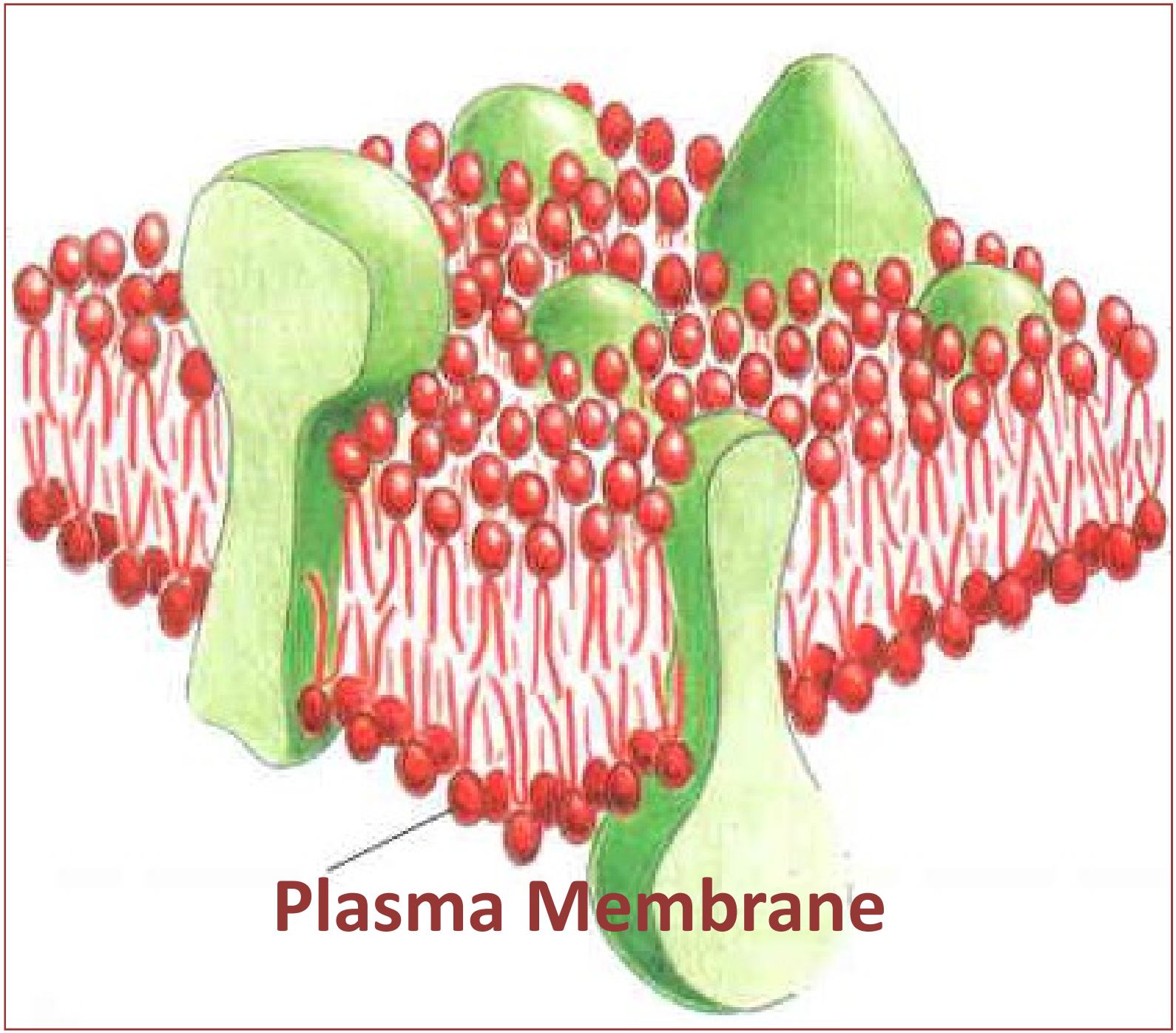

Plasma Membrane

Introduction:

An essential feature of every cell is the presence of **membranes that define the boundaries** of the cell and its various internal compartments. Each cell also includes many sorts of intracellular membranes (*subcellular membranes), such as the endoplasmic reticulum, the inner* and outer membranes of each mitochondrion, and the two closely associated membranes that form the nuclear envelope. These membranes are exceedingly thin, measuring 6–8 nanometers (nm) from one side to the other. They play vitally essential roles nonetheless. They physically compartmentalize systems in functionally essential ways; the cell membrane, for instance, separates the inside of a cell from the cell's surroundings, permitting the inside to have different properties from the outside. In addition, far from being inert barriers, the membranes are dynamic systems that *participate in* cellular and subcellular functions.

The plasma Membrane is an ultra-thin,elastic,living,dynamic and selective transport barrier,that encloses the content of the entire cell.In both Prokaryotes and Eukaryotic cells,it physically separates the cytoplasm from the surrounding environment.The cells of bacteria and plants have the plasma membrane between the cell wall and the cytoplasm.Plasma membrane forms the cell surface foe cells without cell wall(e.g.,mycoplasma and animal cells). The term plasma membrane is also called cytoplasmic membrane,cell membrane,or plasmalemma.The term plasma membrane has been given by J.Q. Plowe in 1931.

An Overview of Membrane Functions:

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

Singer and Nicolson: A Membrane Consists of a Mosaic of Proteins in a Fluid Lipid Bilayer

- The preceding problems with the Davson–Danielli model stimulated considerable interest in the development of new ideas about membrane organization, culminating in 1972 with the **fluid mosaic model proposed by** S. Jonathan Singer and Garth Nicolson.
- This model, which now dominates our view of membrane organization, has two key features, both implied by its name.
- The model envisions a membrane as a mosaic of proteins embedded in, or at least attached to, a fluid lipid bilayer.
- This model retained the basic lipid bilayer structure of earlier models but viewed membrane proteins in an entirely different way—not as thin sheets on the membrane surface but as discrete globular entities within the lipid bilayer**.**
- Three classes of membrane proteins are now recognized based on differences in how the proteins are linked to the bilayer.
- Integral membrane proteins are embedded within the lipid bilayer, where they are held in place by the affinity of hydrophobic segments of the protein for the hydrophobic interior of the lipid bilayer.
- Peripheral proteins are much more hydrophilic and are therefore located on the surface of the membrane, where they are linked noncovalently to the polar head groups of phospholipids and/or to the hydrophilic parts of other membrane proteins.
- Lipid-anchored proteins are essentially hydrophilic proteins and therefore reside on membrane surfaces, but they are covalently attached to lipid molecules that are embedded within the bilayer.

- The fluid nature of the membrane is the second critical feature of the Singer–Nicolson model.
- Rather than being rigidly locked in place, most of the lipid components of a membrane are in constant motion, capable of lateral mobility (i.e., movement parallel to the membrane surface).
- Many membrane proteins are also able to move laterally within the membrane, although some proteins are anchored to structural elements such as the cytoskeleton on one side of the membrane or the other and are therefore restricted in their mobility.

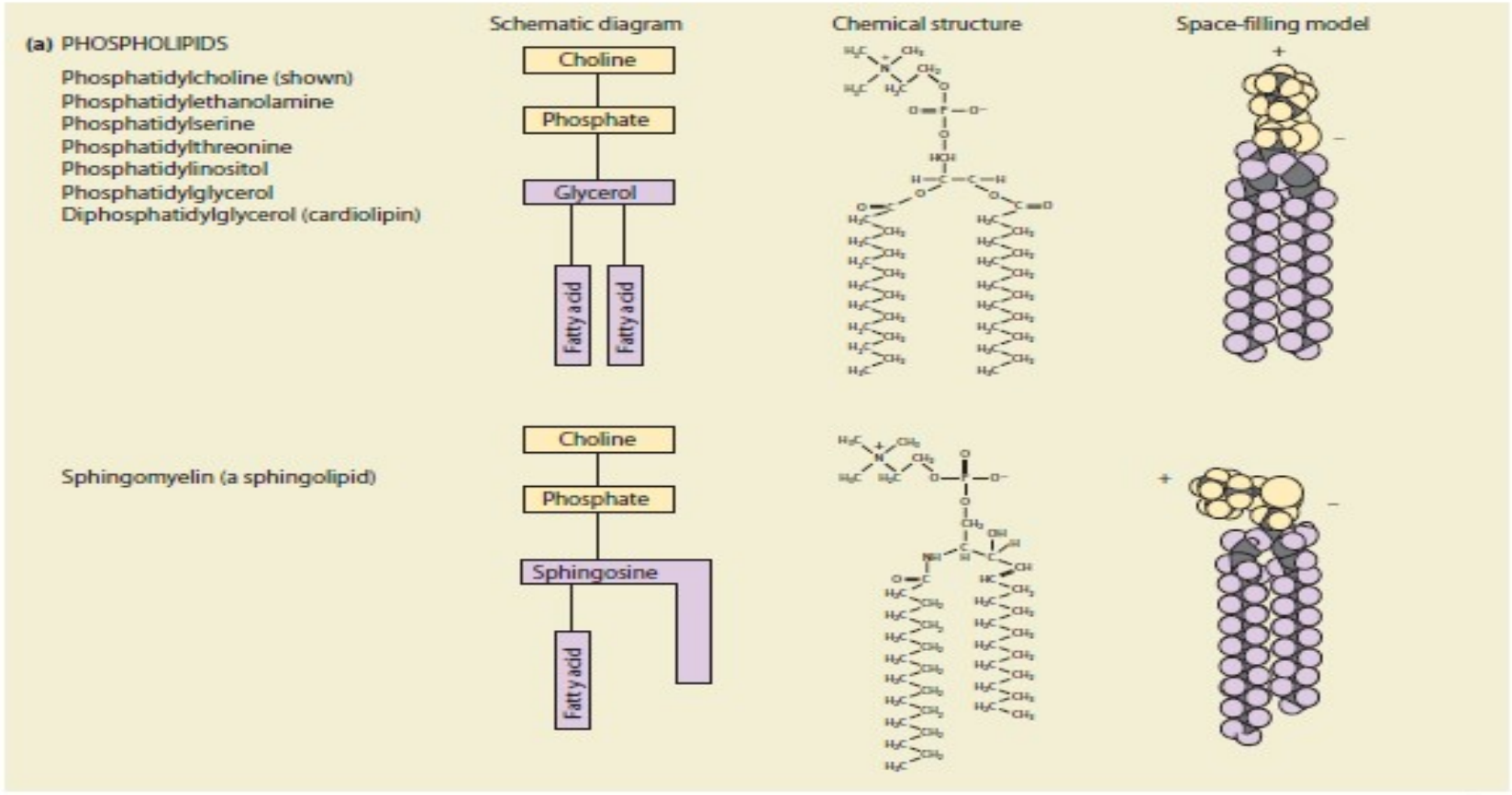
Membrane Lipids("The fluid Part" of the model)

The main classes of membrane lipids are phospholipids,glycolipids and sterols.

1.**Phospholipids**:The most abundant lipids found in membranes are the **phospholipids . Membranes contain many** different kinds of phospholipids, including both the glycerol-based **phosphoglycerides and the sphingosinebased sphingolipids. The most common phosphoglycerides** are phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. A common sphingolipid is sphingomyelin , which is one of the main phospholipids of animal plasma membranes but is absent from the plasma membranes of plants and most bacteria. The kinds and relative proportions of phospholipids present vary significantly among membranes from different sources.

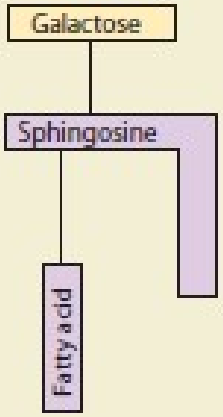
2. **Glycolipids. As their name indicates, glycolipids are** formed by adding carbohydrate groups to lipids. Some glycolipids are glycerol based, and others are derivatives of sphingosine and are therefore called glycosphingolipids. The most common examples are **cerebrosides and gangliosides. Cerebrosides are called neutral glycolipids** because each molecule has a single uncharged sugar as its head group—galactose, in the case of the galactocerebroside.A ganglioside, on the other hand, always has an oligosaccharide head group that contains one or more negatively charged sialic acid residues and gives the molecule a net negative charge. Cerebrosides and gangliosides are especially prominent in the membranes of brain and nerve cells.

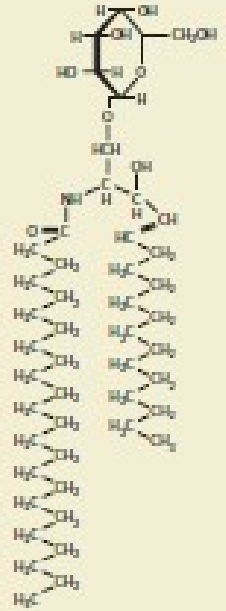
Sterols. Besides phospholipids and glycolipids, the membranes of most eukaryotic cells contain significant amounts of **sterols . The main sterol in animal** cell membranes is **cholesterol, which is necessary for** maintaining and stabilizing membranes in our bodies by acting as a fluidity buffer. Cholesterol 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.

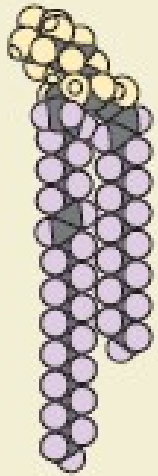


(b) GLYCOLIPIDS

Cerebrosides
(galactocerebroside shown)
Gangliosides

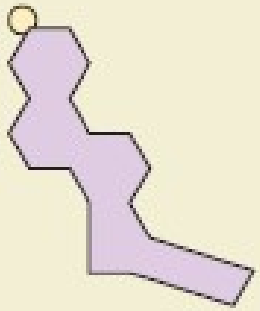


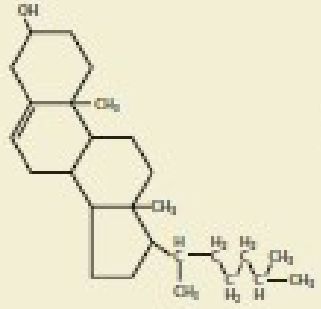


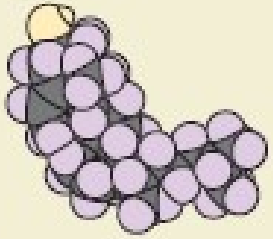


(c) STEROLS

Cholesterol (shown)
Campesterol
Sitosterol
Stigmasterol
} Phytosterols
Ergosterol
Hopanoids







Function of Membrane Lipids:

- Lipid composition can determine the physical state of the membrane and influence the activity of particular membrane proteins.
- Membrane lipids also provide the precursors for highly active chemical messengers that regulate cellular function.
- Membranes form extensive interconnected networks within the cell. Because of the flexibility of the lipid bilayer, membranes are deformable and their overall shape can change, as occurs during locomotion or cell division.
- *The lipid bilayer is* thought to facilitate the regulated fusion or budding of membranes.
- The importance of the lipid bilayer in maintaining the proper internal composition of a cell, in separating electric charges across the plasma membrane,forming recognition sites on cell surface and in many other cellular activities.
- Another important feature of the lipid bilayer is its ability to self-assemble.

Membrane asymmetry:Most Membrane lipids are distributed unequally between the two monolayers

- Chemical studies involving membranes derived from a variety of cell types have revealed that most lipids are unequally distributed between the two monolayers.
- This membrane asymmetry includes differences in both the kinds of lipids present and the degree of unsaturation of the fatty acids in the phospholipid molecules.
- For example, most of the glycolipids present in the plasma membrane of an animal cell are restricted to the outer monolayer. As a result, their carbohydrate groups protrude from the outer membrane surface, where they are involved in various signaling and recognition events.
- Phosphatidylethanolamine(PE), phosphatidylinositol, and phosphatidylserine(PS), on the other hand, are more prominent in the inner monolayer, where they are involved in transmitting various kinds of signals from the plasma membrane to the interior of the cell.
- The outer leaflet has a relatively high concentration of Phosphatidylcholine (and sphingomyelin) and a low concentration of PE and PS.
- Membrane asymmetry is established during membrane biogenesis by the insertion of different lipids, or different proportions of the various lipids, into each of the two monolayers. Once established, asymmetry tends to be maintained.

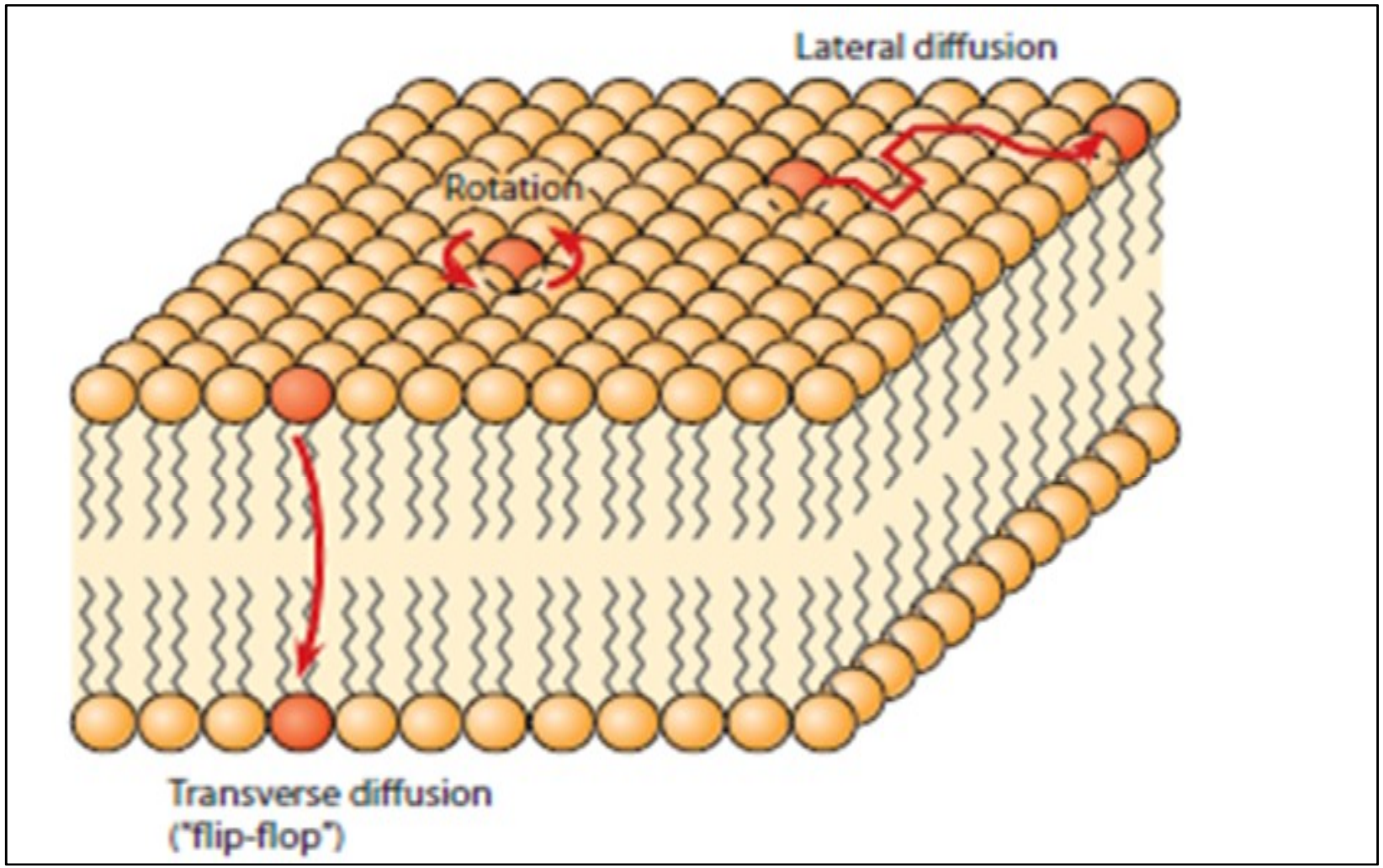
Movements of Phospholipid Molecules Within Membranes: phospholipid molecule is capable of three kinds of movement in a membrane:

Rotation about its long axis

Lateral diffusion by exchanging places with neighboring molecules in the same monolayer

Transverse diffusion or "flip-flop," from one monolayer to the other.

In a pure phospholipid bilayer at 37°C, a typical lipid molecule exchanges places with neighboring molecules about 10 million times per second and can move laterally at a rate of about several micrometers per second. By contrast, an individual phospholipid molecule flip-flops from one layer to the other at a rate ranging from less than once a week in a pure phospholipid bilayer to once every few hours in some natural membranes. The more rapid movement in natural membranes is due to the presence of enzymes called phospholipid translocators, or flippases, that catalyze the transverse diffusion of phospholipid molecules from one monolayer to the other.



Movements of Phospholipid Molecules Within Membranes.

Membrane Functions Properly only in fluid state:
The physical state of the lipid of a membrane is described by its fluidity (or viscosity). Consider a simple artificial bilayer composed of phosphatidylcholine and phosphatidylethanolamine, whose fatty acids are largely unsaturated.
If the temperature of the bilayer is kept relatively warm (e.g., 37C), the lipid exists in a relatively fluid state . At this temperature, the lipid bilayer is best described as a two-dimensional liquid crystal. As in a crystal, the molecules still retain a specified orientation; in this case, the long axes of the molecules tend toward a parallel arrangement, yet individual phospholipids can rotate around their axis or move laterally within the plane of the bilayer. If the temperature is slowly lowered, a point is reached where the bilayer distinctly changes . The lipid is converted from a liquid crystalline phase to a frozen 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.

Effects of Fatty Acid Composition on Membrane Fluidity.

- A membrane's fluidity depends primarily on the kinds of lipids it contains. Two properties of a membrane's lipid makeup are especially important in determining fluidity: the length of the fatty acid side chains and their degree of unsaturation.
- Long-chain fatty acids have higher transition temperatures than do short-chain fatty acids, which means that membranes enriched in long-chain fatty acids tend to be less fluid.
- Membranes containing many unsaturated fatty acids tend to have lower transition temperatures and thus are more fluid than membranes with many saturated fatty acids.
- Saturated fatty acids have the shape of a straight, flexible rod. Cis-unsaturated fatty acids, on the other hand, have crooks in the chain at the sites of a double bond . Consequently, phospholipids with saturated chains pack together more tightly than those containing unsaturated chains.
- The greater the degree of unsaturation of the fatty acids of the bilayer, the lower the temperature before the bilayer gels.

Importance of membrane fluidity:

- Membrane fluidity provides a perfect compromise between a rigid, ordered structure in which mobility would be absent and a completely fluid, nonviscous liquid in which the components of the membrane could not be oriented and structural organization and mechanical support would be lacking.
- In addition, fluidity allows for interactions to take place within the membrane.For example ,membrane fluidity makes it possible for clusters of membrane proteins to assemble at particular sites within the membrane and form specialized structures,such as intercellular junctions, light-capturing photosynthetic complexes, and synapses.
- Because of membrane fluidity, molecules that interact can come together, carry out the necessary reaction, and move apart.
- Fluidity also plays a key role in membrane assembly.
- Many of the most basic cellular processes, including cell movement, cell growth, cell division, formation of intercellular junctions, secretion, and endocytosis, depend on the movement of membrane components and would probably not be possible if membranes were rigid, nonfluid structures.

Effects of Sterols on Membrane Fluidity.

- For eukaryotic cells, membrane fluidity is also affected by the presence of sterols—mainly cholesterol in animal cell membranes and phytosterols in plant cell membranes.
- Sterols are prominent components in the membranes of many cell types. A typical animal cell, for example, contains large amounts of cholesterol—up to 50% of the total membrane lipid on a molar basis.
- Cholesterol molecules are usually found in both layers of the plasma membrane, but a given molecule is localized to one of the two layers. This intercalation of rigid cholesterol molecules into the membrane of an animal cell makes the membrane less fluid at higher temperatures than it would otherwise be.
- However, cholesterol also effectively prevents the hydrocarbon chains of phospholipids from fitting snugly together as the temperature is decreased, thereby reducing the tendency of membranes to gel upon cooling.
- Thus, cholesterol acts as a fluidity buffer: It has the moderating effect of decreasing membrane fluidity at temperatures above the Tm and increasing it at temperatures below theTm.

Lipid Rafts:

- Localized regions of membrane lipids that sequester proteins involved in cell signaling are called either lipid microdomains or, more popularly, **lipid rafts**—and represent areas of lateral heterogeneity within a membrane monolayer.
- Lipid rafts are dynamic structures that change in composition as individual lipids and proteins move in and out of them.
- Lipid rafts in the outer membrane monolayer of animal cells are characterized by elevated levels of cholesterol and glycosphingolipids.
- The glycosphingolipids have longer and more saturated fatty acid tails than those seen in most other membrane lipids.
- The phospholipids present in lipid rafts are more highly saturated than those in the surrounding membrane.
- These properties, plus the rigidity and hydrophobic nature of cholesterol, allow tight packing of the cholesterol and the hydrocarbon tails of the glycosphingolipids and the phospholipids.
- As a result, lipid rafts are thicker and less fluid than the rest of the membrane, thereby distinguishing them as discrete lipid microdomains.
- These regions are less able to be solubilized by nonionic detergents.
- Lipid rafts are thicker and less fluid than the rest of the membrane, thereby distinguishing them as discrete lipid microdomains.These play important role in the detection of, and responses to, extracellular chemical signals. For example, lipid rafts are involved in the transport of nutrients and ions across cell membranes,the binding of activated immune system cells to their microbial targets etc.

Membrane Proteins(“The Mosaic part of the model”)

Membrane proteins differ in their affinity for the hydrophobic interior of the membrane and therefore in the extent to which they interact with the lipid bilayer. That difference in affinity, in turn, determines how easy or difficult it is to extract a given protein from the membrane. Based on the conditions required to extract them—and thus, by extension, on the nature of their association with the lipid bilayer—membrane proteins fall into one of three categories: integral, peripheral, or lipid-anchored.

Membranes Contain Integral,Peripheral and Lipid-Anchored Proteins:

1)Integral Membrane Proteins:

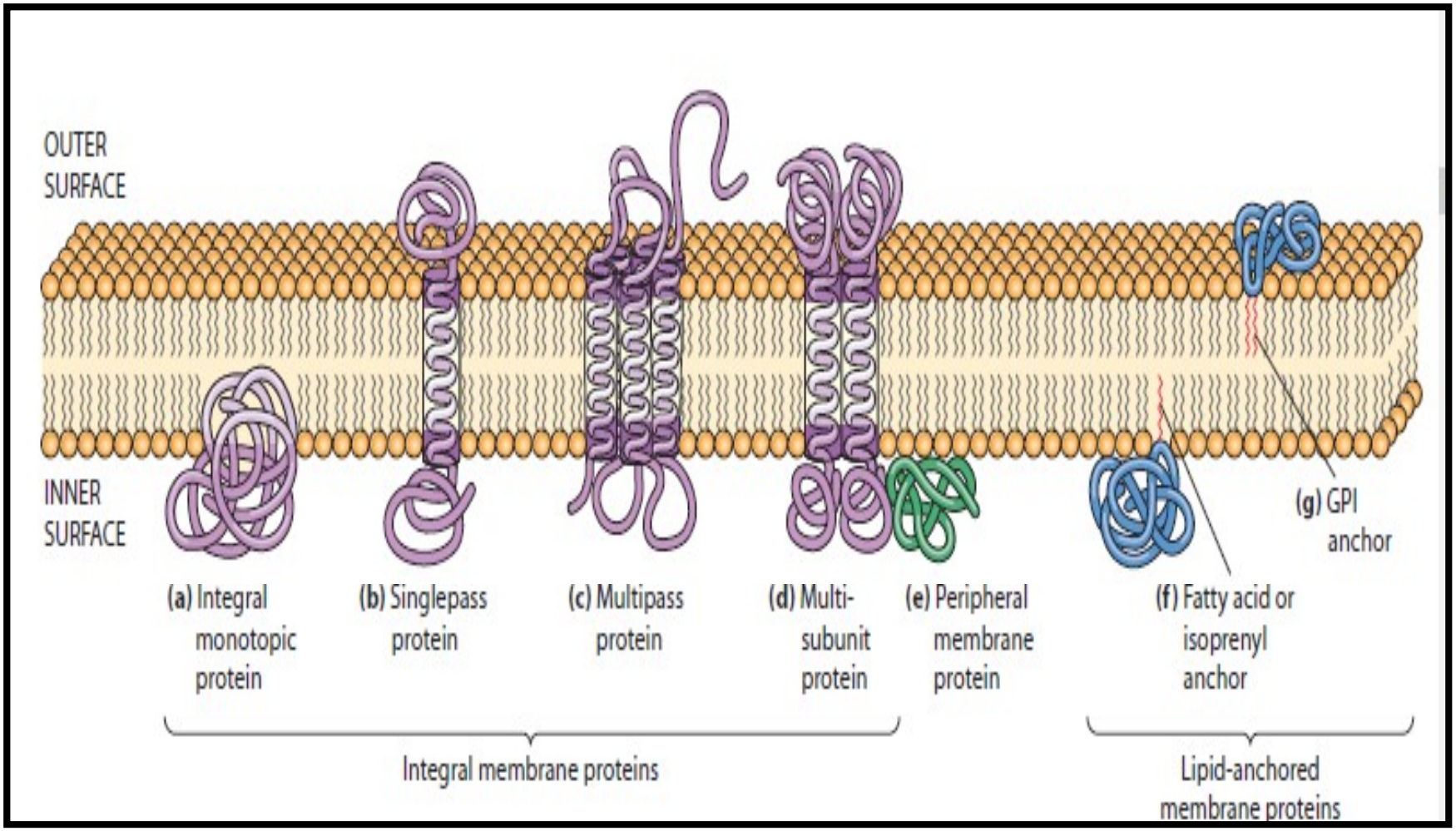
Most membrane proteins are amphipathic molecules possessing one or more hydrophobic regions that exhibit an affinity for the hydrophobic interior of the lipid bilayer. These proteinsare called **integral membrane proteins because their** hydrophobic regions are embedded within the membrane interior in a way that makes these molecules difficult to remove from membranes. However, such proteins also have one or more hydrophilic regions that extend outward from the membrane into the aqueous phase on one or both sides of the membrane. Because of their affinity for the lipid bilayer, integral membrane proteins are difficult to isolate and study by standard protein purification techniques, most of which are designed for water-soluble proteins. Treatment with a detergent that disrupts the lipid bilayer is usually necessary to solubilize and extract integral membrane proteins.

A few integral membrane proteins are known to be embedded in, and therefore to protrude from, only one side of the bilayer. These are called **integral monotopic proteins . However, most integral membrane** proteins are **transmembrane proteins, which means** that they span the membrane and have hydrophilic regions protruding from the membrane on both sides. Such proteins cross the membrane either once (singlepass proteins) or several times (multipass proteins).

Example of integral Membrane protein:Glycophorin,Bacteriorhodopsin

Peripheral Membrane Proteins. In contrast to integral membrane proteins, some membrane-associated proteins lack discrete hydrophobic sequences and therefore do not penetrate into the lipid bilayer. Instead, these **peripheral membrane proteins are bound to membrane surfaces** through weak electrostatic forces and hydrogen bonding with the hydrophilic portions of integral proteins and perhaps with the polar head groups of membrane lipids. Peripheral proteins are more readily removed from membranes than integral proteins and can usually be extracted by changing the pH or ionic strength.
Examples:spectrin, ankyrin of erythrocytic plasma membrane.

Lipid-Anchored Membrane. The polypeptide chains of these **lipid-anchored membrane proteins are located on one of the surfaces of the lipid** bilayer but are covalently bound to lipid molecules embedded within the bilayer.Proteins bound to the inner surface of the plasma membrane are attached by covalent linkage either to a fatty acid or to an isoprene derivative called an isoprenyl group.Many lipid-anchored proteins attached to the external surface of the plasma membrane are covalently linked to glycosylphosphatidylinositol (GPI), a glycolipid found in the outer monolayer of the plasma membrane .
Example:GPI anchored membrane proteins.



Three main classes of membrane proteins

Membrane Carbohydrates

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.In **glycoproteins—membrane proteins with carbohydrate** chains covalently linked to amino acid side chains. The addition of a carbohydrate side chain to a protein is called **glycosylation. This process occurs in the ER and** Golgi compartments of the cell soon after synthesis.Glycosylation involves linkage of the carbohydrate either to the nitrogen atom of an amino group (N-linked glycosylation) or to the oxygen atom of a hydroxyl group (O-linked glycosylation). The most common sugars used in constructing these chains are galactose, mannose,N-acetylglucosamine, and sialic acid. Carbohydrates in plasma membranes which faces outward into the extracellular space play an important role in cell-cell recognition. In many animal cells, the carbohydrate groups of plasma membrane glycoproteins and glycolipids protrude from the cell surface and form a surface coat called the **glycocalyx (meaning "sugar coat").**

Experimental Evidence for Protein Mobility.

Particularly convincing evidence for the mobility of at least some membrane proteins has come from cell fusion experiment.

In these studies**,**David Frye and Michael Edidin took advantage of two powerful techniques, one that enabled them to fuse cells from two different species and another that made it possible for them to label specific proteins on the surfaces of cells with antibodies containing fluorescent dye molecules.

Antibodies are immune system proteins that recognize and bind to specific molecular antigens such as cell surface proteins.

Frye and Edidin prepared two **fluorescent antibodies,** each one having a differently-colored dye linked to it, so that the human and mouse proteins could be distinguished. The anti-mouse antibodies were linked to a green fluorescent dye called fluorescein, whereas the anti-human antibodies were linked to a red fluorescent dye, rhodamine. Thus, under a fluorescence microscope, the mouse cells appeared green and the human cells appeared red due to each antibody recognizing and binding to its specific protein antigens on the surface of the cells (Figure 7-28).

Frye and Edidin fused mouse and human cells using Sendai virus, exposed them to the red and green fluorescent antibodies, and observed the fused cells by fluorescence microscopy. At first, the green fluorescent membrane proteins from the mouse cell were localized on one-half of the hybrid cell surface, and the red fluorescent membrane proteins derived from the human cell were restricted to the other half. In a few minutes, however, the proteins from the two parent cells began to intermix.

After 40 minutes, the separate regions of green and red fluorescence were completely intermingled.

If the fluidity of the membrane was depressed by lowering the temperature below the transition temperature of the lipid bilayer, this intermixing could be prevented. Frye and Edidin therefore concluded that the intermingling of the fluorescent proteins had been caused by lateral diffusion of the human and mouse proteins through the fluid lipid bilayer of the plasma membrane.

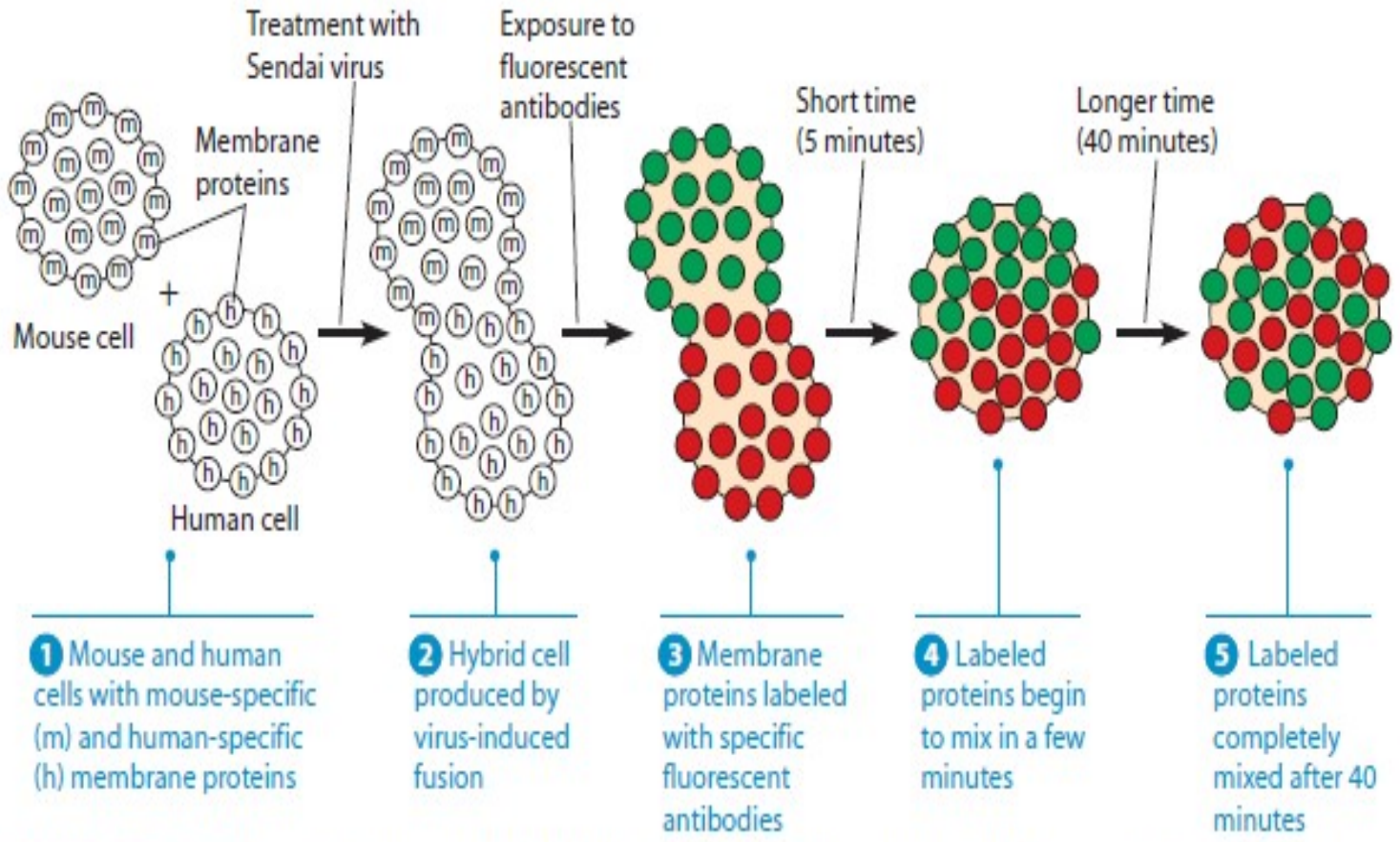


FIGURE 7-28 Demonstration of the Mobility of Membrane Proteins by Cell Fusion. The mobility of membrane proteins can be shown experimentally by the mixing of membrane proteins that occurs when cells from two different species (mouse and human) are fused and the membrane proteins are labeled with specific fluorescent antibodies.

Membrane Transport:
A central aspect of cell function, then, is **transport—**the ability to move ions and organic molecules across membranes selectively. **Solutes Cross Membranes by Simple Diffusion , Facilitated Diffusion and Active Transport.**

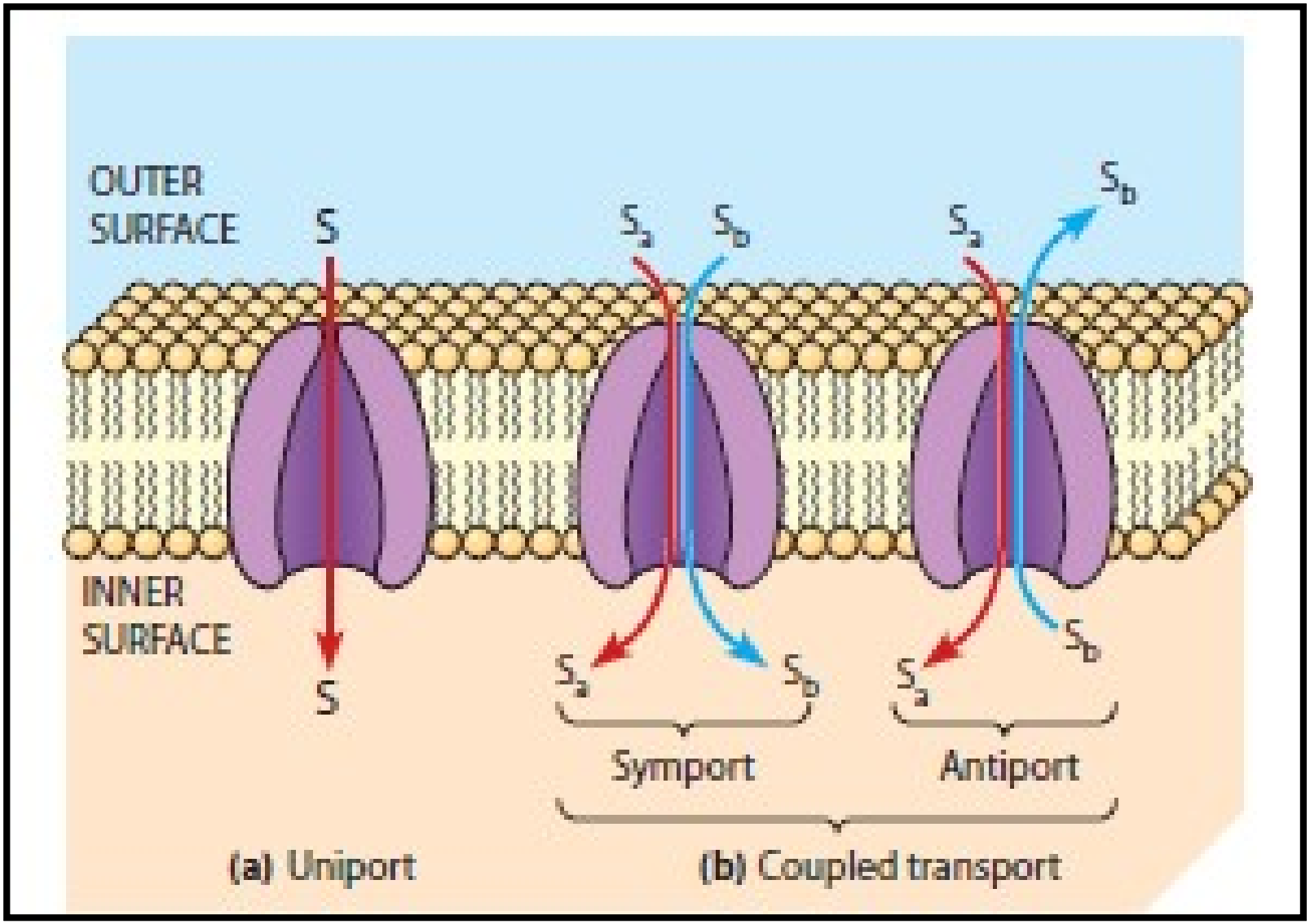
1)Simple Diffusion:Simple diffusion is the direct, unaided movement of solute molecules into and through the lipid bilayer in the direction dictated by the difference in the concentrations of the solute on the two sides of the membrane. It involves exergonic movement "down" the concentration gradient . Because membranes have a hydrophobic interior, simple diffusion is typically a means of transport only for gases,nonpolar molecules , or small polar molecules such as water, glycerol, or ethanol.

2) Facilitated Diffusion: Most substances in cells are too large or too polar to cross membranes at reasonable rates by simple diffusion, even if the process is exergonic. Such solutes can move into and out of cells and organelles at appreciable rates only with the assistance of **transport proteins that mediate the movement** of solute molecules across the membrane. As an example of facilitated diffusion, consider the movement of glucose across the plasma membrane of a cell in your body. The concentration of glucose is typically higher in the blood than in the cell, so the inward transport of glucose is exergonic—that is, it does not require the input of energy. However, glucose is too large and too polar to diffuse across the membrane unaided. A transport protein is required to facilitate its inward movement.

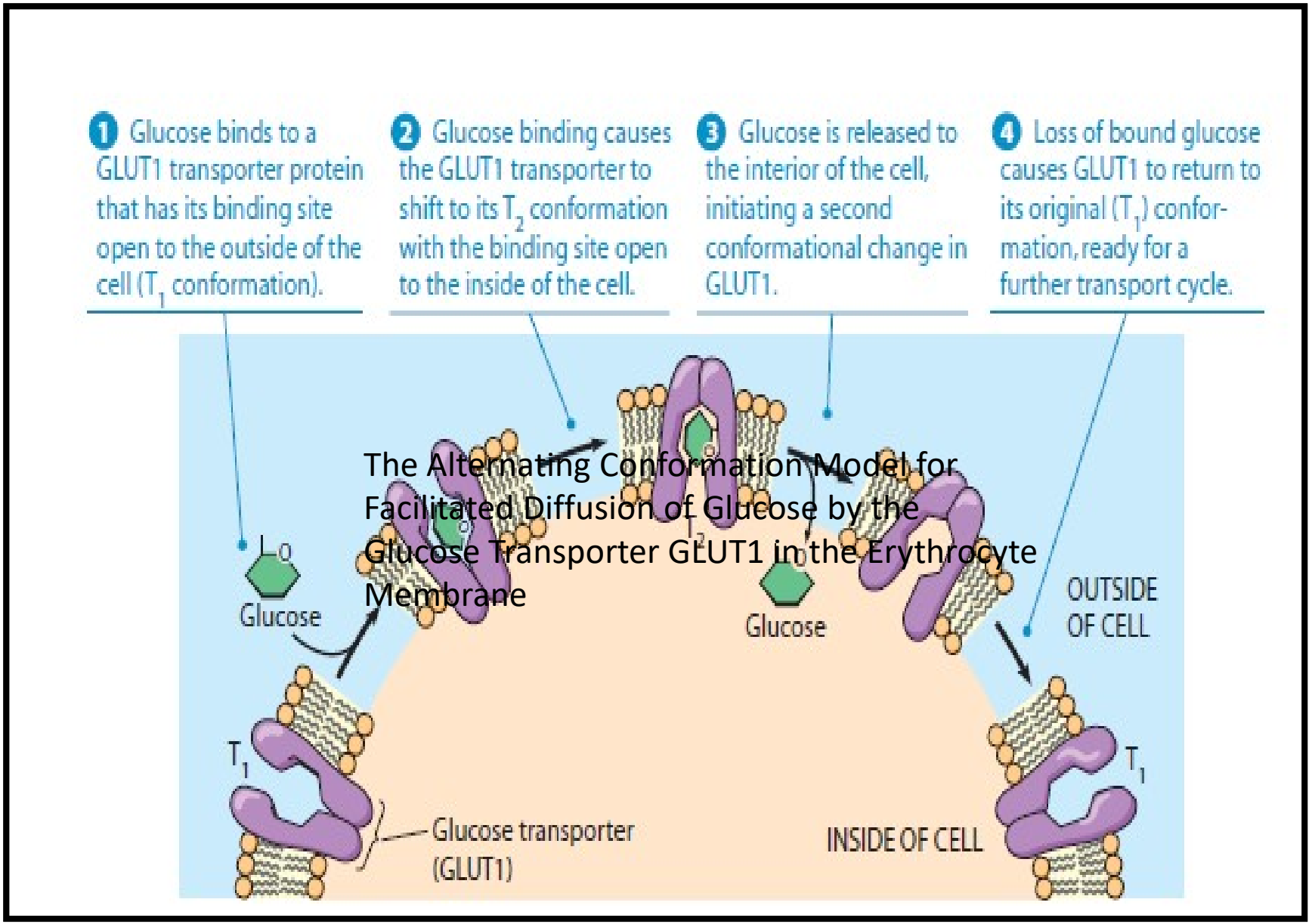
Transport proteins involved in facilitated diffusion of small molecules and ions are integral membrane proteins of two classes:

Carrier proteins (also called transporters or permeases) :

- These proteins bind one or more solute molecules on one side of the membrane and then undergo a conformational change that transfers the solute to the other side of the membrane.
- Carrier Proteins Are Analogous to Enzymes in Their Specificity and Kinetics**.**
- Although carrier proteins are similar in their kinetics and their presumed mechanism of action involving alternate conformations, but they may differ in the number of solutes transported and the direction they move.
- When a carrier protein transports a single solute across the membrane, the process is called **uniport. The glucose** carrier protein GLUT1 in erythrocyte is a uniporter.
- When two solutes are transported simultaneously and their transport is coupled such that transport of either stops if the other is absent, the process is called **coupled transport**.
- Coupled transport is referred to as **symport** (or cotransport) if the two solutes are moved in the same direction or as **antiport (or countertransport) if the two** solutes are moved in opposite directions across the membrane.
- The transport proteins that mediate these processes are called symporters and antiporters, respectively.
- Example of antiporter:**anion exchange protein of the erythrocyte**
- Example of symporter: **Sodium Dependent Glucose Transporters**



Comparison of Uniport, Symport, and Antiport Transport by Carrier Proteins



The Alternating Conformation Model for Facilitated Diffusion of Glucose by the Glucose Transporter GLUT1 in the Erythrocyte Membrane

Channel proteins,:

- These proteins form hydrophilic channels through the membrane that allow the passage of solutes without a major change in the conformation of the protein.
- Some of these channels are relatively large and nonspecific,such as the porins found in the outer membranes of bacteria, mitochondria, and chloroplasts. However, most channels are small and highly selective.
- Most of these smaller channels are involved in the transport of ions rather than molecules and are therefore referred to as ion channels.
- The movement of solutes through ion channels is much more rapid than transport by carrier proteins.
- Most ion channels are highly selective in allowing only one particular type of ion to pass through the pore.
- Most of the ion channels that have been identified can exist in either

an open or a closed conformation; such channels are said to be **gated.**

- The opening and closing of the gates are subject to complex physiologic regulation and can be induced by a variety of factors depending on the particular channel.
- Three major categories of gated channels are distinguished:

1. **Voltage-gated channels whose conformational state depends** on the difference in ionic charge on the two sides of the membrane.Ex-voltage gated Na^+ channels.

2. **Ligand-gated channels** whose conformational state depends on the binding of a specific molecule (the ligand), which is usually not the solute that passes through the channel.Some ligand-gated channels are opened (or closed) following the binding of a molecule to the outer surface of the channel. For example, neurotransmitters, such as acetylcholine, act on the outer surface of certain cation channels.
3. **Mechano-gated channels whose conformational state** depends on mechanical forces (e.g., stretch tension) that are applied to the membrane. Members of one family of cation channels, for example, are opened by the movements of stereocilia on the hair cells of the inner ear in response to sound or motions of the head.

Active Transport: Protein-Mediated Movement Up the Gradient: Active transport makes it possible to move solutes away from thermodynamic equilibrium (that is, up a concentration gradient or against an electrochemical potential). Therefore, it always requires an input of energy. In other words, active transport couples a thermodynamically unfavorable process (movement up a concentration gradient) to an exergonic process (usually ATP hydrolysis). As a result, membrane proteins involved in active transport must provide mechanisms not only for moving desired solute molecules across the membrane but also for coupling such movements to energy-yielding reactions. In contrast to simple or facilitated diffusion, which create conditions that are the same on opposite sides of a membrane, active transport is a means of establishing differences in solute concentration and/or electrical potential across membranes. Active transport, on the other hand, usually has intrinsic **directionality. An active transport system** that moves a solute across a membrane in one direction will not usually move that solute in the other direction. Active transport is therefore said to be a unidirectional process.

Active transport mechanisms can be divided into two related categories that differ primarily in the source of energy and whether or not two solutes are transported simultaneously. Depending on the energy source, active transport is regarded as being either direct or indirect**.**

In direct active transport (also called primary active transport), the accumulation of solute molecules or ions on one side of the membrane is coupled directly to an exergonic chemical reaction, most commonly the hydrolysis of ATP . Transport proteins driven directly by ATP hydrolysis are called transport ATPases or ATPase pumps. Ex- Na^+ -k^+ ATPase, or / pump, uses the exergonic hydrolysis of ATP to drive the endergonic inward transport of potassium ions and the outward transport of sodium ions against their concentration gradients. The Na^+ -k^+ pump is primarily responsible for the asymmetric distribution of ions across the plasma membrane in animal cells.

Indirect active transport also requires energy but depends on the simultaneous transport of two solutes, with the favorable movement of one solute down its gradient driving the unfavorable movement of the other solute up its gradient. The coupling of a favorable process or reaction with an unfavorable one allows both to proceed with an overall decrease in free energy. In most cases, one of the two solutes is an ion that moves exergonically down its electrochemical gradient— in animals and in most other organisms. As it moves, it drives the simultaneous endergonic transport of the second solute (often a monosaccharide or an amino acid) against its concentration gradient or, in the case of ions, its electrochemical potential . Thus indirect active transport is often called secondary active transport. In animals the relatively high extracellular concentration of sodium ions maintained by the Na^+ -k^+ pump serves as the driving force for the uptake of a variety of sugars and amino acids.

Table 8-2 Main Types of Transport ATPases (Pumps)

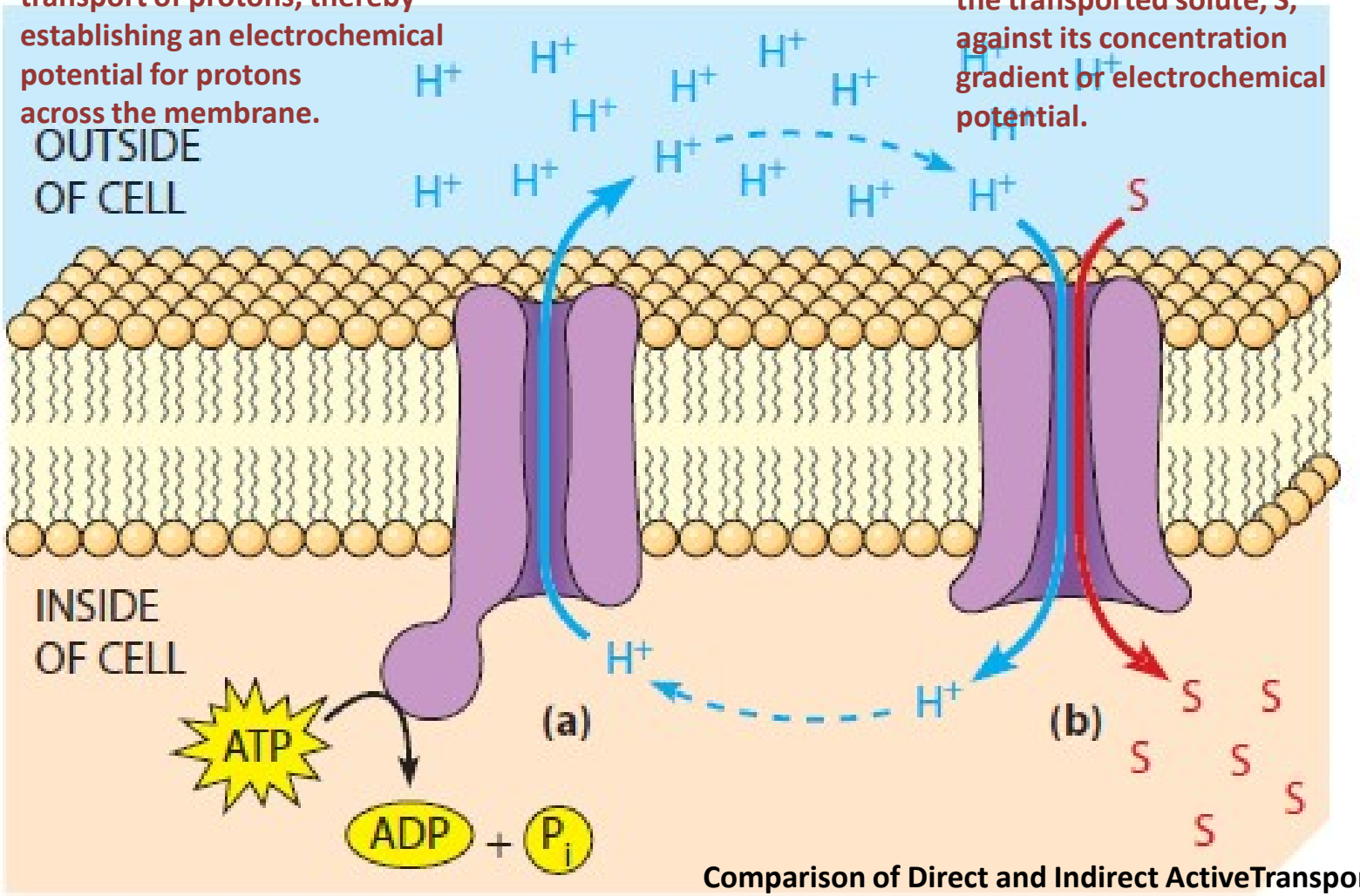
Solutes Transported	Kind of Membrane	Kind of Organisms	Example of ATPase function
P-type ATPases (P for "phosphorylation")			
P_1			
K^+, Cu^+, Zn^{2+}, Cd^{2+}, Pb^{2+}	Plasma membrane	Bacteria, archaea, plants, fungi, animals	Transport of potassium or heavy metal ions
P_2			
Ca^{2+}/H^+	SR* or plasma membrane	Eukaryotes	Keeps $[Ca^{2+}]$ low in cytosol
Na^+/K^+	Plasma membrane	Animals	Maintains membrane potential (−60 mV)
H^+/K^+	Plasma membrane	Animals	Pumps H^+ to acidify stomach
P_3			
H^+	Plasma membrane	Plants, fungi	Pumps protons out of cell to generate membrane potential (−180 mV)
P_4			
Phospholipids	Plasma membrane	Eukaryotes	Flippases that maintain asymmetry in the lipid bilayer
P_5			
Various cations	ER, vacuole, lysosome	Eukaryotes	Not well characterized
V-type ATPases (V for "vacuole")			
H^+	Lysosomes, secretory vesicles	Animals	Keeps pH of compartment low, which activates hydrolytic enzymes
	Vacuolar membrane	Plants, fungi	
F-type ATPases (F for "factor"); also called ATP synthases			
H^+	Inner mitochondrial membrane	Eukaryotes	Uses H^+ gradient to drive ATP synthesis
	Plasma membrane	Bacteria	
	Thylakoid membrane	Plants	
ABC-type ATPases (ABC for "ATP-binding cassette")			
Importers A variety of solutes**	Plasma membrane, organellar membranes	Bacteria	Nutrients such as vitamin B_{12}
Exporters Antitumor drugs, toxins, antibiotics, lipids	Plasma membrane	Bacteria, archaea, eukaryotes	Multidrug resistance transporter removes drugs and antibiotics from cell

*Sarcoplasmic reticulum, a specialized type of ER found in animal muscle cells

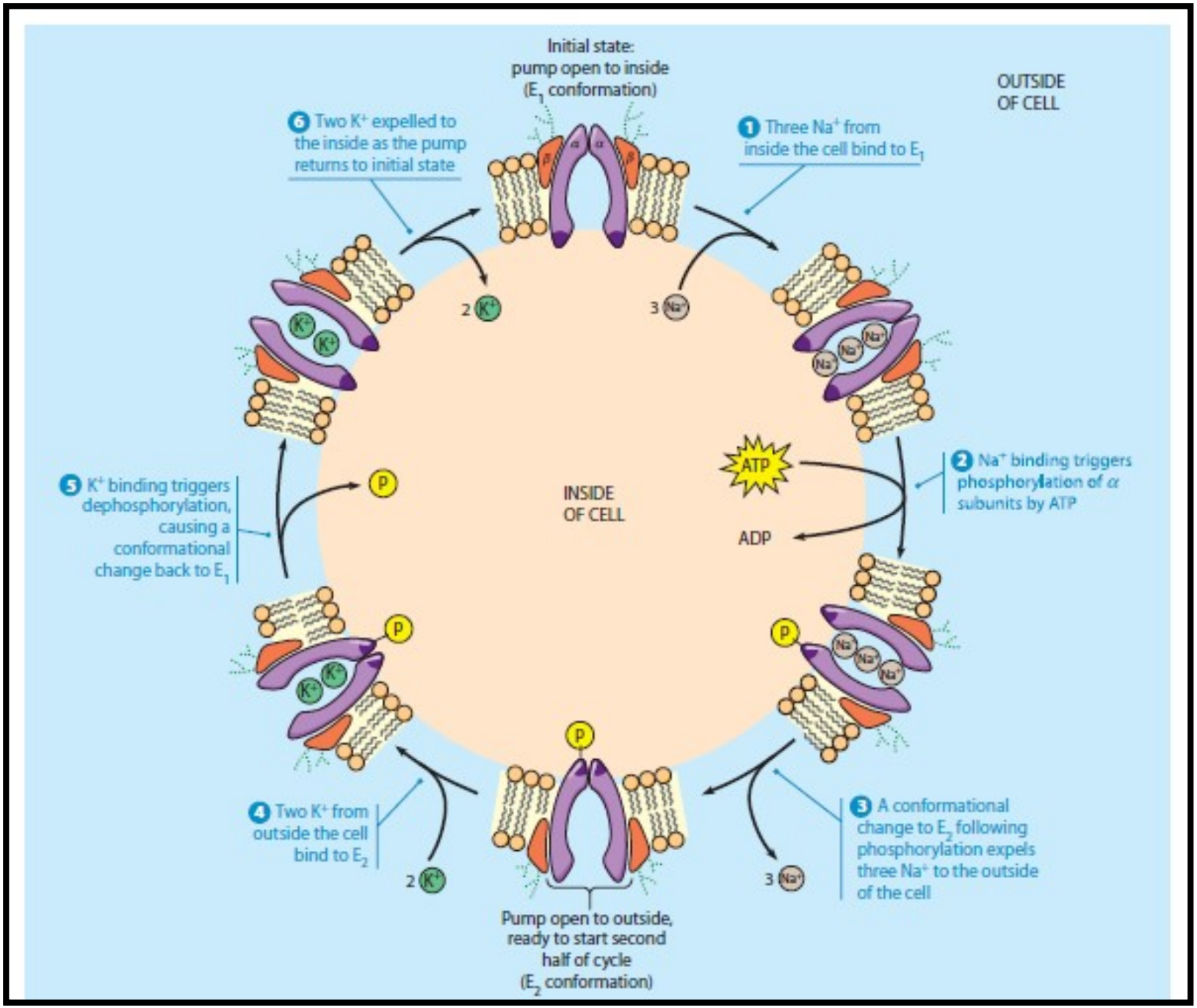
**Solutes include ions, sugars, amino acids, carbohydrates, vitamins, peptides, and proteins.

(a) Direct active transport involves a transport system coupled to an exergonic chemical reaction, most commonly the hydrolysis of ATP. As shown here, ATP hydrolysis drives the outward transport of protons, thereby establishing an electrochemical potential for protons across the membrane.

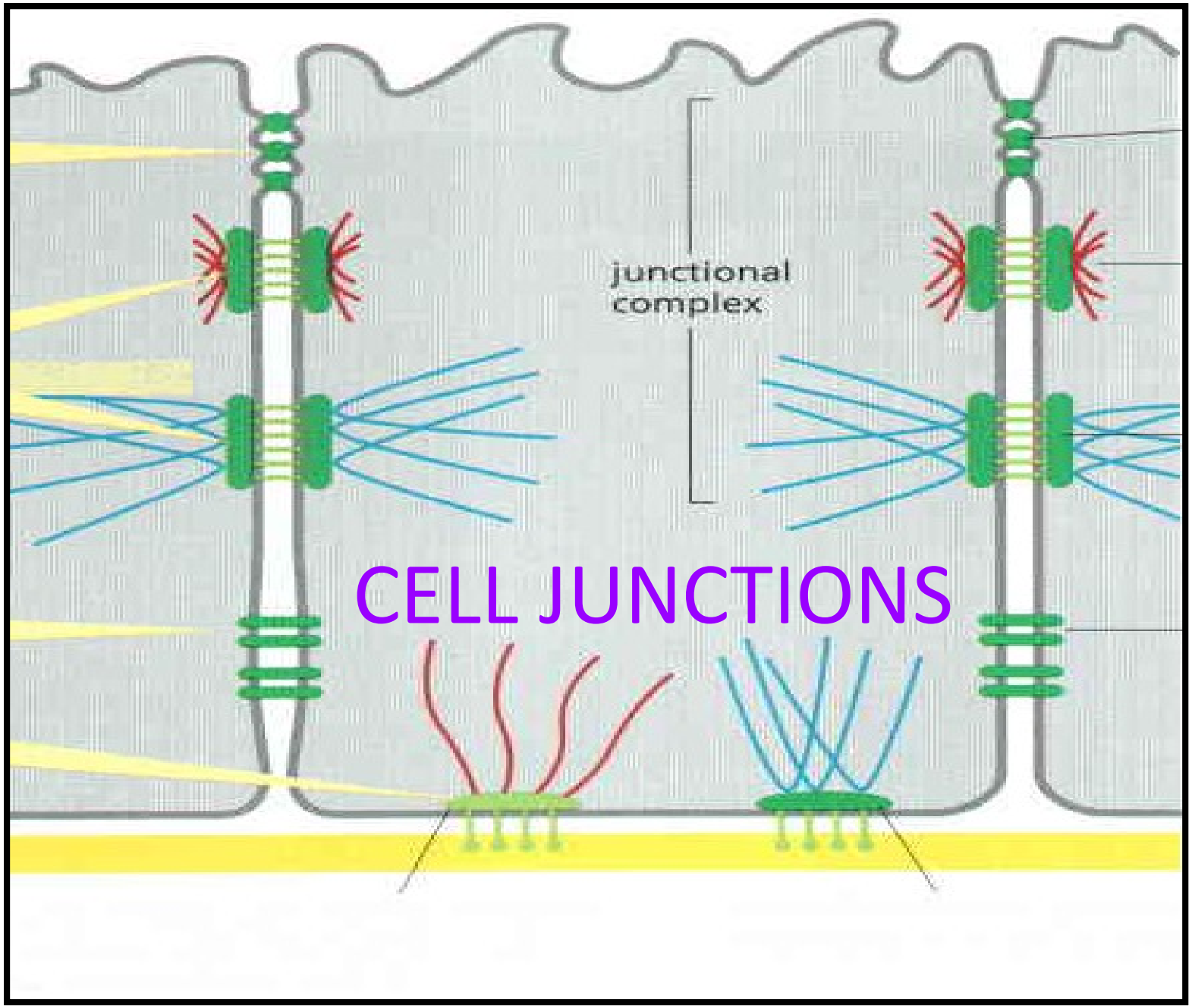
b)Indirect active transport involves the coupled transport of a solute S and ions—protons, in this case. The exergonic inward movement of protons provides the energy to move the transported solute, S, against its concentration gradient or electrochemical potential.



Comparison of Direct and Indirect ActiveTransport



Mechanism of function of Na^+ -K+ Pump



CELL JUNCTIONS

Physical attachment is critical, both in epithelia and in nonepithelial tissues, but junctions between cell and cell or between cells and matrix are diverse in structure and do more than just transmit physical forces. Four main functions can be distinguished, each with a different molecular basis ([redacted] and Table 19–1):

1. **Anchoring junctions**, including both *cell–cell adhesions* and *cell–matrix adhesions*, transmit stresses and are tethered to cytoskeletal filaments inside the cell.
2. **Occluding junctions** seal the gaps between cells in epithelia so as to make the cell sheet into an impermeable (or selectively permeable) barrier.
3. **Channel-forming junctions** create passageways linking the cytoplasms of adjacent cells.
4. **Signal-relaying junctions** allow signals to be relayed from cell to cell across their plasma membranes at sites of cell-to-cell contact.

Table 19–1 A Functional Classification of Cell Junctions

ANCHORING JUNCTIONS
Actin filament attachment sites
1. cell–cell junctions (adherens junctions)
2. cell–matrix junctions (actin-linked cell–matrix adhesions)
Intermediate filament attachment sites
1. cell–cell junctions (desmosomes)
2. cell–matrix junctions (hemidesmosomes)
OCCLUDING JUNCTIONS
1. tight junctions (in vertebrates)
2. septate junctions (in invertebrates)
CHANNEL-FORMING JUNCTIONS
1. gap junctions (in animals)
2. plasmodesmata (in plants)
SIGNAL-RELAYING JUNCTIONS
1. chemical synapses (in the nervous system)
2. immunological synapses (in the immune system)
3. transmembrane ligand–receptor cell–cell signaling contacts (Delta-Notch, ephrin-Eph, etc.). Anchoring, occluding, and channel-forming junctions can all have signaling functions in addition to their structural roles

Cell-cell junctions

By definition, unicellular organisms have no permanent associations between cells (although they can form temporary associations, such as during bacterial swarming or the aggregation of slime mold amoebae). Whereas a single cell is an entity unto itself, multicellular organisms have specific means of joining cells in long-term associations to form tissues and organs. Such associations usually involve specialized modifications of the plasma membrane at the point where two cells come together. These specialized structures are called **cell-cell junctions.** In animals, the three most common kinds of cell junctions are adhesive junctions, tight junctions, and gap junctions.

Table 17-1 Junctions Between Animal Cells

Type of Junction	Main Function	Intermembrane Features	Space	Associated Structures
Adhesive junctions				
Focal adhesion	Cell-ECM adhesion	Localized points of attachment	20–25 nm	Actin microfilaments
Hemidesmosome	Cell–basal lamina adhesion	Localized points of attachment	25–35 nm	Intermediate filaments (tonofilaments)
Adherens junction	Cell-cell adhesion	Continuous zones of attachment	20–25 nm	Actin microfilaments
Desmosome	Cell-cell adhesion	Localized points of attachment	25–35 nm	Intermediate filaments (tonofilaments)
Tight junction	Sealing spaces between cells	Membranes joined along ridges	None	Transmembrane junctional proteins, actin
Gap junction	Exchange of ions and molecules between cells	Connexons (transmembrane protein complexes with 3-nm pores)	2–3 nm	Connexins in one membrane align with those in another to form channels between cells

Desmosomes.

- **Desmosomes are button-like points of** strong adhesion between adjacent cells in a tissue giving the tissue structural integrity, enabling cells to function as a unit and to resist stress.
- Desmosomes are found in many tissues but are especially abundant in skin, heart muscle, and the neck of the uterus.
- In these types of junctions,the plasma membranes of the two adjacent cells are aligned in parallel, separated by a space of about 25–35 nm. The extracellular space between the two membranes is called the desmosome core.
- The desmosome core consists of the desmosomal cadherins, desmocollin and desmoglein. Unlike E-cadherin, desmocollins and desmogleins probably interact heterophilically across the intercellular space. Like other cadherins, linker proteins bind to their cytosolic tail and link them to the cytoskeleton.
- The β-catenin family protein plakoglobin binds to desmocollin. Plakoglobin in turn binds to a protein called desmoplakin. Desmoplakin in turn attaches to tonofilaments, which are composed of intermediate filaments such as vimentin, desmin, or keratin.

- A thick plaque containing these linker proteins and tonofilaments is found just beneath the plasma membrane of each of the two adjoining cells.
- Loss of desmosomal components can be devastating. For example, mice lacking plakoglobin die with heart failure and skin defects.
- Similarly, mutations in desmocollins expressed in the heart can lead to damage to the heart muscle in adult human patients.
- Human patients who develop autoimmune reactions against components of their desmosomes develop blistering diseases of the skin known as pemphigus.

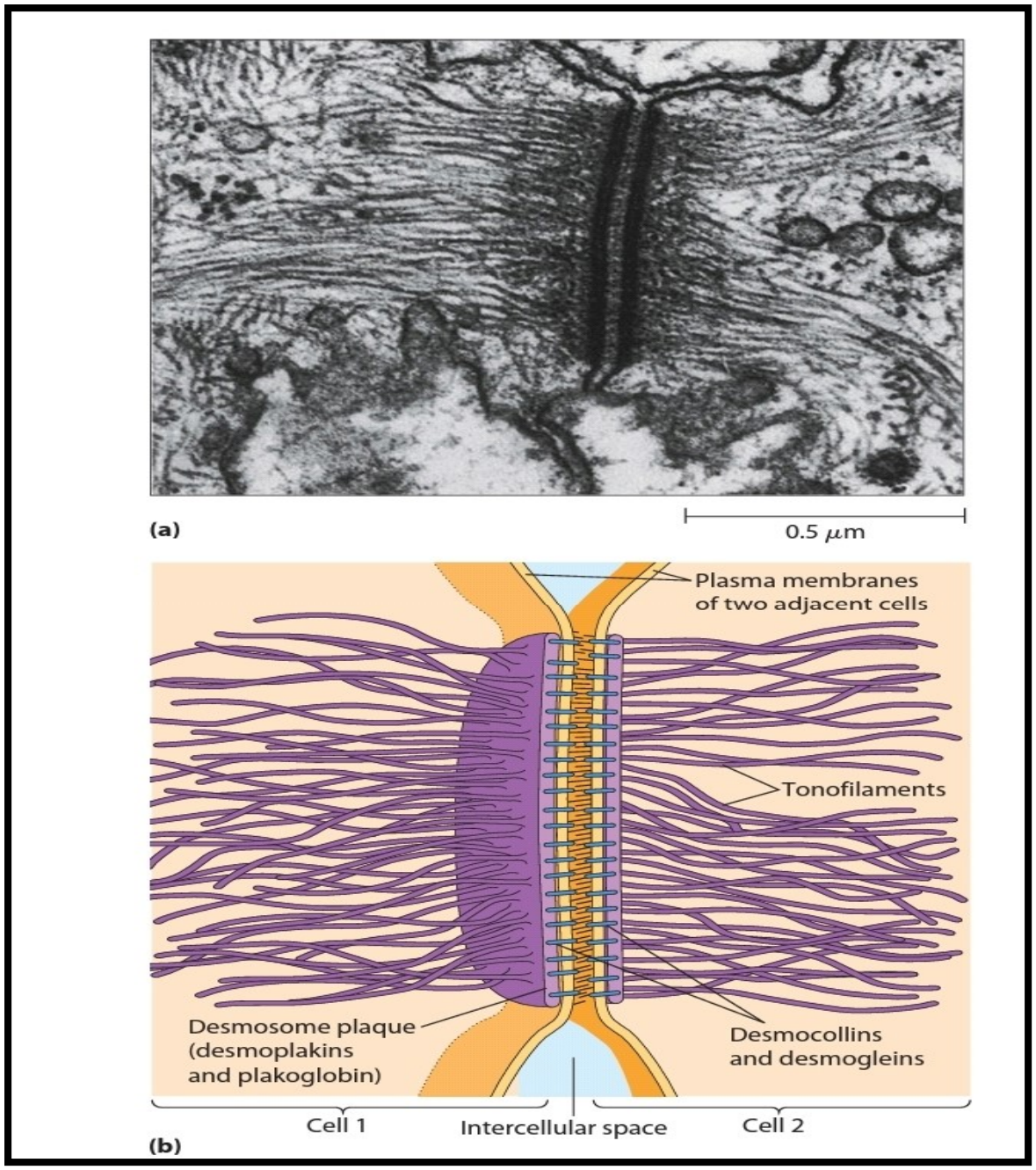


Fig:Desmosome Structure. **(a) An electron** micrograph of a desmosome joining two cells in the skin of a newt (TEM). **(b) A schematic diagram of a desmosome**.

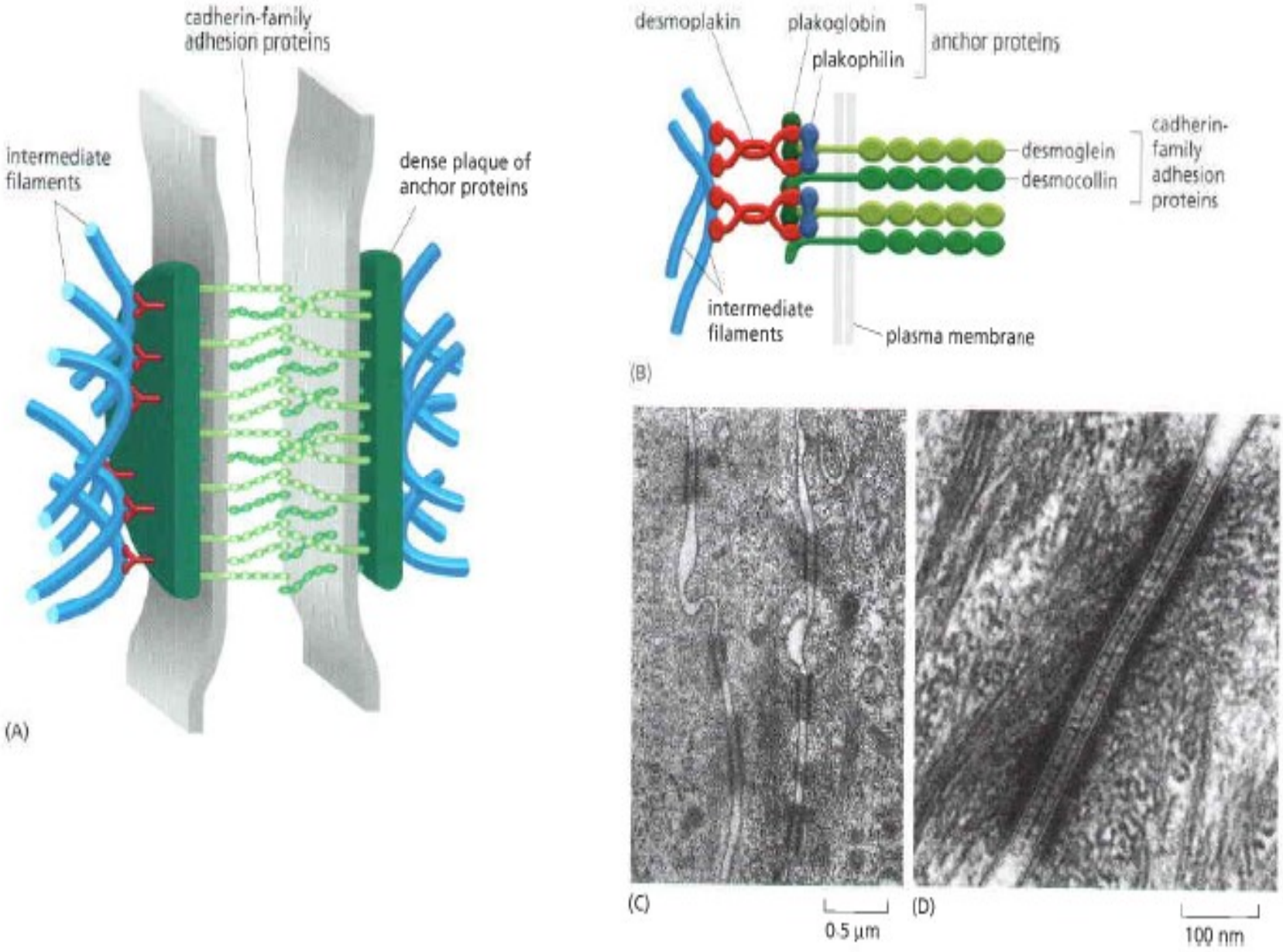

cadherin-family adhesion proteins
intermediate filaments
dense plaque of anchor proteins
(A)
desmoplakin
plakoglobin
plakophilin
anchor proteins
desmoglein
desmocollin
cadherin-family adhesion proteins
intermediate filaments
plasma membrane
(B)
(C)
0.5 µm
(D)
100 nm

Figure [redacted] **Desmosomes.** (A) The structural components of a desmosome. On the cytoplasmic surface of each interacting plasma membrane is a dense plaque composed of a mixture of intracellular anchor proteins. A bundle of keratin intermediate filaments is attached to the surface of each plaque. Transmembrane adhesion proteins of the cadherin family bind to the plaques and interact through their extracellular domains to hold the adjacent membranes together by a Ca^{2+}-dependent mechanism. (B) Some of the molecular components of a desmosome. Desmoglein and desmocollin are members of the cadherin family of adhesion proteins. Their cytoplasmic tails bind *plakoglobin* (γ-catenin) and *plakophilin* (a distant relative of p120-catenin), which in turn bind to *desmoplakin*. Desmoplakin binds to the sides of intermediate filaments, thereby tying the desmosome to these filaments. (C) An electron micrograph of desmosome junctions between epidermal cells in the skin of a baby mouse. (D) Part of the same tissue at higher magnification, showing a single desmosome, with intermediate filaments attached to it. (C and D, from W. He, P. Cowin and D.L. Stokes, *Science* 302:109–113, 2003. With permission from AAAS.)

Tight junctions

- Epithelial cells contain Tight junctions that serve to seal them tightly together and assist the epithelial tissues in forming barriers between the internal cells of the body and the outside world.
- The tight junctions between adjacent cells in an epithelium lining an organ or body cavity form a continuous belt around the apical ends of the lateral surfaces of each cell, just apical to the adherens junction.
- These belts together form a formidable barrier, so that molecules must typically cross the cell layer by passing through the cells themselves.
- Tight junctions are especially prominent in intestinal epithelial cells and are also abundant in the ducts and cavities of glands that connect with the digestive tract, such as the liver and pancreas, as well as in the urinary bladder, where they ensure that the urine stored in the bladder does not seep out between cells.
- .Tight junctions can be seen especially well by freezefracture microscopy, which reveals the inner faces of membranes.Each junction appears as a series of ridges that form an interconnected network extending across the junction. Each ridge consists of a continuous row of tightly packed transmembrane junctional proteins about 3–4 nm in diameter.

- The number of such ridges across a junction correlates well with the tightness of the seal made by the junction.
- In addition to these close membrane appositions, scaffolding proteins at tight junctions recruit cytoskeletal proteins, such as F-actin, to tight junctions.
- Tight junctions act like “gates,” preventing the movement of fluids, ions, and molecules between cells. In addition, tight junctions act like “fences,” blocking the lateral movement of lipids and protein within the membrane.
- Lipid movement is blocked in the outer monolayer only, but the movement of integral membrane proteins is blocked entirely. As a result, different kinds of integral membrane proteins can be maintained in the portions of a plasma membrane on opposite sides of a tight junction belt.
- Epithelial cells can also alter their tight junctions transiently to permit an increased flow of solutes and water through breaches in the junctional barriers.Such paracellular transport is especially important in the absorption of amino acids and monosaccharides from the lumen of the intestine, where the concentration of these nutrients can increase enough after a meal to drive passive transport in the proper direction.
- Tight junctions contain several major transmembrane proteins. These include a transmembrane protein known as occludin and immunoglobulin superfamily proteins known as junctional adhesion molecules (JAMs).

- In addition, tight junctions contain claudins. Claudins have four membrane-spanning domains; the largest extracellular loop contains charged amino acids that are thought to allow passage of specific ions.
- Claudins in the plasma membrane of adjacent cells are thought to interlock to form a tight seal. Charged amino acids in the large extracellular loop of claudins are thought to form ion-selective pores that allow passage of specific ions through the epithelium.
- In addition to their functions in assembling tight junctions, claudins appear to regulate paracellular transport of ions across epithelia.
- Different claudins are expressed in different epithelial tissues and are thought to confer on these tissues different permeability properties.
- Mutations in one claudin (claudin-16) result in familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), an autosomalrecessive disease characterized by severe Mg^{2+} and Ca^{2+} imbalance.

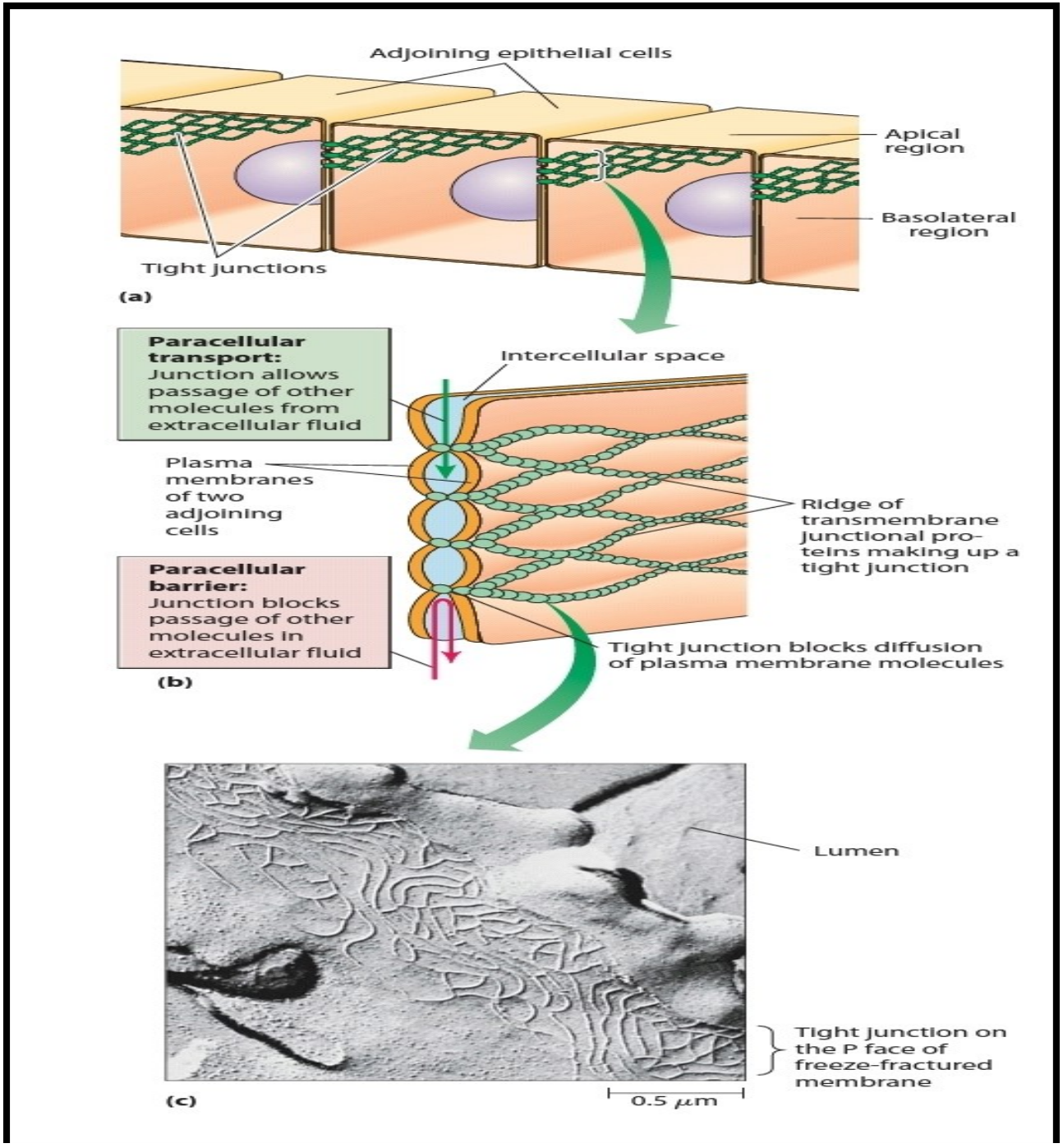

Adjoining epithelial cells
Apical region
Basolateral region
Tight junctions
(a)
Paracellular transport: Junction allows passage of other molecules from extracellular fluid
Intercellular space
Plasma membranes of two adjoining cells
Ridge of transmembrane junctional proteins making up a tight junction
Paracellular barrier: Junction blocks passage of other molecules in extracellular fluid
Tight junction blocks diffusion of plasma membrane molecules
(b)
Lumen
Tight junction on the P face of freeze-fractured membrane
0.5 μm
(c)

Fig:Tight Junction Structure. (a) A schematic representation of several adjoining epithelial cells connected by tight junctions. **(b) Transmembrane junctional proteins** in the plasma membranes of two adjacent cells are clustered along the points of contact, forming ridges of protein particles that join the two plasma membranes together tightly. Tight junctions prevent the passage of extracellular molecules through the spaces between cells (red arrows) and also block lateral movement of transmembrane proteins. **(c) This electron micrograph illustrates tight junctions** between cells in a frog bladder, as revealed by the freeze-fracture technique. Tight junctions appear as raised ridges on the protoplasmic (P) face of the membrane. The lumen is the cavity of the bladder (TEM).

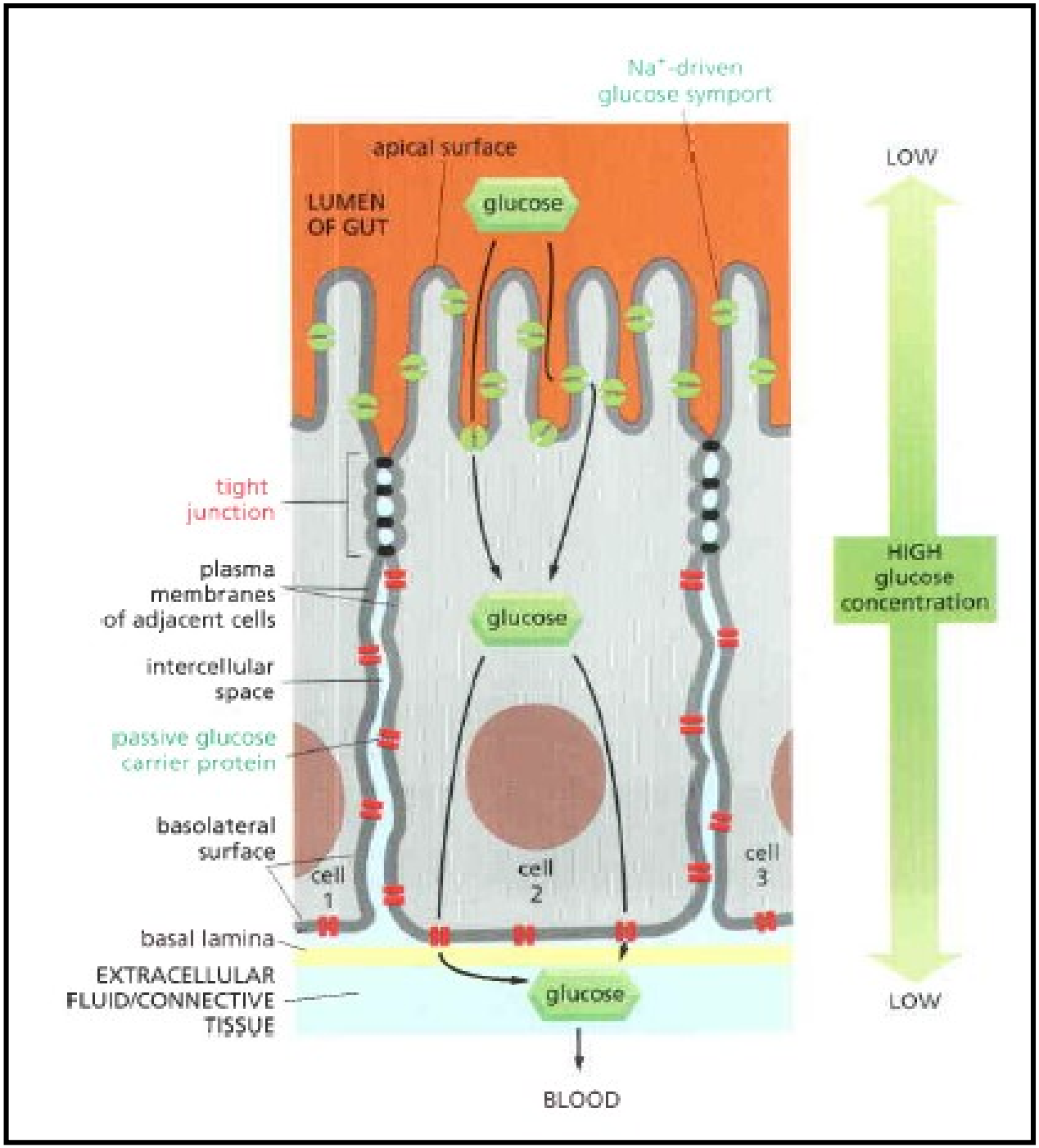

Na+-driven
glucose symport
apical surface
LUMEN
OF GUT
glucose
LOW
tight
junction
plasma
membranes
of adjacent cells
glucose
HIGH
glucose
concentration
intercellular
space
passive glucose
carrier protein
basolateral
surface
cell
1
cell
2
cell
3
basal lamina
EXTRACELLULAR
FLUID/CONNECTIVE
TISSUE
glucose
LOW
BLOOD

Figure:The role of tight junctions in transcellular transport. Transport proteins are confined to different regions of the plasma membrane in epithelial cells of the small intestine.This segregation permits a vectorial transfer of nutrients across the epithelium from the gut lumen to the blood.In the example shown, glucose is actively transported in to the cell by Na+-driven glucose symports at its apical surface and it diffuses out of the cell by facilitated diffusion mediated by glucose carriers in its basolateral membrane.Tight junctions are thought to confine the transport proteins to their appropriate membrane domains by acting as diffusion barriers or"fences"within the lipid bilayer of the plasma membrane; these junctions also block the backflow of glucose from the basal side of the epithelium into the gut lumen.

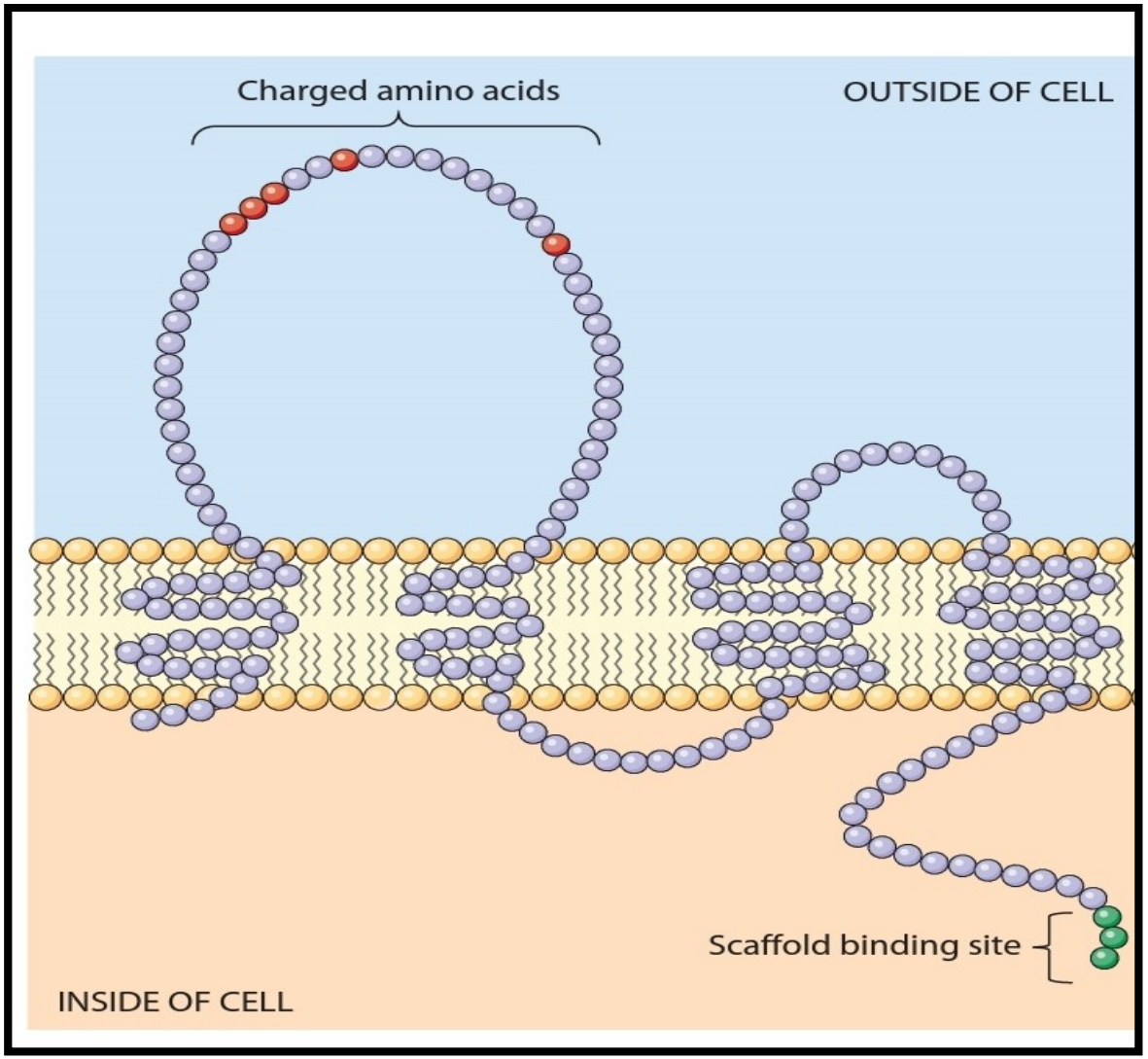


Fig:Claudin Structure. Claudins have four transmembrane domains and characteristic extra- and intracellular loops. The largest extracellular loop contains charged amino acids that are thought to interact with claudins on a neighboring cell to create a paracellular pore through which ions can pass. The C-terminus of claudins can bind scaffolding proteins in the cytosol

Gap junction

- A gap junction is a region where the plasma membranes of two cells are aligned and brought into intimate contact, with a gap of only 2–3 nm in between, spanned by small molecular "pipelines."
- The gap junction thus provides a point of cytoplasmic contact between two adjacent cells through which ions and small molecules can pass. It allows adjacent cells to be in direct electrical and chemical communication with each other.
- At a gap junction, the two plasma membranes from adjacent cells are joined by tightly packed, hollow cylinders called **connexons.**
- A single gap junction may consist of just a few or as many as thousands of clustered connexons. In vertebrates, each connexon is a circular assembly of six subunits of the protein connexin. Invertebrates do not have connexins. Instead, they produce proteins called innexins that appear to serve the same function.
- Many different connexins (more than a dozen types) are found in different tissues, but each one functions similarly in forming connexons.
- The assembly spans the membrane and protrudes into the space, or gap, between the two cells .
- Each connexon has a diameter of about 7 nm and a hollow center that forms a very thin hydrophilic channel through the membrane.
- The channel is about 3 nm in diameter at its narrowest point—just large enough to allow the passage of ions and small molecules but too small to allow proteins, nucleic acids, and organelles through. Included in this range are single sugars, amino acids, and nucleotides—most of the molecules involved in cellular metabolism.

- Conditions inside of the cell, including electrical potential, concentration of second messengers, and other conditions, can influence whether gap junctions are open or closed.
- Gap junctions occur in most vertebrate and invertebrate cells. They are especially abundant in tissues such as muscle and nerve, where extremely rapid communication between cells is required (e.g., in electrical synapses). In heart tissue, gap junctions facilitate the flow of electrical current that causes the heart to beat.
- Several human disorders have been directly linked to defects in gap junctions. These include several types of demyelinating neurodegenerative diseases, various skin disorders,formation of cataracts, and some types of deafness.

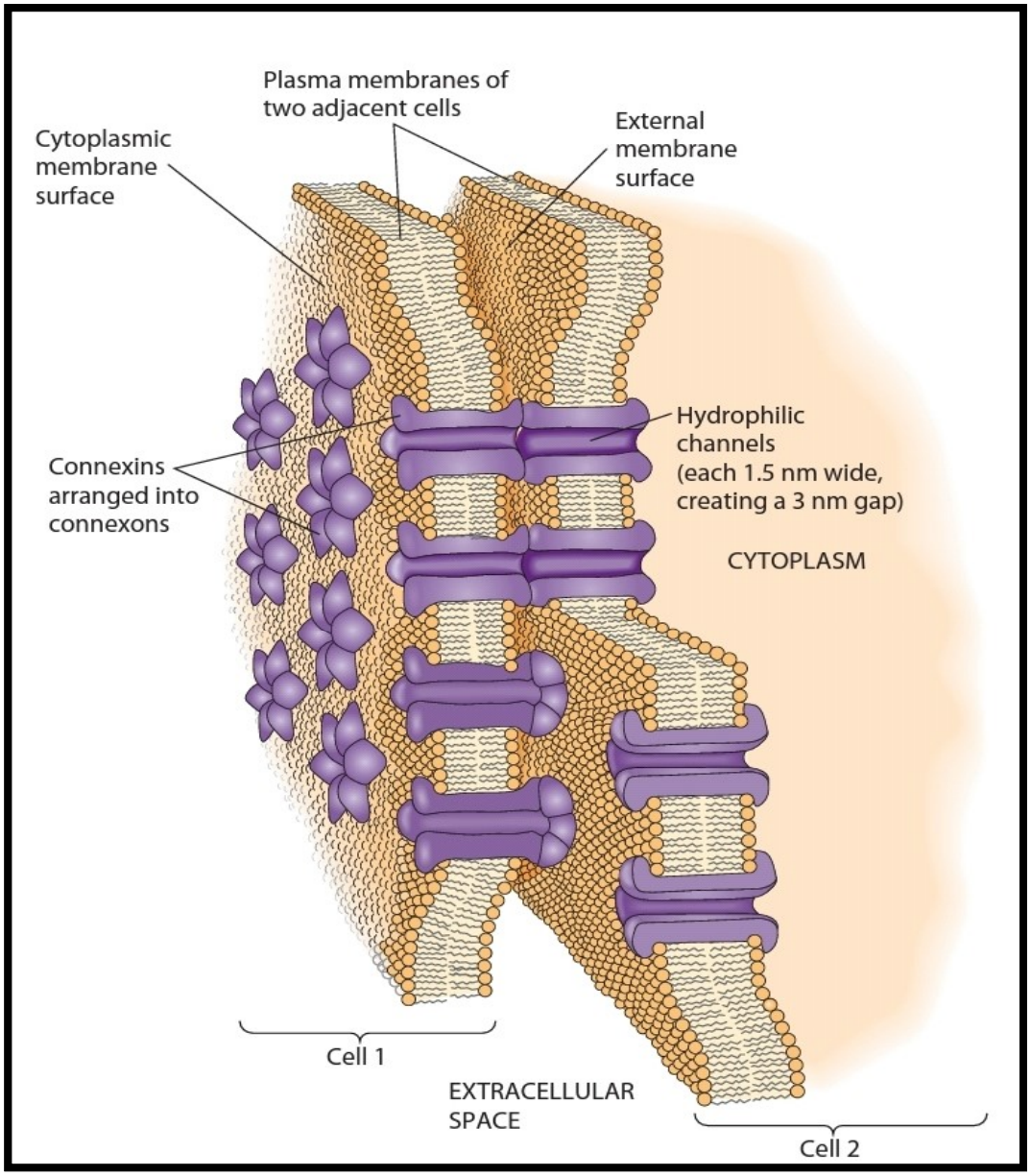
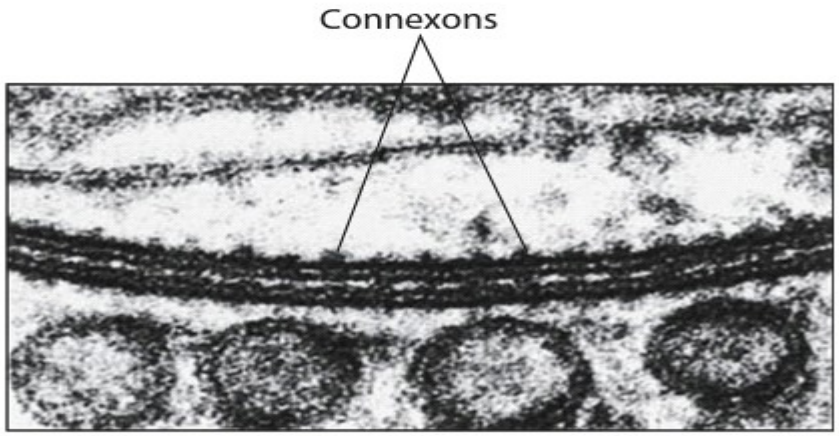
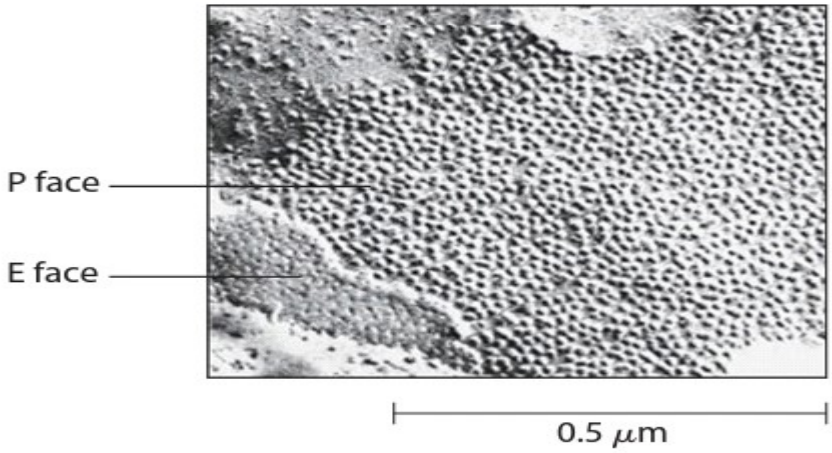


Fig:Gap Junction Structure. (a) A schematic representation of a gap junction. A gap junction consists of a large number of hydrophilic channels formed by the alignment of connexons in the plasma membranes of two adjoining cells.



(b) Electron micrograph of a gap junction



(c) Freeze-fracture of a gap junction