no.

Cytology

Doctor 2019 | Medicine | JU

◉ Sheet ○ Slides

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8.1 : introduction to the plasma membrane

You might expect that the boundary of a living cell to be constructed of an equally tough and impenetrable barrier because it must also protect its delicate internal contents from a non-living and inhospitable environment.

-Plasma membrane : the outer boundary of the cell that separates it from the world is a thin , fragile structure about 5-10 nm thick.

-Not detectable with light microscope need electron microscope.(they can see it at 1950 as three layer(trilaminar) -dark,white,dark— darkly staining inner and outer layers and lightly staining middle layer)

-The 2 dark-staining layers in the electron micrographs correspond primarily to the inner & outer polar surface of the bilayer.

-All membranes examined closely (plasma, nuclear or cytoplasmic) from plants ,animals or microorganisms have the same ultrastructure.

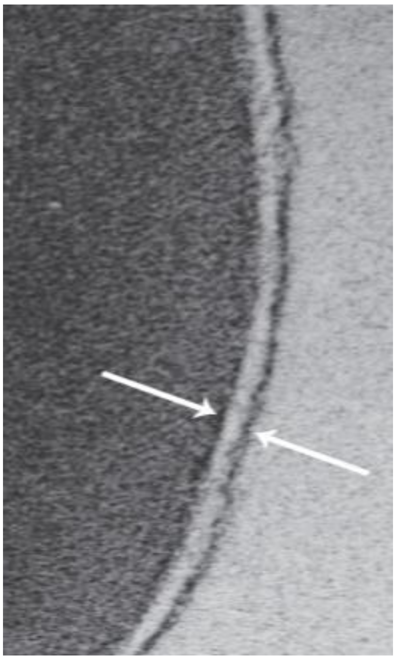


FIGURE 4.1 The trilaminar appearance of membranes. (a) Electron micrograph showing the three-layered (trilaminar) structure of the plasma membrane of an erythrocyte after staining the tissue with the heavy metal osmium. Osmium binds preferentially to the polar head groups of the lipid bilayer, producing the trilaminar pattern. The arrows denote the inner and outer edges of the membrane. (b) The outer edge of a differentiated muscle cell grown in culture showing the similar trilaminar structure of both the plasma membrane (PM) and the membrane of the sarcoplasmic reticulum (SR), a calcium-storing compartment of the cytoplasm.
SOURCE: (a) Courtesy of J. D. Robertson; (b) From Andrew R. Marks, et al., *J. Cell Biol.*, 114, 305, 1991. Reproduced with permission of the Rockefeller University Press.

An overview of membrane function

- **Compartmentalization** Membranes form continuous sheets that enclose intracellular compartments.(it allows specialized activities to proceed without external interference and enables cellular activities to be regulated independently of one another)

- **Scaffold for biochemical activities** Membranes provide a framework that organizes : enzymes for effective interaction. (For reactants floating around in solution, their interactions are dependent on random collisions. In contrast, components that are embedded in a membrane are no longer floating free and can be ordered for effective interaction.)

- **Selectively permeable barrier** Membranes allow regulated exchange of substances : between the compartments they separate.

(for better understanding):The plasma membrane, which encircles a cell, can be compared to a moat around a castle: Both serve as a general barrier, yet both have gated “bridges” that promote the movement of select elements into and out of the enclosed living space.

- **Transporting solutes** : Membrane proteins facilitate the movement of substances (such as amino acids and sugars, that are necessary to fuel its metabolism) between compartments.

The plasma membrane is also able to transport specific ions, thereby establishing ionic gradients across itself. This capability is especially critical for nerve and muscle cells

- **Responding to external signals** : The plasma membrane plays a critical role in the response of a cell to external stimuli (specific molecules (ligands) or respond to other types of stimuli such as light or mechanical tension) a process known as **signal transduction.**

Different types of cells have membranes with different receptors and are, therefore, capable of recognizing and responding to different environmental stimuli.

For example, signals generated at the plasma membrane may tell a cell to manufacture more glycogen, to prepare for cell division, to move toward a higher concentration of a particular compound, to release calcium from internal stores, or possibly to commit suicide.

:• **Intracellular interaction**

Membranes mediate recognition and interaction between adjacent cells. (it allows cells to recognize and signal one another, to adhere when appropriate, and to exchange materials and information.)

- Proteins within the plasma membrane may also facilitate the interaction between extracellular materials and the intracellular cytoskeleton.

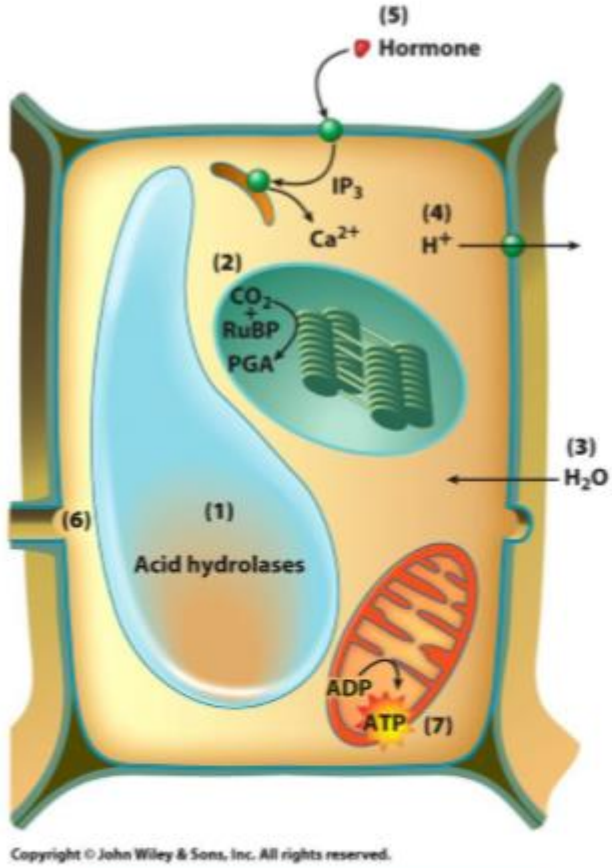
• **Energy transduction** : energy in sunlight is absorbed by membrane-bound pigments, converted into chemical energy, and stored in carbohydrates. Membranes are also involved in the transfer of chemical energy from carbohydrates and fats to ATP .

the processes by which one type of energy is converted to another type (energy transduction).

- ✓ **As a summary:** Membranes transduce photosynthetic energy, convert chemical energy to ATP, and store energy.

- ✓ In eukaryotes, the machinery for these energy conversions is contained within membranes of chloroplasts and mitochondria.

To deeper understanding , take a look to the next figure which includes some examples of plasma membrane functions



A summary of membrane functions in a plant cell.

A Brief History of Studies on Plasma Membrane Structure

- Membranes were found to be mostly composed of lipids because their dissolving power matched that of oil.
- The lipid bilayer accounted for the 2:1 ratio of lipid to cell surface area
- The most energetically favored orientation for polar head groups is facing the aqueous compartments outside of the bilayer.

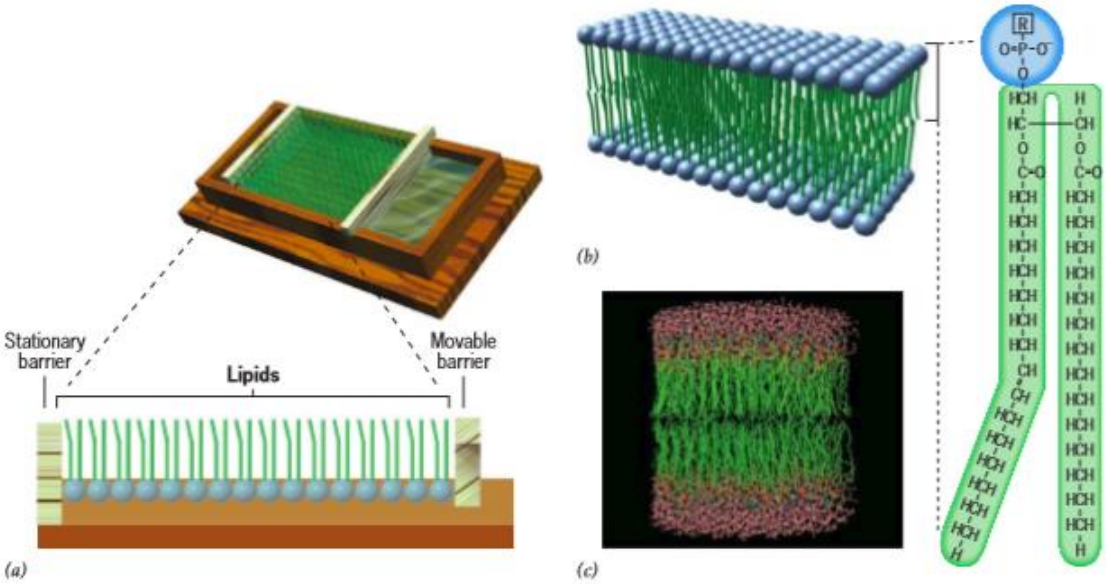


FIGURE 4.3 The plasma membrane contains a lipid bilayer. (a) Calculating the surface area of a lipid preparation. When a sample of phospholipids is dissolved in an organic solvent, such as hexane, and spread over an aqueous surface, the phospholipid molecules form a layer over the water that is a single molecule thick: a monomolecular layer. The molecules in the layer are oriented with their hydrophilic groups bonded to the surface of the water and their hydrophobic chains directed into the air. To estimate the surface area the lipids would cover if they were part of a membrane, the lipid molecules can be compressed into the smallest possible area by means of movable barriers. Using this type of apparatus, which is called a Langmuir trough after its inventor, Gorter and Grendel concluded that red blood cells contained enough lipid to form a layer over their surface that was two molecules thick: a bilayer. (b) As Gorter and Grendel first proposed, the core of a membrane contains a bimolecular layer of phospholipids oriented with their water-soluble head groups facing the outer surfaces and their hydrophobic fatty acid tails facing the interior. The structures of the head groups are given in Figure 4.6a. (c) Simulation of a fully hydrated lipid bilayer composed of the phospholipid phosphatidylcholine. Phospholipid head groups are purple, water molecules are blue, fatty acid chains are green.

توضيح بسيط : لما اجو يدرسوا مكونات الخلية اختارو الخلية الاخف تعقيدا فكانت خلية الدم الحمراء :

Gorter and Grendel extracted the lipid from human red blood cells and measured the amount of surface area the lipid would cover when spread over the surface of water .

. Because mature mammalian red blood cells lack both nuclei and cytoplasmic organelles, the plasma membrane is the only lipid-containing structure in the cell. Consequently, all of the lipids .extracted from the cells can be assumed to have resided in the cells' plasma membranes.

Cell physiologists determined that there must be more to the structure of membranes than simply a lipid bilayer, because:

I. Lipid solubility was not the sole determining factor as to whether a substance could penetrate the plasma membrane.
II. Surface tensions of membranes were calculated to be much lower than those of pure lipid structures explained by the presence of protein in the membrane .

❖ Protein is present in the form of individual protein molecules and protein complexes that penetrate a fluid lipid bilayer and extend out into the surrounding aqueous environment .

❖ Due to lipid bilayer fluidity , membranes are dynamic structures in which the components are mobile and capable of coming together to engage in various types of transient or semipermanent interactions.

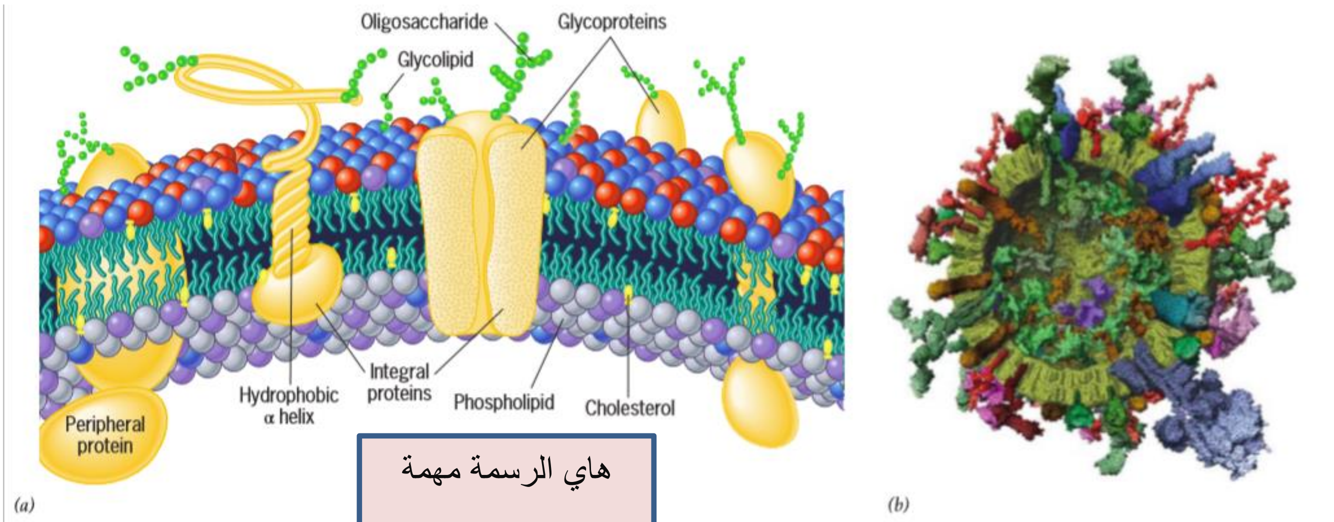


FIGURE 4.4 Plasma mebranes as lipid plus proteins. (a) A representation of the plasma membrane showing the organization of proteins embedded in the lipid bilayer. The external surface of most membrane proteins, as well as a small percentage of the phospholipids, contain short chains of sugars, making them glycoproteins and glycolipids. Those portions of the polypeptide chains that extend through the lipid bilayer typically occur as α helices composed of hydrophobic amino acids. The two leaflets of the bilayer contain different types of lipids as indicated by the differently colored head groups. (b) Molecular model of the membrane of a synaptic vesicle constructed using known structures of the various proteins along with information on their relative numbers obtained from the analysis of purified synaptic vesicles. The high protein density of the membrane is apparent. Most of the proteins in this membrane are required for the interaction of the vesicle with the plasma membrane. The large blue protein at the lower right pumps H^+ ions into the vesicle.

The Lipid Composition of Membranes

Membranes are lipid-protein assemblies held together by <u>noncovalent</u> bonds.

- The lipid bilayer is a structural backbone and <u>barrier to prevent random movement of material into and out of the cells.</u>

- Proteins carry out many functions in the cell. Each type of cells has a <u>unique</u> complement of membrane proteins which contributes to the specialized activities of that cell type.

- The ratio of lipid to proteins varies depending on the type of cellular membrane, type of organism and the type of cell.

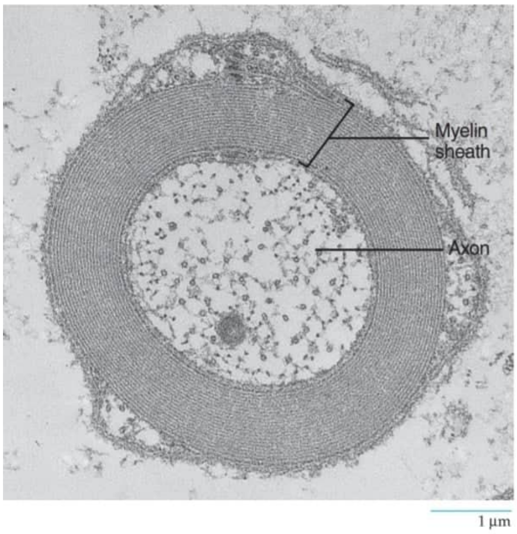
Example: The ratio of protein/lipid on these cells is in this order :

Inner mitochondrial membrane>> red blood cell plasma membrane >>membrane of myelin sheath**

**myelin sheath (غمد ميليني)

Form a multilayered wrapping around nerve cell. The myelin sheath acts as electrical insulation for the nerve cell , best carried out by a thick lipid layer of high electrical resistance with an minimal content of protein, which increase the velocity of impulses along the axon.

(زي العازل الموجود على اسلاك الكهربا -بحافظ عالشحنات جواته-)



Electron micrograph of a nerve cell axon

- The difference in ratio above is not random, but it fits to the cell function. For example, the inner mitochondrial membrane contains proteins of the electron transport chain (high protein/lipid ratio). Also in example for that is the myelin sheath membrane which discussed above (low protein/lipid ratio**).**

- Membranes also contain carbohydrates , which are attached to the lipids and proteins.

Membrane lipids

- Membrane lipids are <u>amphipathic</u>** with three main types :

****Recall that amphipathic molecule is a molecule with both hydrophobic and hydrophilic regions**

<u>Concentrate on colors!!</u>

1<u>. **phosphoglycerides**</u> : (figure 4.6 on the next pages) are diacylglycerides with small functional head groups linked to the glycerol backbone by phosphate <u>ester</u> bonds.

- Lipids + phosphate = <u>phospholipids</u>
- Phospholipids built on a glycerol backbone are called <u>phosphoglycerides</u>
- Unlike triglycerides, which have 3 fatty acids and are not amphipathic, membrane glycerides are <u>diglycerides</u> . Only two of the three hydroxyl groups

of the glycerol are esterified **to fatty acids**, the third one is esterified to a **hydrophilic phosphate group.**

- Because phosphate group has a partial negative charge, it can bond to another group such as choline, ethanolamine, serine and inositol.
Each one of these group is hydrophilic and small and, together with the negative charge of the phosphate group, forms a highly water-soluble domain at one end of the molecule, called the Head Group.

Phosphate group + Choline = (PC) head group
Phosphate group + Ethanolamine = (PE) head group
Phosphate group + Serine = (PS) head group
Phosphate group + Inositol = (PI) head group

Inositol:

حلقة سداسية تتضمن 6 (OH)

(للفهم من الريكورد)

- If nothing bind to the phosphate group we call it **phosphatidic acid**

- PS and PI have an overall negative charge
PC and PE are neutral

- The fatty acyl (glycerol + fatty acid) chains are hydrophobic, unbranched hydrocarbons approximately 16 to 22 carbon in length.

- The fatty acid may be fully saturated (lack double bonds) , monounsaturated (have one double bond) or polyunsaturated (have more than one double bond) . phosphoglycerides often contain one unsaturated and one saturated fatty acyl chain.

- Lately , some studies proved that the unsaturated fatty acids (EPA and DHA) , which found in fish oil and incorporated primarily into PC and PE molecules, have many benefits to our body specially on brain and retina.

- With fatty acid chains at one end and a polar head group at the other end, all of the **phosphoglycerides** exhibit a distinct amphipathic character.

2. Sphingolipids: (figure 4.6 on the next page) are derivatives of sphingosine (an amino alcohol that contains along hydrocarbon chains). They are amphipathic and consist of sphingosine linked to a fatty acid by its amino group , called ceramide

- The sphingosine-based lipids have additional group esterified to terminal alcohol :

1. If the substitution is phosphorylcholine, the molecule is **sphingomyelin**
2. If the substitution is a carbohydrate, the molecule is **glycolipid**

   a. If the carbohydrate is a simple sugar, the glycolipid is a **cerebroside**

   b. If the carbohydrate is a small cluster of sugars that includes sialic acid, the glycolipid is **ganglioside**

- Sphingolipids is basically like the structure of phosphoglycerides. However, sphingolipids fatty acyl chains tend to be longer and more highly saturated than those on phosphoglycerides

- The nervous system is rich in glycolipids, myelin sheath contains a high content of glucocerebroside.

- Mice lacking the enzyme that makes the glycolipids exhibit severe muscular tremors and eventual paralysis. Humans unable to synthesize ganglioside suffer from a serious neurological disease characterized by severe seizures and blindness

- Glycolipids play a role in infectious diseases; toxins that cause cholera and botulism both enter their target cell by first binding to cell-surface gangliosides, as does the influenza virus.

3. Cholesterol: (figure 4.7 below) is a smaller and less amphipathic lipid that is only found in animals.

- A steroid that makes up to 50% of animal membrane lipids .
- The -OH group is oriented toward membrane surface.

Carbon rings are flat and rigid; interfere with movement of phospholipid fatty acid tails

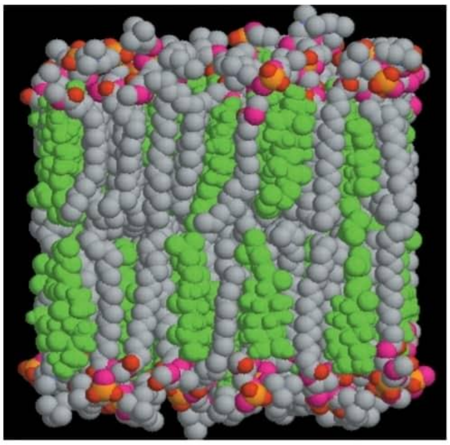


FIGURE 4.7 The cholesterol molecules (shown in green) of a lipid bilayer are oriented with their small hydrophilic end facing the external surface of the bilayer and the bulk of their structure packed in among the fatty acid tails of the phospholipids. The placement of cholesterol molecules interferes 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).

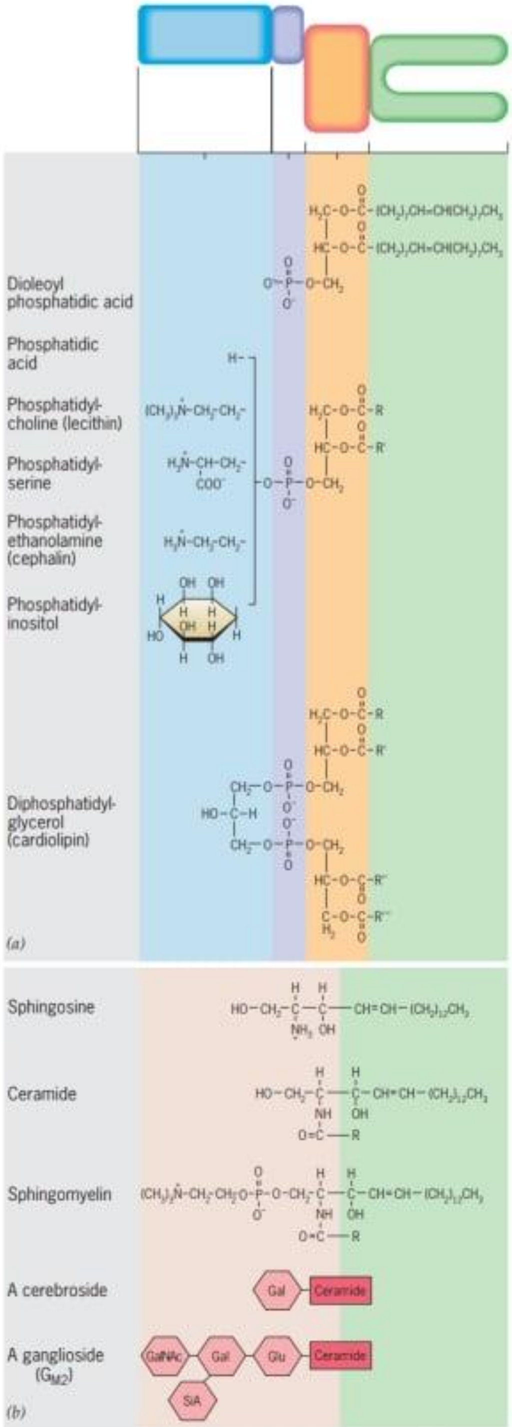
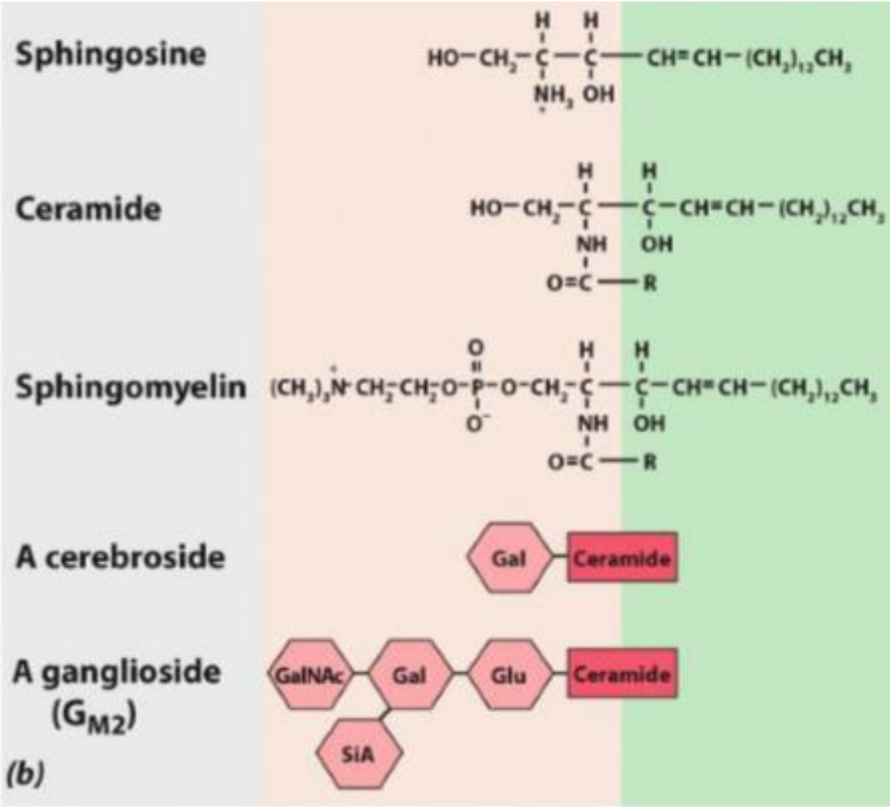


FIGURE 4.6 The chemical structures of membrane lipids. (a) The structures of phosphoglycerides (see also Figure 2.22). (b) The structures of sphingolipids. Sphingomyelin is a phospholipid; cerebrosides and gangliosides are glycolipids. A third membrane lipid is cholesterol, which is shown in the next figure. (R = fatty acyl chain). [The green portion of each lipid, which represents the hydrophobic tail(s) of the molecule, is actually much longer than the hydrophilic head group (see Figure 4.23).]



The chemical structure of membrane lipids.

(for sphingolipids)

#The Nature and importance of the lipid Bilayer:

Each type of cellular membrane has its own characteristic lipid composition,

The differences between them:

1. The type of lipids .
2. The nature of the head groups.
3. The particular species of fatty acyl chain(s).

These differences due to some biological membrane contain hundreds of chemically distinct species of phospholipids, which can be catalogued by **mass spectrometry.**

- The importance of the lipid Bilayer
    1. They can have important effect on the biological properties of a membrane
    2. Their composition can determine the physical state of the membrane & influence the activity of particular membrane proteins
    3. They provide the precursors for highly active chemical messengers that regulates cellular function

The percentages of some of the major types of lipids of a variety of membranes are given in this table.

Table 8.1 Lipid Compositions of Some Biological Membranes*

Lipid	Human erythrocyte	Human myelin	Beef heart mitochondria	*E. coli*
Phosphatidic acid	1.5	0.5	0	0
Phosphatidylcholine	19	10	39	0
Phosphatidyl-ethanolamine	18	20	27	65
Phosphatidylgycerol	0	0	0	18
Phosphatidylserine	8.5	8.5	0.5	0
Cardiolipin	0	0	22.5	12
Sphingomyelin	17.5	8.5	0	0
Glycolipids	10	26	0	0
Cholesterol	25	26	3	0

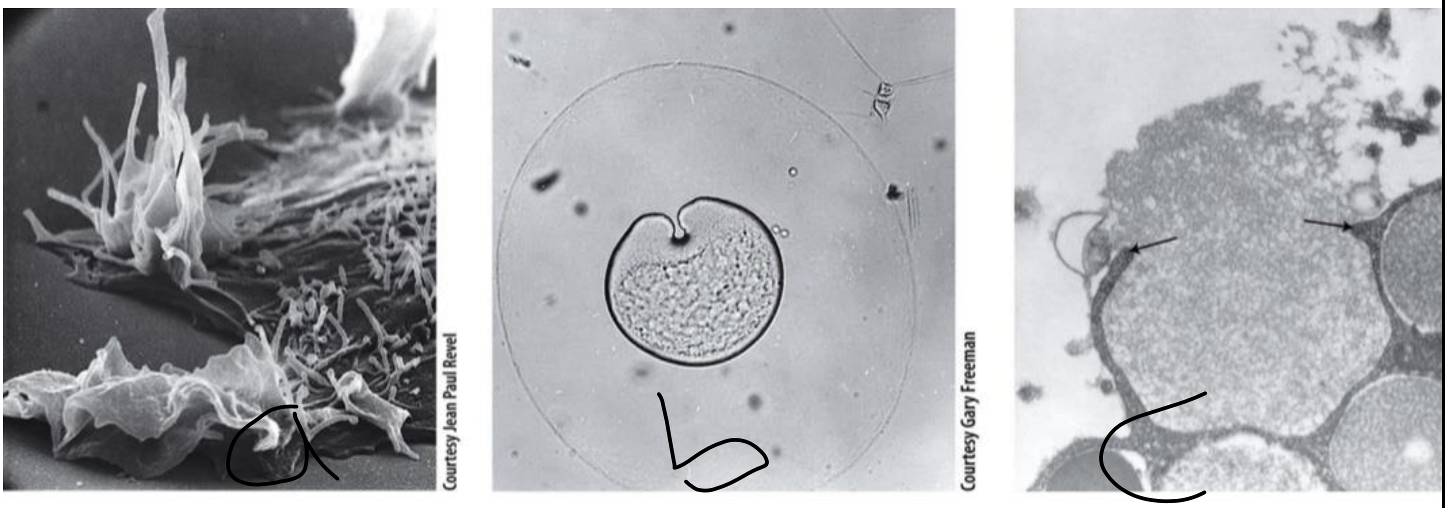
*The values given are weight percent of total lipid.
Source: C. Tanford, *The Hydrophobic Effect*, p. 109, copyright 1980, John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

#Various types of measurements indicate that:

- the combined fatty acyl chains of both leaflets of the lipid bilayer span a width of about 30 , each row of head groups (with its adjacent shell of water molecules) adds another 15 Å
- → the entire lipid bilayer is only about 60 Å (6 nm) thick.

The dynamic properties of plasma membrane

- the hydrocarbon chains of the lipid bilayer are never exposed to the surrounding aqueous solution ,because of thermodynamic considerations .Consequently, membranes are never seen to have a free edge; they are always continuous, unbroken structures, As a result, membranes form extensive interconnected networks within the cell.



a)Movement: The leading edge of a moving cell often contains sites where the plasma membrane displays undulating ruffles

b) Division of a cell is accompanied by the deformation of the plasma membrane as it is pulled center of the cell Unlike most dividing cells, the cleavage furrow of this dividing ctenophore egg begins at one pole and moves unidirectionally through the egg.

(c) Membranes are capable of fusing with other membranes. This electron micrograph shows a secretory granule discharging its contents after fusion with the overlying plasma membrane (arrows)..

The importance of the lipid bilayer(addition):

1. maintaining the proper internal composition of a cell

2. separating electric charges across the plasma membrane.

3. its ability to self-assemble, which can be demonstrated more easily within a test- tube than a living cell.

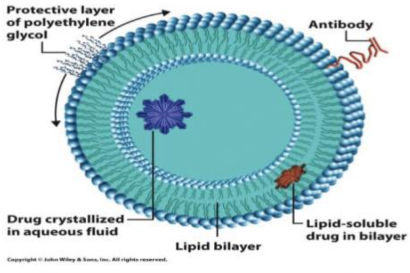
Liposomes:

- Phospholipid molecules assemble spontaneously to form the walls of fluid-filled spherical vesicles, called liposomes.
- Liposomes have proven invaluable in membrane research.
- Membrane proteins can be inserted into liposomes and their function studied in a much simpler environment than that of a natural membrane
    - ✓ the walls of the liposomes are constructed to contain specific proteins (such as antibodies or hormones) that allow the liposomes to bind selectively to the surfaces of particular target cells where the drug or DNA is intended to go.(vehicles for DNA or drugs)

Most of the early clinical studies with liposomes met with failure because the injected . vesicles were rapidly removed by phagocytic cells of the immune system. This obstacle has been overcome with the development of so-called stealth liposomes

stealth liposomes: that contain an outer coating of a synthetic polymer that protects the liposomes from immune destruction.

- . One important example for stealth liposomes is Caelyx, a stealth liposome containing the chemotherapy drug doxorubicin. Caelyx is now an accepted therapy for treatment of metastatic breast cancer.



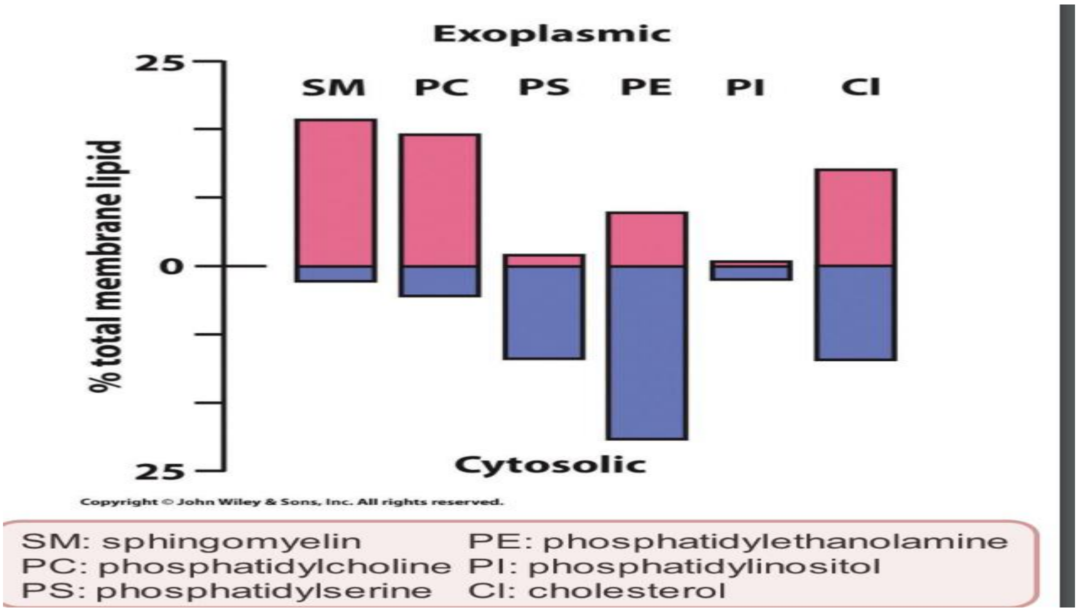
#The Asymmetry of Membrane Lipids

- The lipid bilayer consists of two distinct leaflets that have a distinctly different lipid composition ,that led to the fact that lipid -digesting enzymes cannot penetrate the plasma membrane and, consequently, are only able to digest lipids that reside in the outer leaflet of of bilayer.
- Compared to the inner leaflet, the outer leaflet has a relatively high concentration of PC (and sphingomyelin) and a low concentration of PE and PS:

~80% of the membrane phosphatidylcholine (PC) is hydrolyzed, but only ~20% of membrane phosphatidylethanolamines (PE) & <10% of its phosphatidylserines (PS) are attacked.

- Thus, one can think of the lipid bilayer as 2 more-or-less stable, independent monolayers with different physical & chemical properties

- The lipid bilayer is composed of two semi-stable, independent monolayers having different physical and chemical properties.
- The different classes of lipids exhibit different properties:
  1. All glycolipids of plasma membrane are in outer leaflet - often serve as receptors for extracellular ligands
  2. PE, concentrated in the inner leaflet, tends to promote the curvature of the membrane, which is important in membrane budding & fusion
  3. PS (concentrated in inner leaflet) – it has a net"-" charge at physiologic pH, so it may bind "+" charged lysine & arginine residues.
  4. PI, mostly in inner leaflet, is involved in signal transduction across the membrane; it can be phosphorylated at different sites on the inositol ring.



The end.

Some notes from the record :

-the hydrocarbon tails of the phospholipids make a hydrophobic interaction, while the hydrophilic part make an ionic ,hydrogen....bonds .

-للفهم:البروتين بكون محب او كاره للمي بناء على الاحماض الامينية و الي بنميزها من (R Group) كالتالي:

When it terminates by -CH- it is nonpolar.

When it terminates by -OH,NH,SH,=O- it is polar.

When it terminates by-amino or carboxyl group- it is polar.

-the sugars located attached to lipids or proteins away from cytosol.

-cholesterol is more hydrophobic than lipids because it has only one region for hydrophilic side (OH).

الفرق بين di,bis :

Di:المجموعتين مرتبطات بنفس ذرة الكربون.

Bis:كل مجموعة مرتبطة بذرة كربون بتختلفز