The Cell Components

The Structure and Function of the Plasma Membrane

- Cells are separated from the external world by a thin, fragile structure called the plasma membrane that is only 5 to 10 nm wide.

- Membranes serves various functions in the cell.

- **1. Compartmentalization.** Membranes are continuous, unbroken sheets and, as such, inevitably enclose compartments.

- The plasma membrane encloses the contents of the entire cell, whereas the nuclear and cytoplasmic membranes enclose diverse intracellular spaces.

- The various membrane-bounded compartments of a cell possess markedly different contents.

- Membrane compartmentalization allows specialized activities to proceed without external interference and enables cellular activities to be regulated independently of one another.

- **2. Scaffold for biochemical activities.** Membranes not only enclose compartments but are also a distinct compartment themselves.

- As long as reactants are present in solution, their relative positions cannot be stabilized and their interactions are dependent on random collisions.

- Because of their construction, membranes provide the cell with an extensive framework or scaffolding within which components can be ordered for effective interaction.

- **3. Providing a selectively permeable barrier.** Membranes prevent the unrestricted exchange of molecules from one side to the other.

- At the same time, membranes provide the means of communication between the compartments they separate.

- 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.

❖ 4. Transporting solutes.

- ❖ The plasma membrane contains the machinery for physically transporting substances from one side of the membrane to another, often from a region where the solute is present at low concentration into a region where that solute is present at much higher concentration.

- ❖ The membrane's transport machinery allows a cell to accumulate substances, such as sugars and amino acids, that are necessary to fuel its metabolism and build its macromolecules.

- ❖ 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.

- **5. Responding to external stimuli.** The plasma membrane plays a critical role in the response of a cell to external stimuli, a process known as signal transduction.

- Membranes possess receptors that combine with specific molecules (ligands) or respond to other types of stimuli such as light or mechanical tension.

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

- The interaction of a plasma membrane receptor with an external stimulus may cause the membrane to generate a signal that stimulates or inhibits internal activities.

- 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.

- **6. Intercellular interaction.** Situated at the outer edge of every living cell, the plasma membrane of multicellular organisms mediates the interactions between a cell and its neighbors.

- The plasma membrane allows cells to recognize and signal one another, to adhere when appropriate, and to exchange materials and information.

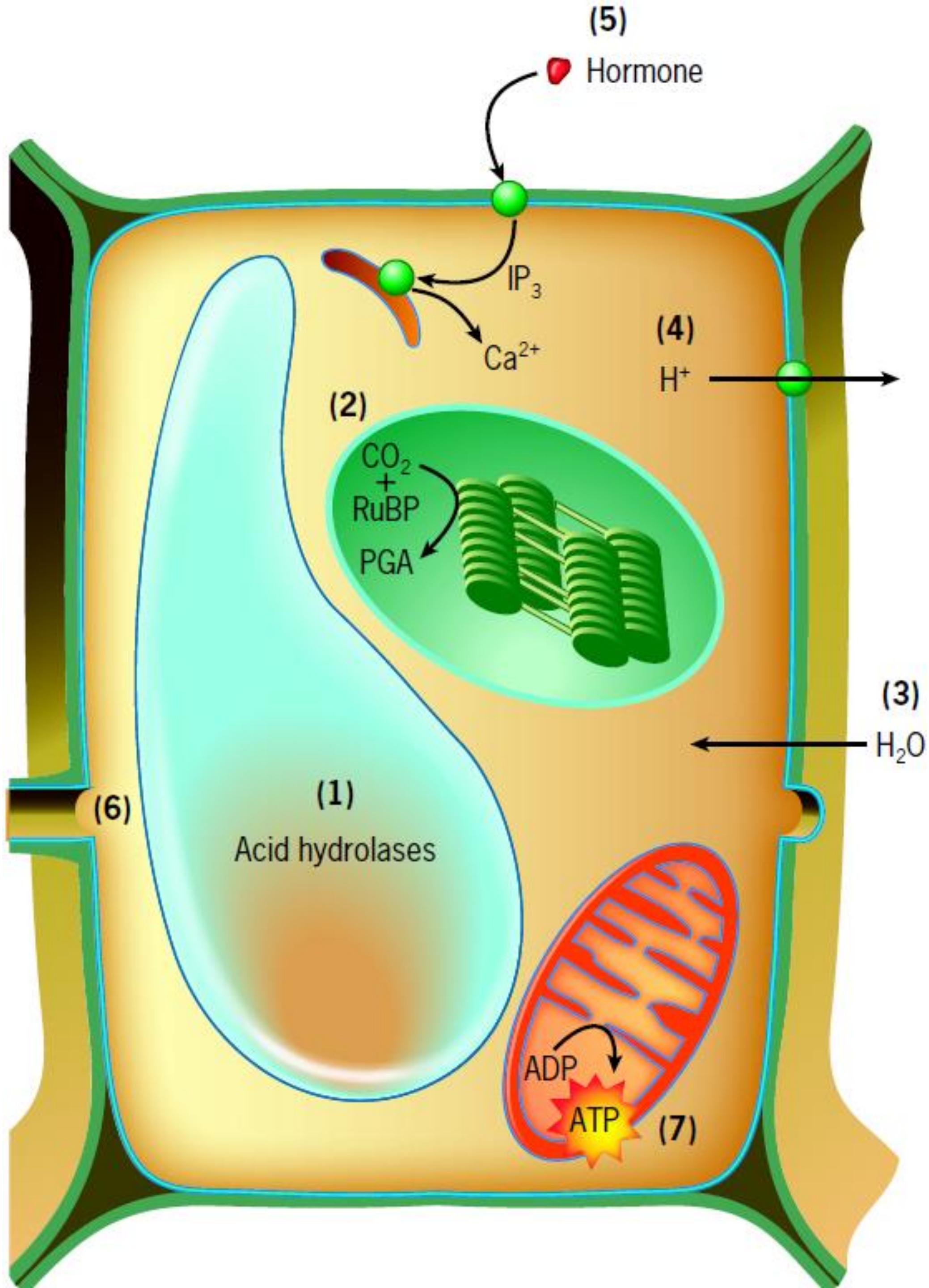
- Proteins within the plasma membrane may also facilitate the interaction between extracellular materials and the intracellular cytoskeleton.

- **7. Energy transduction.** Membranes are intimately involved in the processes by which one type of energy is converted to another type (energy transduction).

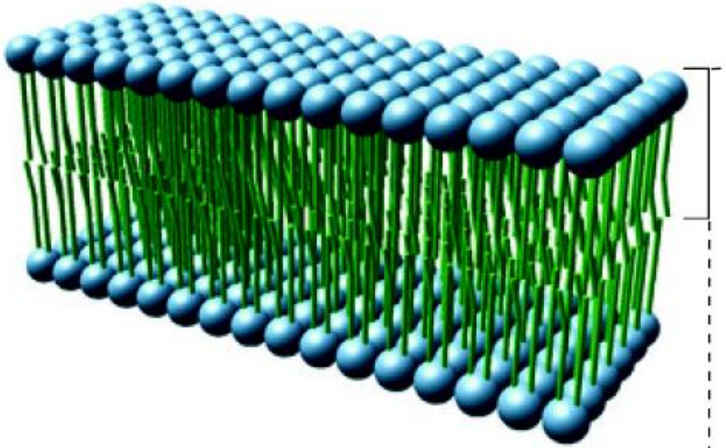
- The most fundamental energy transduction occurs during photosynthesis when energy in sunlight is absorbed by membrane-bound pigments, converted into chemical energy, and stored in carbohydrates.

- Membranes are also involved in the transfer of chemical energy from carbohydrates and fats to ATP.

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



(1) An example of membrane compartmentalization (2) An example of the role of cytoplasmic membranes as a site of enzyme localization. The fixation of CO_2 by the plant cell is catalyzed by an enzyme that is associated with the outer surface of the thylakoid membranes of the chloroplasts. (3) An example of the role of membranes as a selectively permeable barrier. (4) An example of solute transport. Hydrogen ions, which are produced by various metabolic processes in the cytoplasm, are pumped out of plant cells. (5) An example of the involvement of a membrane in the transfer of information from one side to another (signal transduction). (6) An example of the role of membranes in cell–cell communication. Openings between adjoining plant cells, called plasmodesmata, allow materials to move directly from the cytoplasm of one cell into its neighbors. (7) An example of the role of membranes in energy transduction.



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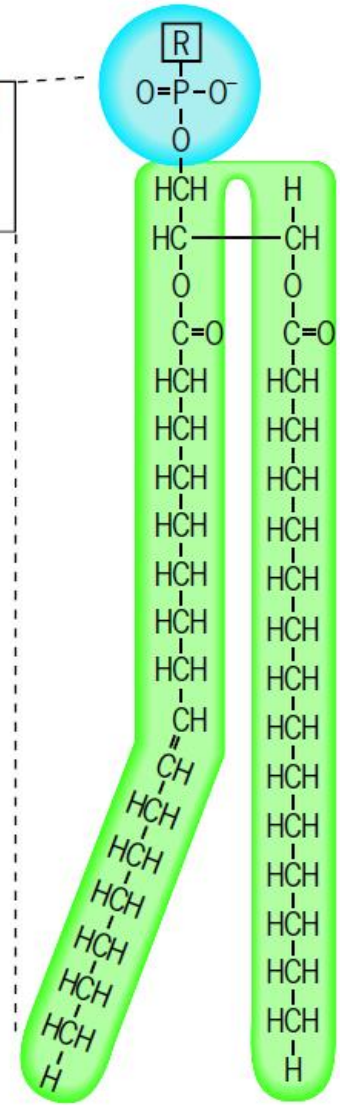

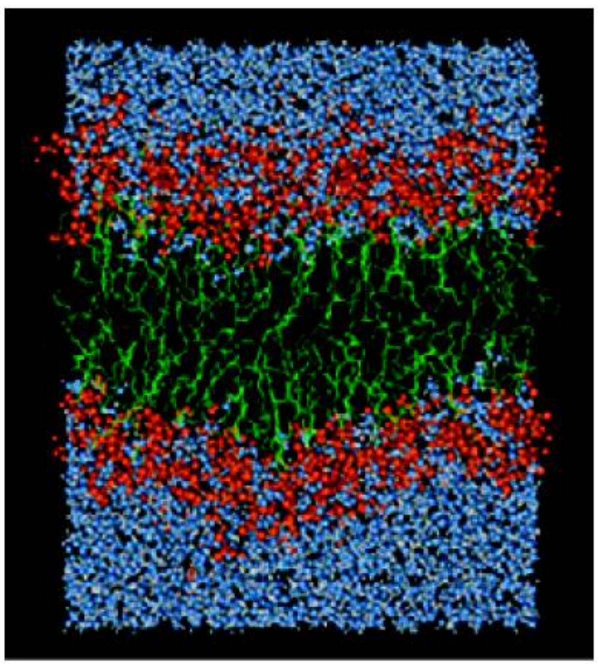

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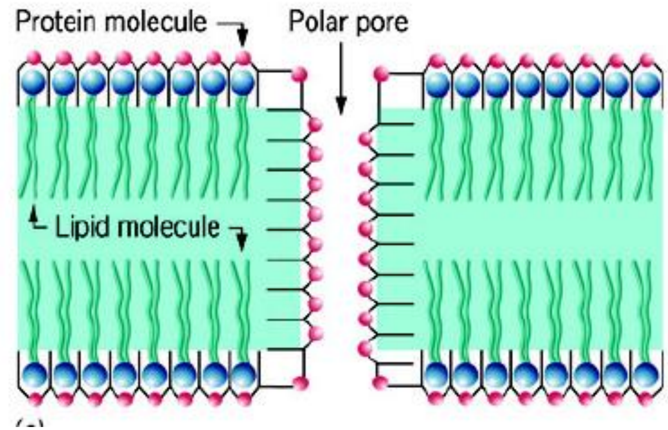

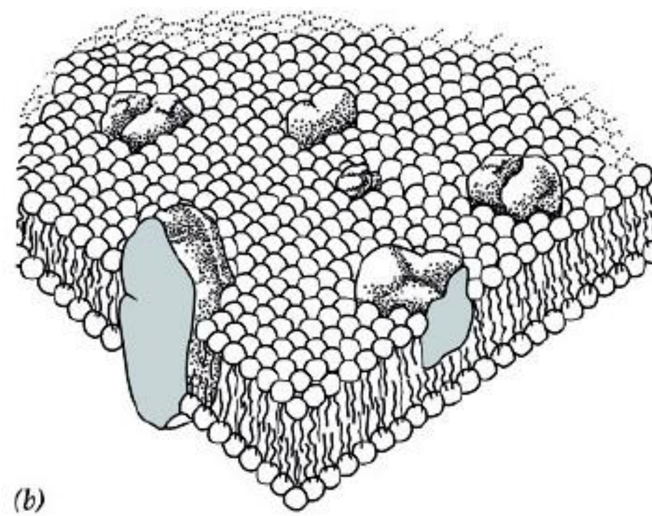

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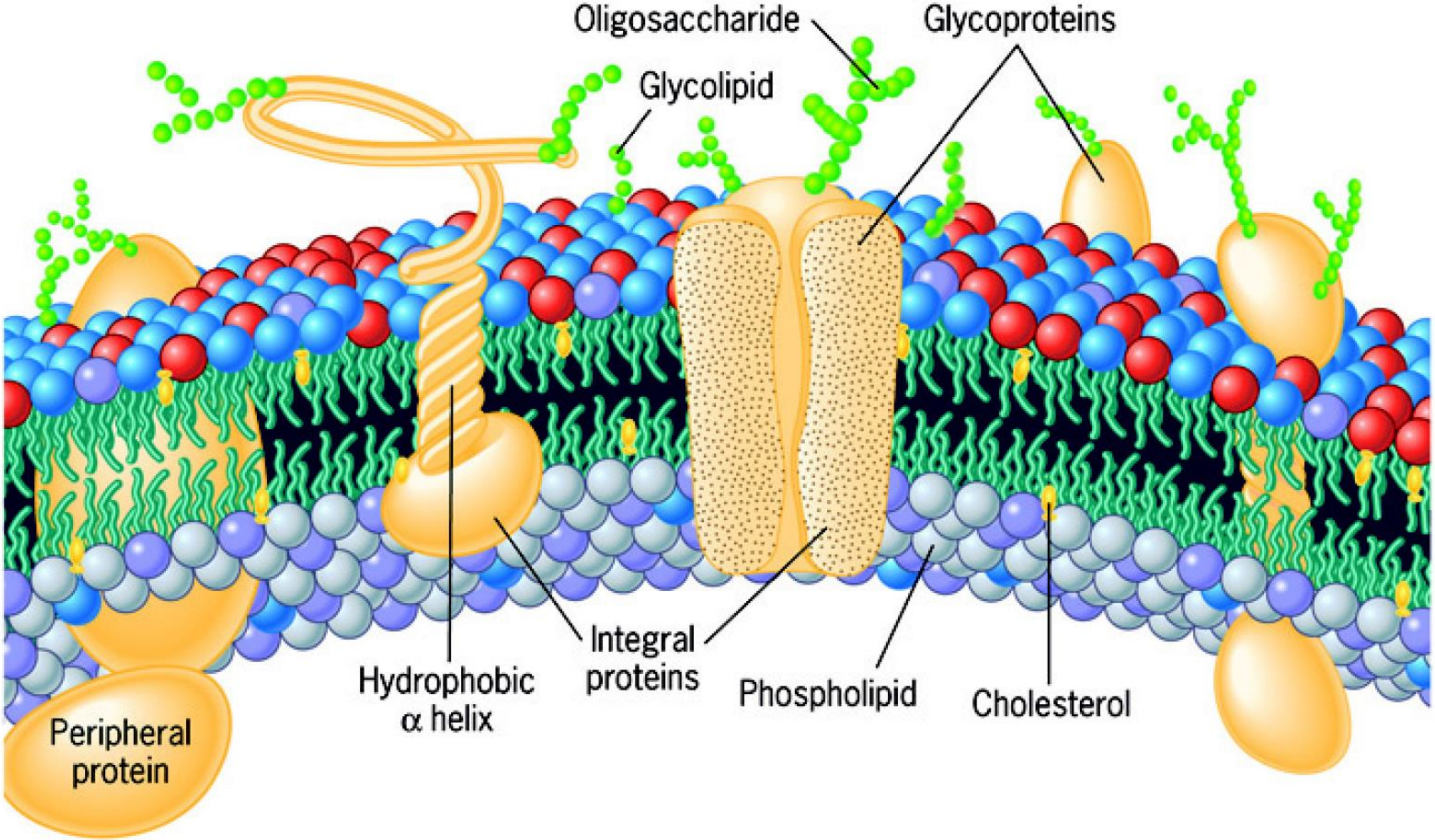

Oligosaccharide
Glycoproteins
Glycolipid
Integral proteins
Hydrophobic α helix
Phospholipid
Cholesterol
Peripheral protein

- The first insights into the chemical nature of the outer boundary layer of a cell were obtained by Ernst Overton of the University of Zürich during the 1890s.

- He discovered that the more lipid-soluble the solute, the more rapidly it would enter the root hair cells.

- He concluded that the dissolving power of the outer boundary layer of the cell matched that of a fatty oil.

- The first proposal that cellular membranes might contain a lipid bilayer was made in 1925 by two Dutch scientists, E. Gorter and F. Grendel.

- In the 1920s and 1930s, cell physiologists obtained evidence that there must be more to the structure of membranes than simply a lipid bilayer

- Experiments conducted in the late 1960s led to a new concept of membrane structure, as detailed in the fluid mosaic model proposed in 1972 by S. Jonathan Singer and Garth Nicolson of the University of California, San Diego.

- In the fluid-mosaic model, which has served as the “central dogma” of membrane biology for more than three decades, the lipid bilayer remains the core of the membrane, but attention is focused on the physical state of the lipid.

- Unlike previous models, the bilayer of a fluid-mosaic membrane is present in a fluid state, and individual lipid molecules can move laterally within the plane of the membrane.

- The structure and arrangement of membrane proteins in the fluid-mosaic model differ from those of previous models in that they occur as a “mosaic” of discontinuous particles that penetrate the lipid sheet.

- Most importantly, the fluid-mosaic model presents cellular membranes as dynamic structures in which the components are mobile and capable of coming together to engage in various types of transient or semipermanent interactions.

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

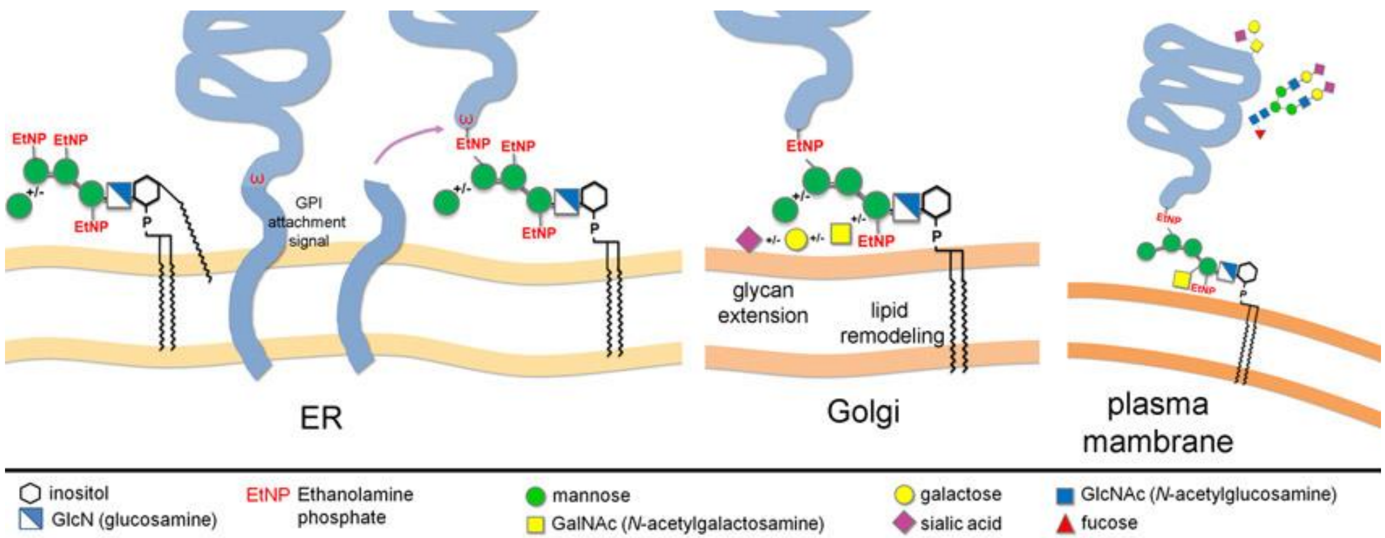
- The ratio of lipid to protein in a membrane varies, depending on the type of cellular membrane (plasma vs. endoplasmic reticulum vs. Golgi), the type of organism (bacterium vs. plant vs. animal), and the type of cell (cartilage vs. muscle vs. liver).

- Membranes also contain carbohydrates, which are attached to the lipids and 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 glycosyl-phosphatidylinositol linkage are called GPI-anchored proteins.

❖ They were discovered when it was shown that certain membrane proteins could be released by a phospholipase that specifically recognized and cleaved inositol-containing phospholipids



- Membrane Lipids

- Membranes contain a wide diversity of lipids, all of which are amphipathic; that is, they contain both hydrophilic and hydrophobic regions. There are three main types of membrane lipids: phosphoglycerides, sphingolipids, and cholesterol.

- Most membrane lipids contain a phosphate group, which makes them phospholipids. Because most membrane phospholipids are built on a glycerol backbone, they are called phosphoglycerides

- A less abundant class of membrane lipids, called sphingolipids, are derivatives of sphingosine, an amino alcohol that contains a long hydrocarbon chain.

- Sphingolipids consist of sphingosine linked to a fatty acid by its amino group. This molecule is a ceramide.

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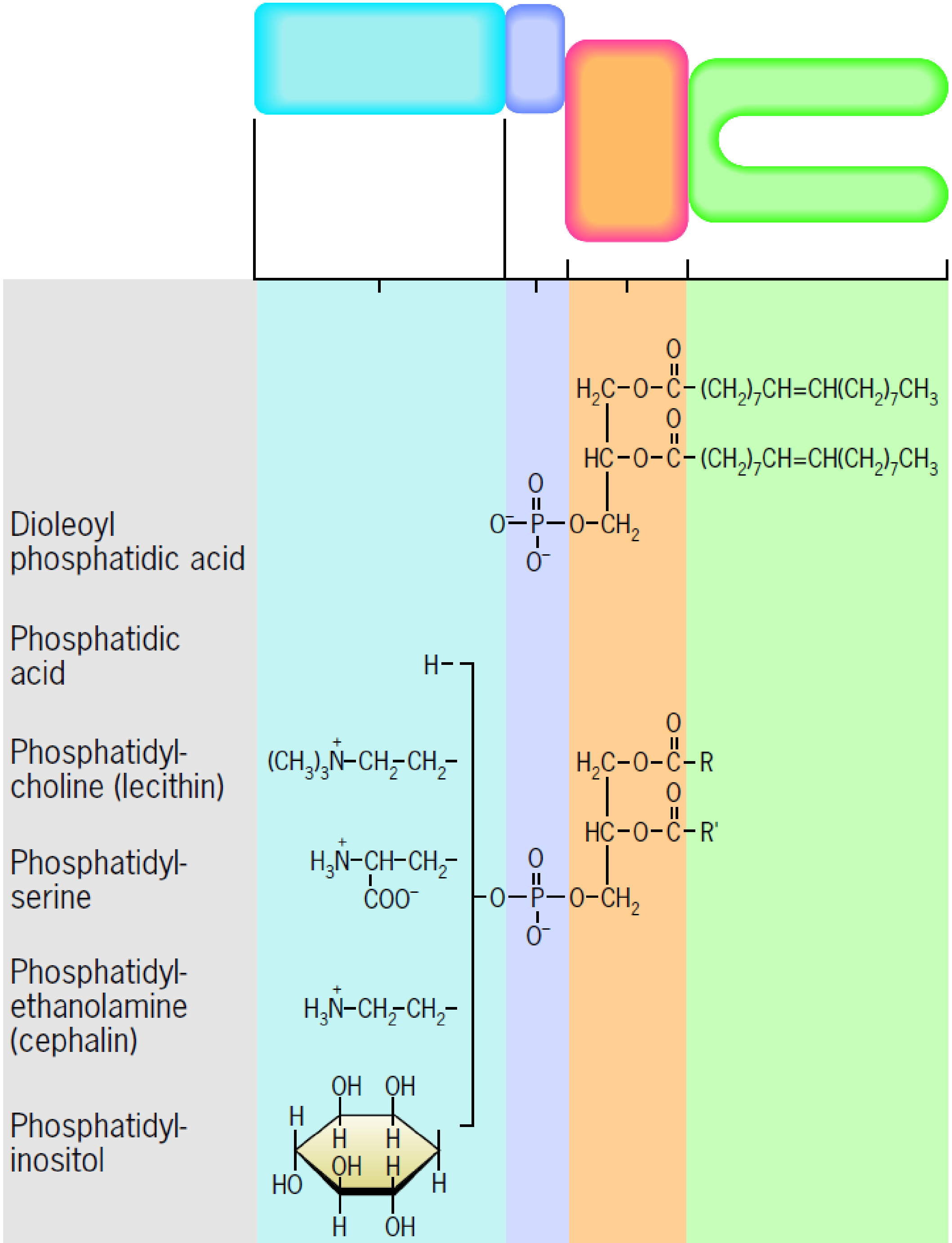
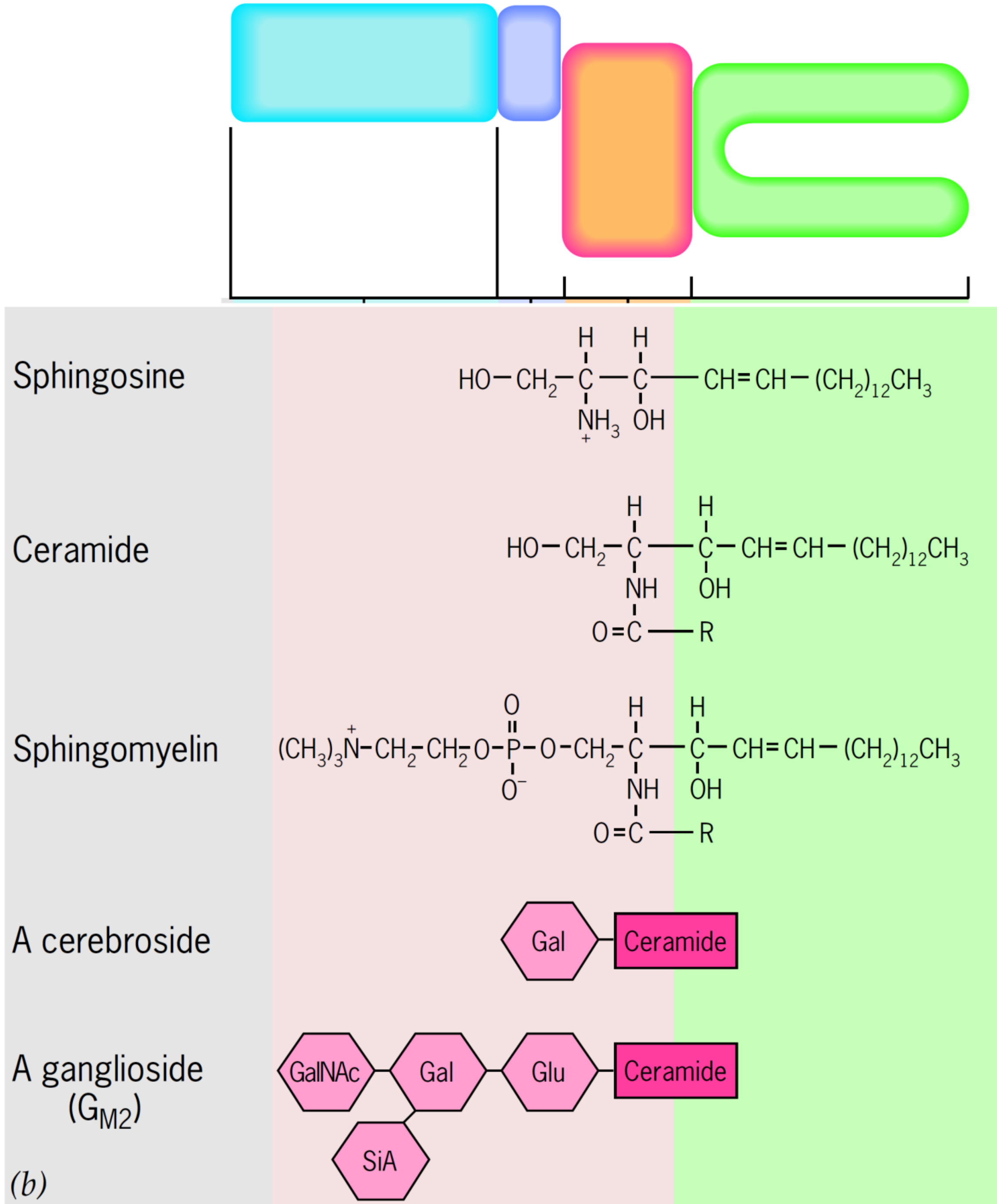

Dioleoyl phosphatidic acid
Phosphatidic acid
Phosphatidyl-choline (lecithin)
Phosphatidyl-serine
Phosphatidyl-ethanolamine (cephalin)
Phosphatidyl-inositol
H–
$(CH_3)_3\overset{+}{N}–CH_2–CH_2–$
$H_3\overset{+}{N}–CH–CH_2–$
COO^-
$H_3\overset{+}{N}–CH_2–CH_2–$
$H_2C–O–C(=O)–(CH_2)_7CH=CH(CH_2)_7CH_3$
$HC–O–C(=O)–(CH_2)_7CH=CH(CH_2)_7CH_3$
$O^-–P(=O)(O^-)–O–CH_2$
$H_2C–O–C(=O)–R$
$HC–O–C(=O)–R'$
$–O–P(=O)(O^-)–O–CH_2$


Sphingosine
HO−CH2−C(H)(NH3+)−C(H)(OH)−CH=CH−(CH2)12CH3
Ceramide
HO−CH2−C(H)(NH−C(=O)−R)−C(H)(OH)−CH=CH−(CH2)12CH3
Sphingomyelin
(CH3)3N+−CH2−CH2−O−P(=O)(O−)−O−CH2−C(H)(NH−C(=O)−R)−C(H)(OH)−CH=CH−(CH2)12CH3
A cerebroside
Gal
Ceramide
A ganglioside
(GM2)
GalNAc
Gal
Glu
Ceramide
SiA
(b)

- 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.

- Plant cells contain cholesterol-like sterols, but biologists disagree as to whether or not they completely lack 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 movements of the fatty acid tails of the phospholipids.

- Each type of cellular membrane has its own characteristic lipid composition, differing from one another in the types of lipids, the nature of the head groups, and the particular species of fatty acyl chain(s).

Table 4.1 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.

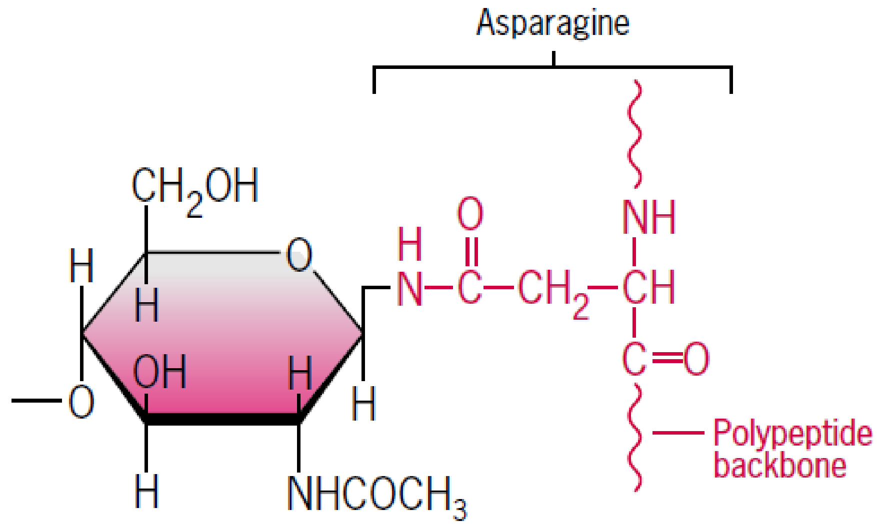
- The plasma membranes of eukaryotic cells also contain carbohydrate.

- Depending on the species and cell type, the carbohydrate content of the plasma membrane ranges between 2 and 10 percent by weight.

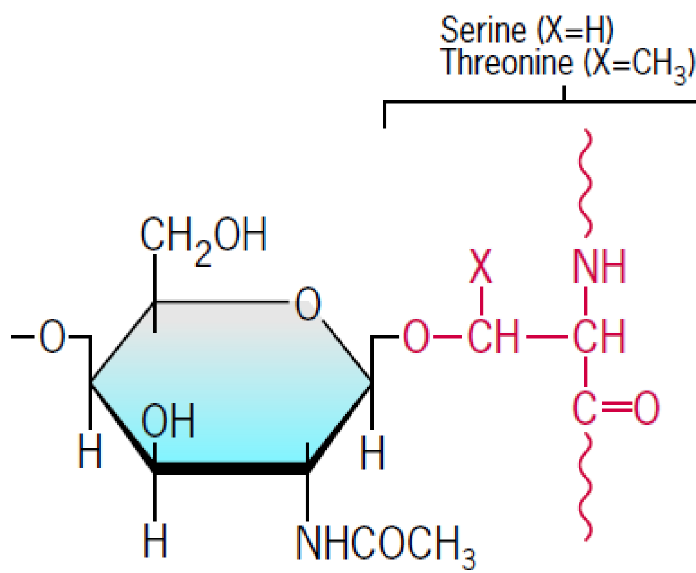
- More than 90 percent of the membrane’s carbohydrate is covalently linked to proteins to form glycoproteins; the remaining carbohydrate is covalently linked to lipids to form glycolipids.

- 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.



***N*-Acetylglucosamine**



***N*-Acetylgalactosamine**

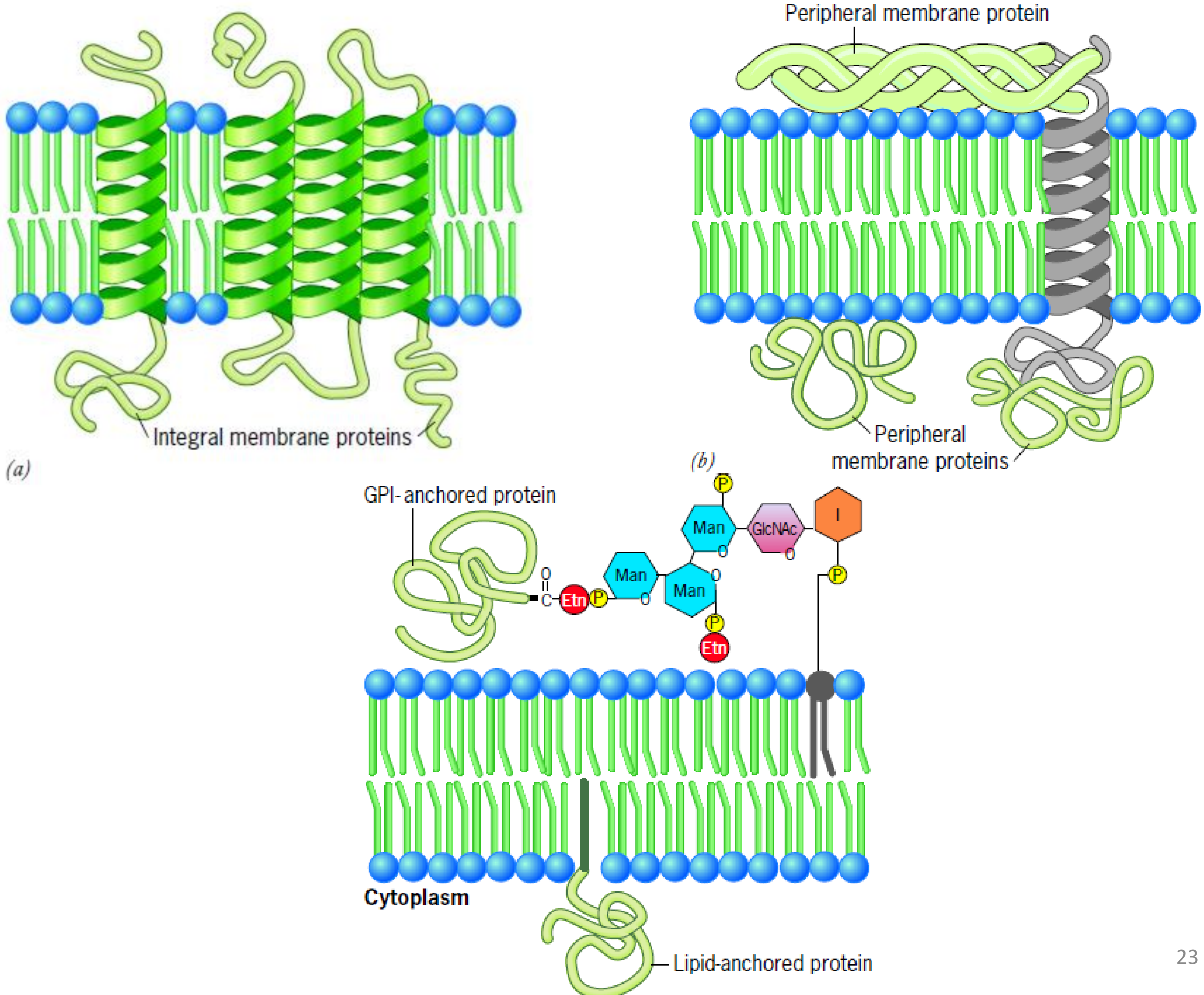
- Depending on the cell type and the particular organelle within that cell, a membrane may contain hundreds of different proteins.

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

- **1. Integral proteins** that 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. Some integral proteins have only one membrane-spanning segment, whereas others are multispanning.

- **2. Peripheral proteins** that are located entirely outside of the lipid bilayer, on either the cytoplasmic or extracellular side, yet are associated with the surface of the membrane by noncovalent bonds.

- **3. Lipid-anchored proteins** that are 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.


Peripheral membrane protein
Integral membrane proteins
(a)
(b)
Peripheral
membrane proteins
GPI-anchored protein
O
C
Etn
P
Man
O
Man
O
P
Etn
P
Man
O
GlcNAc
O
I
P
Cytoplasm
Lipid-anchored protein

- Most integral membrane proteins function in the following capacities: as receptors that bind specific substances at the membrane surface, as channels or transporters involved in the movement of ions and solutes across the membrane, or as agents that transfer electrons during the processes of photosynthesis and respiration.

- Like the phospholipids of the bilayer, integral membrane proteins are also amphipathic, having both hydrophilic and hydrophobic portions.

- 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.

- As a result, the permeability barrier of the membrane is preserved, the protein is anchored within the bilayer, and the protein is brought into direct contact with surrounding lipid molecules.

- 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.

- In actual fact, the distinction between integral and peripheral proteins is blurred because many integral membrane proteins consist of several polypeptides, some that penetrate the lipid bilayer and others that remain on the periphery.

- The best studied peripheral proteins are located on the internal (cytosolic) surface of the plasma membrane, where they form a fibrillar network that acts as a membrane “skeleton”.

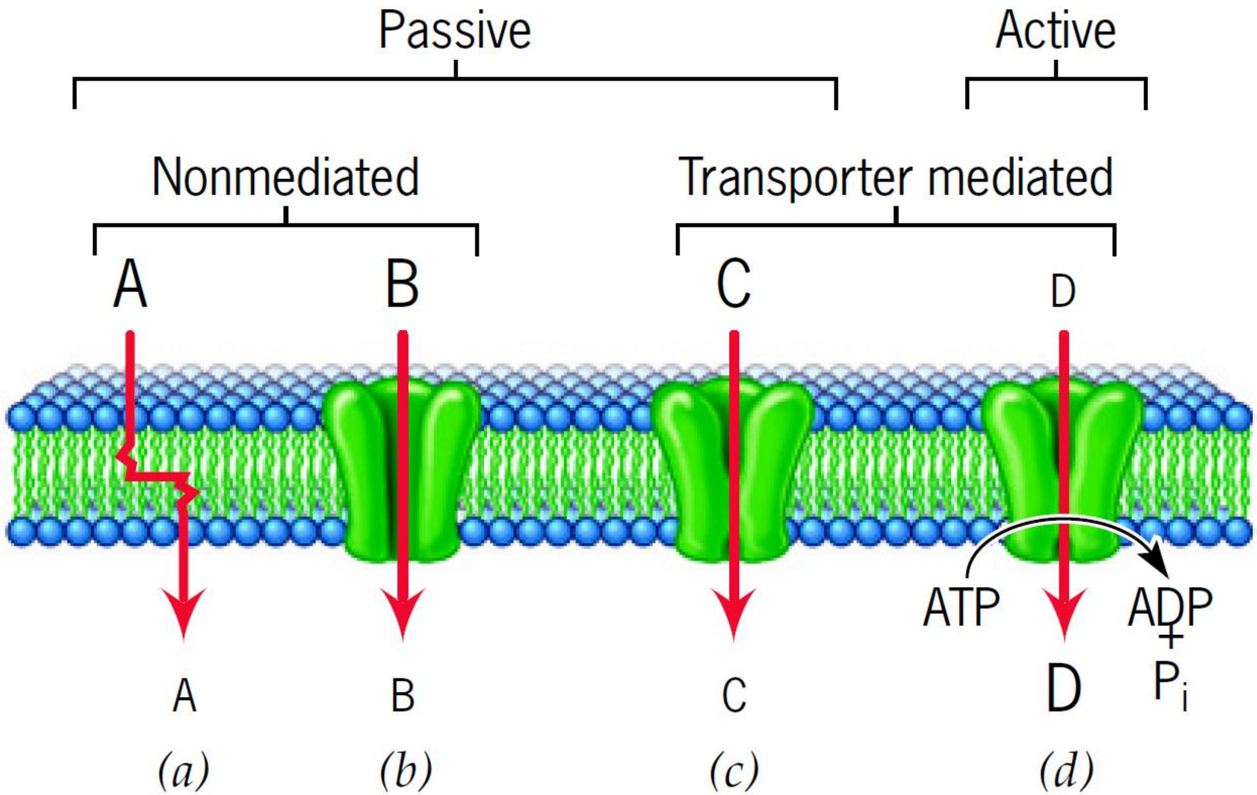
- These proteins provide mechanical support for the membrane and function as an anchor for integral membrane proteins.

- Several types of lipid-anchored membrane proteins can be distinguished.

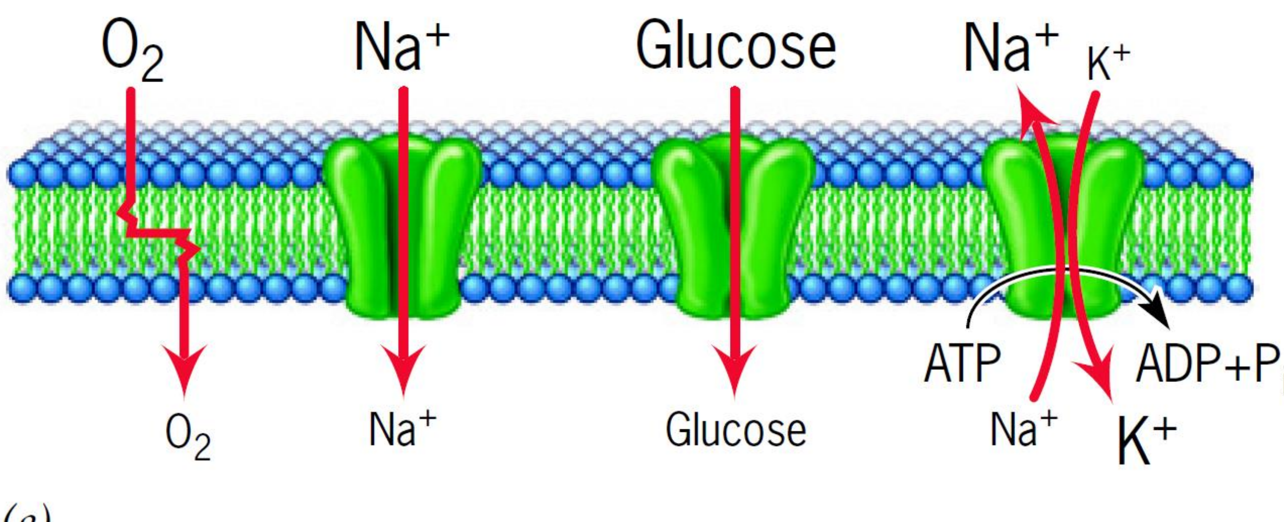
- Numerous proteins present on the external face of the plasma membrane are bound to the membrane by a small, complex oligosaccharide linked to a molecule of phosphatidylinositol that is embedded in the outer leaflet of the lipid bilayer.

- Peripheral membrane proteins containing this type of glycosyl-phosphatidylinositol linkage are called GPI-anchored proteins.

- They were discovered when it was shown that certain membrane proteins could be released by a phospholipase that specifically recognized and cleaved inositol-containing phospholipids



Passive
Active
Nonmediated
Transporter mediated
A
B
C
D
ATP
ADP
+
P_i
A
B
C
D
(a)
(b)
(c)
(d)



O_2
Na^+
Glucose
Na^+
K^+
ATP
$ADP+P_i$
O_2
Na^+
Glucose
Na^+
K^+

Four basic mechanisms by which solute molecules move across membranes. The relative sizes of the letters indicate the directions of the concentration gradients.

(a) Simple diffusion through the bilayer, which always proceeds from high to low concentration.

(b) Simple diffusion through an aqueous channel formed within an integral membrane protein or a cluster of such proteins. As in a, movement is always down a concentration gradient.

(c) Facilitated diffusion in which solute molecules bind specifically to a membrane protein carrier (a facilitative transporter). As in a and b, movement is always from high to low concentration.

(d) Active transport by means of a protein transporter with a specific binding site that undergoes a change in affinity driven with energy released by an exergonic process, such as ATP hydrolysis. Movement occurs against a concentration gradient.

(e) Examples of each type of mechanism as it occurs in the membrane of an erythrocyte.

- Several severe, inherited disorders have been traced to mutations in genes that encode ion channel proteins (Table 1).

- Most of the disorders listed in Table 1 affect the movement of ions across the plasma membranes of excitable cells (i.e., muscle, nerve, and sensory cells), reducing the ability of these cells to develop or transmit impulses.

- In contrast, cystic fibrosis, the best studied and most common inherited ion channel disorder, results from a defect in the ion channels of epithelial cells.

Table 1

Inherited disorder	Type of channel	Gene	Clinical consequences
Familial hemiplegic migraine (FHM)	Ca^{2+}	*CACNL1A4*	Migraine headaches
Episodic ataxia type-2 (EA-2)	Ca^{2+}	*CACNL1A4*	Ataxia (lack of balance and coordination)
Hypokalemic periodic paralysis	Ca^{2+}	*CACNL1A3*	Periodic myotonia (muscle stiffness) and paralysis
Episodic ataxia type-1	K^+	*KCNA1*	Ataxia
Benign familial neonatal convulsions	K^+	*KCNQ2*	Epileptic convulsions
Nonsyndromic dominant deafness	K^+	*KCNQ4*	Deafness
Long QT syndrome	K^+ Na^+	*HERG* *KCNQ1, or SCN5A*	Dizziness, sudden death from ventricular fibrillation
Hyperkalemic periodic paralysis	Na^+	*SCN4A*	Periodic myotonia and paralysis
Liddle Syndrome	Na^+	*B-ENaC*	Hypertension (high blood pressure)
Myasthenia gravis	Na^+	*nAChR*	Muscle weakness
Dent's disease	Cl^-	*CLCN5*	Kidney stones
Myotonia congenita	Cl^-	*CLC-1*	Periodic myotonia
Bartter's syndrome type IV	Cl^-	*CLC-Kb*	Kidney dysfunction, deafness
Cystic fibrosis	Cl^-	*CFTR*	Lung congestion and infections
Cardiac arrhythmias	Na^+ K^+ Ca^{2+}	many different genes	Irregular or rapid heartbeat

- On average, 1 out of every 25 persons of Northern European descent carries one copy of the mutant gene that can cause cystic fibrosis.

- Because they show no symptoms of the mutant gene, most heterozygotes are unaware that they are carriers.

- Consequently, approximately 1 out of every 2500 infants in this Caucasian population is homozygous recessive at this locus and born with cystic fibrosis (CF).

- Although cystic fibrosis affects various organs, including the intestine, pancreas, sweat glands, and reproductive tract, the respiratory tract usually exhibits the most severe effects.

- Victims of CF produce a thickened, sticky mucus that is very hard to propel out of the airways.

- Afflicted individuals typically suffer from chronic lung infections and inflammation, which progressively destroy pulmonary function.

- The gene responsible for cystic fibrosis was isolated in 1989. Once the sequence of the CF gene was determined and the amino acid sequence of the corresponding polypeptide was deduced, it was apparent that the polypeptide was a member of the ABC transporter superfamily.

- The protein was named cystic fibrosis transmembrane conductance regulator (CFTR), an ambiguous term that reflected the fact that researchers weren't sure of its precise function.

- The question was thought to be answered after the protein was purified, incorporated into artificial lipid bilayers, and shown to act as a cyclic AMP-regulated chloride channel, not a transporter.

- Because the movement of water out of epithelial cells by osmosis follows the movement of salts, abnormalities in the flux of Cl-, HCO3 - , and/or Na+ caused by CFTR deficiency leads to a decrease in the fluid that bathes the epithelial cells of the airways .
- A reduction in volume of the surface liquid, and a resulting increase in viscosity of the secreted mucus, impair the function of the cilia that push mucus and bacteria out of the respiratory tract.

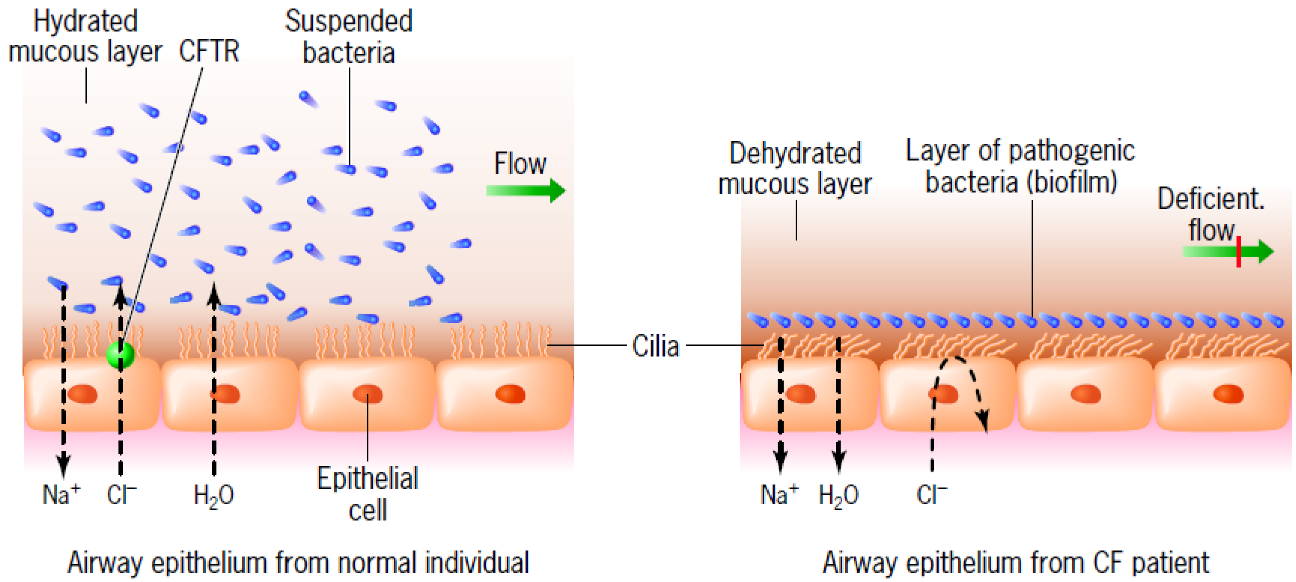


Figure 1 **An explanation for the debilitating effects on lung function from the absence of the CFTR protein.** In the airway epithelium of a normal individual, water flows out of the epithelial cells in response to the outward movement of ions, thus hydrating the surface mucous layer. The hydrated mucous layer, with its trapped bacteria, is readily moved out of the airways. In the airway epithelium of a person with cystic fibrosis, the abnormal movement of ions causes water to flow in the opposite direction, thus dehydrating the mucous layer. As a result, trapped bacteria cannot be moved out of the airways, which allows them to proliferate as a biofilm (page 13) and cause chronic infections.

- In the past decade, researchers have identified more than 1000 different mutations that give rise to cystic fibrosis.

- However, approximately 70 percent of the alleles responsible for cystic fibrosis in the United States contain the same genetic alteration (designated F508)—they are all missing three base pairs of DNA that encode a phenylalanine at position 508, within one of the cytoplasmic domains of the CFTR polypeptide.

- Ever since the isolation of the gene responsible for CF, the development of a cure by gene therapy—that is, by replacement of the defective gene with a normal version—has been a major goal of CF researchers.

- Cystic fibrosis is a good candidate for gene therapy because the worst symptoms of the disease result from the defective activities of epithelial cells that line the airways and, therefore, are accessible to agents that can be delivered by inhalation of an aerosol.

- To date, none of the clinical trials of gene therapy has resulted in significant improvement of either physiologic processes or disease symptoms.

- The development of more effective DNA delivery systems, which are capable of genetically altering a greater percentage of airway cells, will be required if a treatment for CF based on gene therapy is to be achieved.