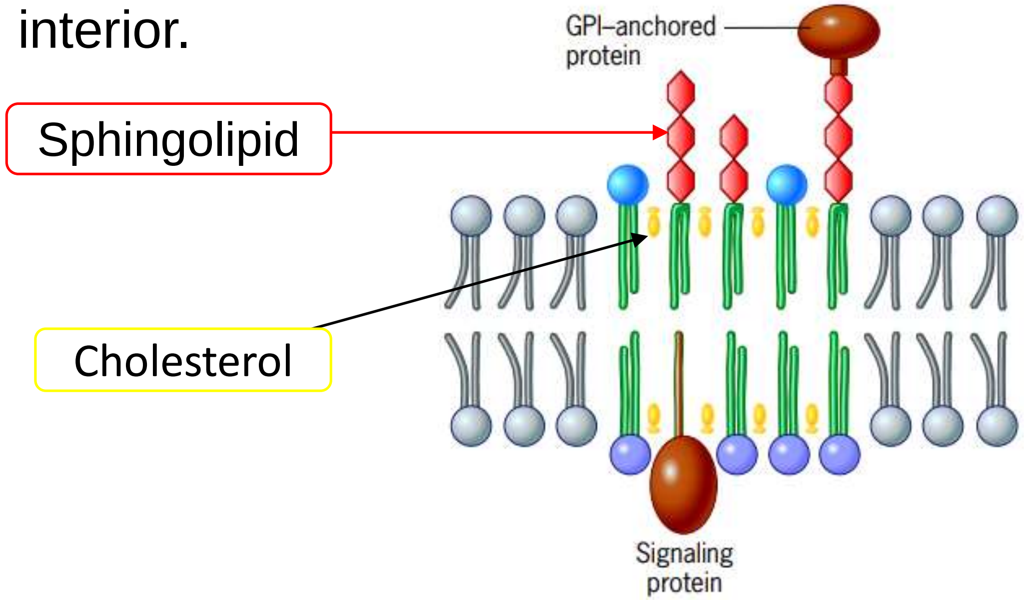
- Degree of unsaturation: the greater the degree of unsaturation of the fatty acids of the bilayer, lower is the melting temperature
- FA chain length: the shorter the fatty acyl chains of a phospholipid, the lower its melting temperature
- Cholesterol: maintains fluidity- cold, mains rigidity- hot



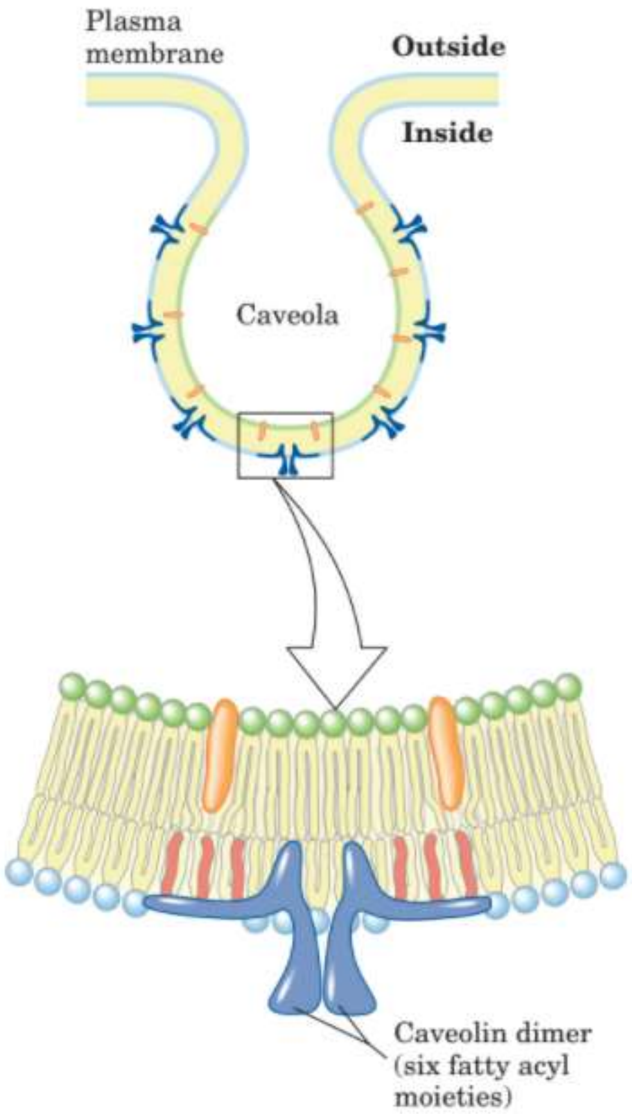
Lipid Rafts

- Lipid rafts = Sphingolipids + Cholesterol
- Lipid rafts are thought to provide a favorable local environment for cell-surface receptors to interact with other membrane proteins that transmit signals from the extracellular space to the cell interior.





Special Class of Membrane Rafts: Caveolins



- Caveolin binds cholesterol in the membrane, and the presence of caveolin forces the associated lipid bilayer to curve inward, forming caveolae ("little caves") in the surface of the cell

- Caveolae→ cellular functions includes:
  - ➢ membrane trafficking within cells
  - ➢ transduction of external signals into cellular responses

- The receptors for insulin and other growth factors, as well as certain GTP-binding proteins and protein kinases associated with transmembrane signaling, appear to be localized in rafts and perhaps in caveolae.

The Asymmetry of Membrane Lipids

- The lipid bilayer consists of two distinct leaflets that have a distinctly different lipid composition.
- inner leaflet: PE (tends to promote the curvature of the membrane, which is important in membrane budding and fusion)
- inner leaflet: PS (negatively charged, interacts with lys & arg residues of membrane protein)
- outer leaflet: PC (and sphingomyelin)

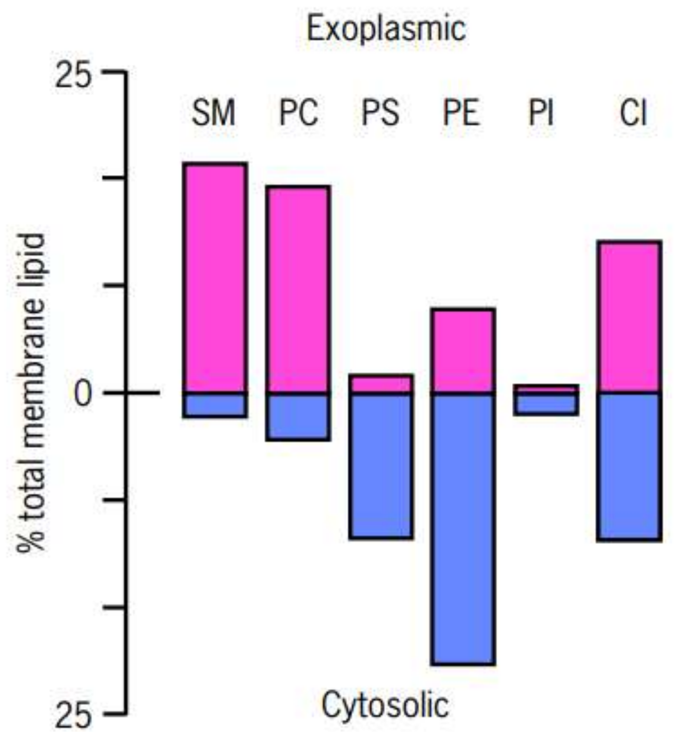


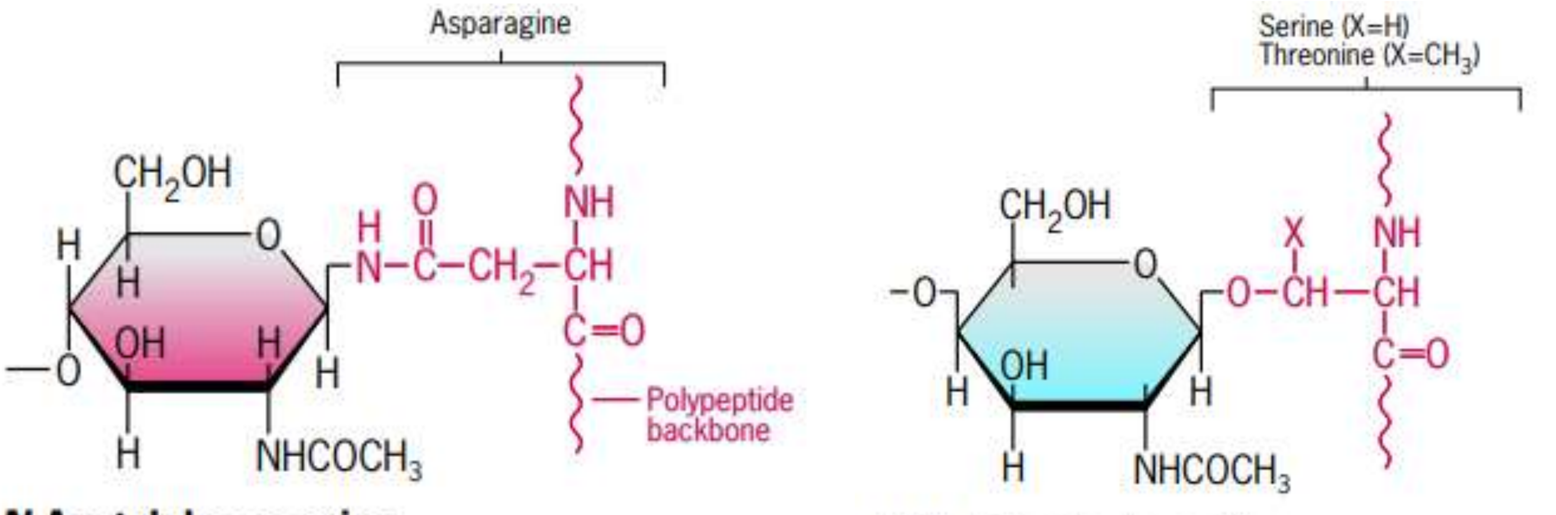
Figure 4.10 **The asymmetric distribution of phospholipids (and cholesterol) in the plasma membrane of human erythrocytes.** (SM, sphingomyelin; PC, phosphatidylcholine; PS, phosphatidylserine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; Cl, cholesterol.)

The Asymmetry of Membrane Lipids

- inner leaflet: PI (transfer of stimuli from the plasma membrane to cytoplasm)
- All the glycolipids→ outer leaflet where they often serve as receptors for extracellular ligands
- The appearance of PS on the outer surface of aging lymphocytes marks the cells for destruction by macrophages
- The appearance of PS on the outer surface of platelets leads to blood coagulation

Membrane Carbohydrates

- More than 90 percent of the membrane's carbohydrate is covalently linked to proteins to form glycoproteins
- All of the carbohydrate of the plasma membrane faces outward into the extracellular space
- Oligosaccharides may be attached to several different amino acids by two major types of linkages: N-linked & O-linked

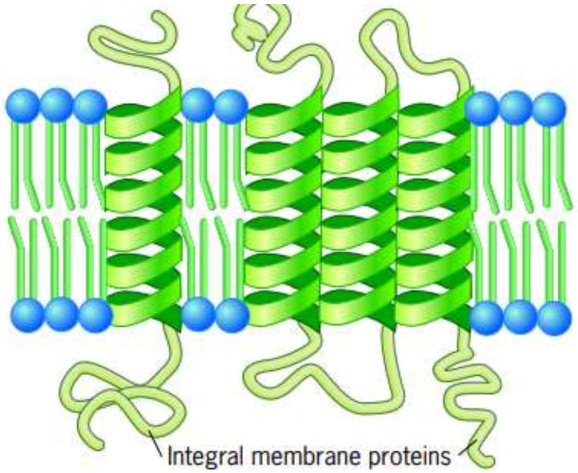


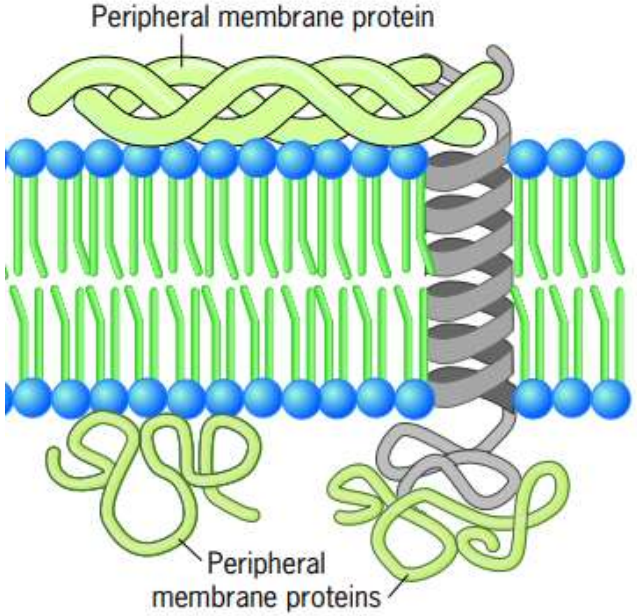
***N*-Acetylglucosamine**   ***N*-Acetylgalactosamine**

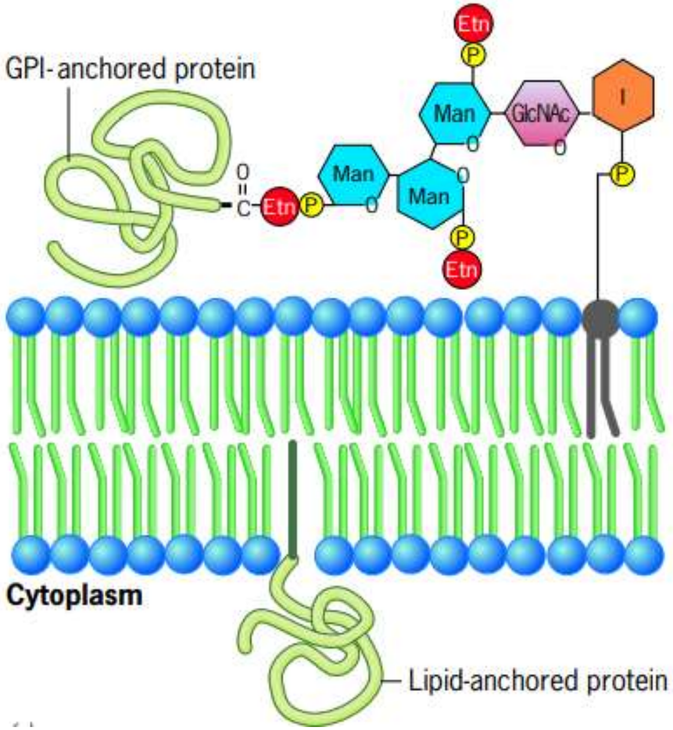
Membrane Proteins

- Membrane proteins can be grouped into three distinct classes distinguished by the intimacy of their relationship to the lipid bilayer:

1. Integral proteins (transmembrane proteins)
2. Peripheral proteins
3. Lipid-anchored proteins





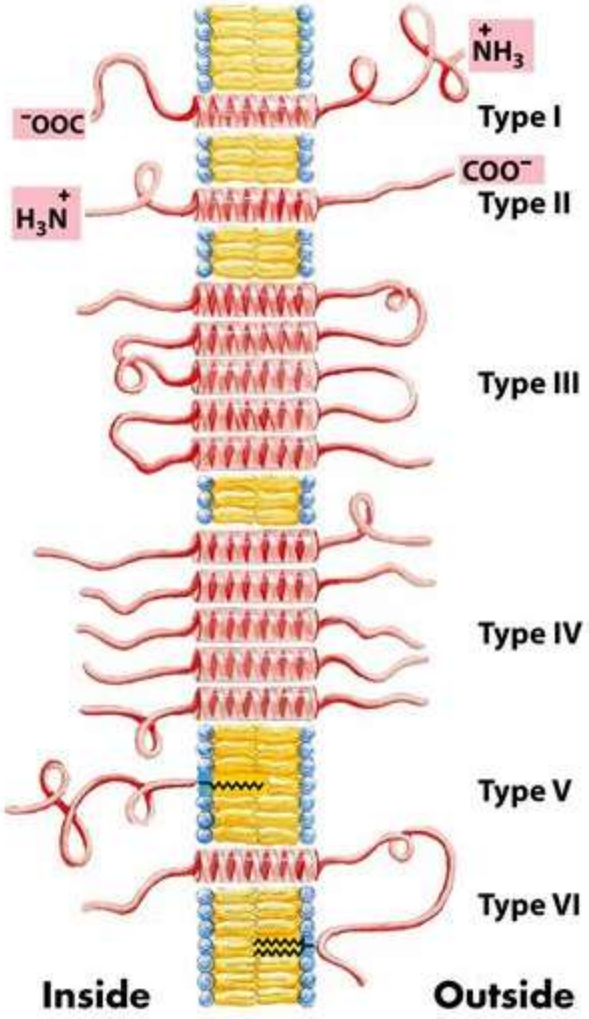


Membrane Proteins: Integral Proteins

- Receptors
- Channels or Transporters
- Agents that transfer electrons during the processes of photosynthesis and respiration
- Amphipathic
- Transmembrane domains—tend to have a hydrophobic character
- Amino acid residues in transmembrane domains form van der waals interactions with the fatty acyl chains of the bilayer, which seals the protein into the lipid “wall” of the membrane.

Types of Integral Membrane Proteins

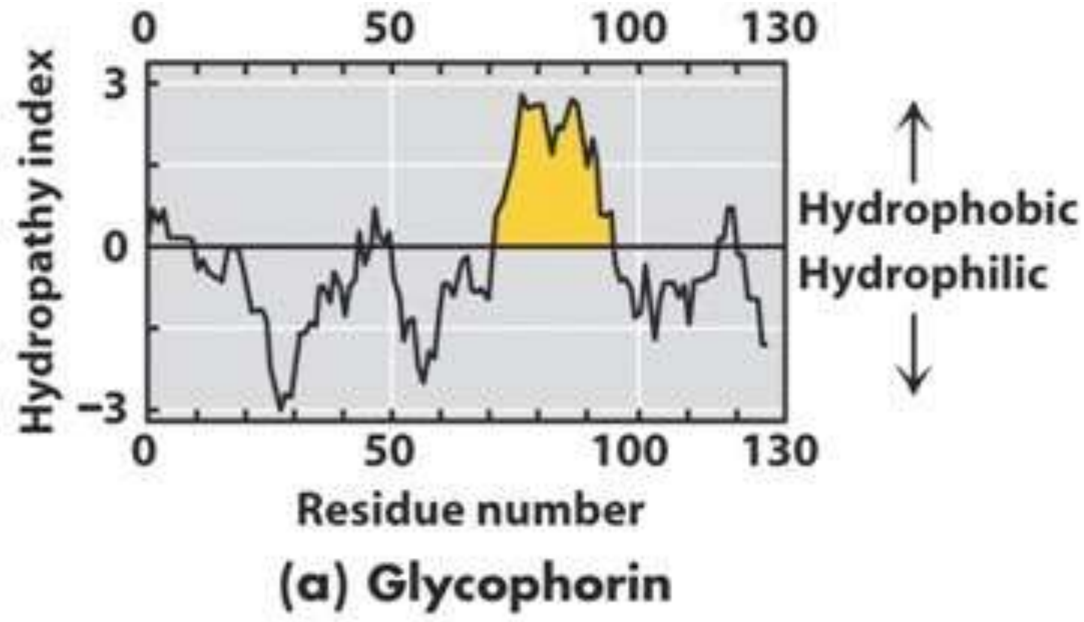
- Type I – one transmembrane helix, N-term outside
- Type II – one transmembrane helix, C-term outside
- Type III – multiple transmembrane helices on single polypeptide
- Type IV – multiple transmembrane helices on separate polypeptides
- Type V – proteins covalently bound to lipid
- Type VI – proteins with covalently bound lipid and transmembrane helix

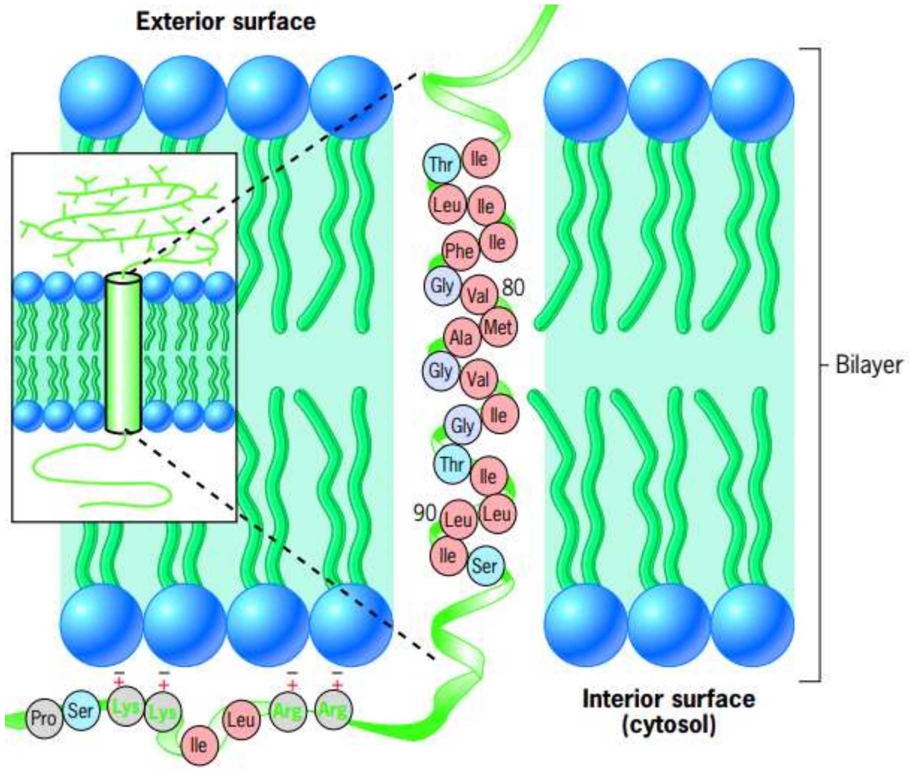


Identifying Transmembrane Domains: Hydropathy Index/Plot

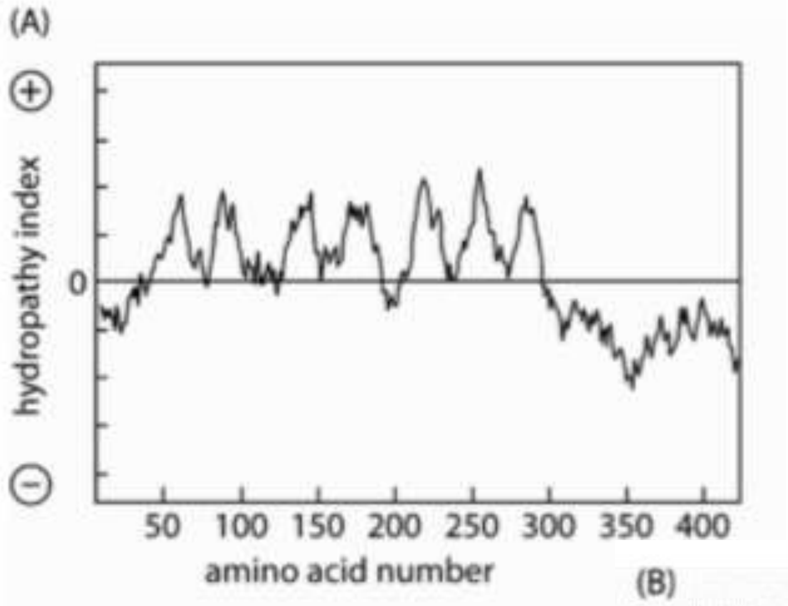
- Transmembrane domains consist of a string of about 20-30 predominantly nonpolar amino acids that span the core of the lipid bilayer as an helix

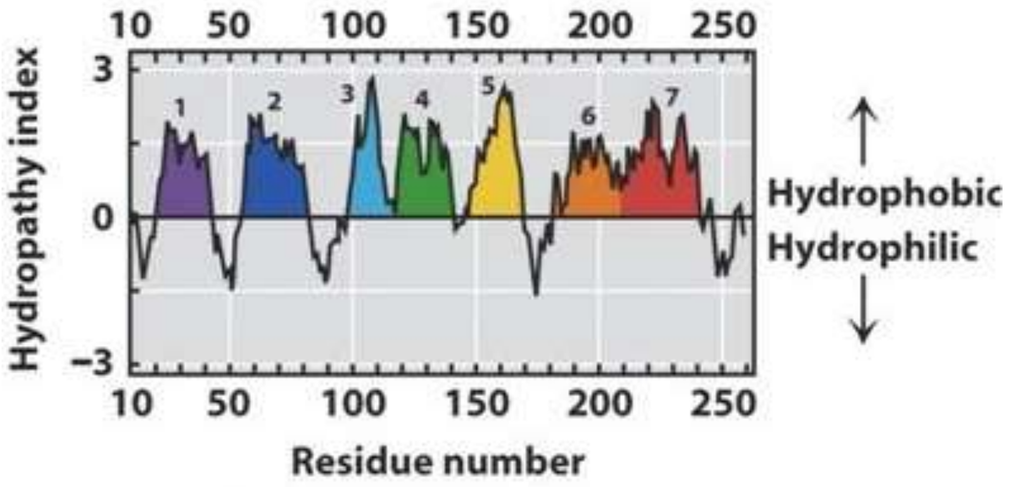
- Example: Glycophorin A, amino acids 73-92 , non-polar and/or uncharged (hydrophobic)



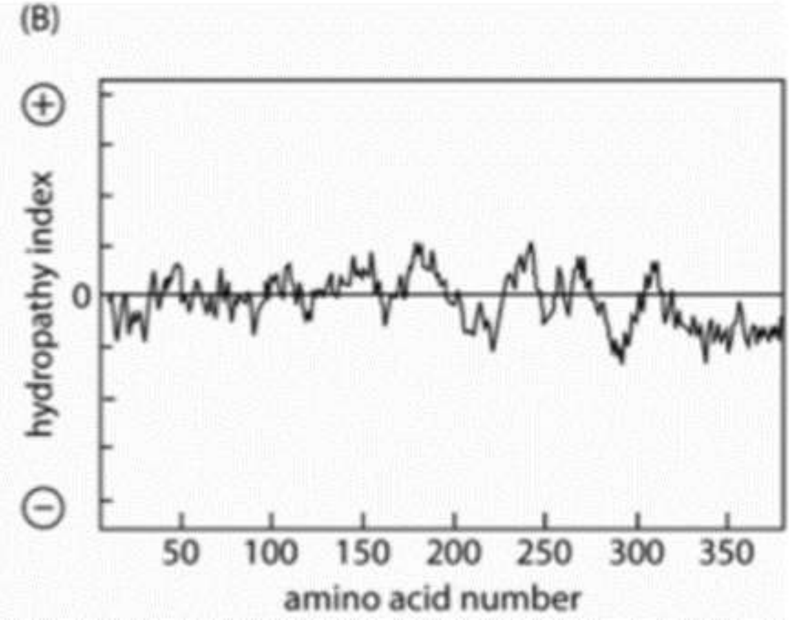


Hydropathy Plot





(b) Bacteriorhodopsin

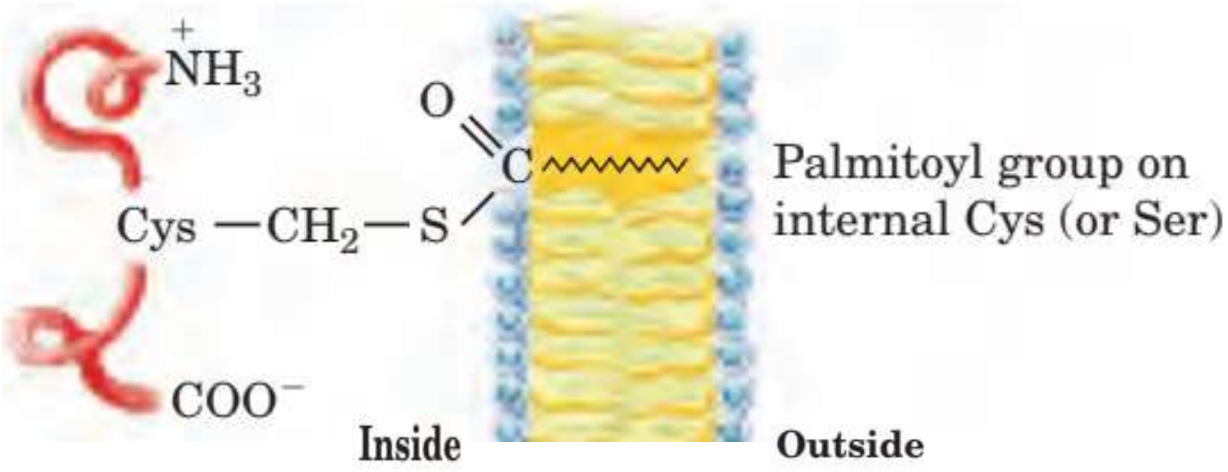


Peripheral Proteins

- Peripheral proteins associate with the membrane through electrostatic interactions and hydrogen bonding with the hydrophilic domains of integral proteins and with the polar head groups of membrane lipids
- Peripheral proteins located on the internal (cytosolic) surface of the plasma membrane, where they form a fibrillar network that acts as a membrane “skeleton”.
- These proteins provide mechanical support for the membrane and function as an anchor for integral membrane proteins
- Other peripheral proteins on the internal plasma membrane surface function as enzymes, or factors that transmit transmembrane signals

Lipid-anchored proteins

- Some membrane proteins contain one or more covalently linked lipids of several types: long-chain fatty acids, isoprenoids, sterols, or glycosylated derivatives of phosphatidylinositol (GPI)

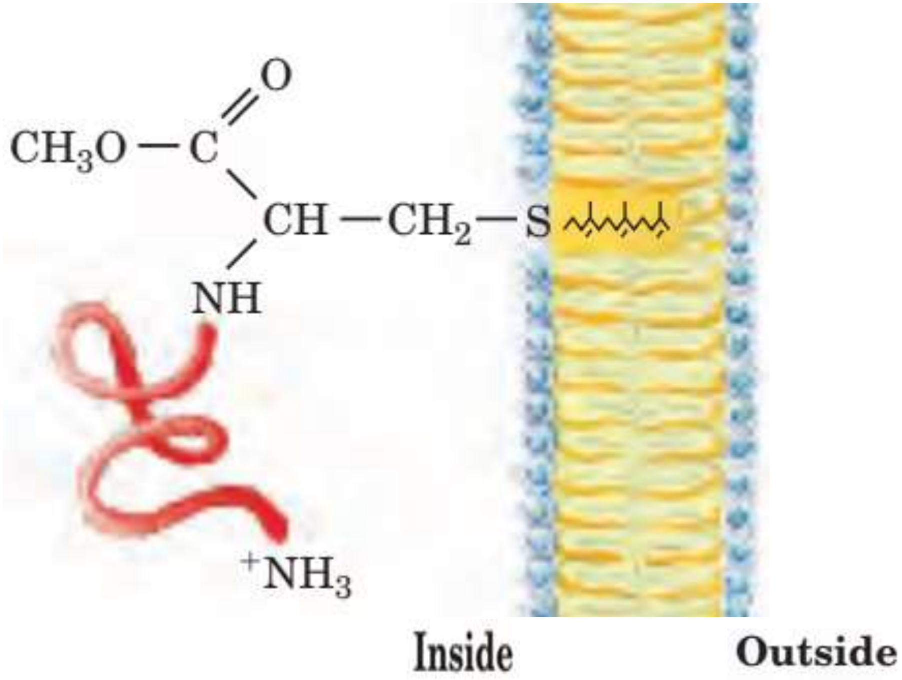


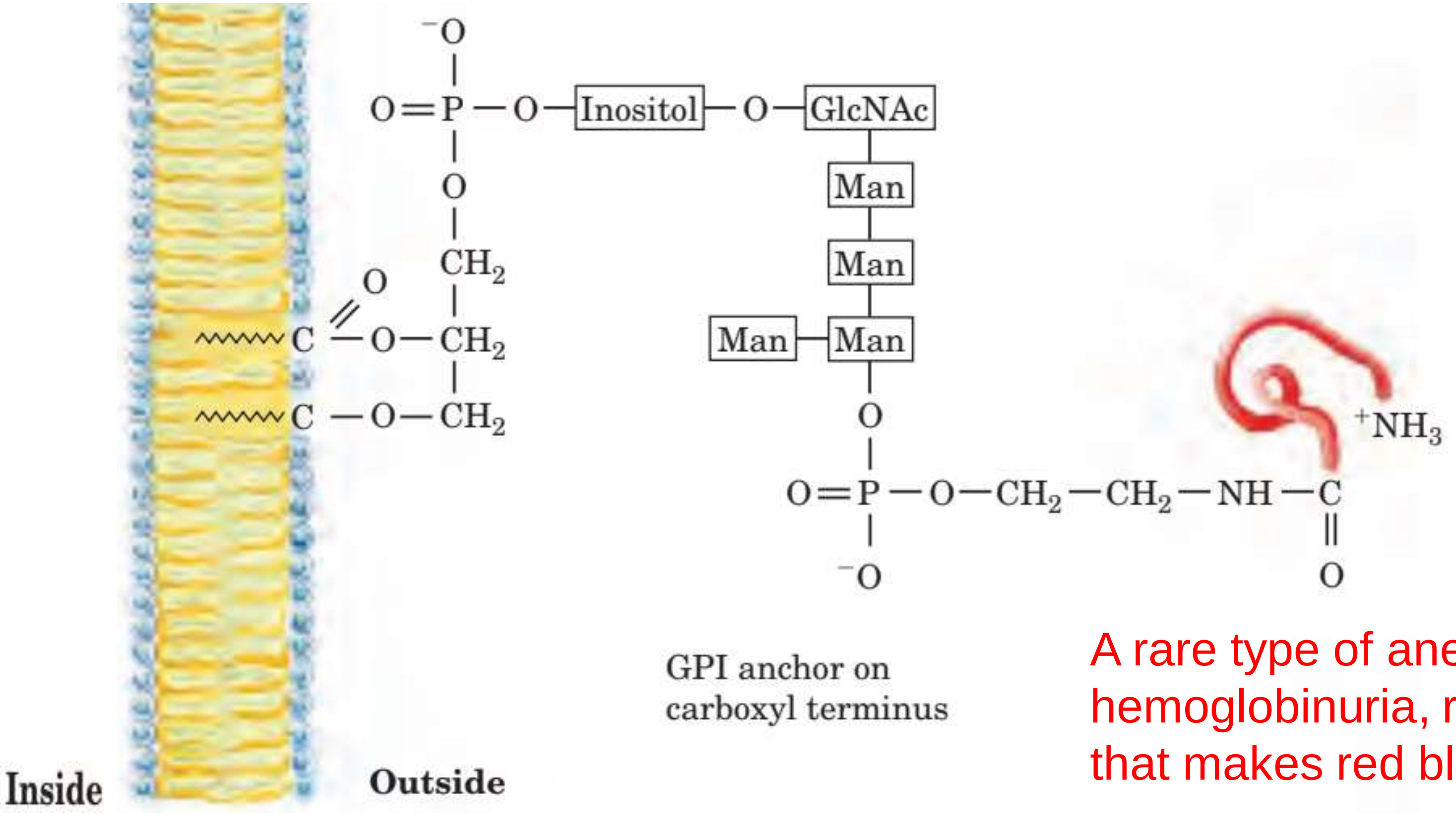
- The attached lipid provides a hydrophobic anchor that inserts into the lipid bilayer and holds the protein at the membrane surface

Lipid-anchored proteins

proteins associated with the plasma membrane in this way (Src and Ras)

Farnesyl (or geranylgeranyl) group on carboxyl-terminal Cys

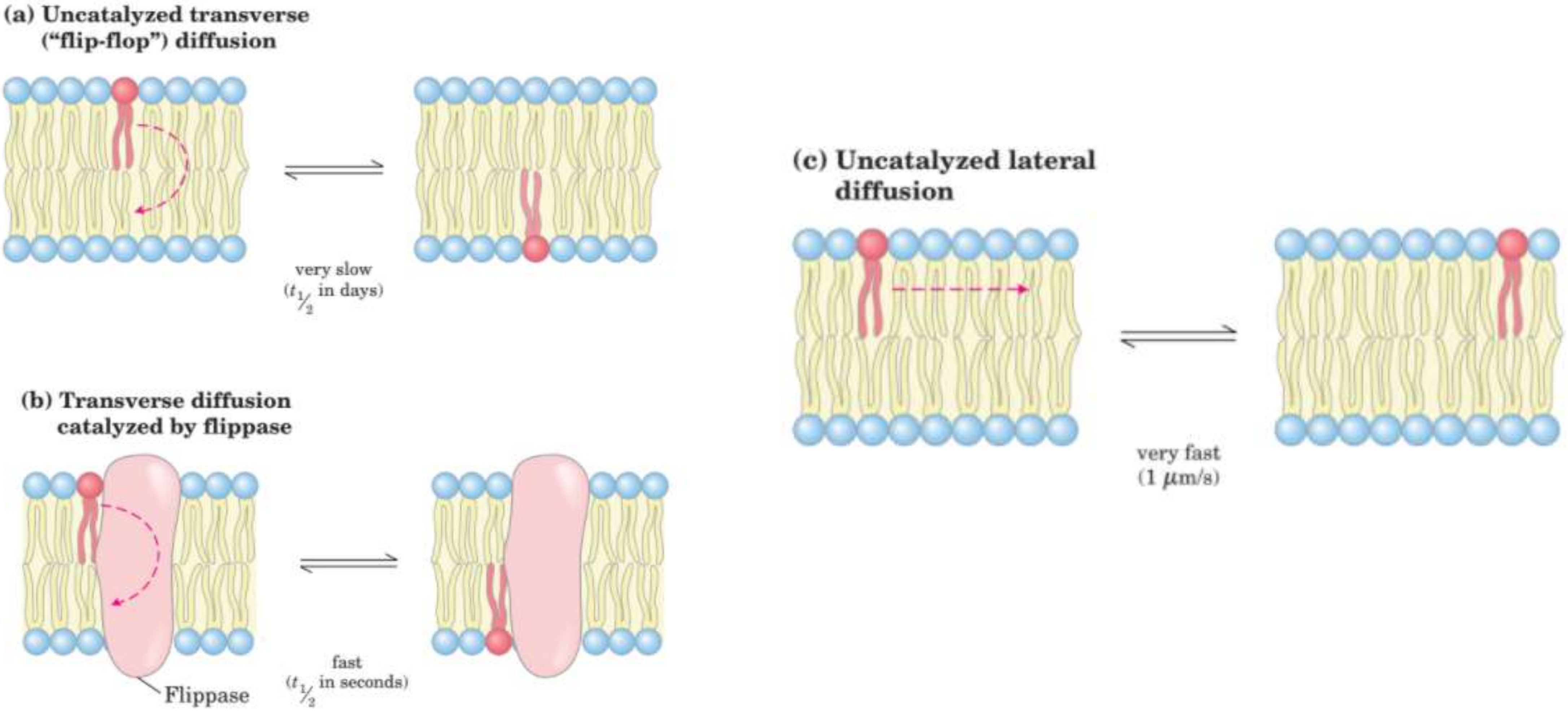


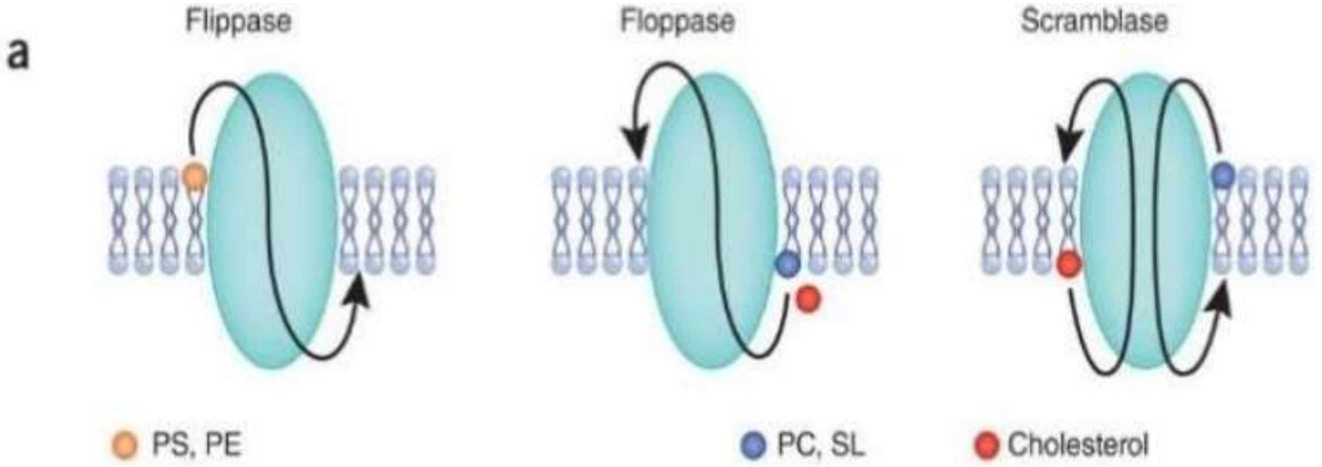


GPI anchor on carboxyl terminus

A rare type of anemia, paroxysmal nocturnal hemoglobinuria, results from a deficiency in GPI synthesis that makes red blood cells susceptible to lysis.

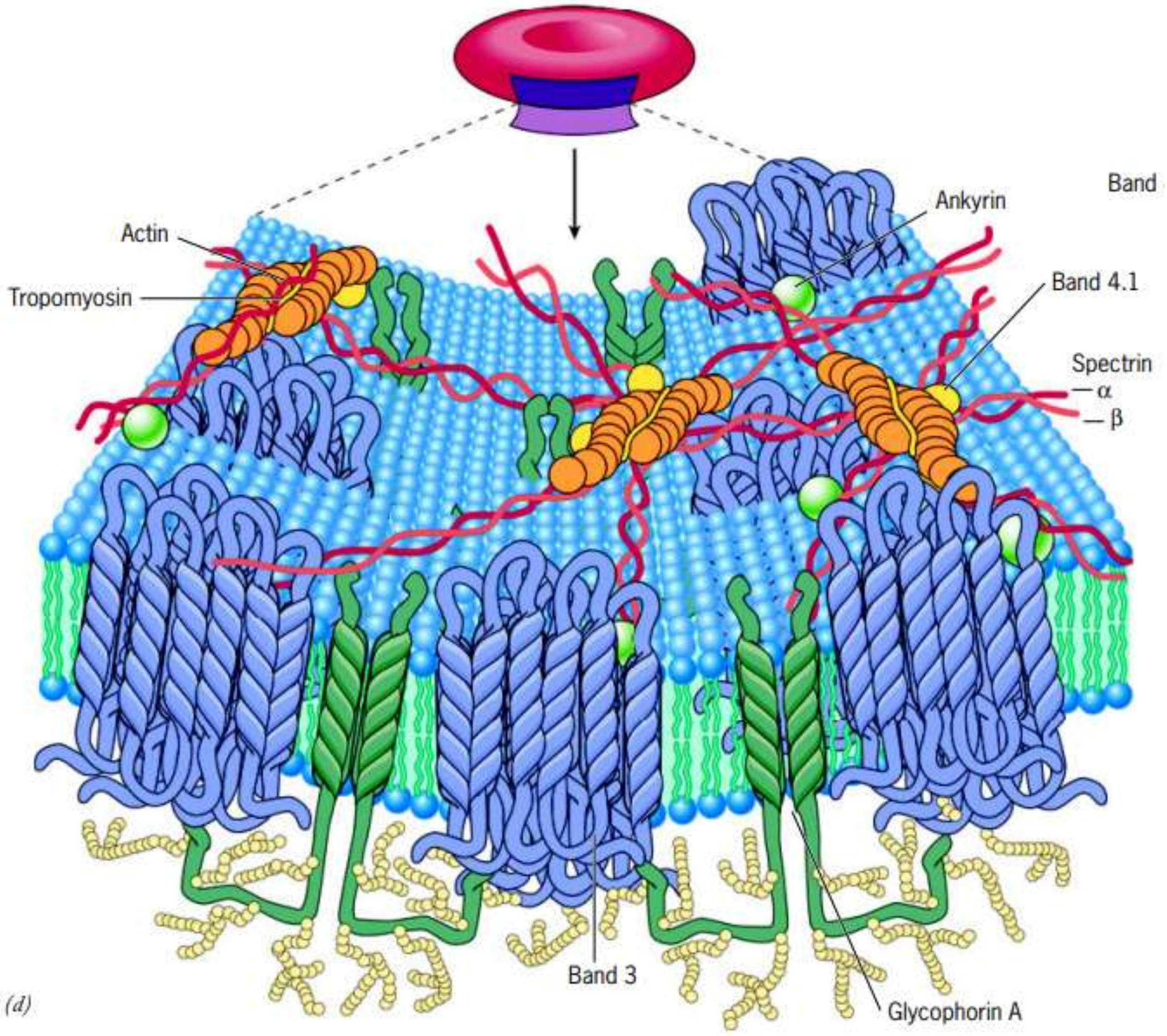
Dynamic Nature of the Plasma Membrane





Comparison of the functions of flippases, floppases and scramblases in the plasma membrane. Flippases (left) use ATP to move the aminophospholipids PS and, to a lesser extent, phosphatidylethanolamine (PE), from the outer leaflet to the inner leaflet of the PM against a concentration gradient. Floppases (middle) use ATP to transport substrates such as phosphatidylcholine (PC), sphingolipid (SL) and cholesterol against concentration gradients in the opposite direction. Scramblases (right) are ATP independent and less substrate specific and facilitate the movement of lipids along concentration gradients.

The Red Blood Cell: An Example of Plasma Membrane Structure



- ➢ Integral membrane proteins:
- Band 3
- Glycophorin A
- ➢ Erythrocyte Membrane Skeleton
- Spectrin
- Ankyrin
- Actin
- Tropomyosin

Integral Proteins of the Erythrocyte Membrane

- Band 3: is present as a dimer (a homodimer)
- Band 3 protein serves as a channel for the passive exchange of anions across the membrane
- Each subunit spans the membrane at least a dozen times and contains a relatively small amount of carbohydrate (6–8 percent of the molecule's weight)
- The reciprocal movement of HCO_3^- and Cl^- occurs through a channel in the center of each band 3 dimer.

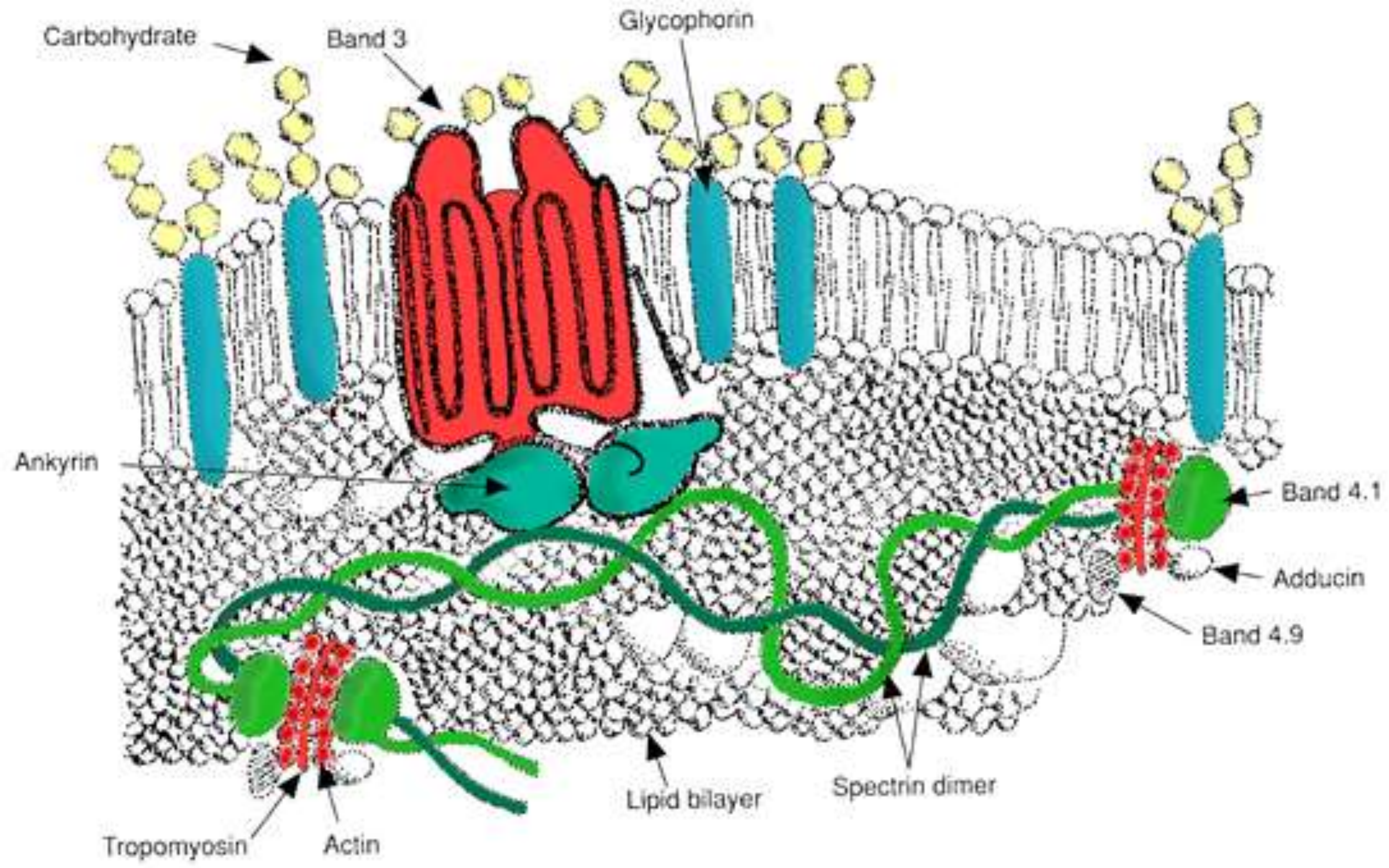
$$H_2O + CO_2 \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$$

Integral Proteins of the Erythrocyte Membrane

Glycophorin A:

- Dimer, spans the membrane only once
- 16 oligosaccharide chains that together make up about 60 percent of the molecule's weight
- Presence of negative charges (sialic acid)→ prevents the cells from clumping
- Glycophorin→ receptor of malarial protozoan
- Differences in glycophorin amino acid sequence determine whether a person has an MM, MN, or NN blood type.

Erythrocyte Membrane Skeleton



- Spectrin is a heterodimer, consisting of an alpha and beta subunit that curl around one another
- Ankyrin- link between spectrin and band 3
- Actin
- Tropomyosin

- A number of genetic diseases (hemolytic anemias) characterized by fragile, abnormally shaped erythrocytes have been traced to mutations in ankyrin or spectrin.

Part B: Question 1

The mobility of integral proteins can be measured by physical state of the ________________

a) amino acids
b) external phospholipids
c) membrane phospholipids
d) membrane appendages

Part B: Question 2

According to Roberston’s unit membrane model of plasma membrane:

a. Proteins on cytoplasmic & non cytoplasmic sides are same.
b. All proteins are transmembrane proteins.
c. There is no space between lipid bilayers.
d. None of above.

Part B: Question 3

Which of the following membranes has the largest amount of proteins:

a. Erythrocyte membrane
b. Myelin sheath membrane
c. Inner mitochondrial membrane
d. Outer mitochondrial membrane

Part C: Question 1

77. Both sphingomyelin and phosphoglycerides are phospholipids. Which one of the following statements is **NOT** correct?

1. While one has a fatty acid tail attached via an ester bond, in another, the fatty acid tail is attached via an amide bond.
2. The hydrophilicity of both is dependent on the phosphate group and other head groups attached to the phosphate group.
3. Only one of them may contain a carbon-carbon double bond (C=C).
4. Both may have choline as head group.

Part C: Question 2

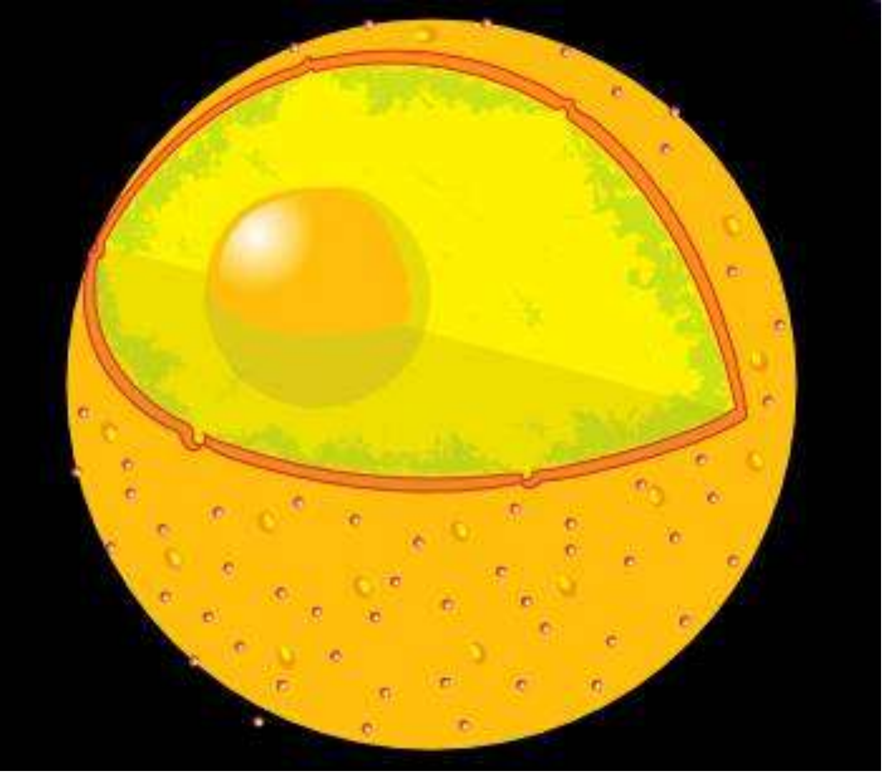
- Q.8. When bacteria growing at 20°C are warmed at 37°C, they are most likely to synthesize membrane lipids with more? (CSIR-June 2015)

1. short chain saturated fatty acids
2. short chain unsaturated fatty acids
3. long chain saturated fatty acids
4. long chain unsaturated fatty acids

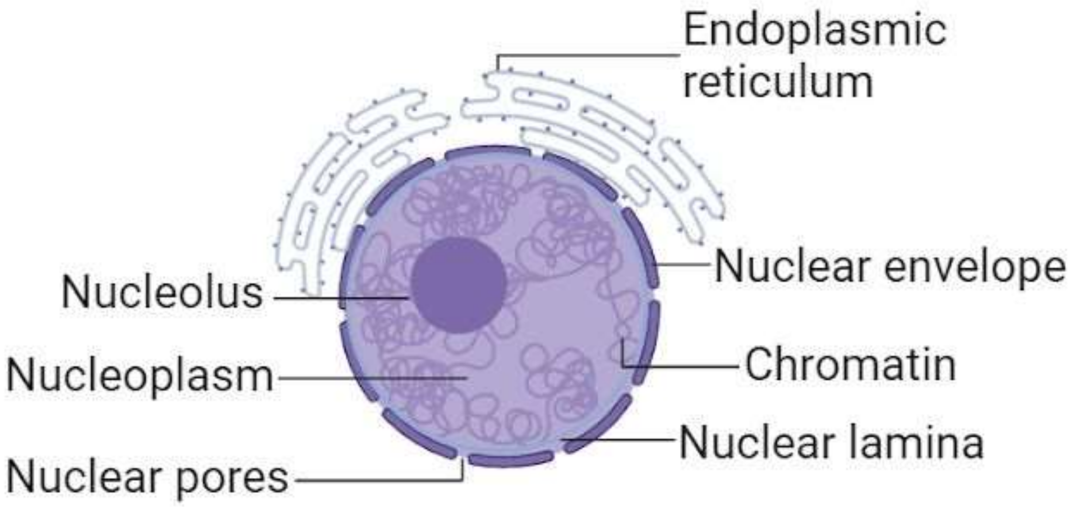
Part C: Question 3

Sphingolipids (S) and cholesterol (C) molecules of the lipid bilayer aggregate into multiple tiny rafts instead of a single large one. Considering that size of a lipid raft depends on the affinity of S and C for one another and other lipids in the membrane, choose the option that best describes this property.

1. S and C bind to one another tightly and independent of any other lipid molecules.
2. S and C bind to one another with same affinity as they bind to other lipid species of the membrane.
3. S and C bind to one another with high affinity under the influence of some cytoskeletal elements.
4. S and C have slightly higher affinity than other lipid molecules of the membrane and are in dynamic equilibrium with their free forms.



Nucleus



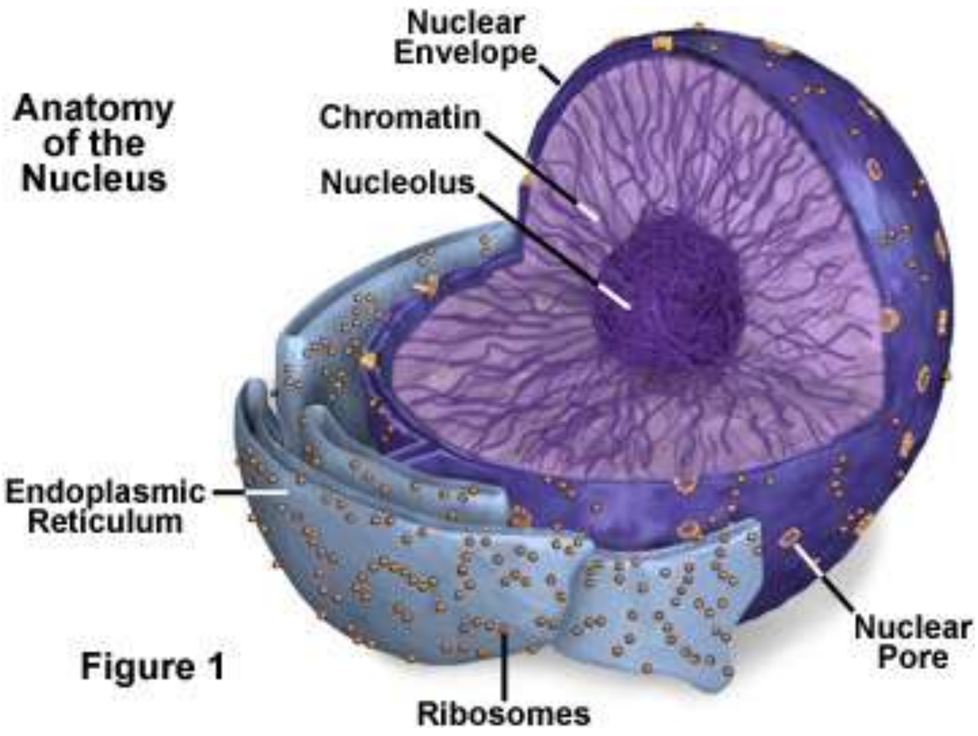


Figure 1

Nucleus

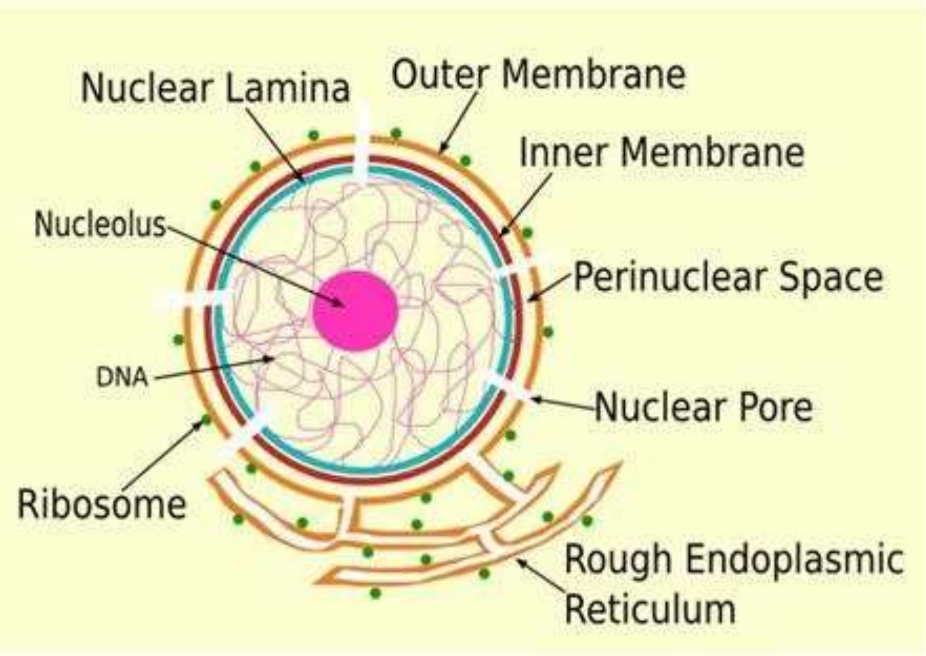
- The Nucleus is a membrane-enclosed organelle (nuclear envelop) which houses most of the genetic information and regulatory machinery responsible for providing the cell with its unique characteristics.

Functions of the Nucleus

- It stores the cell's hereditary material, or DNA.
- Site of DNA replication
- Site of DNA transcription to mRNA
- Ribosomal formation
  - Nucleolus: RNA & protein required for ribosomal synthesis

Nuclear Envelop

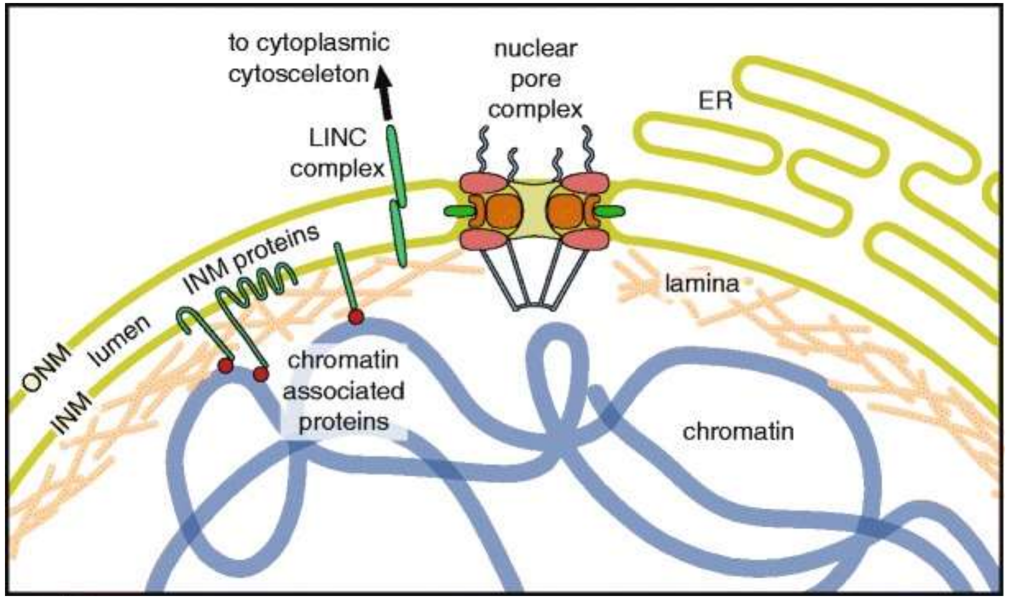
- Consists of two cellular membranes, separated by 10-50 nm
- Serve as a barrier; prevents free movement of ions, solutes and macromolecules from the nucleus to cytoplasm
- Two membranes are fused at sites forming circular pores that contain assemblies of proteins (nuclear pores)



- The outer nuclear membrane is continuous with the membrane of the rough endoplasmic reticulum (RER), and is similarly studded with ribosomes.
- The space between the membranes is called the perinuclear space.

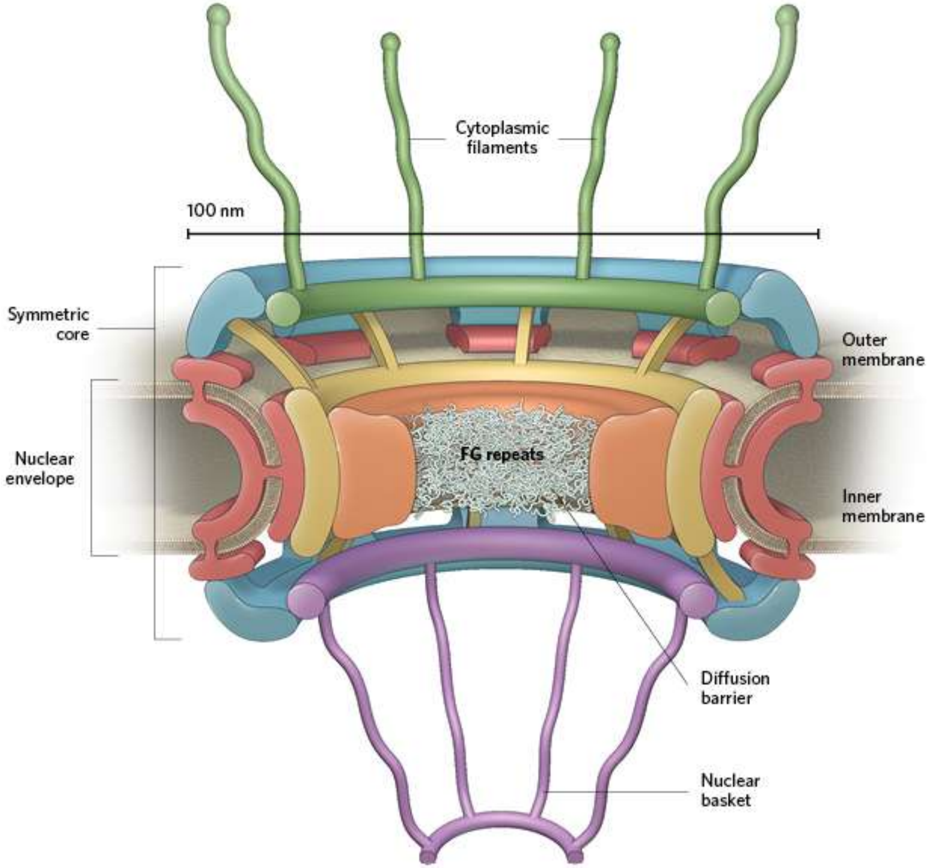
Nuclear Lamina

- The inner surface of the nuclear envelope is lined by a thin filamentous network (lamins polypeptide) called the nuclear lamina
- The nuclear lamina provides mechanical supports to the nuclear envelope: Gives shape and stability to nuclear envelope
- The nuclear lamina is composed of polypeptides called lamins.
- The integrity of the nuclear lamina is regulated by phosphorylation and dephosphorylation.
- Mutation in laminin genes leads to rare form of Muscular Dystrophy (EDM2) and Hutchinson-Gilford progeria syndrome (HGPS)



Nuclear Pore Complex (NPC)

- Nuclear pores are gateways which mediates the movement of RNAs and proteins in both directions between the nucleus and the cytoplasm
- The nucleus of a typical mammalian cell has about 3000 to 4000 pores throughout its envelope.
- Contain about 30-50 different proteins called nucleoporins that line the central channel of the NPC
- Each pore contains a donut-shaped, eightfold-symmetric ring-shaped structure at a position where the inner and outer membranes fuse.



Nuclear Transport

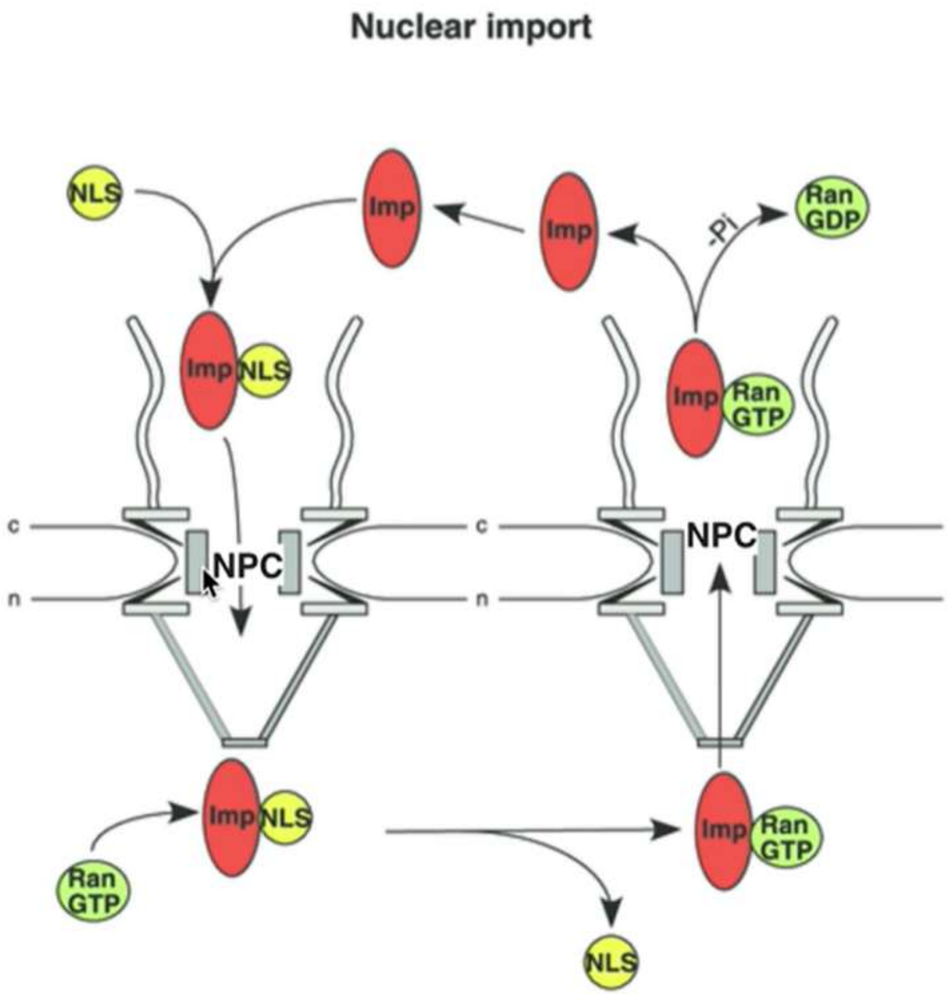
- A family of proteins (karyopherins) function as transport receptors:

➢ Importins: move macromolecules from cytoplasm to nucleus

➢ Exportins: move macromolecules from nucleus to cytoplasm

- NLS (Nuclear Localization Signal) and NES (Nuclear Export Signal) containing proteins are only transported across the nucleus
- Importins binds to only NLS containing proteins, whereas Exportins binds to NES containing proteins
- Importin (heterodimeric, α/β) resides in cytoplasm, Exportins resides in nucleus.

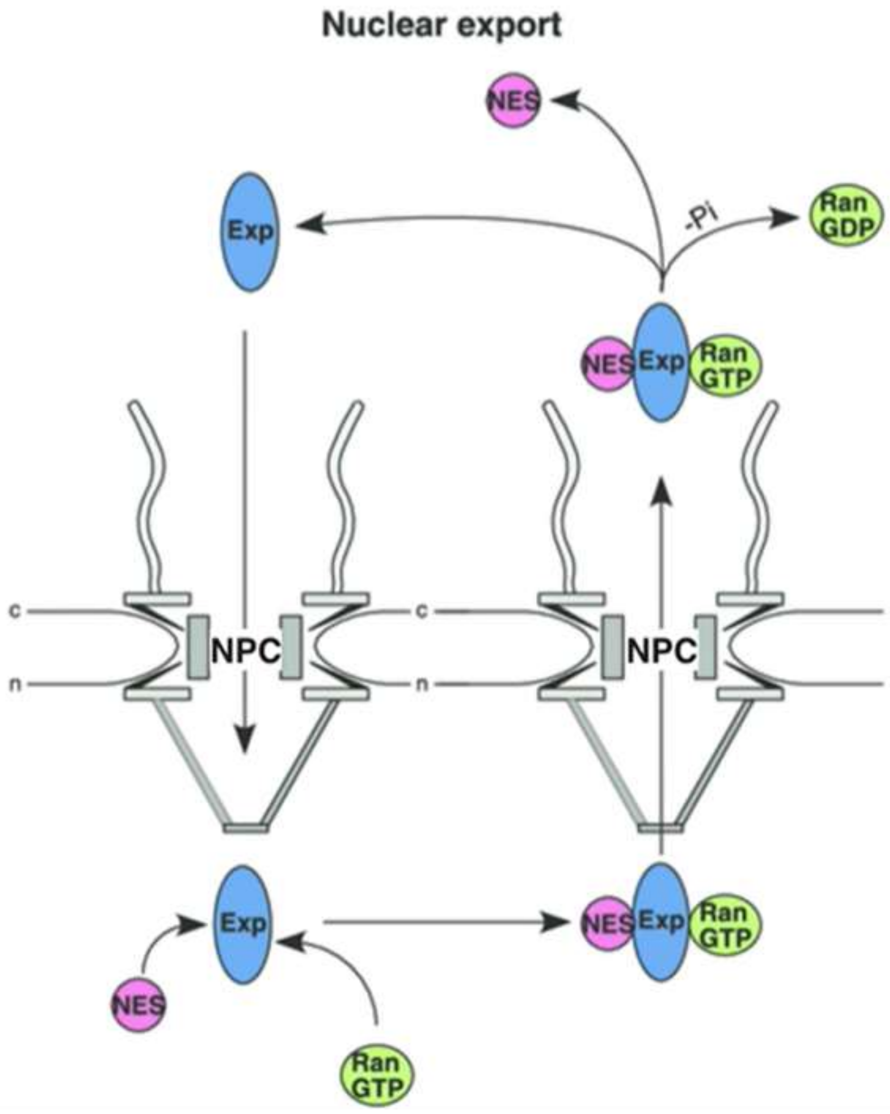
Nuclear Transport: Import



NLS of Nucleoplasmin = KR[PAATKKAGQA]KKKK

- Importin binds to protein containing NLS sequence
- NLS sequences are rich in Lysine (positively charged), which facilitates its binding to importin.

Nuclear Transport: Export



NES = $L_{xxx}L_{xx}L_{x}L$

- Exportin binds to protein containing NES sequence

- NES sequences are rich in Leucine (hydrophobic in nature), which facilitates its binding to exportin.

– RCC1 sequestered in the nucleus, promotes the conversion of Ran-GDP to Ran-GTP

– RanGAP1-resides in the cytoplasm, promotes the hydrolysis of Ran-GTP to Ran-GDP


KEEP
LEARNING.
KEEP
GROWING.