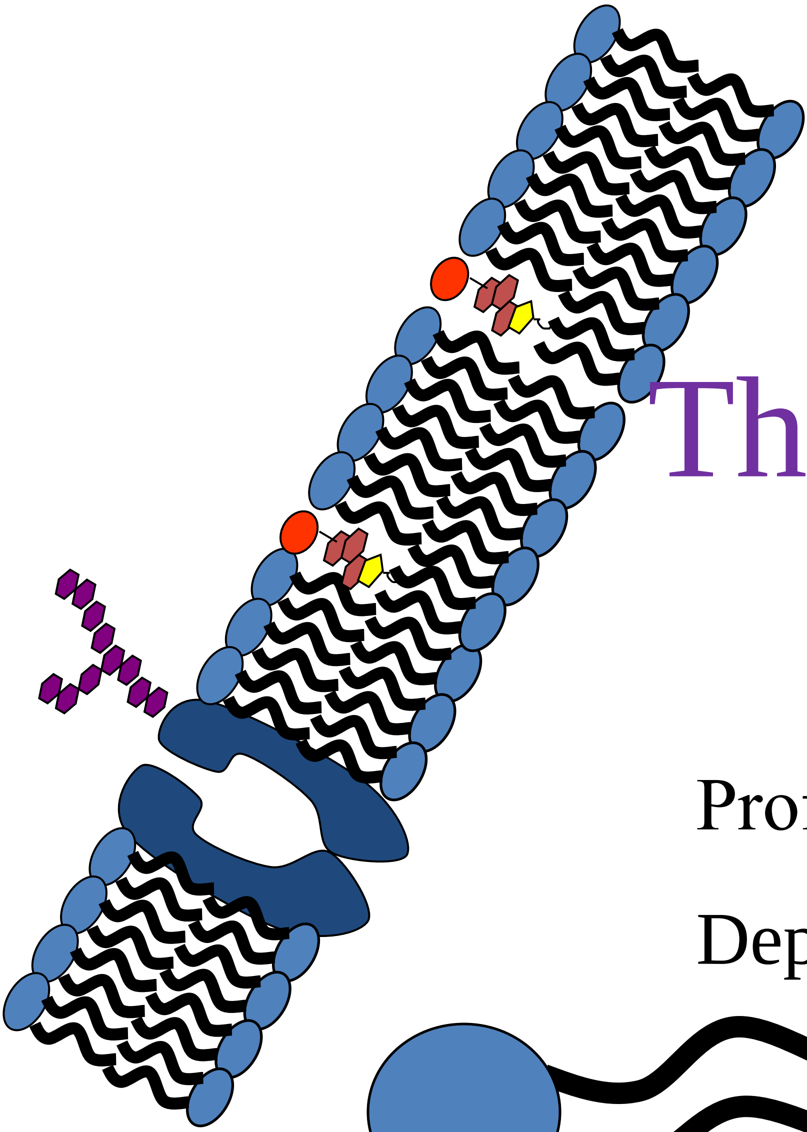
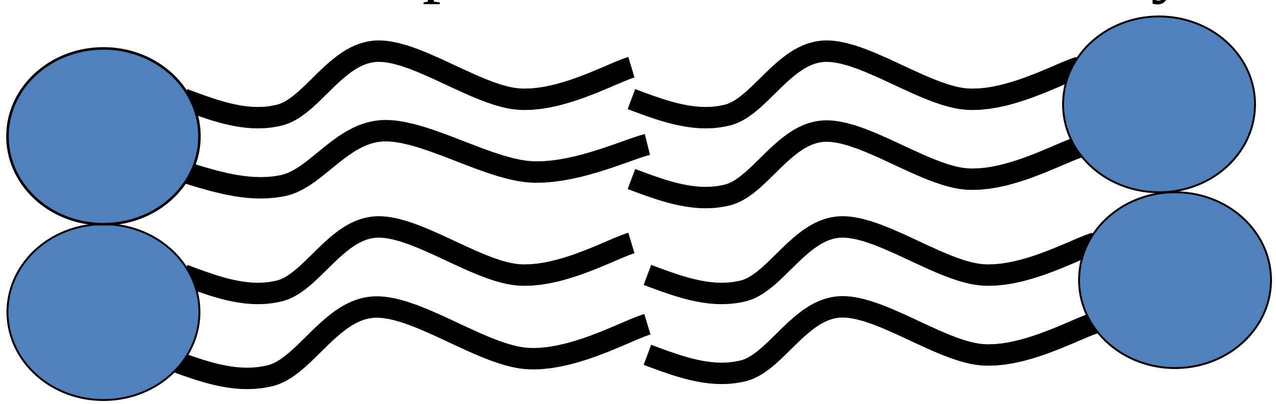


The Structure of Cell Membrane

Prof. Dr. Nurten ÖZSOY

Department of Biochemistry



Suggestions for doing well

- Come to class!
- Read the assignment before lecture
- Stay current with problems
- Seek help if needed
- You are responsible for content of lectures and readings

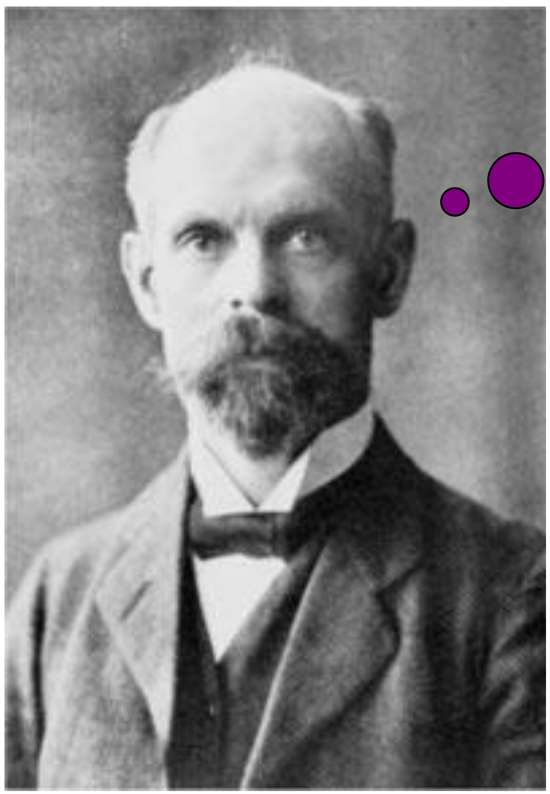
Learning objectives

At the completion of this lesson, students will be able to:

- Define plasma membrane
- Review the history of membrane models
- Explain the fluid mosaic model of cellular membranes
- Identify the functions of the plasma membrane
- Outline the composition of the plasma membrane, including all main components.
- Describe the structures of the major types of membrane lipids including the phosphoglycerides, sphingomyelin, and the glycolipids.
  - ➢ Identify the polar (hydrophilic) and nonpolar (hydrophobic) regions of a phospholipid.
  - ➢ Explain the meaning of the statement that phospholipids and most other membrane constituents (e.g., proteins, cholesterol) are amphipathic molecules.
  - ➢ Distinguish glycerophospholipids from sphingophospholipids.
  - ➢ Distinguish phospholipids from glycolipids.
  - ➢ Explain how the phospholipid molecules form the bilayer of the cell membrane.
  - ➢ Identify the structures lipids form in water (micelle, liposomes)

- Explain the possible movements of phospholipids in a membrane
- Describe the fluidity of the components of a cell membrane and explain how membrane fluidity is influenced by temperature and membrane composition.
- Explain how cholesterol resists changes in membrane fluidity as temperatures change.
- Describe the structure of integral and peripheral membrane proteins.
- Distinguish between peripheral and integral membrane proteins.
- Summarize the major functions of membrane proteins.
- Describe the glycocalyx and the significance of glycoproteins and glycolipids.
- Explain the role of membrane carbohydrates in cell-cell recognition.

The History of Plasma Membrane

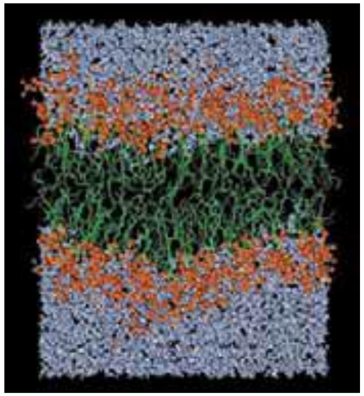


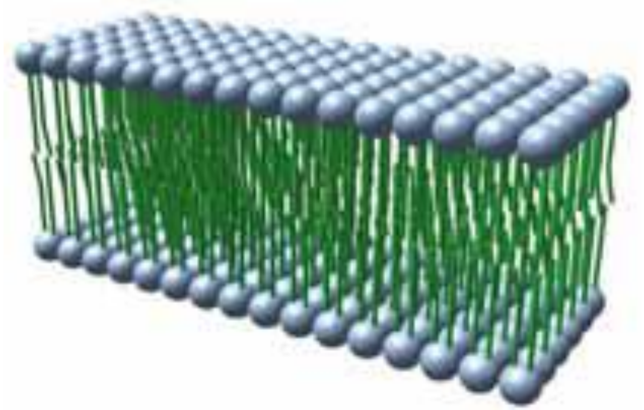
Hmm… I wonder what it's made of??

Charles Overton, 1895- Hypothesizes that membranes are made of lipids after noticing that lipid soluble compounds enter cells more readily.

Overton’s Hypothesis Confirmed

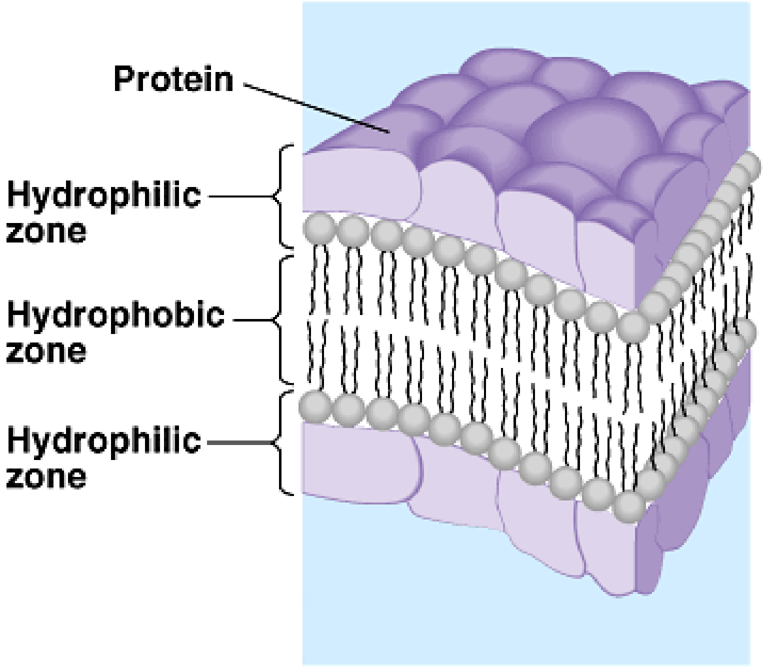
- In 1925-Dutch scientists E. Gorter and F. Grendel concluded that the plasma membrane contained a bimolecular layer of phospholipids, that is, a lipid bilayer. They also suggested that the polar groups of each molecular layer (or **leaflet**) were directed outward toward the aqueous environment. This would be the thermodynamically favored arrangement because the polar head groups of the lipids could interact with surrounding water molecules, just as the hydrophobic fatty acyl chains would be protected from contact with the aqueous environment.





The Davson-Danielli Model (1935)

- In 1935, Hugh Davson and James Danielli proposed a sandwich model in which the phospholipid bilayer lies between two layers of globular proteins.



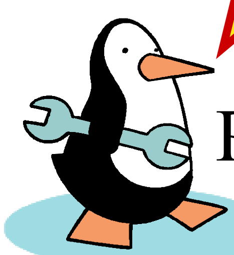
(a) The Davson-Danielli model

Two Problems:

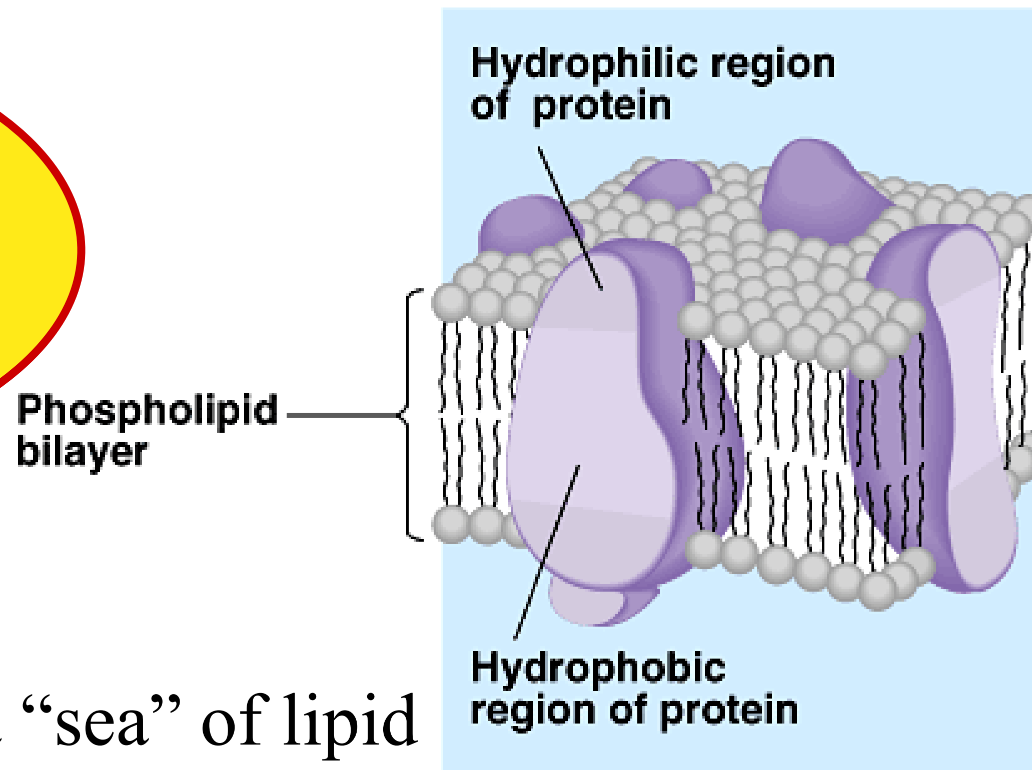
1. Later studies found problems with this model, particularly the placement of membrane proteins, which have hydrophilic and hydrophobic regions so could not be exposed to water.
2. Not all membranes look alike! Cell membranes with different function differ in chemical composition and structure.

More than lipids…

- In 1972, S.J. Singer & G. Nicolson of the University of California, San Diego, proposed that the membrane is a mosaic of proteins dispersed within the fluid bilayer of phospholipids, with only the hydrophilic regions exposed to water.



Proteins "float" in a "sea" of lipid



Membrane Structure

The fluid mosaic model of membrane structure has two components:

1. Phospholipids arranged in a bilayer
2. Globular proteins inserted in the lipid bilayer

Membranes are lipid–protein assemblies in which the components are held together in a thin sheet by noncovalent bonds.

What are some of the functions of biological membrane?

- **Cell membrane <u>separates</u> living cell from aqueous environment** *(Compartmentalization)*
  - Compartmentalize and segregate intracellular events, and separate cells from one another
  - Boundaries around cells (Plasma Membrane)
  - Boundaries round distinct sub-cellular compartments (Nucleus, Mitochondria, Lysosomes, Golgi bodies, etc.)
  - **<u>Provides a selectively permeable barrier</u>**

  (allows some substances to cross more easily than others)

- **Transports solutes:** The cell membrane is a dynamic structure that controls traffic in & out of the cell. Plasma membrane contains specific pumps, channels, transporters used for exchange of nutrients and other materials with the environment
- **Membranes are involved in signalling processes:**
    - Contain specific receptors for external stimuli
    - It is involved in chemical and electrical signal generation
- **Allow cell recognition** – antigens are localized on membranes

The basic components in biological membrane?

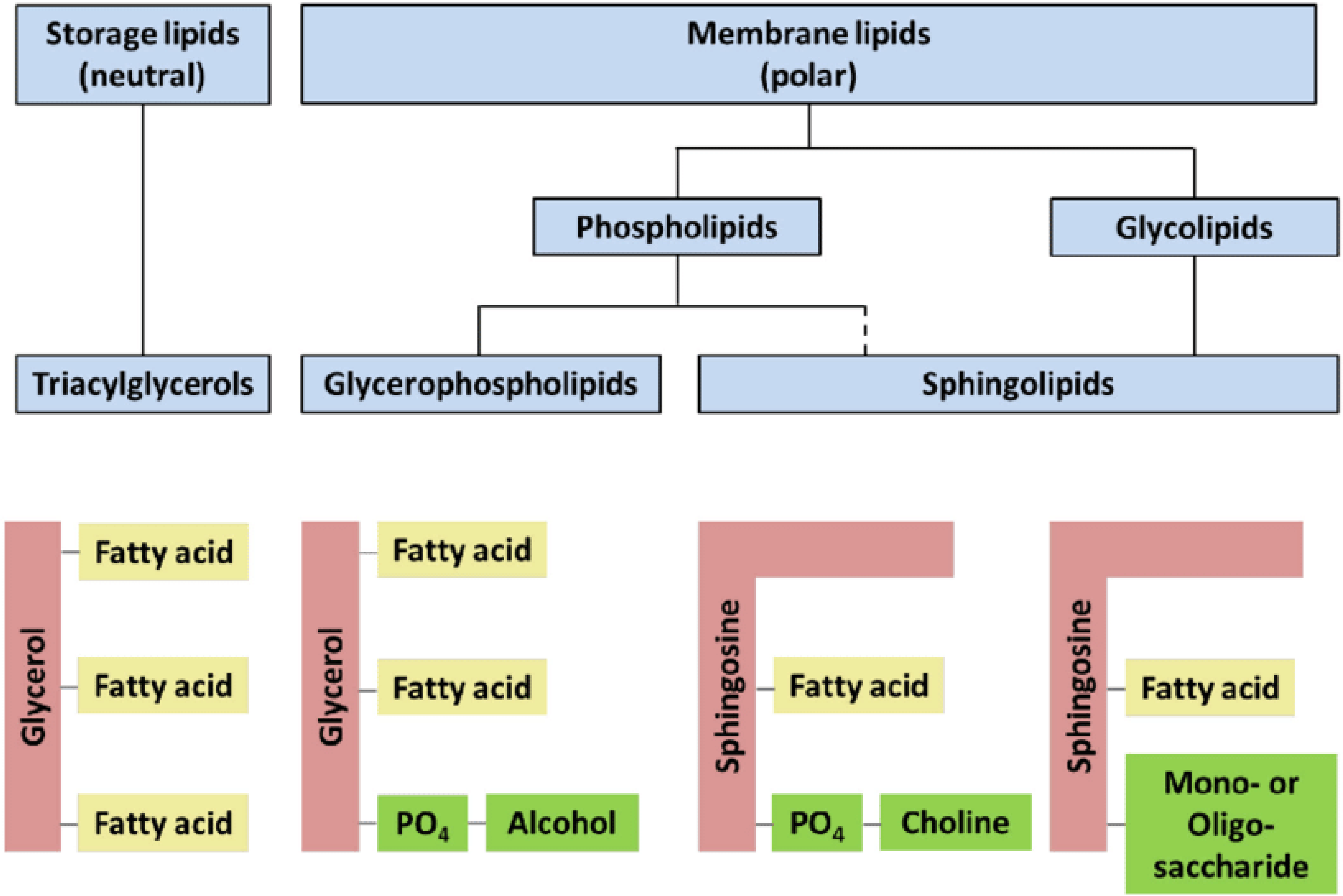
- Made of **phospholipids, proteins and carbohydrates**

- Proteins ……………………….55%
- Lipids ……………………….. 41%
  - Phospholipids…… 25 %
  - Cholesterol……….12 %
  - Glycolipids …….. 4 %
- Carbohydrates……………… 3%

Essential Questions

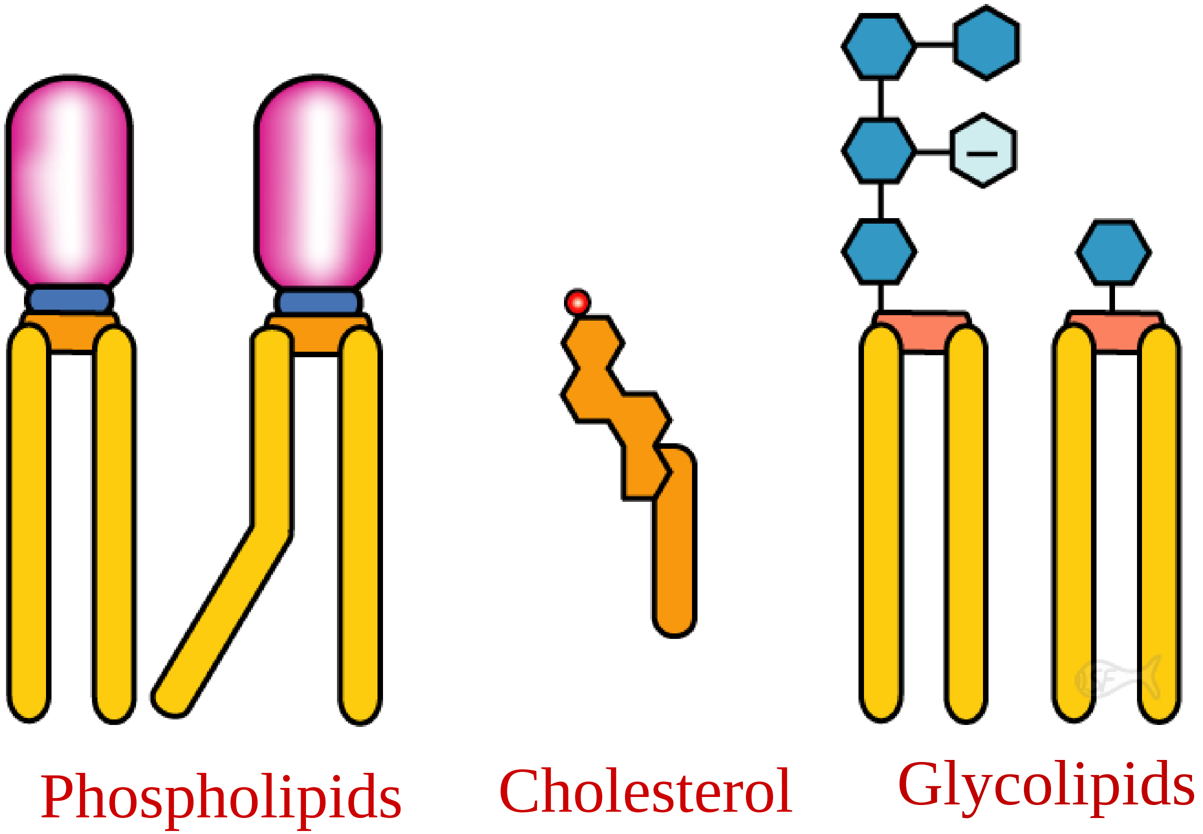
- *Describe some of the important roles of membranes*
- *Summarize some of the major steps leading to the current model of membrane structure. How does each new model retain certain basic principles of earlier models?*
- *What are the basic components in biological membrane?*

What are the major lipids in the biological membrane?



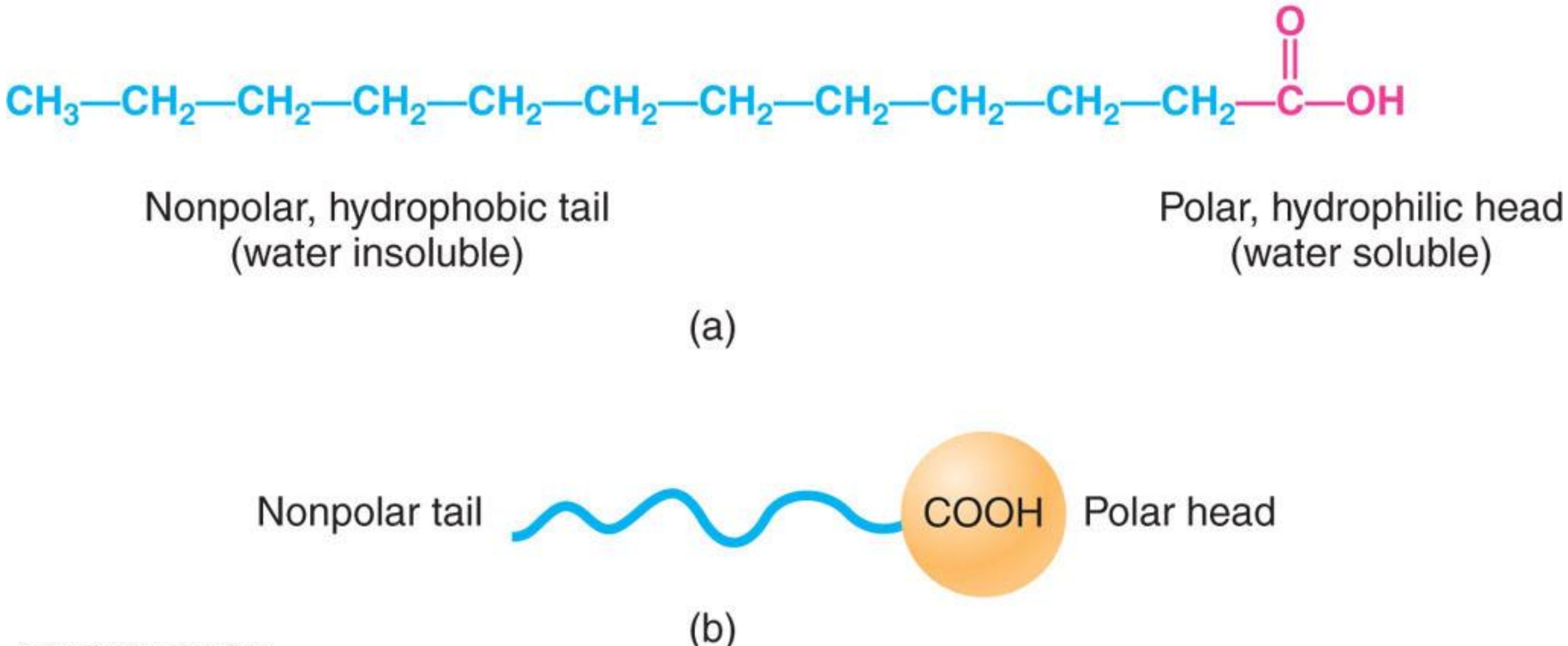
All these lipids have either glycerol or sphingosine as the backbone.

- Major lipids in biological membranes are:
- Phospholipids,
- Glycolipids, and
- Cholesterol

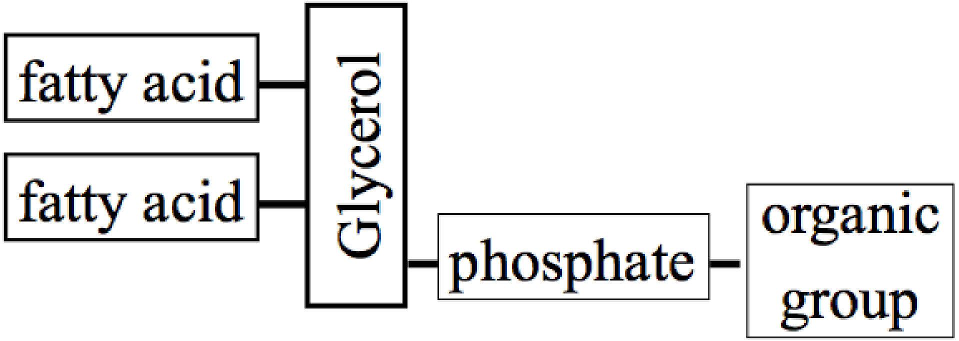


Fatty acids are carboxylic acids with long-chain hydrocarbon chains

Fatty acids are **amphipathic** molecules composed of a **hydrophilic ("water-loving", polar, ionized) head** (formed by the carboxyl group) and a **hydrophobic ("water-fearing", non-polar, non-ionized) tail** formed by the hydrocarbon chain).

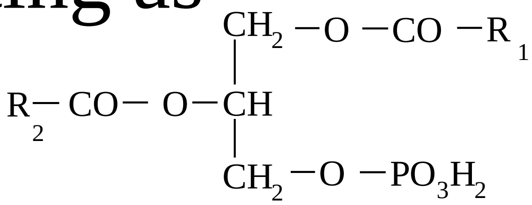


Phospholipids



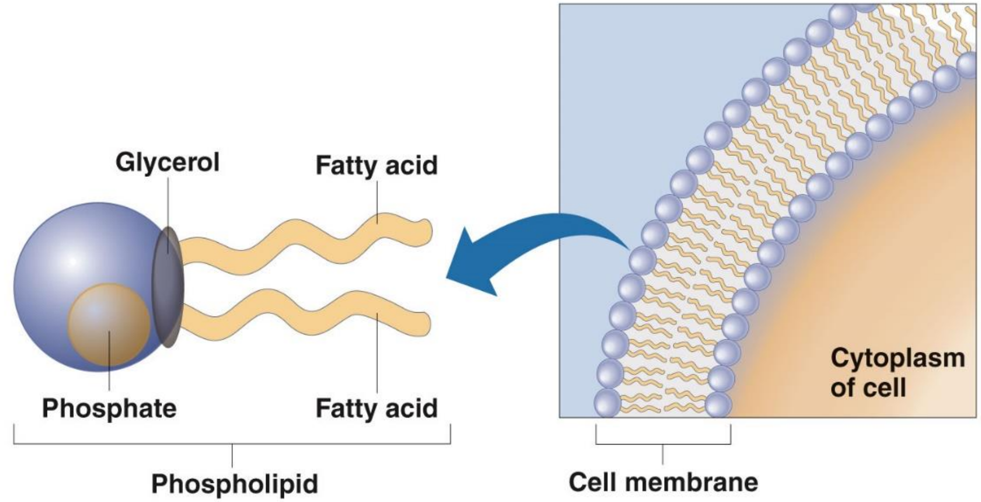
Phospholipid Structure

-glycerol – a 3-carbon polyalcohol acting as a backbone for the phospholipid



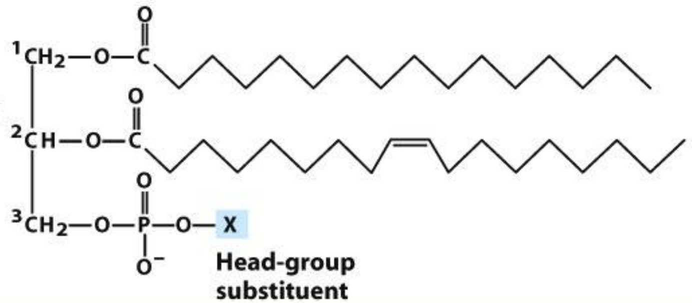
-2 fatty acids attached to the glycerol

-phosphate group attached to the glycerol



Without any additional substitutions beyond the phosphate and the two fatty acyl chains, the molecule is called phosphatidic acid, which is virtually absent in most membranes.

Instead, membrane phosphoglycerides have an additional group linked to the phosphate, most commonly either choline (forming phosphatidylcholine, PC), ethanolamine (forming phosphatidylethanolamine, PE), serine (forming phosphatidylserine, PS), or inositol (forming phosphatidylinositol, PI). Each of these groups is small and hydrophilic and, together with the negatively charged phosphate to which it is attached, forms a highly water-soluble domain at one end of the molecule, called the head group.



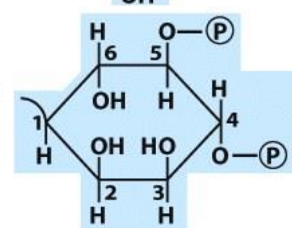
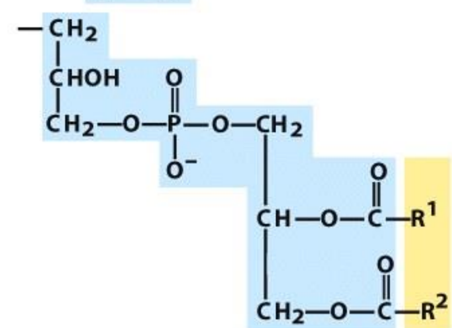
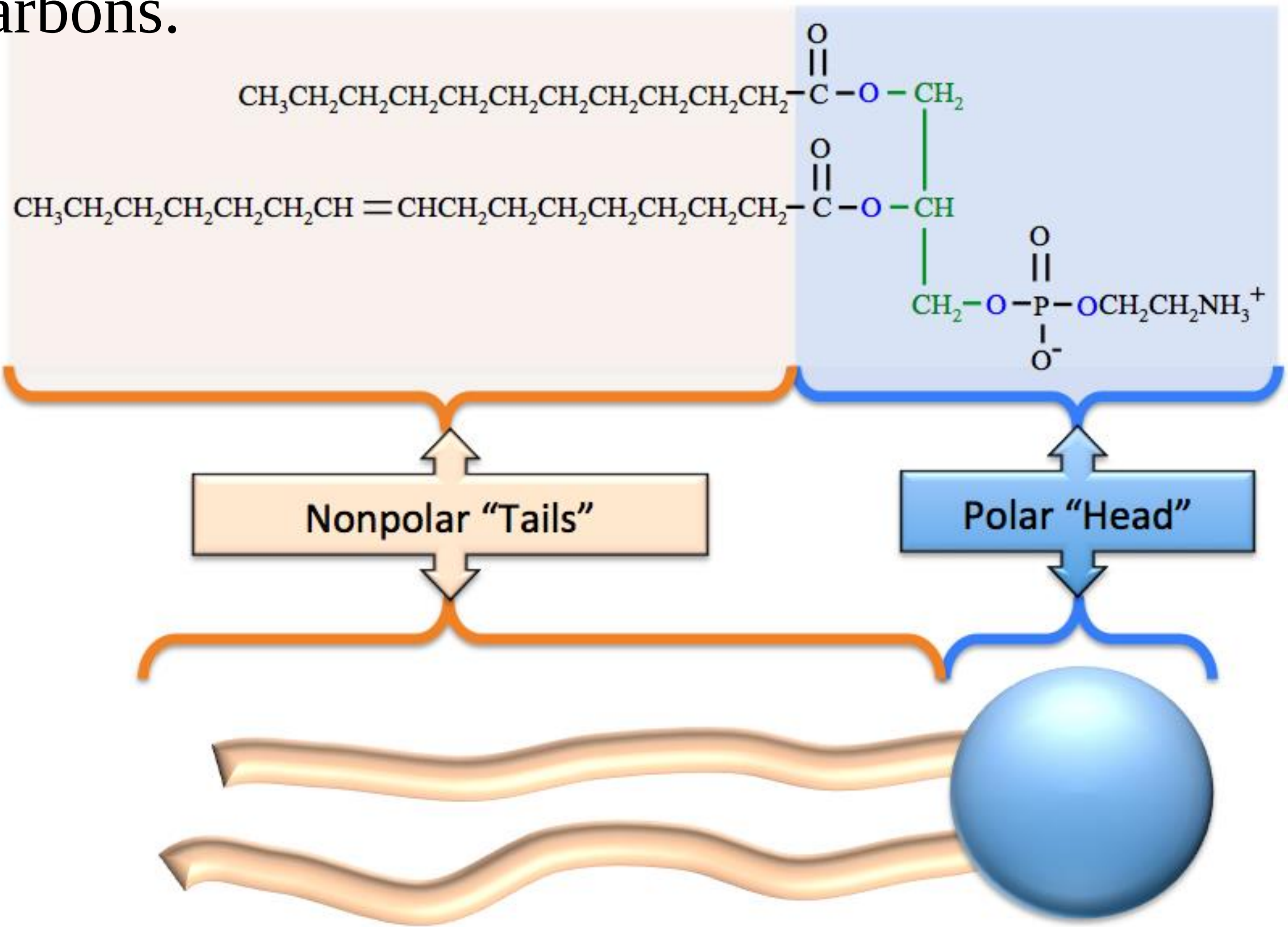
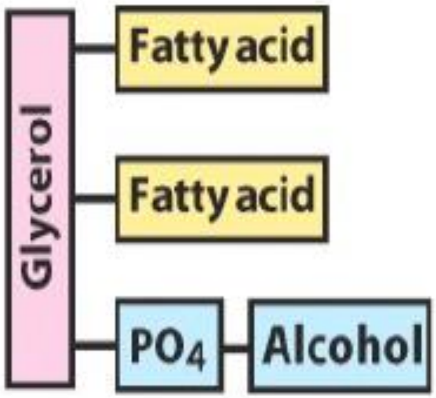
Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	$-H$	−1
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$	0
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$	0
Phosphatidylserine	Serine	$-CH_2-CH(COO^-)-\overset{+}{N}H_3$	−1
Phosphatidylglycerol	Glycerol	$-CH_2-CH(OH)-CH_2-OH$	−1
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		−4
Cardiolipin	Phosphatidyl-glycerol		−2

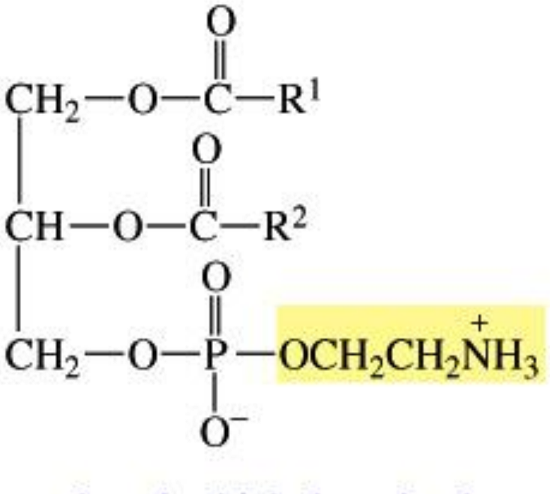
Figure 10-9
Lehninger Principles of Biochemistry, Fifth Edition

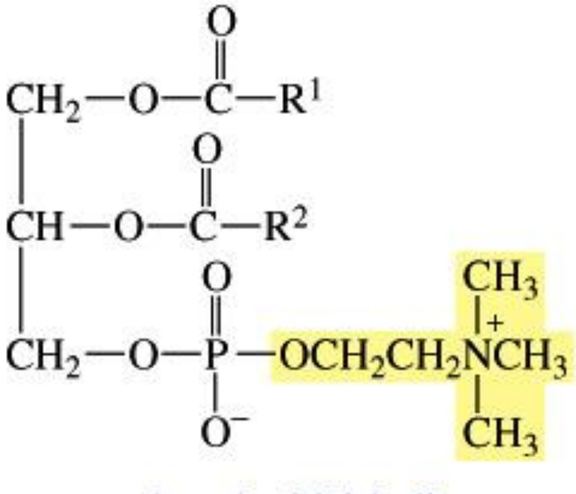
Like fatty acids, **phospholipids** are amphipathic in nature. That is, each has a hydrophilic head, which is the phosphate group plus whatever alcohol is attached to it and a long, hydrophobic tail containing fatty acids or fatty acid–derived hydrocarbons.

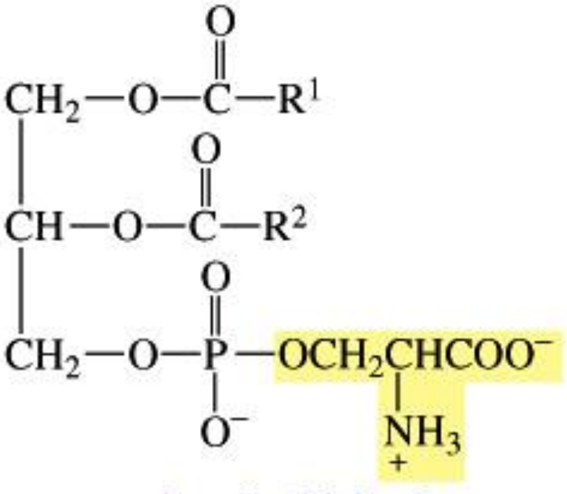


Glycerophospholipids

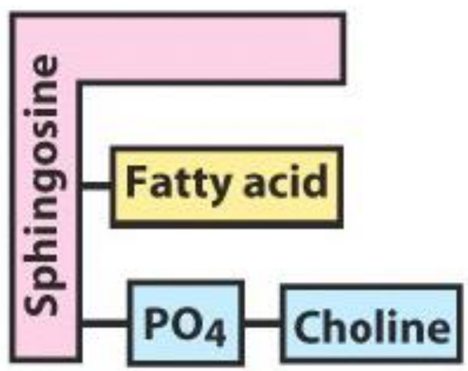








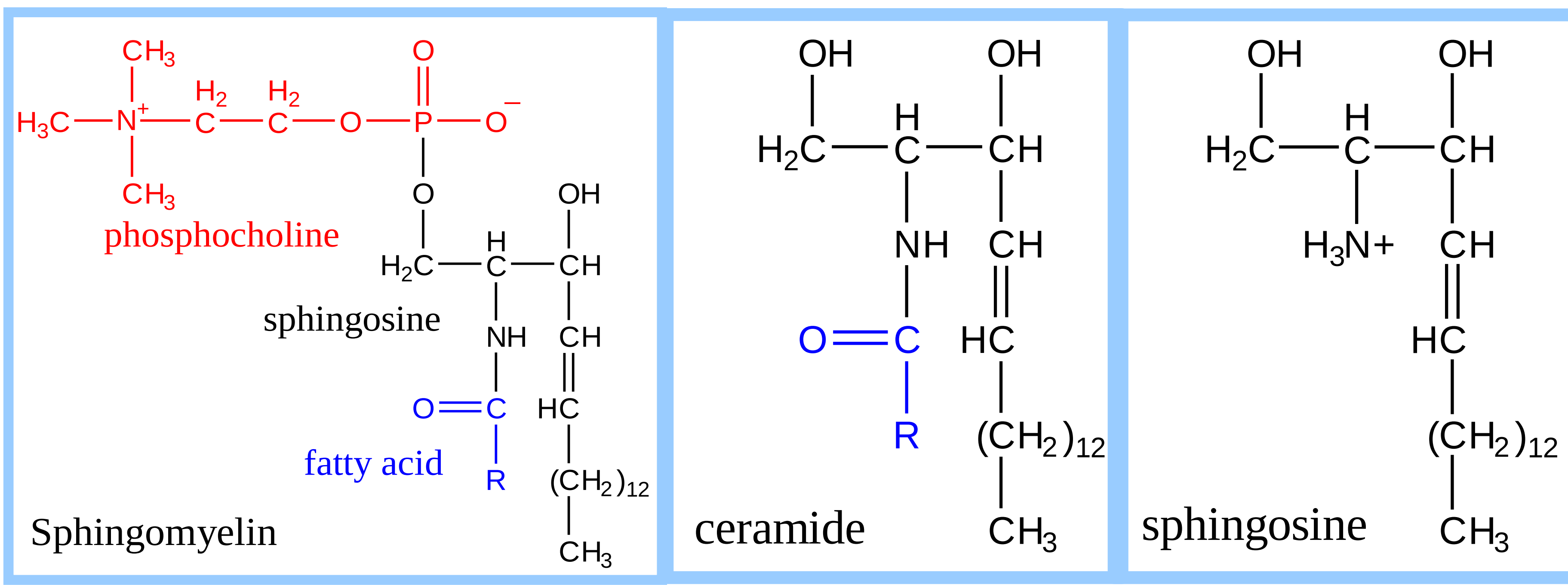
Sphingophospholipids



Sphingolipids, are derivatives of sphingosine, an amino alcohol that contains a long hydrocarbon chain. Sphingolipids consist of sphingosine linked to a fatty acid (R) by its amino group. This molecule is a ceramide. The various sphingosine-based lipids have additional groups esterified to the terminal alcohol of the sphingosine moiety.

If the substitution is phosphocholine, the molecule is sphingomyelin

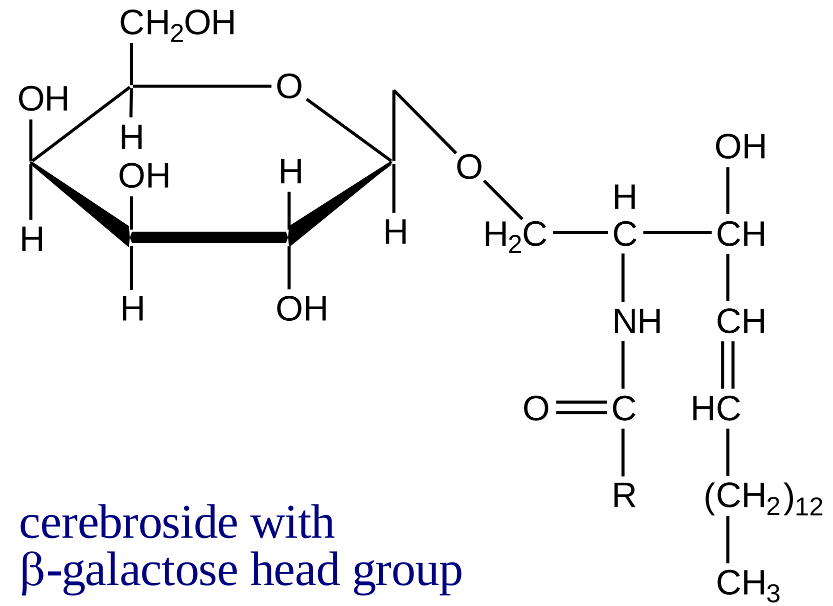
- **Sphingosine replaces glycerol, so only 1 FA tail**



Since all sphingolipids have long, hydrophobic hydrocarbon chain at one end and a hydrophilic region at the other, they are also amphipathic and basically similar in overall structure to the phosphoglycerides.

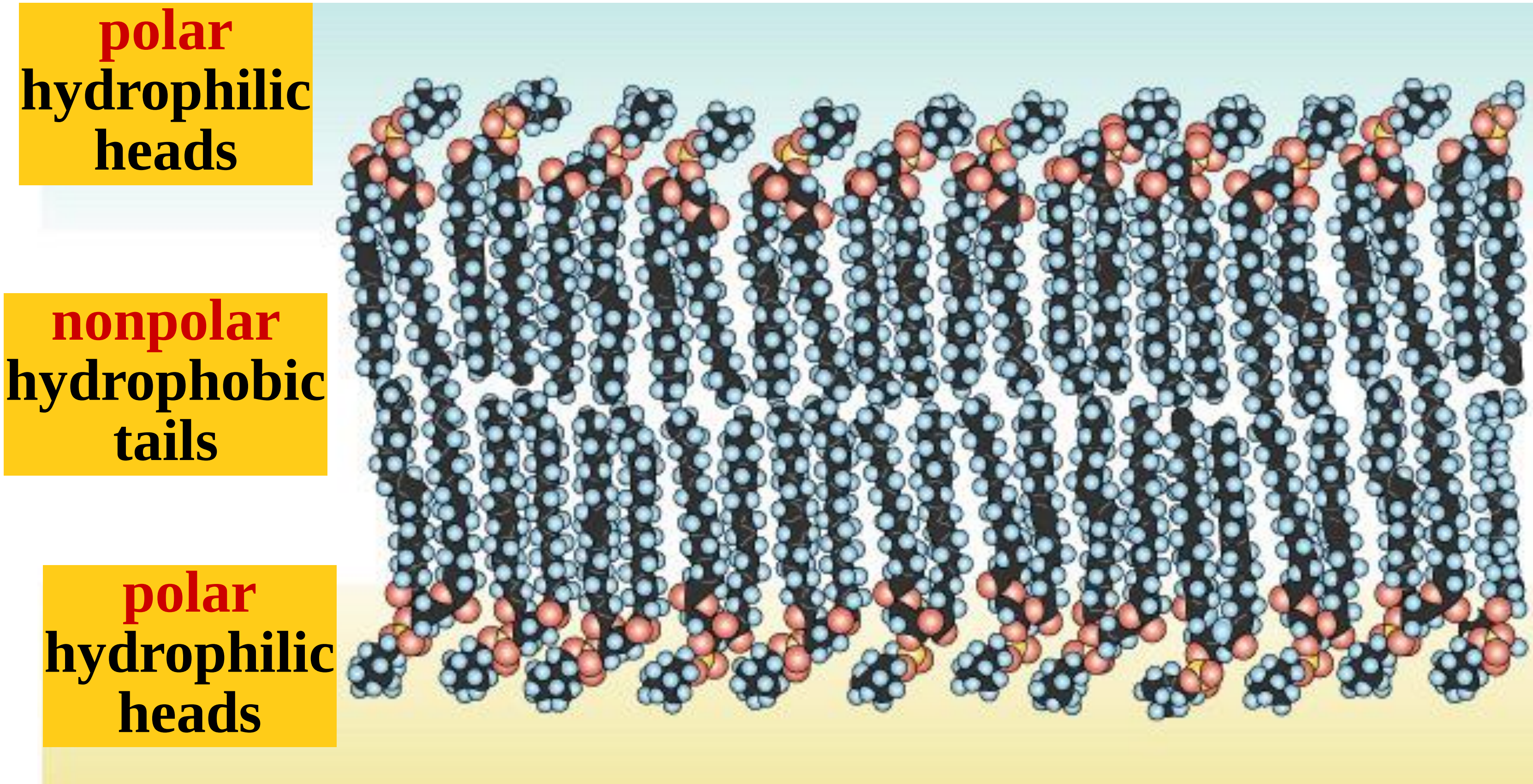
Glycolipids

- Glycolipids have a carbohydrate bound to the alcohol of a lipid via a glycosidic link.
- Frequently a glucose or galactose is bound to the primary alcohol of a ceramide. The compound is called a cerebroside. If it is an oligosaccharide, the glycolipid is called a ganglioside.
- These compounds are found in the cell membranes of nerve and brain cells.
- Glycolipids have **no phosphate**.



cerebroside with
β-galactose head group

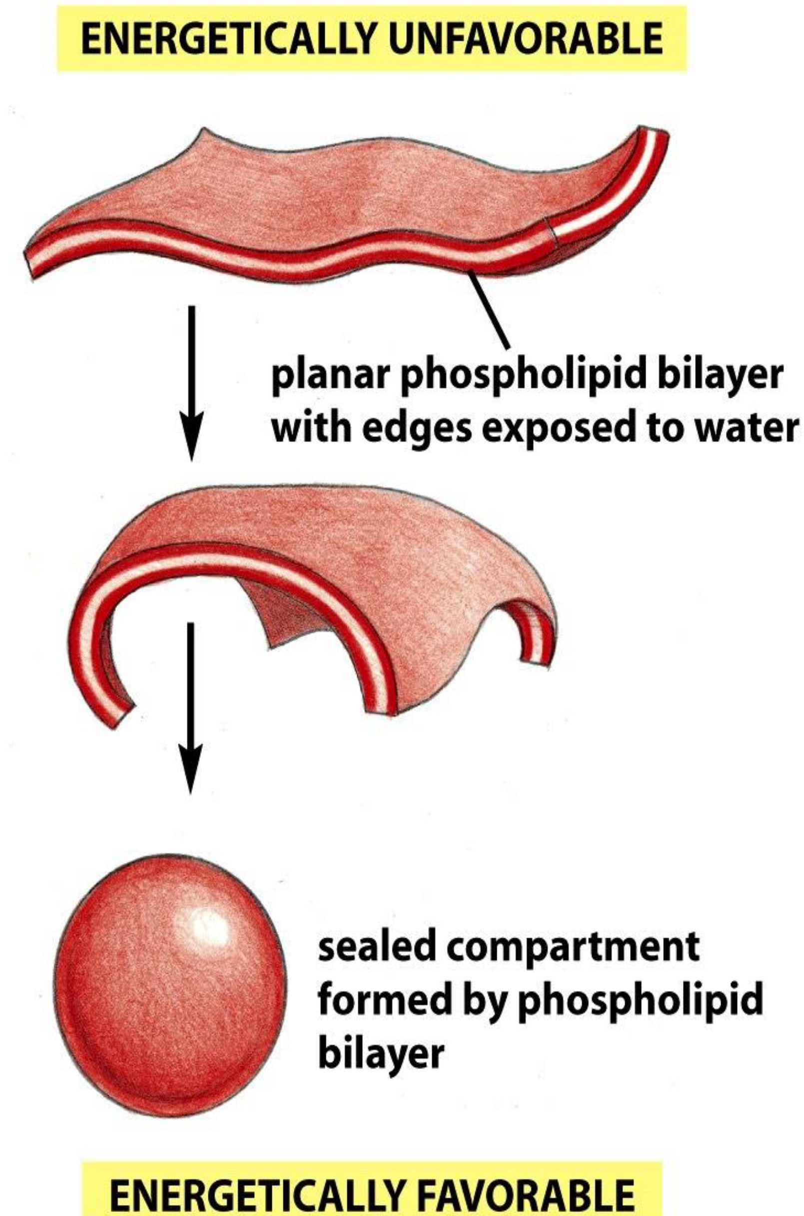
Phospholipid bilayer



Amphipathic phospholipids form a lipid bilayer, with the nonpolar regions of lipids facing each other at the core of the bilayer and their polar head groups facing outward. The lipid bilayer serves primarily as a structural backbone of the membrane and provides the barrier that prevents random movements of water-soluble materials into and out of the cell.

The bilayer ends are exposed to water so curve around to form a ball.

Because of thermodynamic considerations, the hydrocarbon chains of the lipid bilayer are never exposed to the surrounding aqueous solution. Consequently, membranes are never seen to have a free edge; they are always continuous, unbroken structures.



Lipids aggregate into structures in water

- Structures formed depend on:
  - type of lipid
  - concentration
- Micelles
- Liposomes
- Bilayers

Lipid Bilayer Structure

- Lipids assemble to segregate polar end nonpolar substituents
  - Micelles are globular
    - Exterior polar head group, Interior hydrophobic tail
    - Favored by single acyl chains
  - Vesicles or liposomes have an internal aqueous compartments
    - Inner and Outer leaflets
  - Bilayers are locally planar structures
    - Inner and Outer leaflets are asymmetrical
    - Bio membranes are ~3 nm (30 Angstroms) thick

sonication generates liposomes

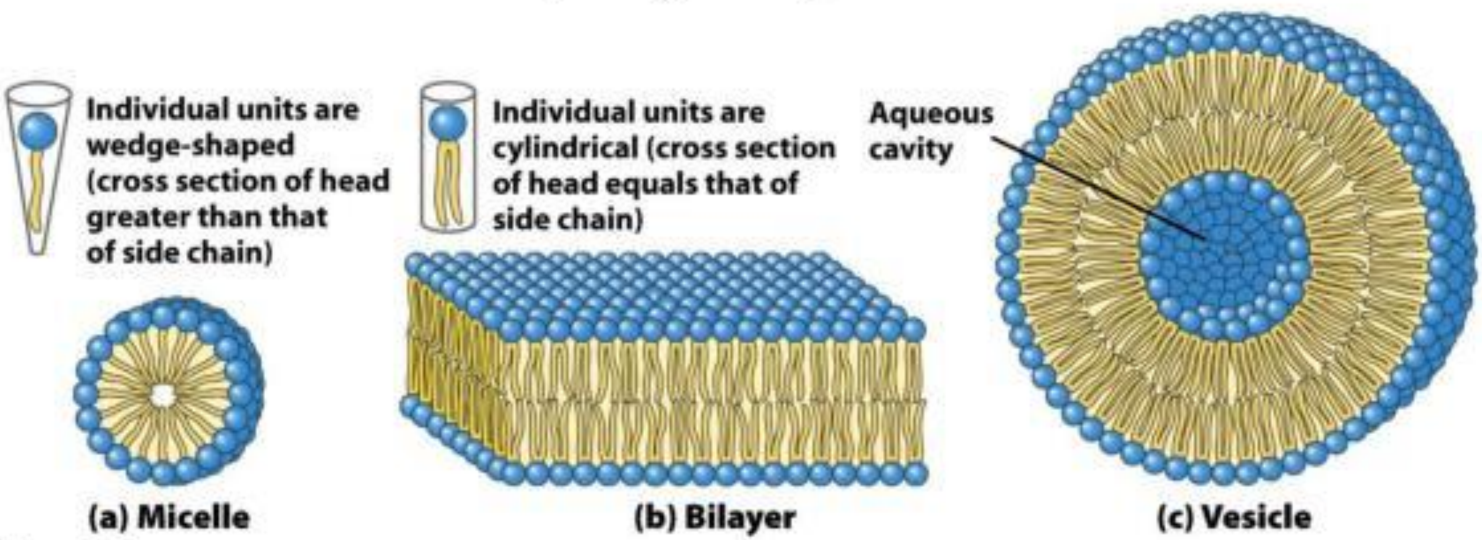
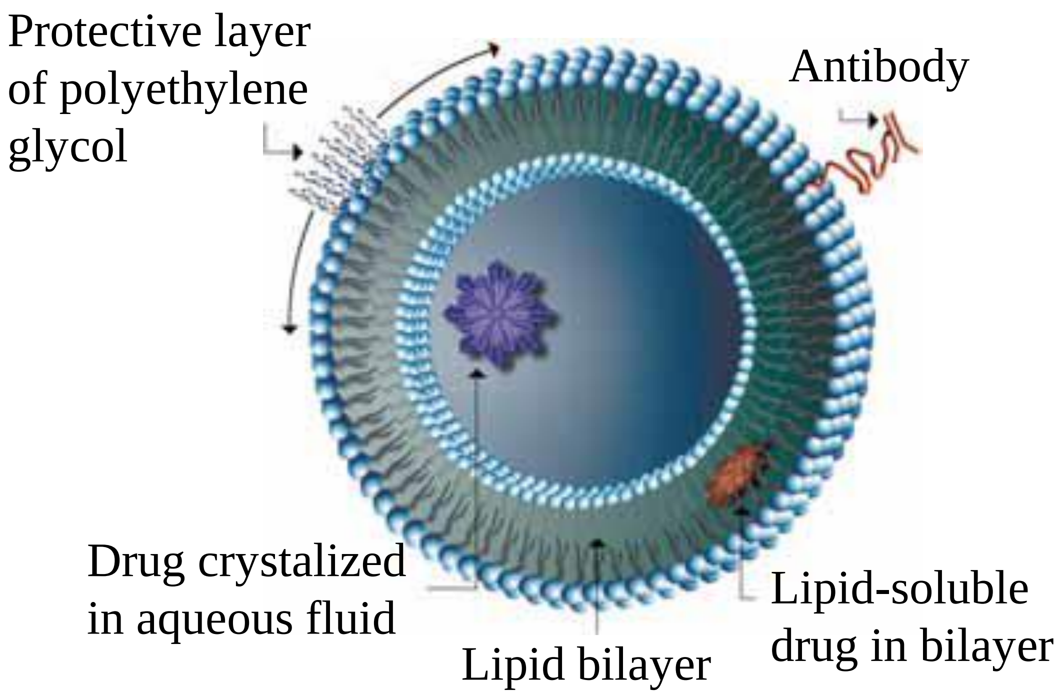


Figure 11-4
Lehninger Principles of Biochemistry, Fifth Edition

Liposomes are also being tested as vehicles to deliver drugs or DNA molecules within the body. The drugs or DNA can be linked to the wall of the liposome or contained at high concentration within its lumen.



Liposomes. A schematic diagram of a stealth liposome containing a hydrophilic polymer (such as polyethylene glycol) to protect it from destruction by immune cells, antibody molecules that target it to specific body tissues, a water-soluble drug enclosed in the fluid-filled interior chamber, and a lipid-soluble drug in the bilayer.

Essential Questions

- *What are the major lipids in the biological membrane?*
- *Which lipids are phospholipids?*
- *Which are glycolipids?*
- *How do sphingolipids differ from glycerolipids?*
- *How are these lipids organized into a bilayer?*
- *How is the bilayer important for membrane activities?*
- *What is a micelle?*
- *What is a liposome? How are liposomes used in medical therapies?*

The possible movements of phospholipids in a membrane

- ***Lateral diffusion***
- Refers to the lateral movement of lipids or proteins
  - o Very fast

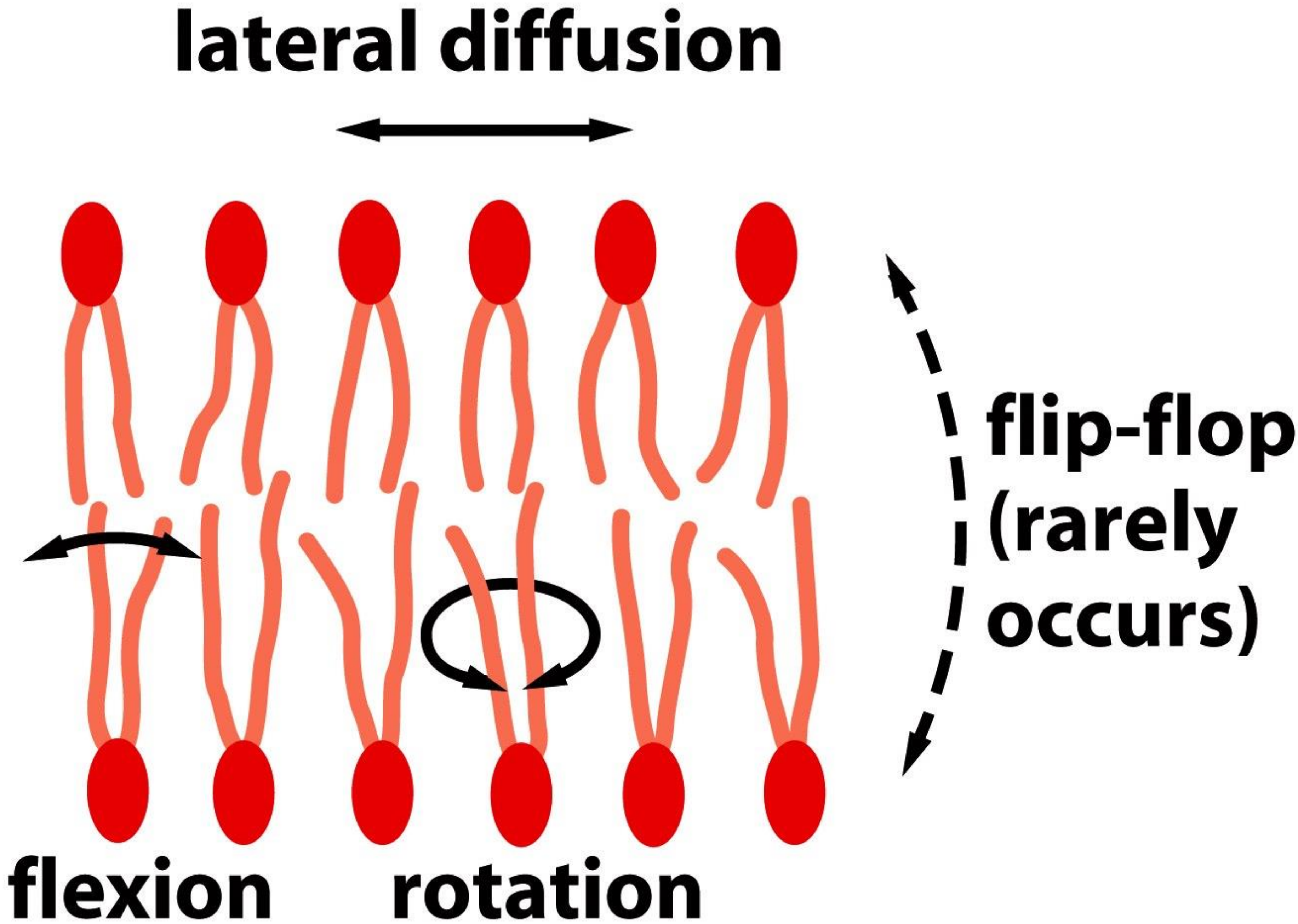
o Phosphate can diffuse 2 mm in 1 second

- ***Transverse diffusion***

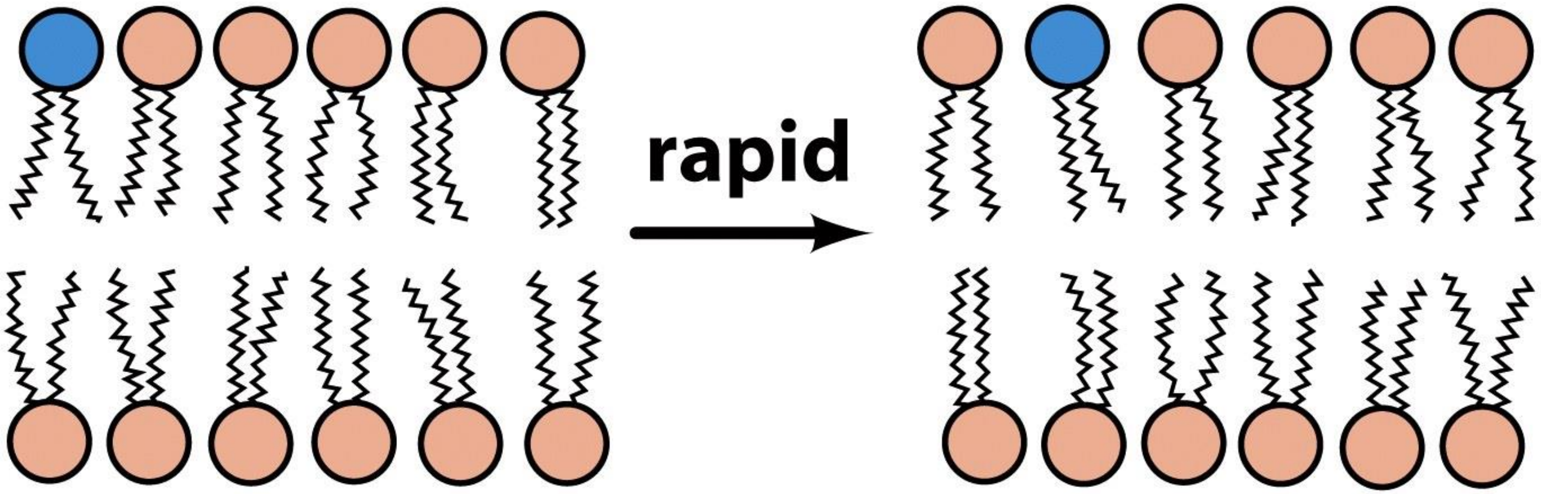
Or **flip-flop** involves the movement of a lipid or protein from one membrane surface to the other. It is a fairly ***slow*** process due to the fact that a relatively significant amount of energy is required for flip-flopping to occur.

o Once every several hours

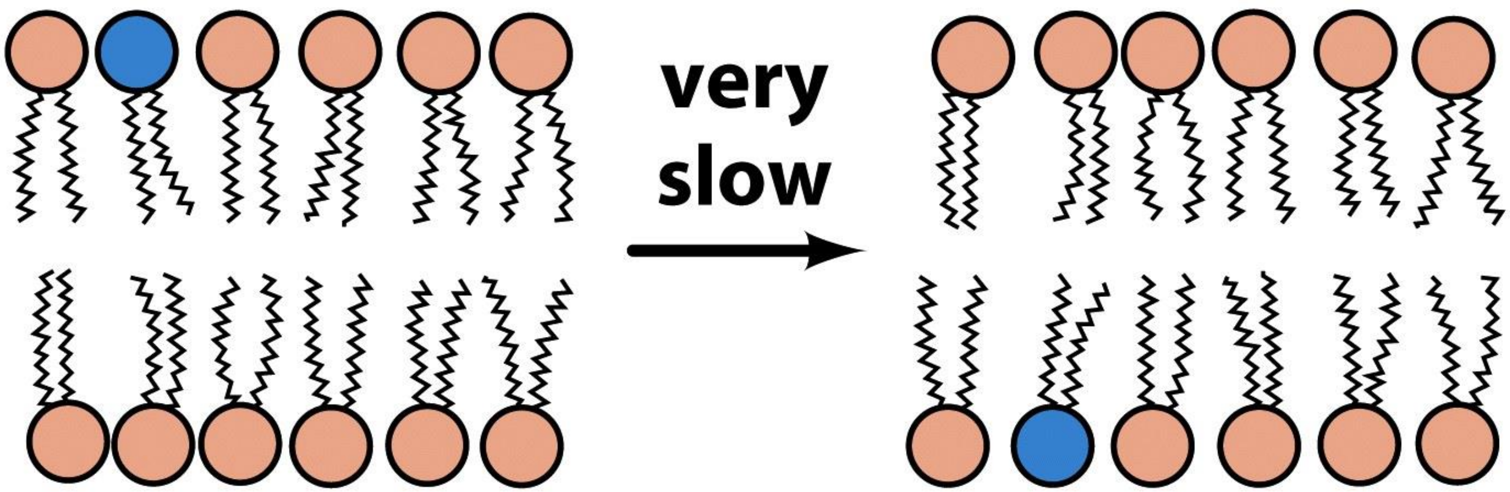
- ***Rotational diffusion (rapid)***
- ***Flexing of acyl chains (rapid: ~ 10^9 sec^{-1})***


lateral diffusion
flip-flop
(rarely
occurs)
flexion
rotation

Lateral diffusion



Transverse diffusion (flip-flop)



Membrane fluidity

Membranes are fluid: lipids & proteins move in the plane of the bilayer.

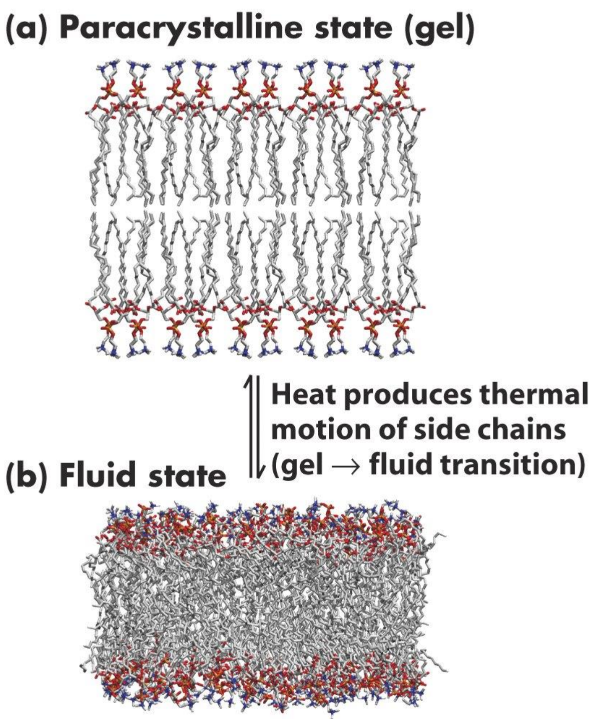
The interactions among lipids, and between lipids and proteins, are noncovalent, leaving individual lipid and protein molecules free to move laterally in the plane of the membrane.

The degree of fluidity depends on lipid composition and temperature

❑ Temperature

Membranes can transition from Gels to Fluids

If the temperature of the bilayer is kept relatively warm (e.g., $37^{o}C$) the lipid exists in a relatively fluid state. At low temperature the lipid is converted from a liquid phase to a crystalline gel in which the movement of the phospholipid fatty acid chains is greatly restricted. The temperature at which this change occurs is called the **transition temperature.**



Gel State

⬍

Liquid Ordered

⬍

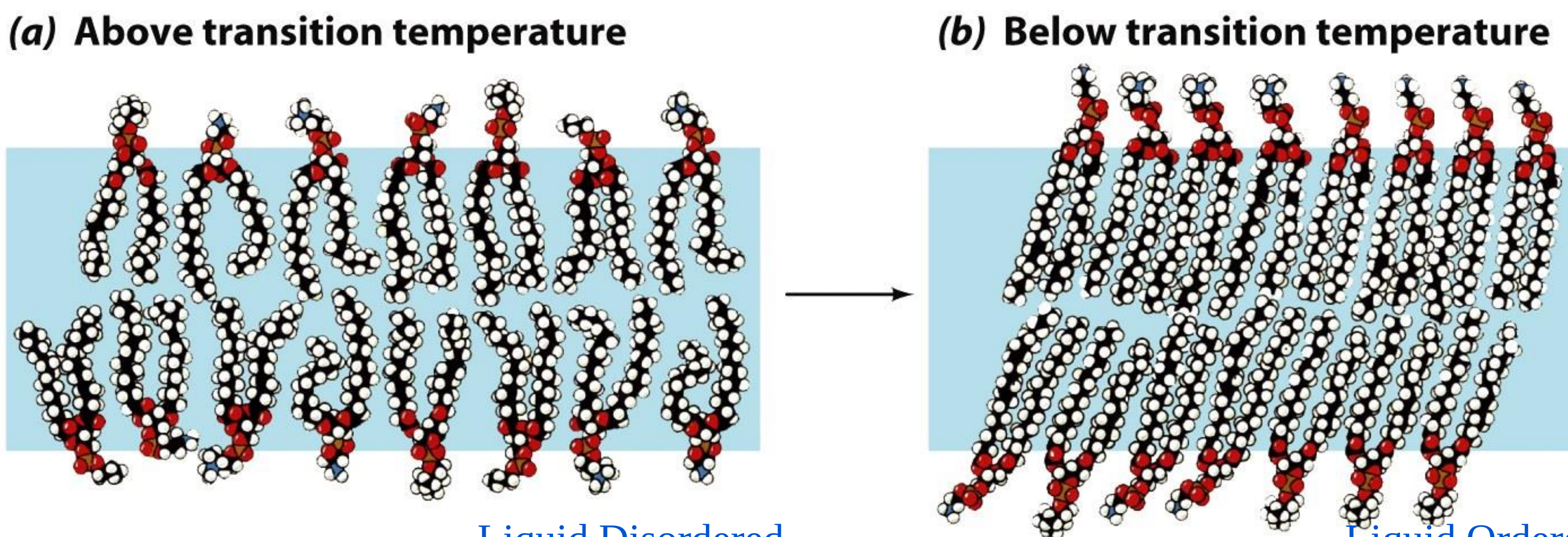
Liquid Disordered

The structure of the lipid bilayer depends on the temperature.

The bilayer shown here is composed of two phospholipids: phosphatidylcholine and phosphatidylethanolamine.

(*a*) Above the transition temperature, the lipid molecules and their hydrophobic tails are free to move in certain directions, even though they retain a considerable degree of order.

(*b*) Below the transition temperature, the movement of the molecules is greatly restricted, and the entire bilayer can be described as a crystalline gel.



❑ Lipid composition of the membrane

- ✓ The more unsaturated, the more fluid
- ✓ Double bonds are always in the cis conformation

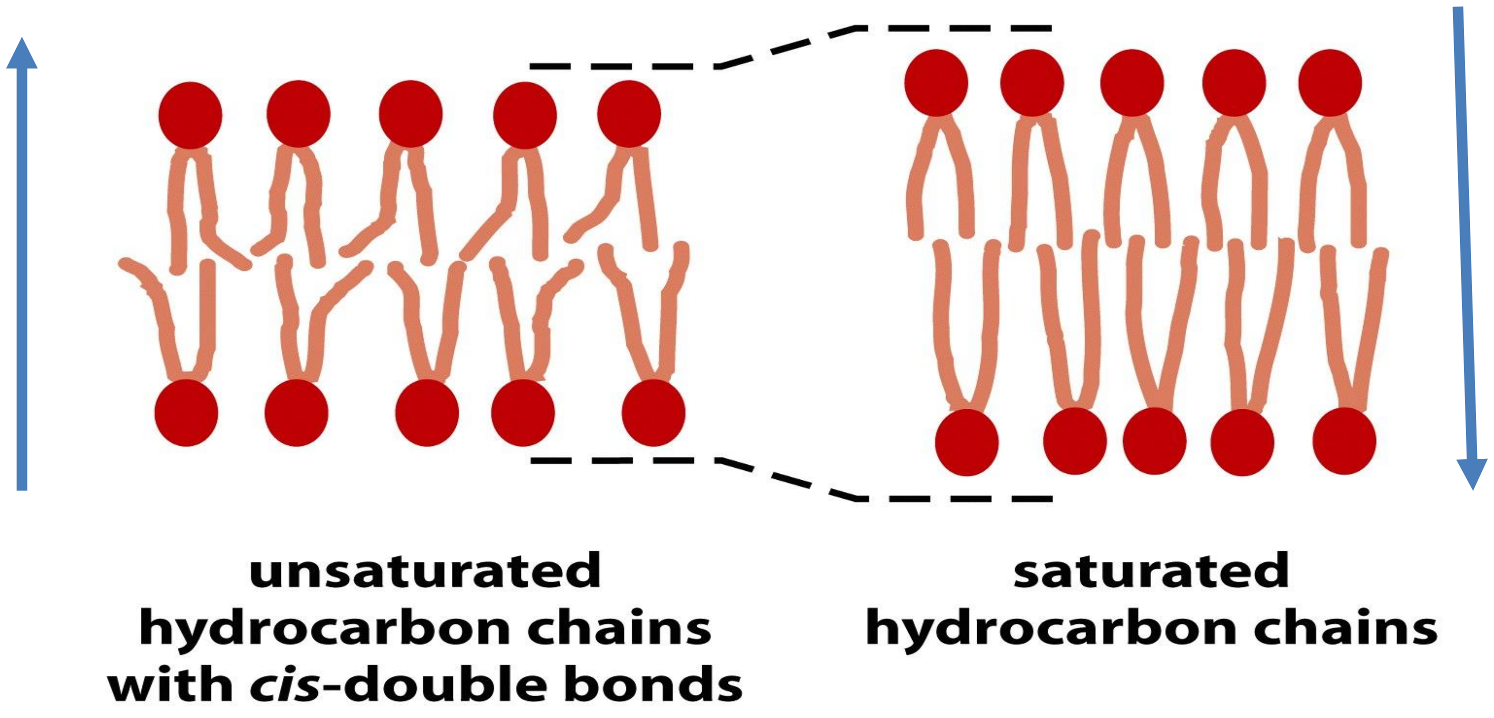
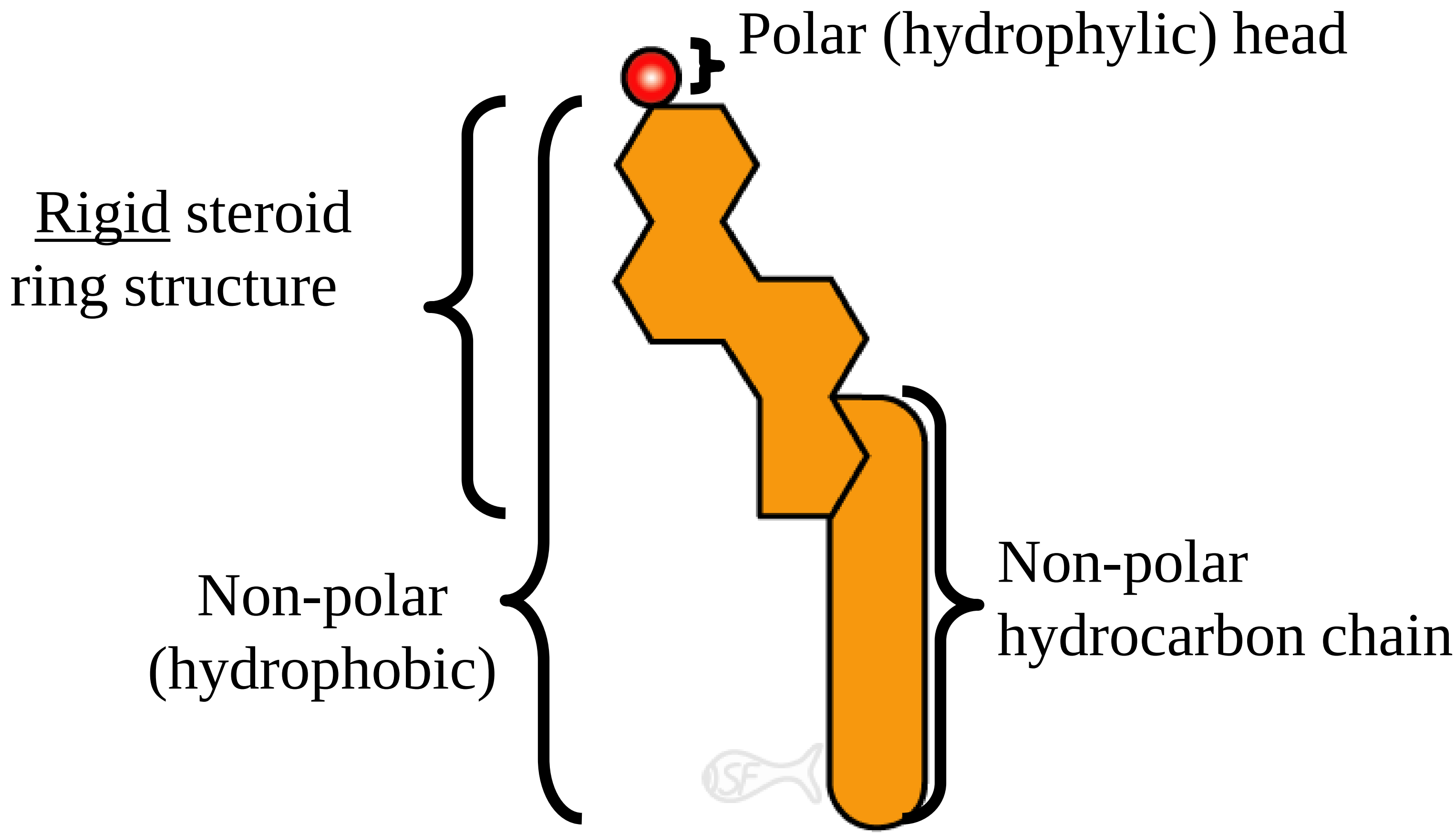


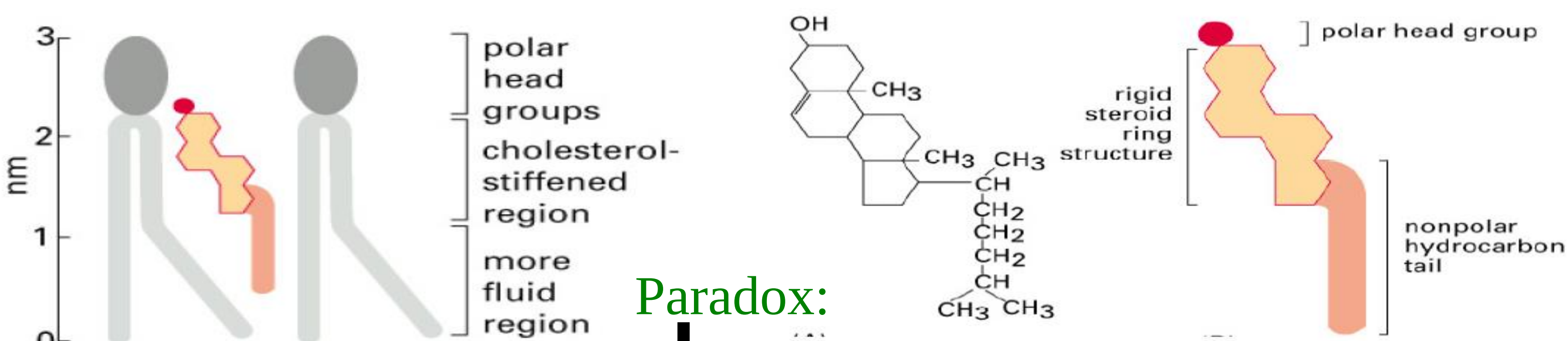
Figure 10-12 Molecular Biology of the Cell 5/e (© Garland Science 2008)

❑ Cholesterol

Another lipid component of certain membranes is the sterol **cholesterol**, which in certain animal cells may constitute up to 50 percent of the lipid molecules in the plasma membrane. Cholesterol is smaller than the other lipids of the membrane and less amphipathic.



- 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.
- Wedged between phospholipid molecules in the plasma membrane of animal cells. The hydrophobic rings of a cholesterol molecule are flat and rigid, and they interfere with the movements of the fatty acid tails of the phospholipids.
- At warm temperatures (such as 37°C), cholesterol restrains the movement of phospholipids and reduces fluidity.
- At cool temperatures, it maintains fluidity by preventing tight packing
- Thus, **cholesterol acts as a "temperature or fluidity buffer**" for the membrane, resisting changes in membrane fluidity as temperature changes.



Paradox:

a) ↓ fluidity at <u>high</u> temp.

b) ↑ fluidity at <u>low</u> temp.

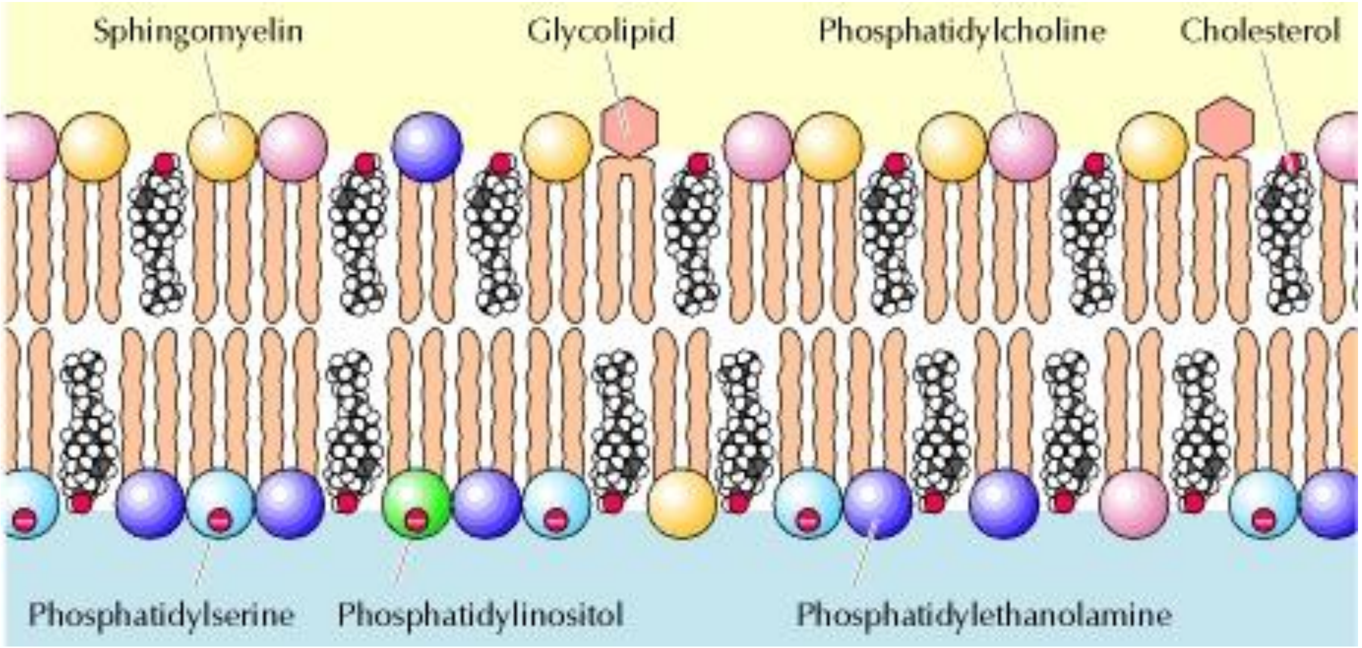
Membranes have assymetric lipid distribution

Proteins and lipids are <u>asymmetrically</u> distributed in the bilayers

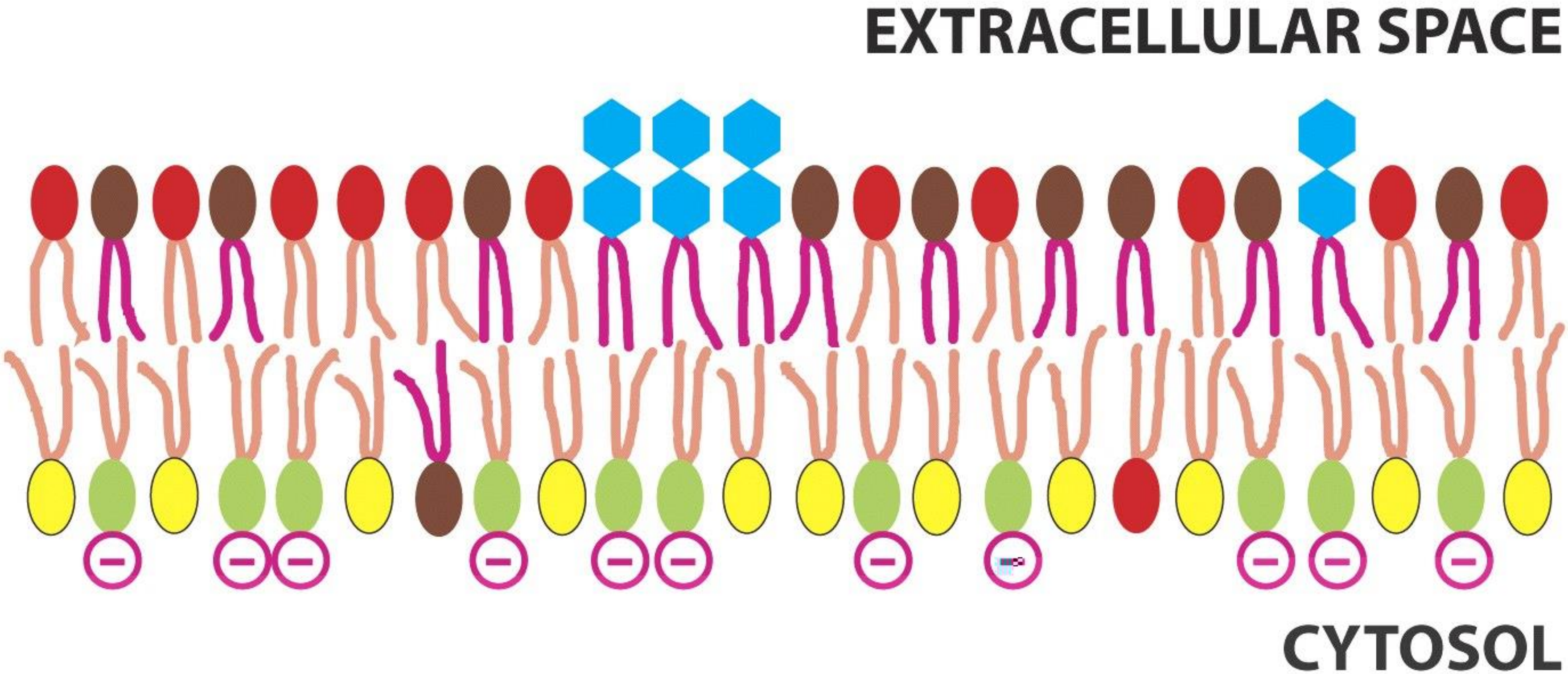
Plasma membrane of erythrocytes contains:

Sphingomyelin and Phosphatidylcholine which are preferentially located in the Outer leaflet,

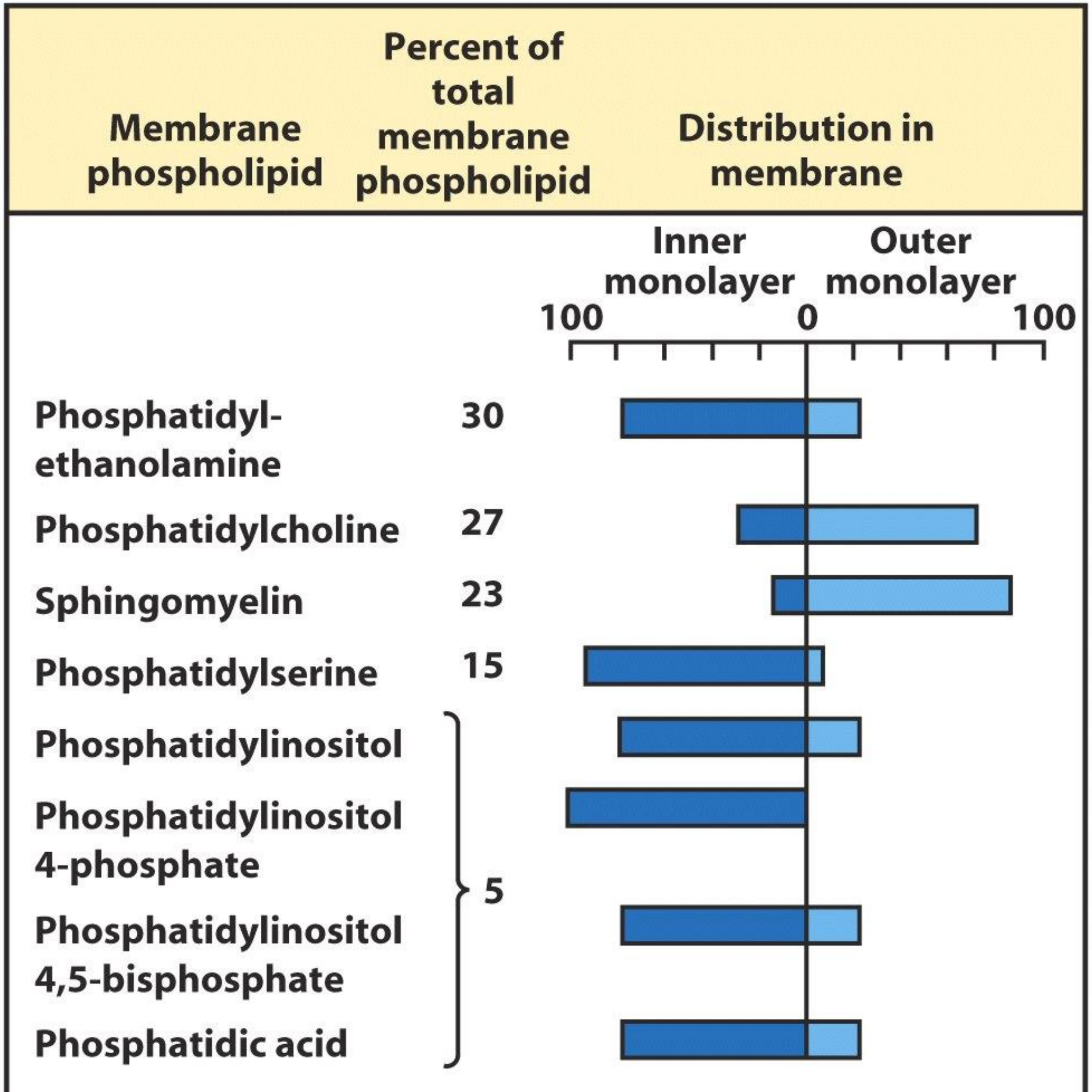
• Phosphatidylethanolamine and Phosphatidylserine which are mainly in the Inner leaflet



Phosphatidylinositol and phosphatidylserine, which are concentrated in the inner leaflet, have a net negative charge at physiologic pH



Asymmetric distribution of phospholipids in erythrocyte membrane

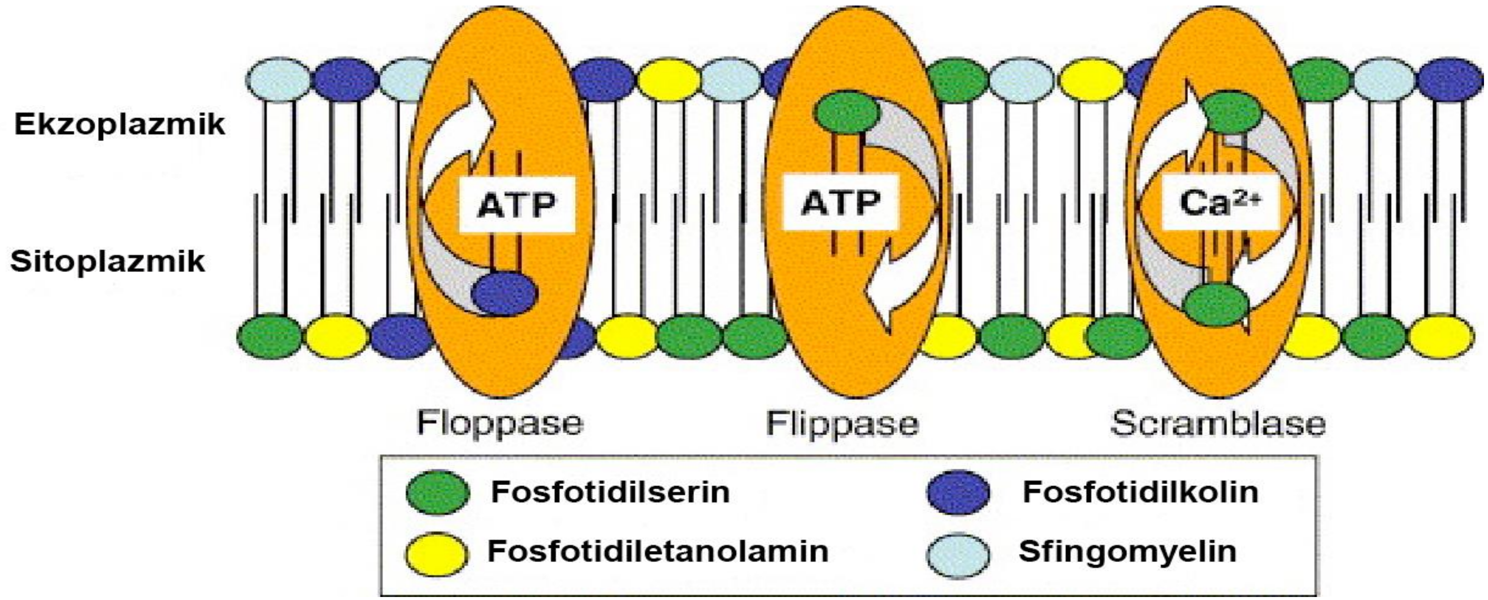


Transporters that move lipids across the plasma membrane

Maintenance and regulation of the asymmetric lipid distribution across the plasma membrane is governed by the concerted action of specific membrane proteins controlling lipid movement across the bilayer.

Phospholipid flippases, are proteins able to translocate phospholipids from one side of a membrane to the other even against a gradient of concentration and thereby able to establish, a transmembrane asymmetrical lipid distribution.

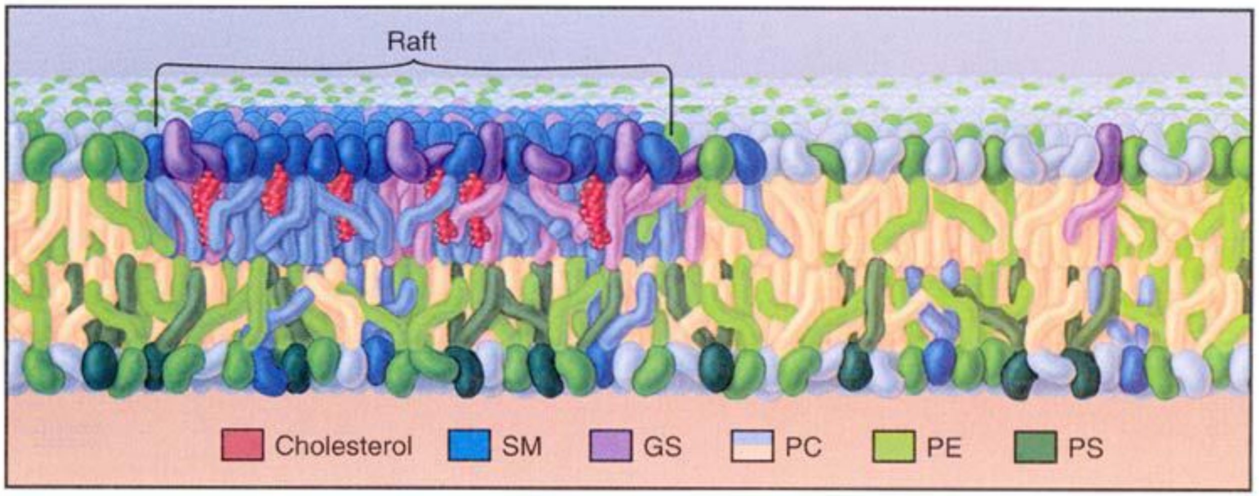
- Couples ATP hydrolysis to move lipids against concentration gradient.
- Flippases catalyse flipping of specific phospholipids from the exoplasmic to the cytoplasmic monolayer, while **floppases** transport in the reverse direction.
- **Scramblase** translocates phospholipids between two monolayers randomly (bi-directional movement), resulting in equal distribution



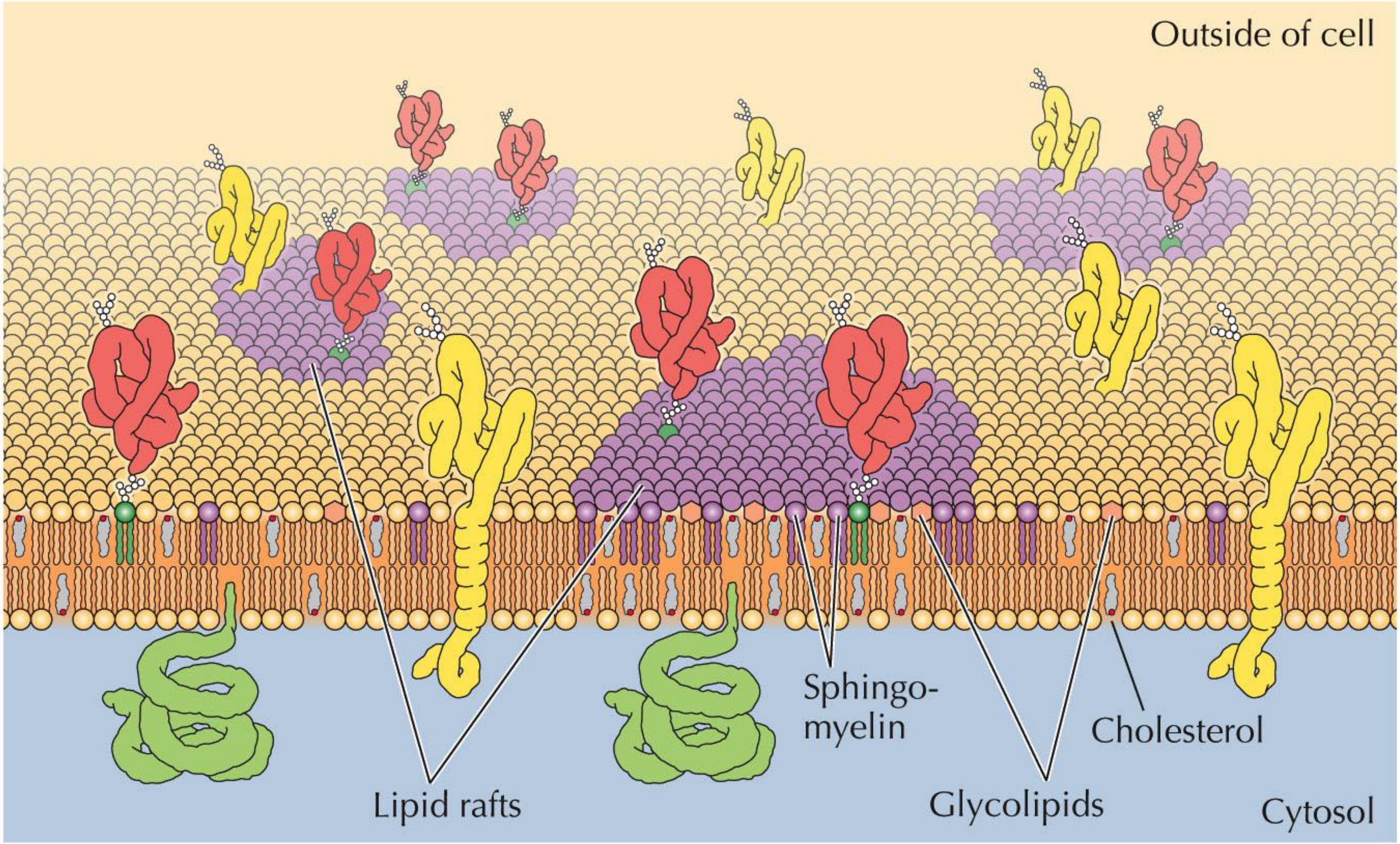
Lipid microdomains (RAFTS)

Lipid micro domains are:

- Enriched in sphingolipids
- Enriched in cholesterol



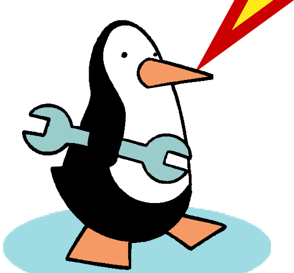
Cholesterol and sphingolipids tend to pack together tightly to form microdomains that are more gelated and highly ordered than surrounding regions consisting primarily of phosphoglycerides. This segregation is important for signalling pathways and cascades

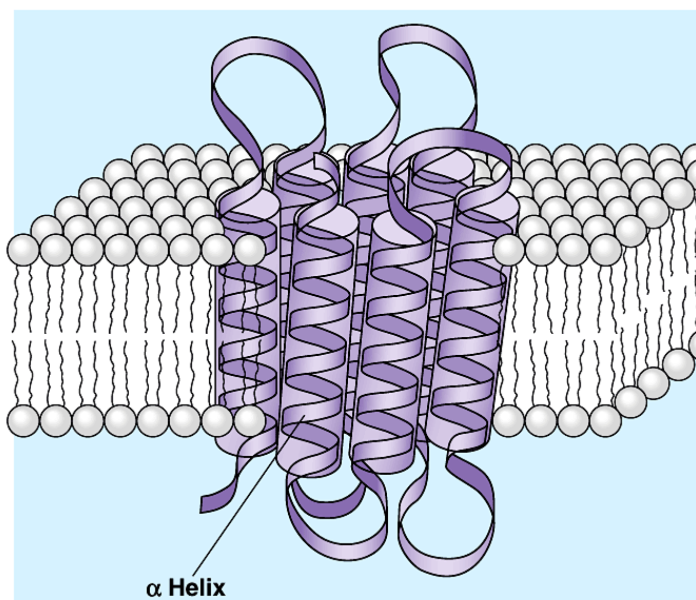

Outside of cell
Sphingo-
myelin
Cholesterol
Lipid rafts
Glycolipids
Cytosol

Essential Questions

1. *What is the importance of fatty acid unsaturation for membrane fluidity?*
2. *What is meant by a membrane's transition temperature and how is it affected by the degree of saturation or length of fatty acyl chains?*
3. *Why is membrane fluidity important to a cell?*
4. *How can the two sides of a lipid bilayer have different ionic charges?*

Why are <u>proteins</u> the perfect molecule to build structures in the cell membrane?





Membrane Proteins

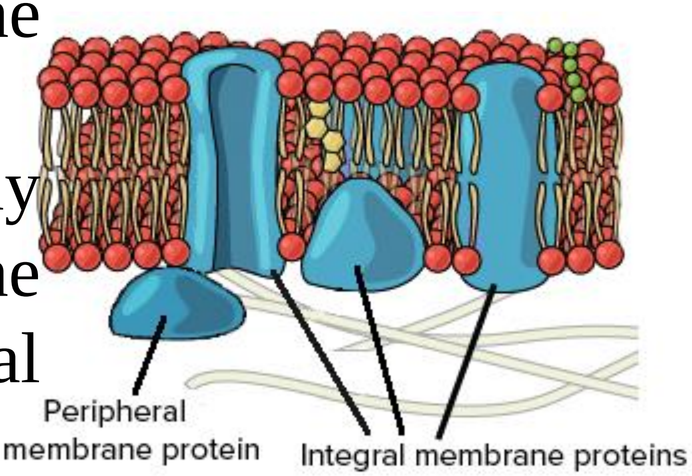
Proteins determine membrane's specific functions

- cell membrane & organelle membranes each have unique collections of proteins

Three classes of membrane proteins:

1. Peripheral proteins:

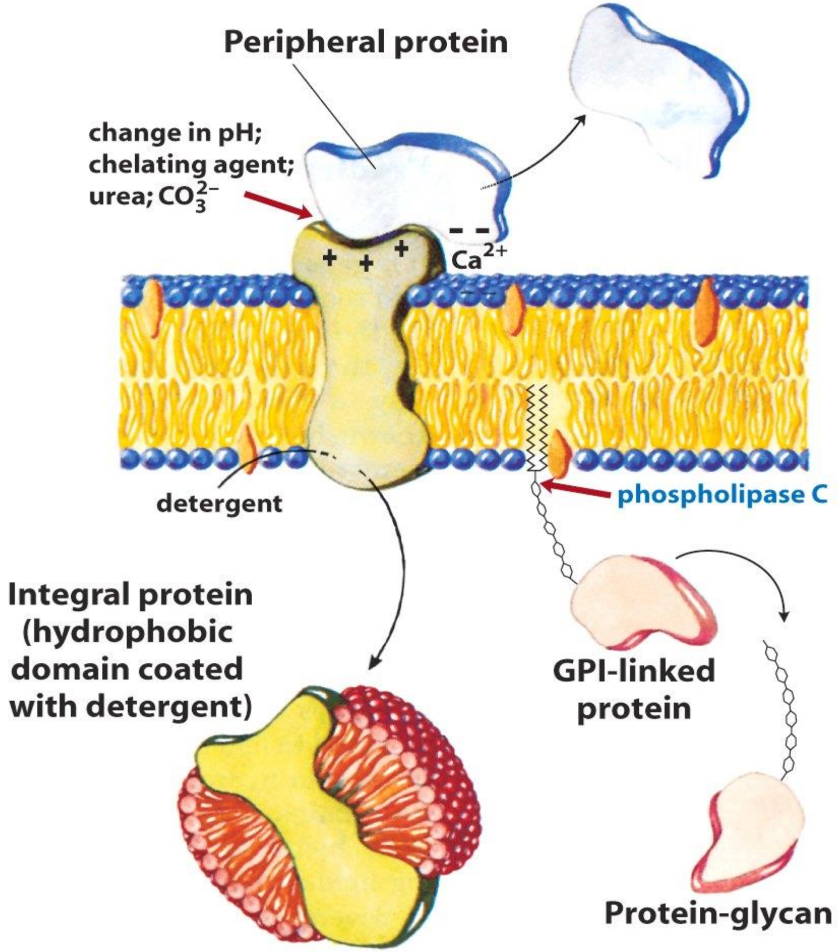
- Peripheral proteins are located entirely outside of the lipid bilayer, on the cytoplasmic or extracellular side
- Peripheral proteins are noncovalently bonded to the polar head groups of the lipid bilayer and/or to an integral membrane protein.



- Cell surface identity marker (antigens).

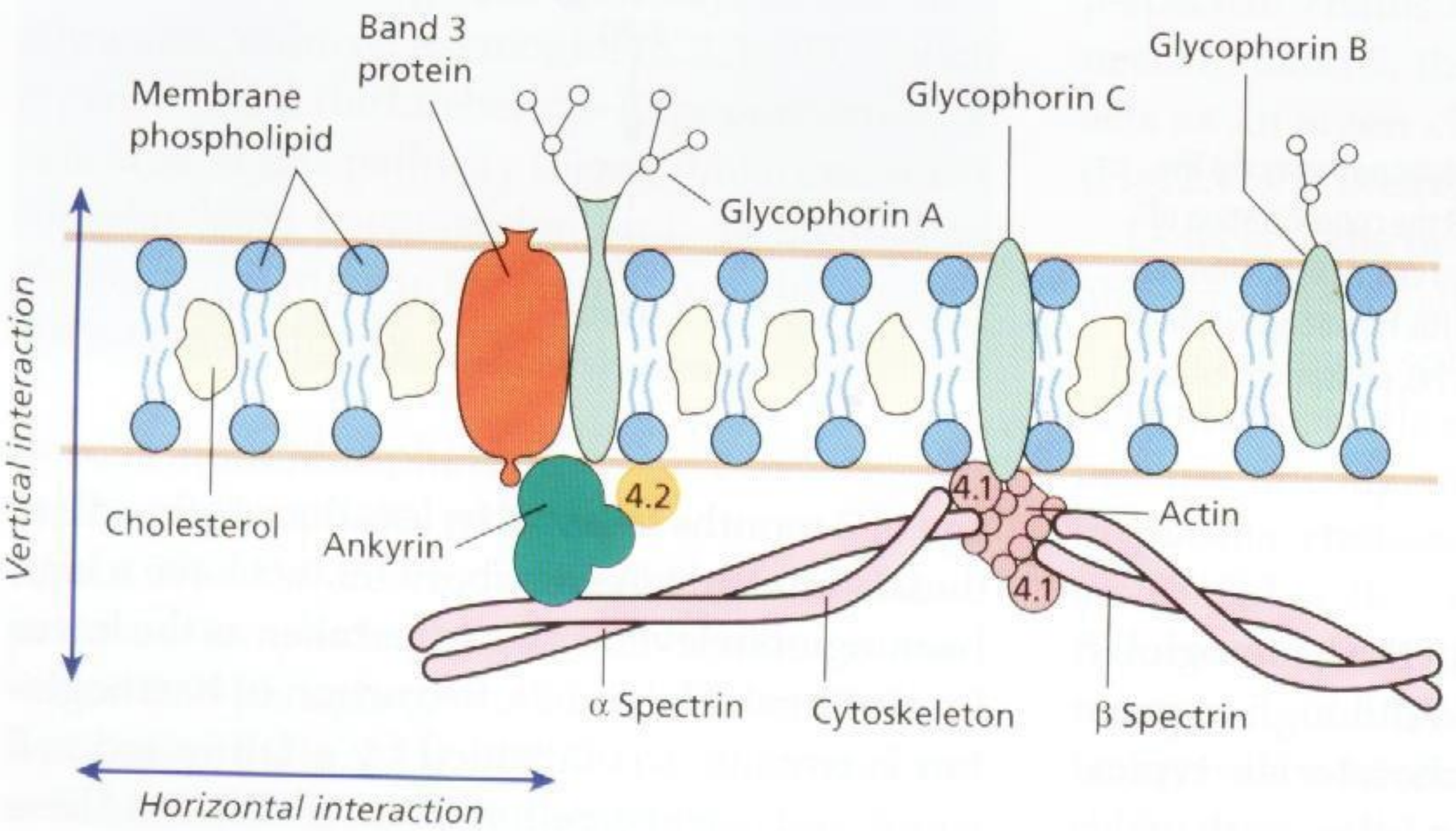
- Peripheral proteins are associated with the membrane by weak electrostatic bonds. Peripheral proteins can usually be solubilized by extraction with high-concentration salt solutions that weaken the electrostatic bonds holding peripheral proteins to a membrane

- They are not amphipatic



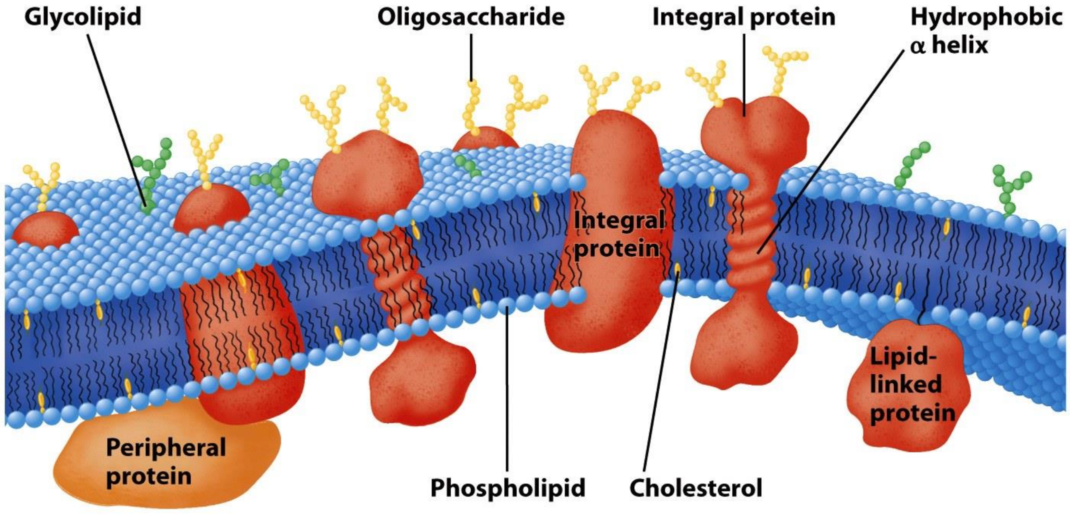
Example

Spectrin-peripheral protein of the red cell membrane



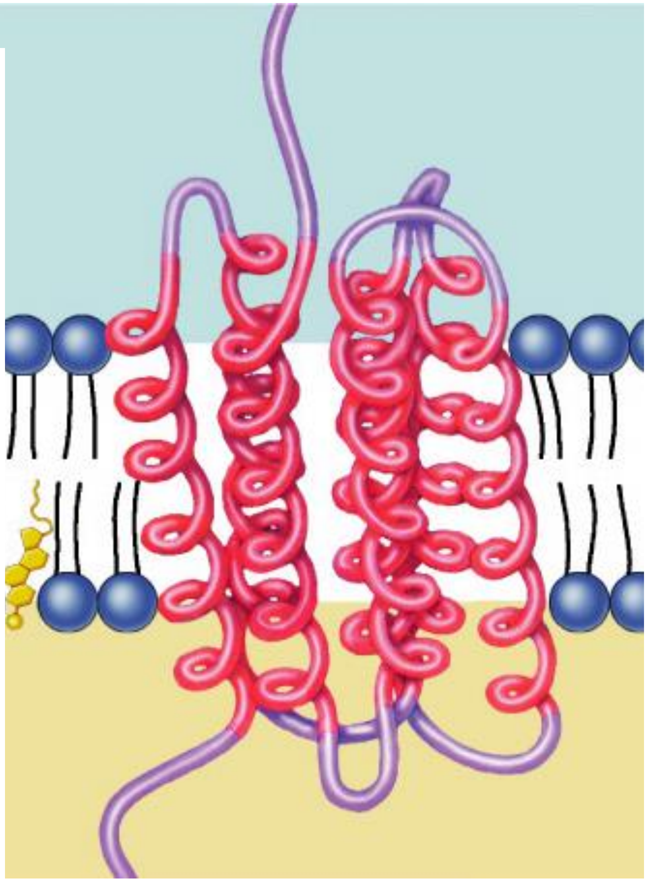
❑ Integral proteins

- Penetrate the lipid bilayer.
- Integral proteins are **transmembrane proteins**; that is, they pass entirely through the lipid bilayer and thus have domains that protrude from both the extracellular and cytoplasmic sides of the membrane.
- Like the phospholipids of the bilayer, integral membrane proteins are also amphipathic, having both hydrophilic and hydrophobic portions.

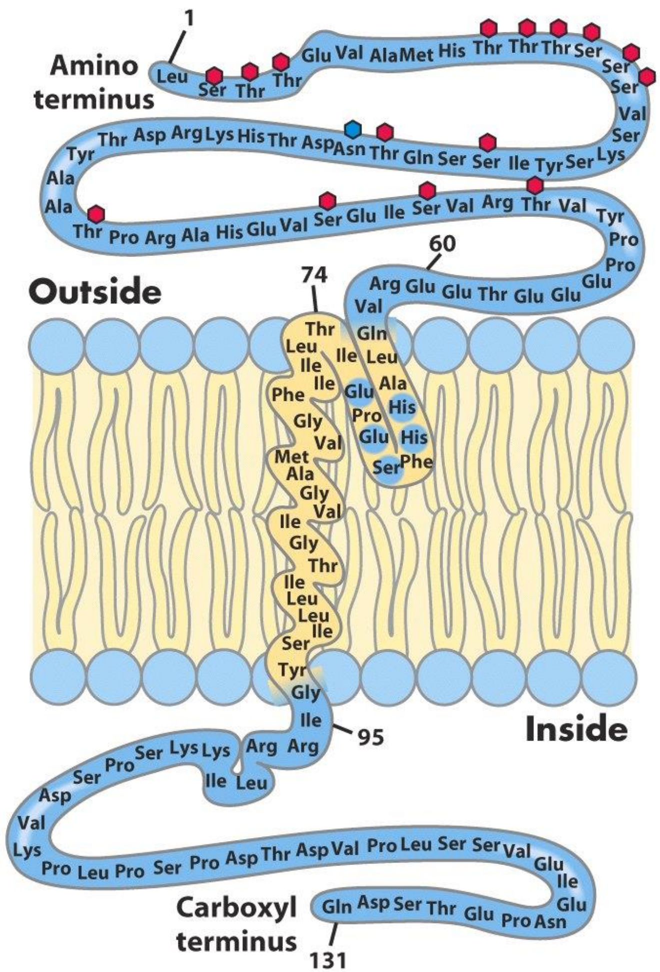


Transmembrane domains (TMD): Segments of the polypeptide chain that are actually embedded in the lipid bilayer

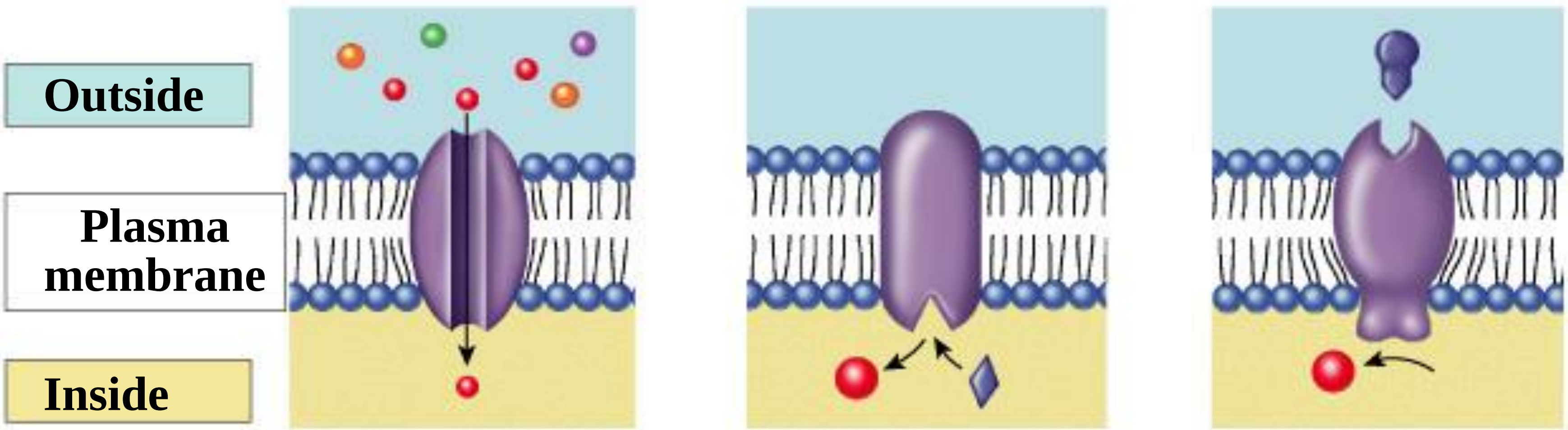
- Within membrane
    - Have a hydrophobic character
    - amino acid residues in TMD are nonpolar
    - anchor proteins into membrane
- On outer surfaces of membrane
    - Have a hydrophilic character
    - amino acids residues are polar
    - extend into extracellular fluid & into cytosol



Glycophorin A, the major integral protein of the erythrocyte plasma membrane is **an integral protein with a single transmembrane domain.** The single helix that passes through the membrane consists predominantly of hydrophobic residues.



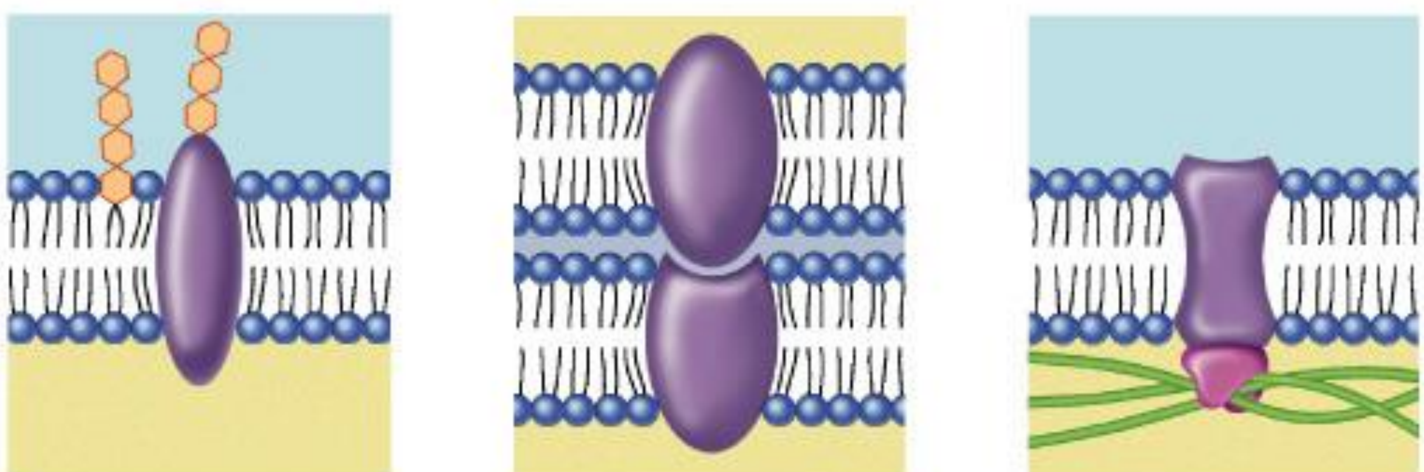
Many Functions of Membrane Proteins



channel

enzyme

Cell surface receptor

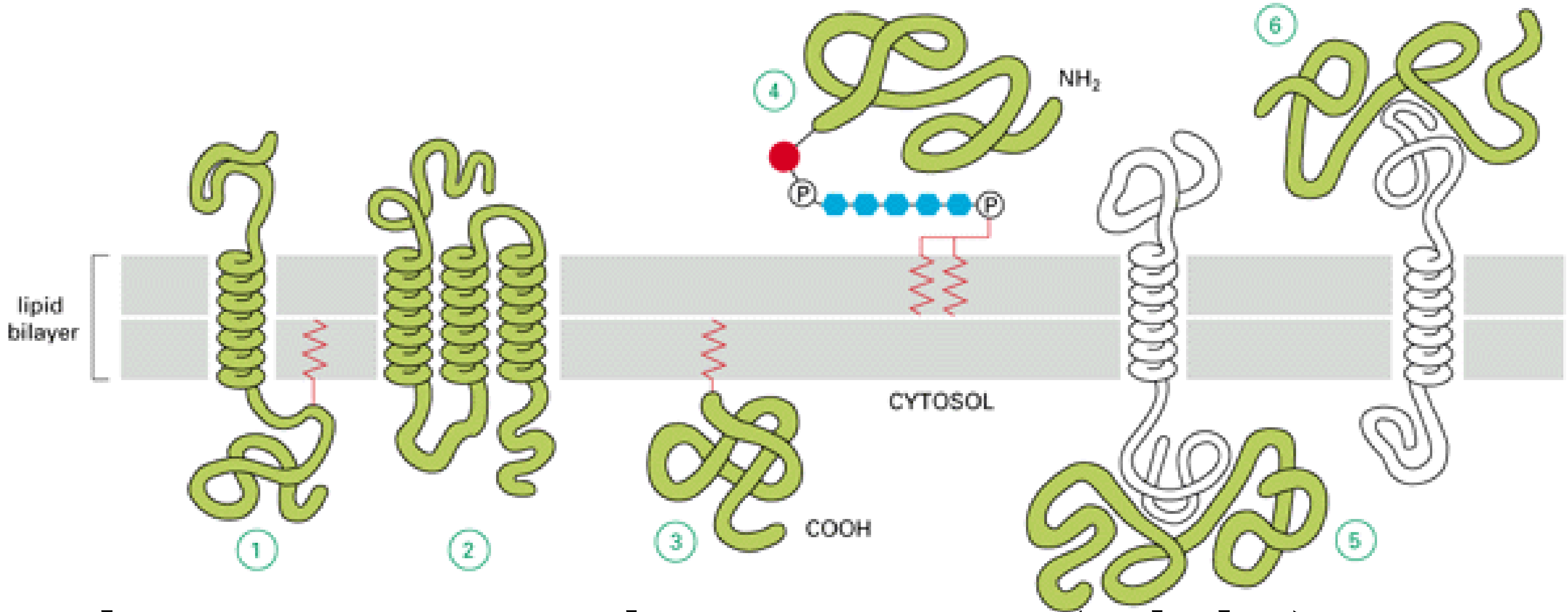


Cell surface identity marker antigen

cell to cell adhesion molecule

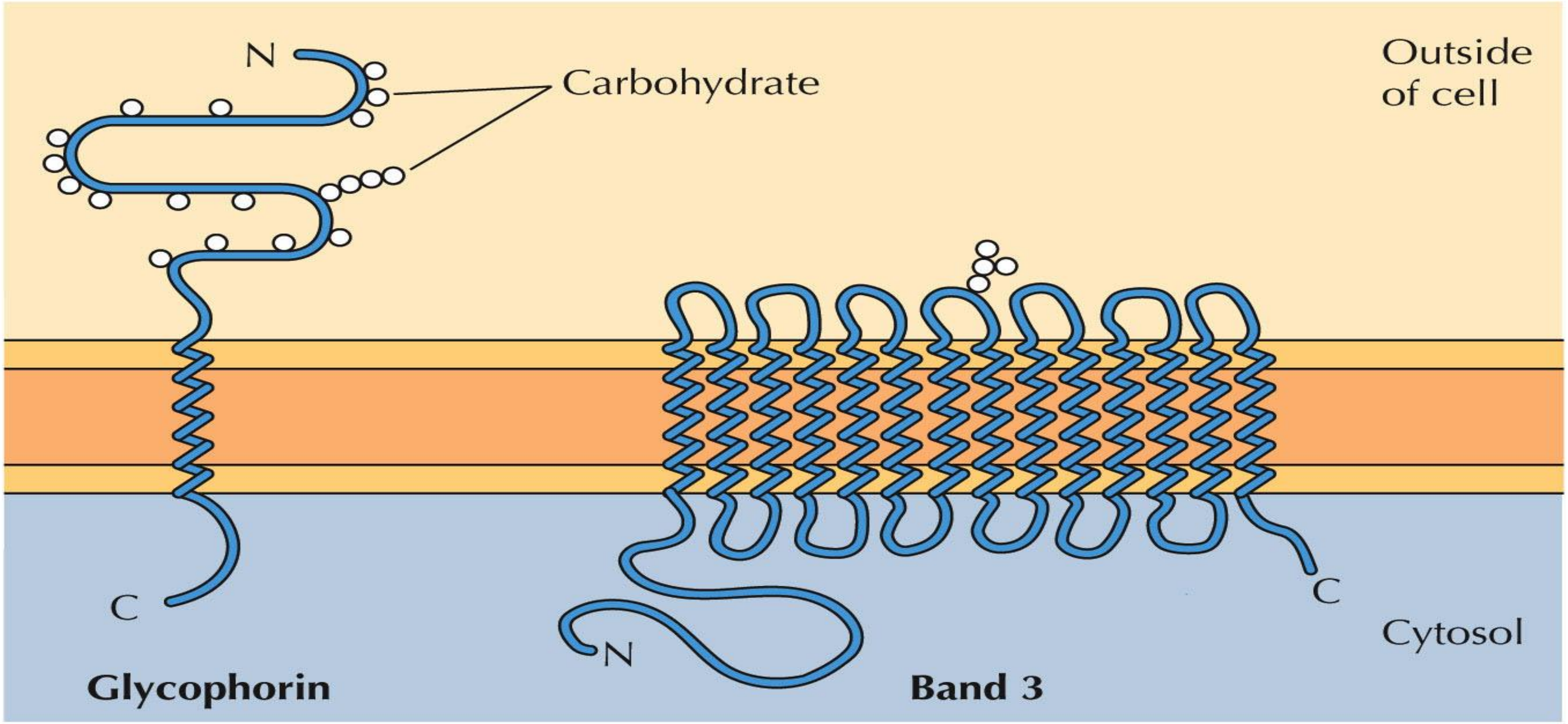
Attachment to the cytoskeleton

Types of membrane proteins



1. Single pass transmembrane protein (α-helix): cross the plasma membrane only once.
2. Multi-pass transmembrane protein (α-helix)
3. Prenylated (covalently attached to lipid) protein
4. GPI anchor (covalently attached to glycolipid)

5-6. Peripheral membrane protein (non-covalent interaction)



THE CELL, Fourth Edition, **Figure 13.6**

❑ Lipid-anchored proteins

Located outside the lipid bilayer, on either the extracellular or cytoplasmic surface, but are covalently linked to a lipid molecule that is situated within the bilayer. The lipid can be phosphatidylinositol, a fatty acid, or a prenyl group (a long-chain hydrocarbon built from five-carbon isoprenoid units).

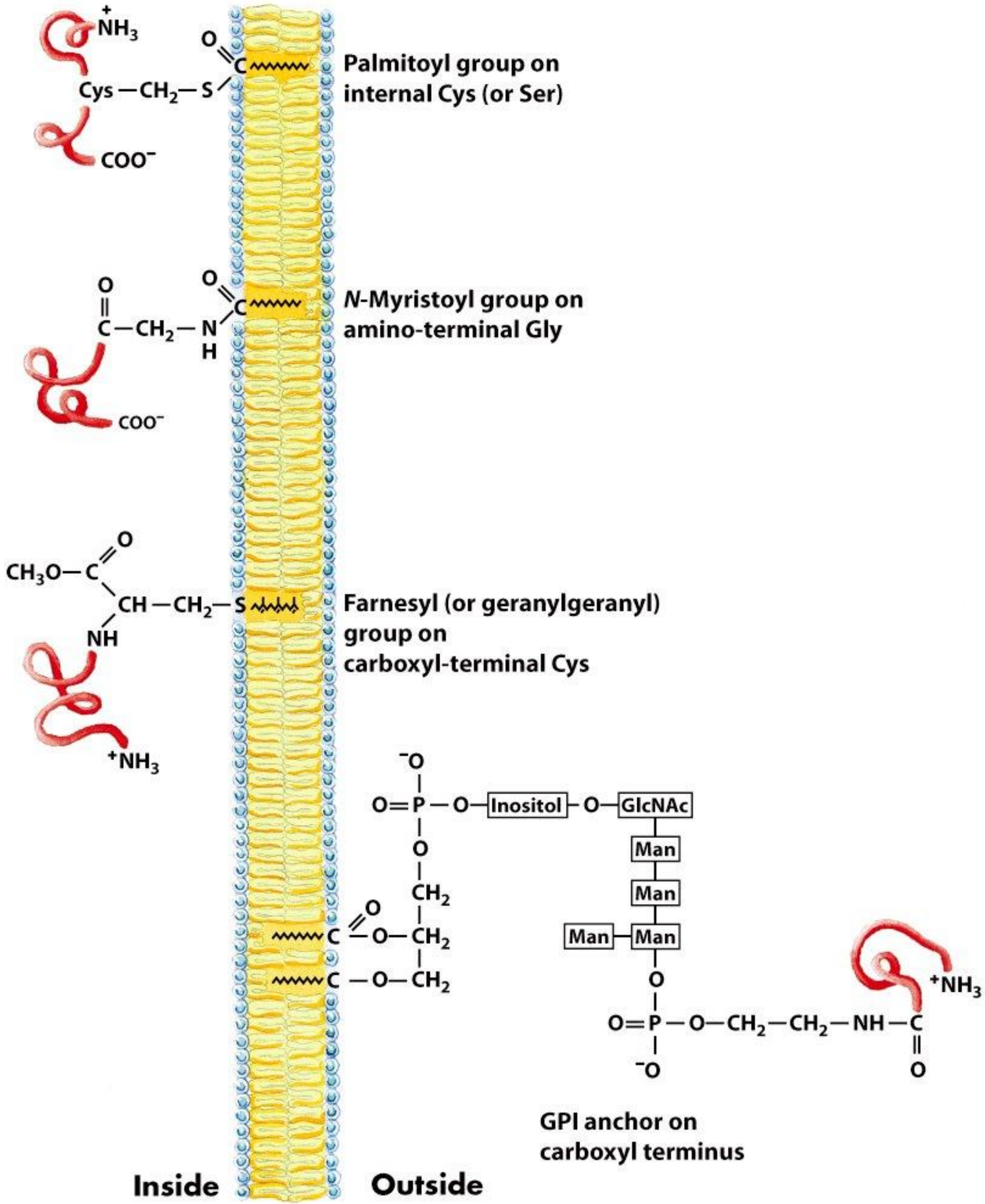
LIPID MODIFICATIONS OF PROTEINS:

1. Anchoring the outside (lumenal leaflet) of cell membrane:

- GPI (Glycosyl phosphatidyl inositol) anchored proteins

2. Anchoring to the inside of the cell:

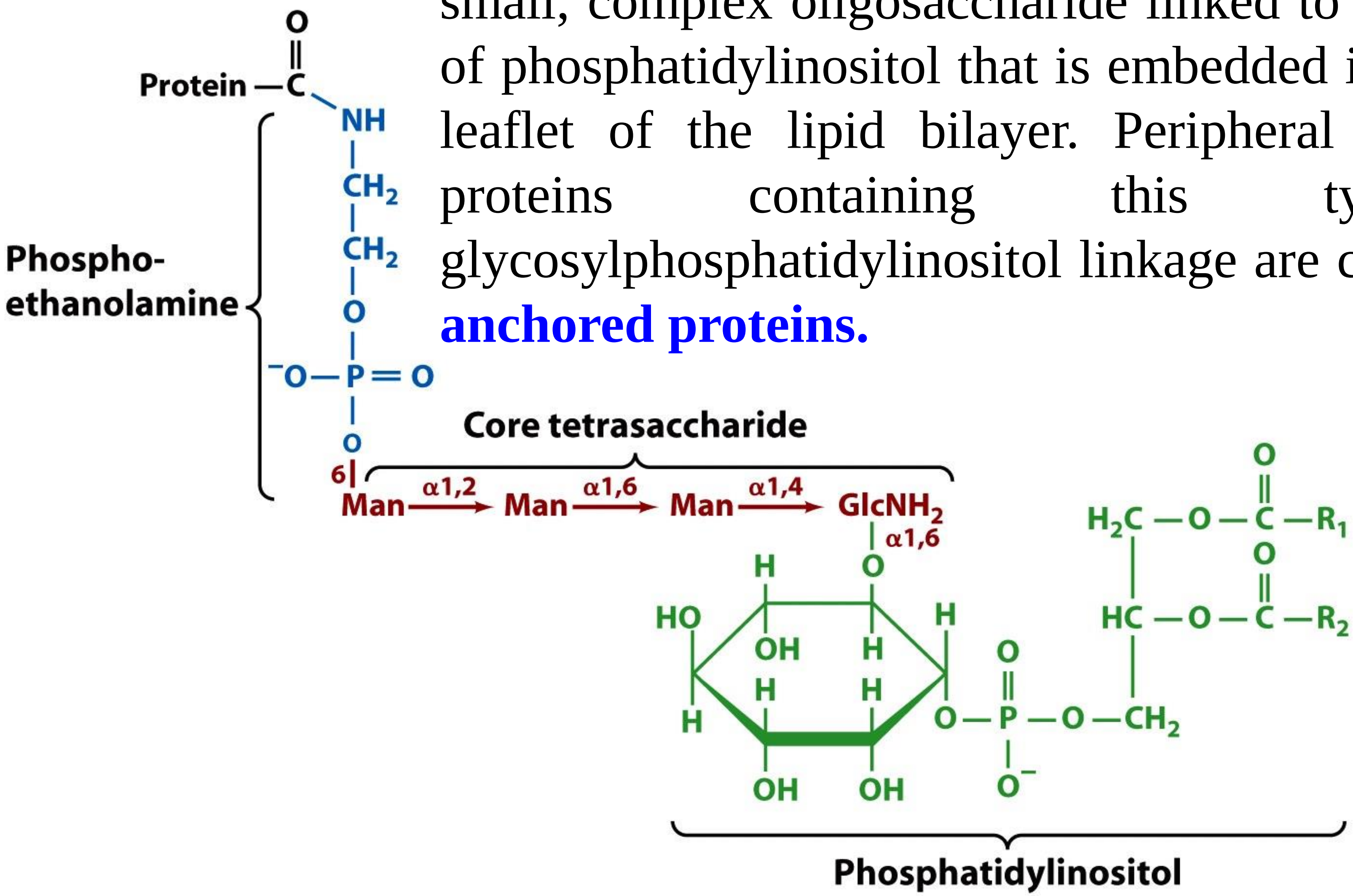
- **N-terminal myristoylation:** Myristoyl group is covalently attached by an amide bond to a glycine residue in the N-terminal of protein
- **Palmitoylation of cysteine residues:** covalently attachment of fatty acids e.g. palmitic acid to cysteine residues in proteins
- **Prenylatıon of C-terminus:** Post translational thioester linkage of farnesyl and geranylgeranyl groups.



Palmitoyl group on internal Cys (or Ser)
N-Myristoyl group on amino-terminal Gly
Farnesyl (or geranylgeranyl) group on carboxyl-terminal Cys
GPI anchor on carboxyl terminus
Inositol
GlcNAc
Man
Man
Man
Man
Inside
Outside

GPI (Glycosyl phosphatidyl inositol) anchored proteins

Numerous proteins present on the external face of the plasma membrane are bound to the membrane by a small, complex oligosaccharide linked to a molecule of phosphatidylinositol that is embedded in the outer leaflet of the lipid bilayer. Peripheral membrane proteins containing this type of glycosylphosphatidylinositol linkage are called **GPI-anchored proteins.**



Essential Questions

- *Describe the properties of the three classes of membrane proteins (integral, peripheral, and lipid-anchored), how they differ from one another, and how they vary among themselves.*

Membrane carbohydrates

The plasma membranes of eukaryotic cells contain carbohydrates. More than 90 percent of the membrane's carbohydrate is covalently linked to proteins to form **glycoproteins**; the remaining carbohydrate is covalently linked to lipids to form **glycolipids**

- Play a key role in cell-cell recognition
  - ability of a cell to distinguish one cell from another
    - antigens
  - important in organ & tissue development
  - basis for rejection of foreign cells by immune system

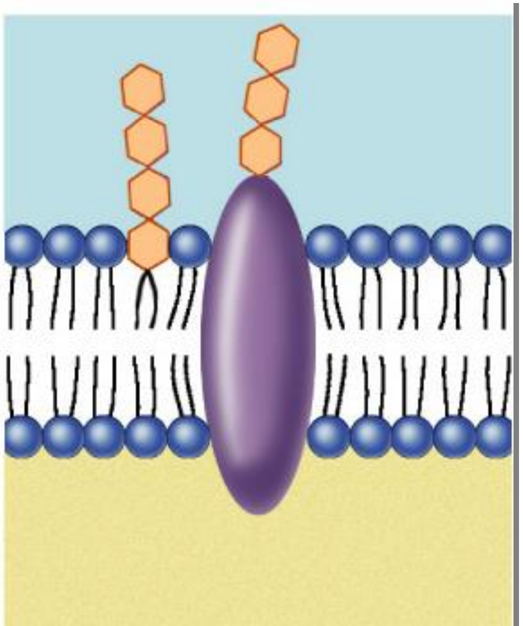
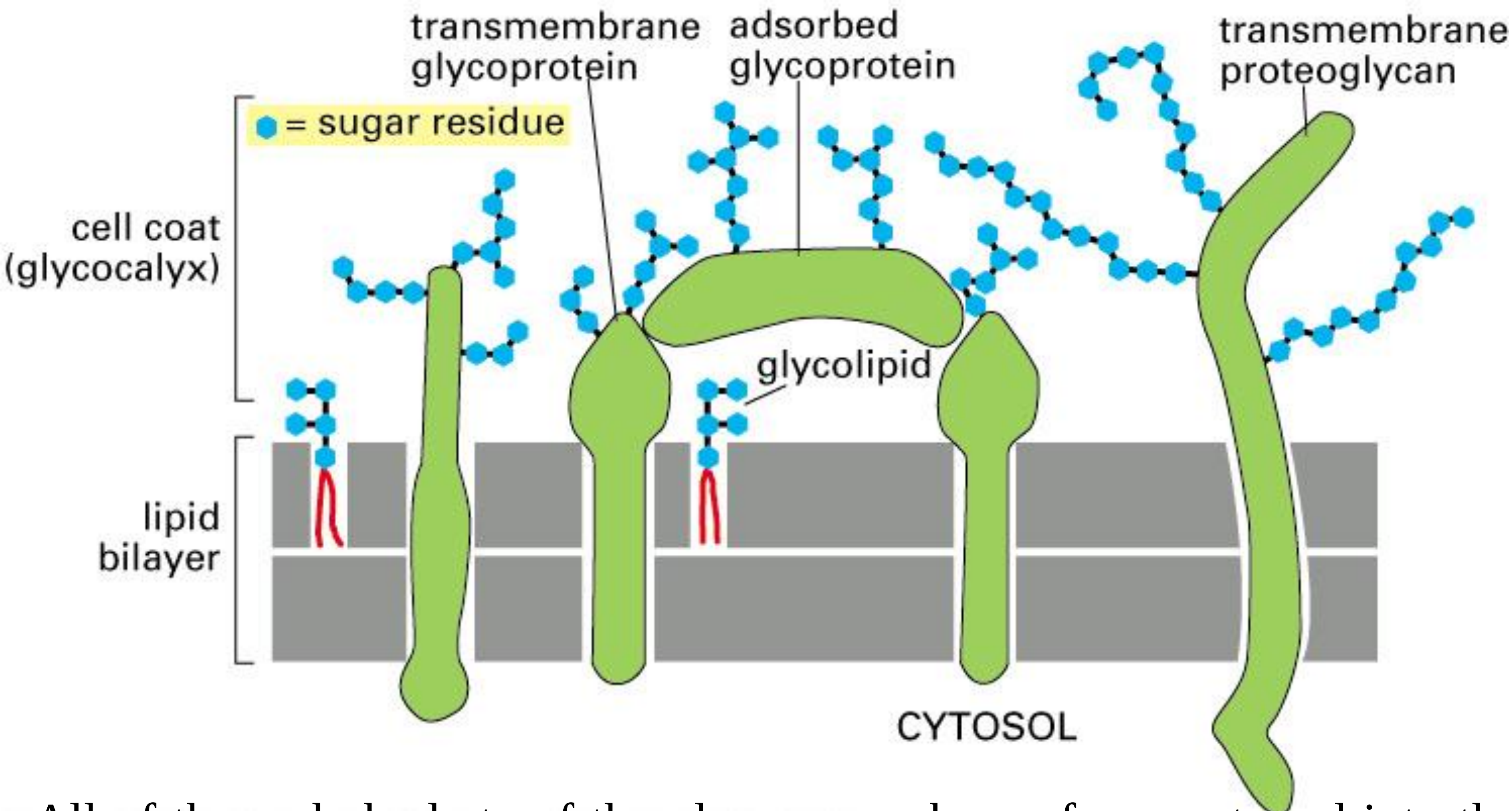
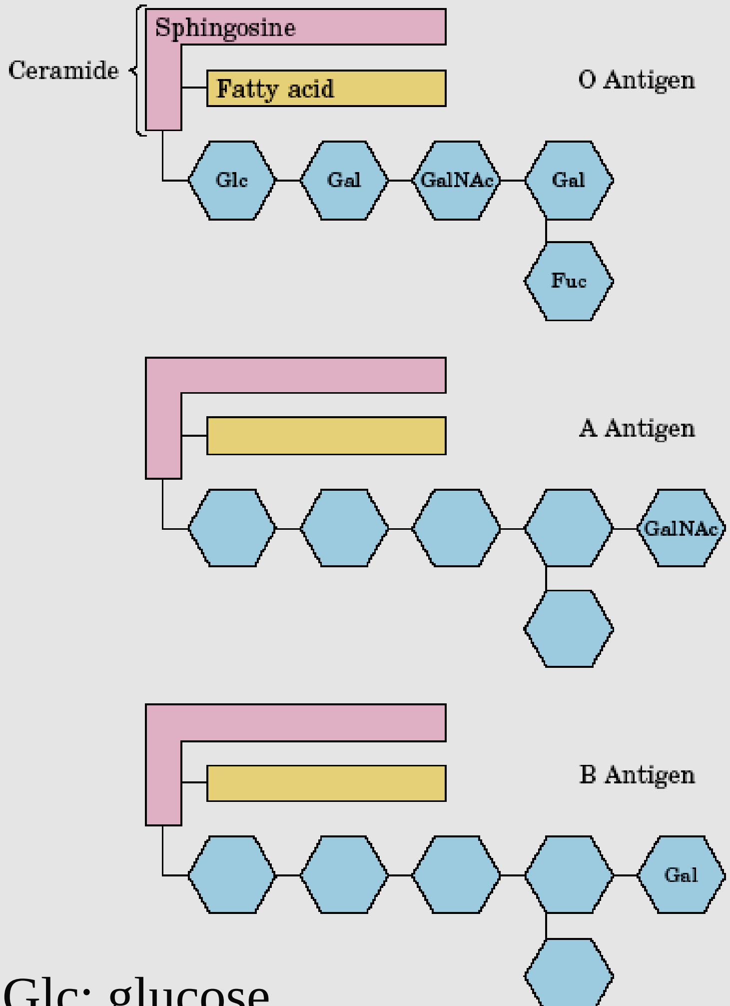


Diagram of glycocalyx (glycoproteins + glycolipids)



All of the carbohydrate of the plasma membrane faces outward into the extracellular space. The carbohydrate of internal cellular membranes also faces away from the cytosol

Glycosphingolipids as determinants of blood groups



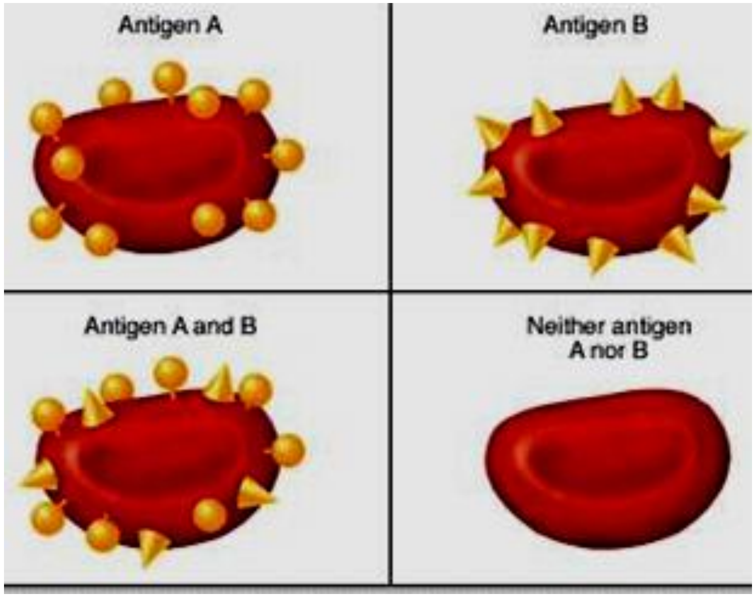
The carbohydrates of the glycolipids of the red blood cell plasma membrane determine whether a person's blood type is A, B, AB, or O.

A person having blood type A has an enzyme that adds an *N* acetylgalactosamine to the end of the chain, whereas a person with type B blood has an enzyme that adds galactose to the chain terminus. People with AB blood type possess both enzymes, whereas people with O blood type lack enzymes capable of attaching either terminal sugar.

Glc: glucose
Gal: galactose
GalNAc: N-Acethyl-D-galactosamine
Fuc: Fucose

If you belong to the blood group A you have A antigens on the surface of your RBCs and B antibodies in your blood plasma

If you belong to the blood group B you have B antigens on the surface of your RBCs and A antibodies in your blood plasma

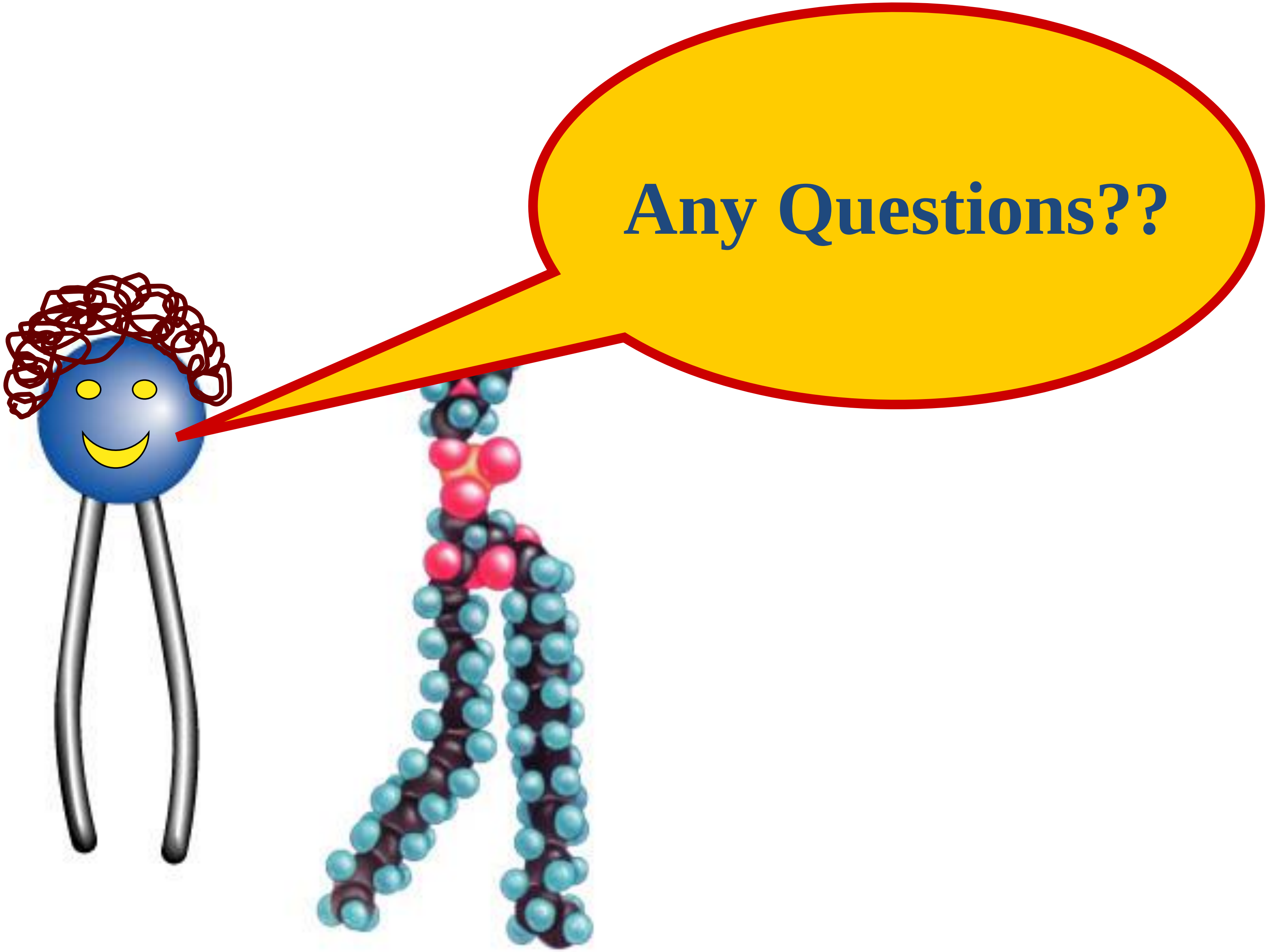


If you belong to the blood group AB you have A and B antigens on the surface of your RBCs and no A or B antibodies in your blood plasma

If you belong to the blood group O you have neither A or B antigens on the surface of your RBCs and but you have both A and B antibodies in your blood plasma

Essential Questions

- *How oligosaccharides are linked to membrane proteins?*
- *How they are related to human blood types?*


Any Questions??