

10

Membrane Structure

In This Chapter

THE LIPID BILAYER	617
MEMBRANE PROTEINS	629

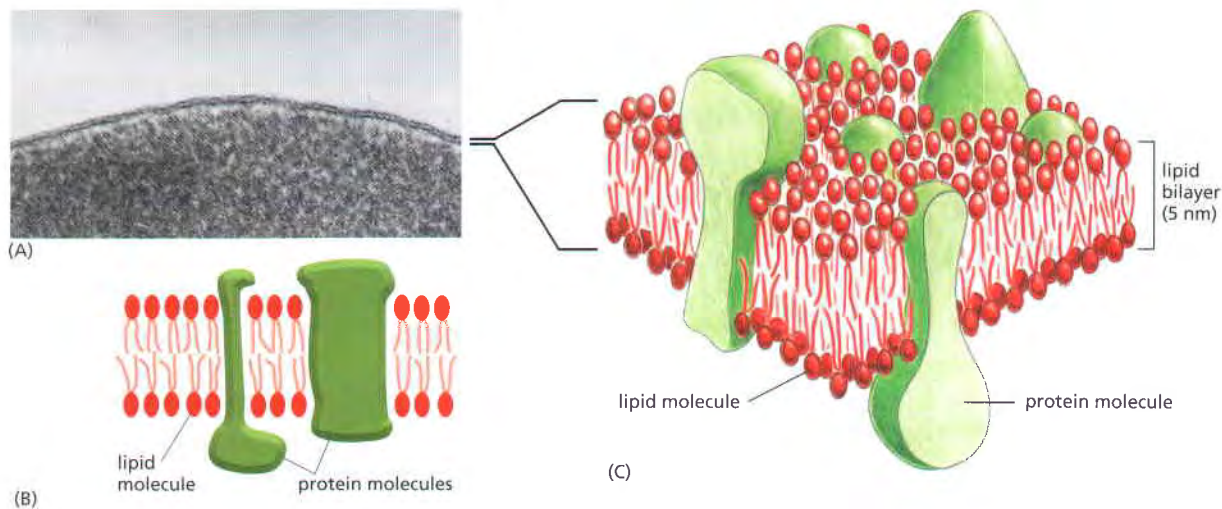
Cell membranes are crucial to the life of the cell. The **plasma membrane** encloses the cell, defines its boundaries, and maintains the essential differences between the cytosol and the extracellular environment. Inside eucaryotic cells, the membranes of the endoplasmic reticulum, Golgi apparatus, mitochondria, and other membrane-enclosed organelles maintain the characteristic differences between the contents of each organelle and the cytosol. Ion gradients across membranes, established by the activities of specialized membrane proteins, can be used to synthesize ATP, to drive the transmembrane movement of selected solutes, or, as in nerve and muscle cells, to produce and transmit electrical signals. In all cells, the plasma membrane also contains proteins that act as sensors of external signals, allowing the cell to change its behavior in response to environmental cues, including signals from other cells; these protein sensors, or *receptors*, transfer information—rather than molecules—across the membrane.

Despite their differing functions, all biological membranes have a common general structure: each is a very thin film of lipid (fatty) and protein molecules, held together mainly by noncovalent interactions (**Figure 10–1**). Cell membranes are dynamic, fluid structures, and most of their molecules move about in the plane of the membrane. The lipid molecules are arranged as a continuous double layer about 5 nm thick. This *lipid bilayer* provides the basic fluid structure of the membrane and serves as a relatively impermeable barrier to the passage of most water-soluble molecules. Protein molecules that span the lipid bilayer (*transmembrane proteins*; see **Figure 10–1**) mediate nearly all of the other functions of the membrane, transporting specific molecules across it, for example, or catalyzing membrane-associated reactions such as ATP synthesis. In the plasma membrane, some transmembrane proteins serve as structural links that connect the cytoskeleton through the lipid bilayer to either the extracellular matrix or an adjacent cell, while others serve as receptors to detect and transduce chemical signals in the cell's environment. As would be expected, it takes many different membrane proteins to enable a cell to function and interact with its environment, and it is estimated that about 30% of the proteins encoded in an animal cell's genome are membrane proteins.

In this chapter, we consider the structure and organization of the two main constituents of biological membranes—the lipids and the proteins. Although we focus mainly on the plasma membrane, most concepts discussed apply to the various internal membranes in cells as well. The functions of cell membranes are considered in later chapters: their role in ATP synthesis, for example, is discussed in Chapter 14; their role in the transmembrane transport of small molecules in Chapter 11; and their roles in cell signaling and cell adhesion in Chapters 15 and 19, respectively. In Chapters 12 and 13, we discuss the internal membranes of the cell and the protein traffic through and between them.

THE LIPID BILAYER

The **lipid bilayer** provides the basic structure for all cell membranes. It is easily seen by electron microscopy, and its structure is attributable exclusively to the



special properties of the lipid molecules, which assemble spontaneously into bilayers even under simple artificial conditions.

Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

Lipid molecules constitute about 50% of the mass of most animal cell membranes, nearly all of the remainder being protein. There are approximately 5×10^6 lipid molecules in a $1 \mu\text{m} \times 1 \mu\text{m}$ area of lipid bilayer, or about 10^9 lipid molecules in the plasma membrane of a small animal cell. All of the lipid molecules in cell membranes are **amphiphilic**—that is, they have a **hydrophilic** (“water-loving”) or *polar* end and a **hydrophobic** (“water-fearing”) or *nonpolar* end.

The most abundant membrane lipids are the **phospholipids**. These have a polar head group and two hydrophobic *hydrocarbon tails*. In animal, plant, and bacterial cells, the tails are usually fatty acids, and they can differ in length (they normally contain between 14 and 24 carbon atoms). One tail typically has one or more *cis*-double bonds (that is, it is *unsaturated*), while the other tail does not (that is, it is *saturated*). As shown in **Figure 10-2**, each *cis*-double bond creates a small kink in the tail. Differences in the length and saturation of the fatty acid tails influence how phospholipid molecules pack against one another, thereby affecting the fluidity of the membrane, as we discuss later.

The main phospholipids in most animal cell membranes are the **phosphoglycerides**, which have a three-carbon *glycerol* backbone (see **Figure 10-2**). Two long-chain fatty acids are linked through ester bonds to adjacent carbon atoms of the glycerol, and the third carbon atom is attached to a phosphate group, which in turn is linked to one of several different types of head group. By combining several different fatty acids and head groups, cells make many different phosphoglycerides. *Phosphatidylethanolamine*, *phosphatidylserine*, and *phosphatidylcholine* are the main ones in mammalian cell membranes (**Figure 10-3A–C**).

Another important phospholipid, called *sphingomyelin*, is built from *sphingosine* rather than glycerol (**Figure 10-3D–E**). Sphingosine is a long acyl chain with an amino group (NH_2) and two hydroxyl groups (OH) at one end of the molecule. In sphingomyelin, a fatty acid tail is attached to the amino group, and a phosphocholine group is attached to the terminal hydroxyl group, leaving one hydroxyl group free. The free hydroxyl group contributes to the polar properties of the adjacent head group, as it can form hydrogen bonds with the head group of a neighboring lipid, with a water molecule, or with a membrane protein. Together, the phospholipids phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and sphingomyelin constitute more than half the mass of lipid in most mammalian cell membranes (see **Table 10-1**).

Figure 10-1 Three views of a cell membrane. (A) An electron micrograph of a plasma membrane (of a human red blood cell) seen in cross section. (B and C) These drawings show two-dimensional and three-dimensional views of a cell membrane and the general disposition of its lipid and protein constituents. (A, courtesy of Daniel S. Friend.)

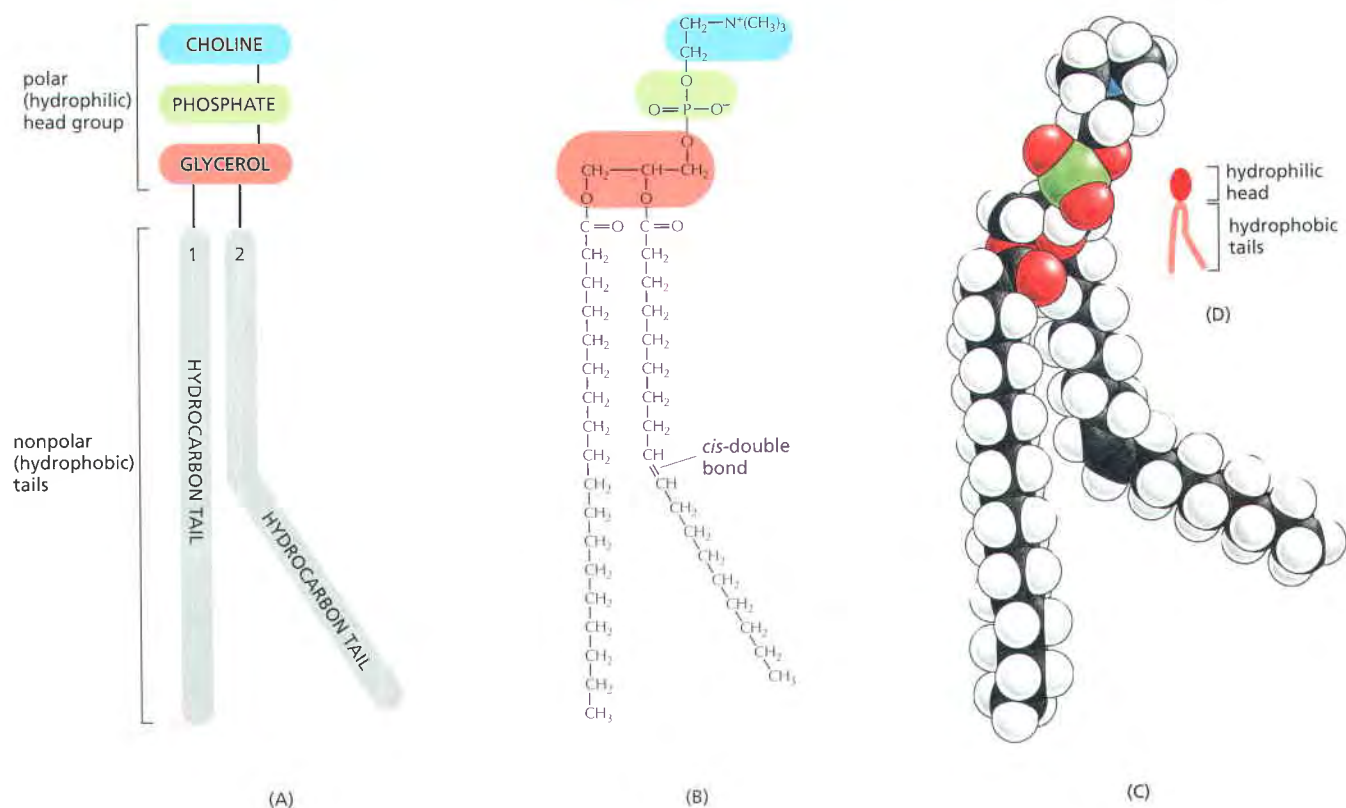


Figure 10-2 The parts of a phosphoglyceride molecule. This example is a phosphatidylcholine, represented (A) schematically, (B) by a formula, (C) as a space-filling model, and (D) as a symbol. The kink resulting from the *cis*-double bond is exaggerated for emphasis.

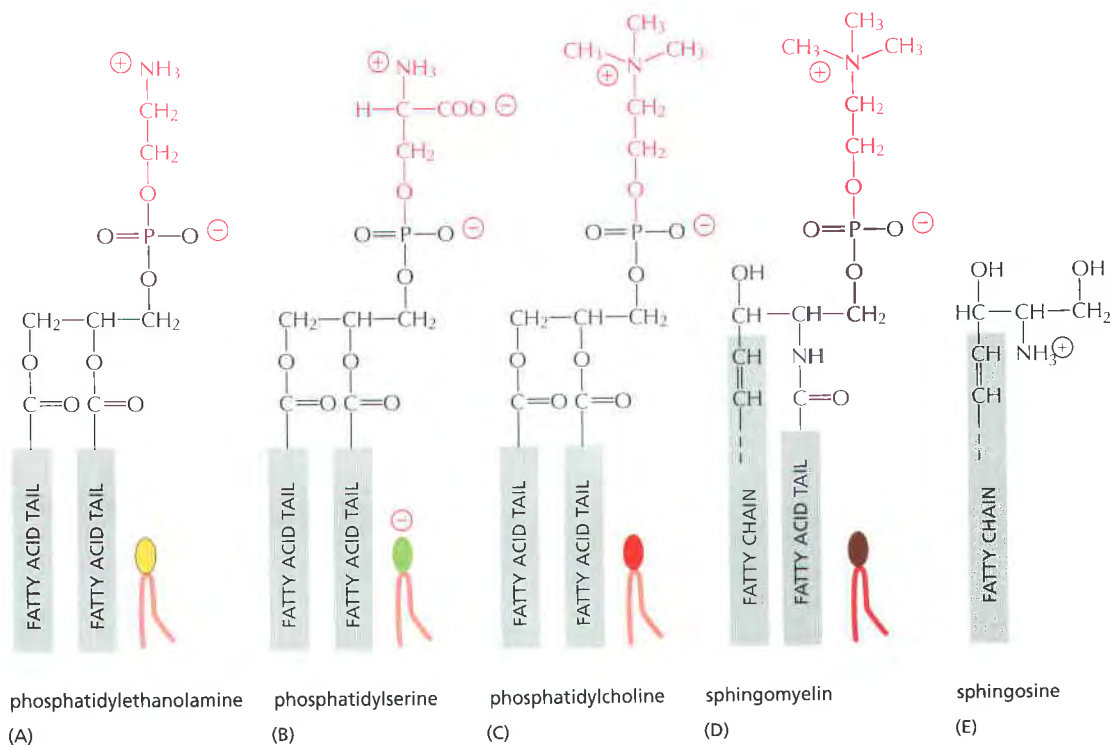


Figure 10-3 Four major phospholipids in mammalian plasma membranes. Different head groups are represented by different colors in the symbols. The molecule in (D) is sphingomyelin, which is derived from sphingosine (E) and is therefore a sphingolipid. Note that only phosphatidylserine carries a net negative charge, the importance of which we discuss later; the other three are electrically neutral at physiological pH, carrying one positive and one negative charge.

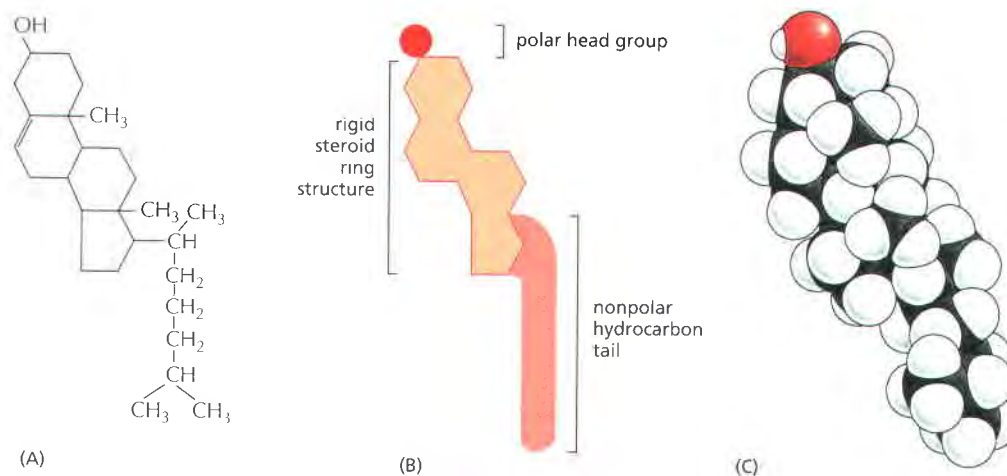


Figure 10-4 The structure of cholesterol. Cholesterol is represented (A) by a formula, (B) by a schematic drawing, and (C) as a space-filling model.

In addition to phospholipids, the lipid bilayers in many cell membranes contain *cholesterol* and *glycolipids*. Eucaryotic plasma membranes contain especially large amounts of **cholesterol** (Figure 10-4)—up to one molecule for every phospholipid molecule. Cholesterol is a *sterol*. It contains a rigid ring structure, to which is attached a single polar hydroxyl group and a short nonpolar hydrocarbon chain. The cholesterol molecules orient themselves in the bilayer with their **hydroxyl group** close to the polar head groups of adjacent phospholipid molecules (Figure 10-5).

Phospholipids Spontaneously Form Bilayers

The shape and amphiphilic nature of the phospholipid molecules cause them to form bilayers spontaneously in aqueous environments. As discussed in Chapter 2, hydrophilic molecules dissolve readily in water because they contain charged groups or uncharged polar groups that can form either favorable electrostatic interactions or hydrogen bonds with water molecules. Hydrophobic molecules, by contrast, are insoluble in water because all, or almost all, of their atoms are uncharged and nonpolar and therefore cannot form energetically favorable interactions with water molecules. If dispersed in water, they force the adjacent water molecules to reorganize into ice-like cages that surround the hydrophobic molecule (Figure 10-6). Because these cage structures are more ordered than the surrounding water, their formation increases the free energy. This free energy cost is minimized, however, if the hydrophobic molecules (or the hydrophobic portions of amphiphilic molecules) cluster together so that the smallest number of water molecules is affected.

The hydrophobic and hydrophilic regions of lipid molecules behave in the same way. Thus, lipid molecules spontaneously aggregate to bury their hydrophobic hydrocarbon tails in the interior and expose their hydrophilic heads to water. Depending on their shape, they can do this in either of two ways: they can form spherical *micelles*, with the tails inward, or they can form double-layered sheets, or *bilayers*, with the hydrophobic tails sandwiched between the hydrophilic head groups (Figure 10-7).

Being cylindrical, phospholipid molecules spontaneously form bilayers in aqueous environments. In this energetically most favorable arrangement, the hydrophilic heads face the water at each surface of the bilayer, and the hydrophobic tails are shielded from the water in the interior. The same forces that drive phospholipids to form bilayers also provide a self-healing property. A small tear in the bilayer creates a free edge with water; because this is energetically unfavorable, the lipids tend to rearrange spontaneously to eliminate the free edge. (In eucaryotic plasma membranes, the fusion of intracellular vesicles repairs larger tears.) The prohibition of free edges has a profound consequence: the only way for a bilayer to avoid having edges is by closing in on itself and forming a sealed compartment (Figure 10-8). This remarkable behavior, fundamental

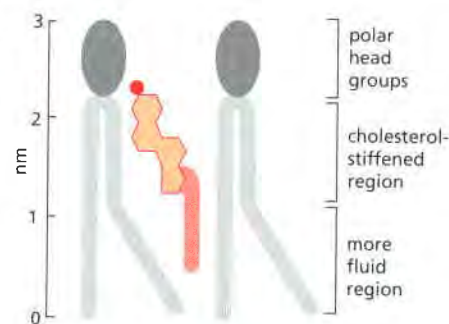


Figure 10-5 Cholesterol in a lipid bilayer. Schematic drawing of a cholesterol molecule interacting with two phospholipid molecules in one monolayer of a lipid bilayer.

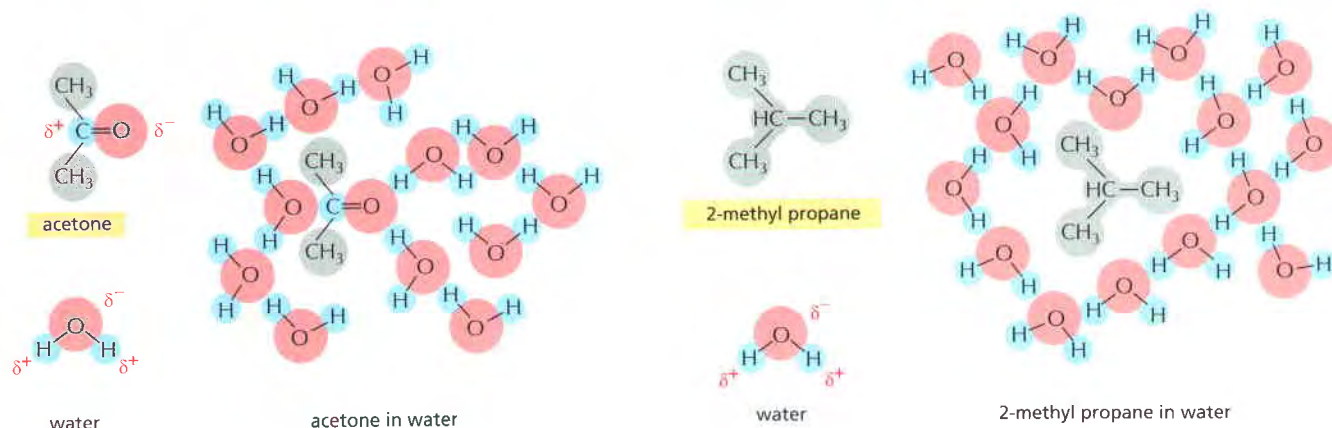


Figure 10-6 How hydrophilic and hydrophobic molecules interact differently with water. (A) Because acetone is polar, it can form favorable electrostatic interactions with water molecules, which are also polar. Thus, acetone readily dissolves in water. (B) By contrast, 2-methyl propane is entirely hydrophobic. Because it cannot form favorable interactions with water, it would force adjacent water molecules to reorganize into icelike cage structures, which increases the free energy. This compound is therefore virtually insoluble in water. The symbol δ^- indicates a partial negative charge, and δ^+ indicates a partial positive charge. Polar atoms are shown in color and nonpolar groups are shown in gray.

to the creation of a living cell, follows directly from the shape and amphiphilic nature of the phospholipid molecule.

A lipid bilayer also has other characteristics that make it an ideal structure for cell membranes. One of the most important of these is its fluidity, which is crucial to many membrane functions.

The Lipid Bilayer Is a Two-dimensional Fluid

Around 1970, researchers first recognized that individual lipid molecules are able to diffuse freely within lipid bilayers. The initial demonstration came from studies of synthetic lipid bilayers. Two types of preparations have been very useful in such studies: (1) bilayers made in the form of spherical vesicles, called **liposomes**, which can vary in size from about 25 nm to 1 μm in diameter

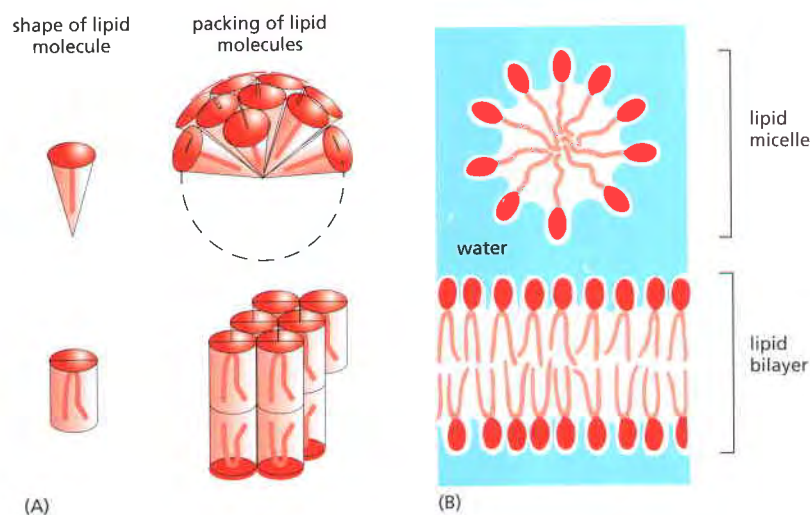


Figure 10-7 Packing arrangements of lipid molecules in an aqueous environment. (A) Cone-shaped lipid molecules (*above*) form micelles, whereas cylinder-shaped phospholipid molecules (*below*) form bilayers. (B) A lipid micelle and a lipid bilayer seen in cross section. Lipid molecules spontaneously form one or the other structure in water, depending on their shape.

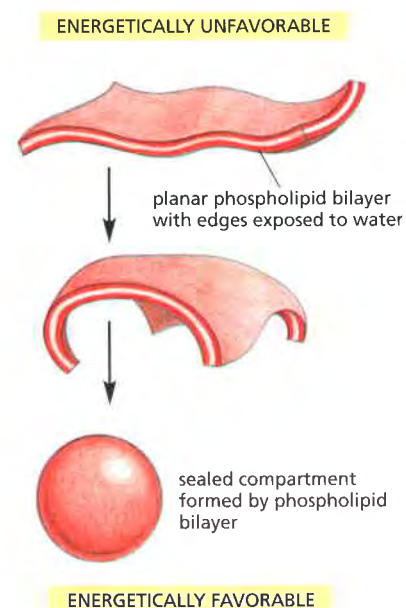


Figure 10-8 The spontaneous closure of a phospholipid bilayer to form a sealed compartment. The closed structure is stable because it avoids the exposure of the hydrophobic hydrocarbon tails to water, which would be energetically unfavorable.

depending on how they are produced (Figure 10–9); and (2) planar bilayers, called **black membranes**, formed across a hole in a partition between two aqueous compartments (Figure 10–10).

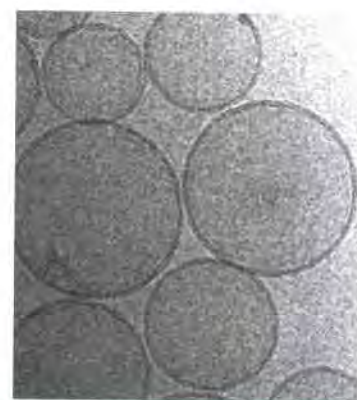
Various techniques have been used to measure the motion of individual lipid molecules and their components. One can construct a lipid molecule, for example, with a fluorescent dye or a small gold particle attached to its polar head group and follow the diffusion of even individual molecules in a membrane. Alternatively, one can modify a lipid head group to carry a “spin label,” such as a nitroxyl group (>N-O); this contains an unpaired electron whose spin creates a paramagnetic signal that can be detected by electron spin resonance (ESR) spectroscopy. (The principles of this technique are similar to those of nuclear magnetic resonance, discussed in Chapter 8.) The motion and orientation of a spin-labeled lipid in a bilayer can be deduced from the ESR spectrum. Such studies show that phospholipid molecules in synthetic bilayers very rarely migrate from the monolayer (also called a *leaflet*) on one side to that on the other. This process, known as “flip-flop,” occurs less than once a month for any individual molecule, although cholesterol is an exception to this rule and can flip-flop rapidly. In contrast, lipid molecules readily exchange places with their neighbors *within* a monolayer ($\sim 10^7$ times per second). This gives rise to a rapid lateral diffusion, with a diffusion coefficient (D) of about $10^{-8} \text{ cm}^2/\text{sec}$, which means that an average lipid molecule diffuses the length of a large bacterial cell ($\sim 2 \mu\text{m}$) in about 1 second. These studies have also shown that individual lipid molecules rotate very rapidly about their long axis and have flexible hydrocarbon chains. Computer simulations show that lipid molecules in membranes are very disordered, presenting an irregular surface of variously spaced and oriented head groups to the water phase on either side of the bilayer (Figure 10–11).

Similar mobility studies on labeled lipid molecules in isolated biological membranes and in living cells give results similar to those in synthetic bilayers. They demonstrate that the lipid component of a biological membrane is a two-dimensional liquid in which the constituent molecules are free to move laterally. As in synthetic bilayers, individual phospholipid molecules are normally confined to their own monolayer. This confinement creates a problem for their synthesis. Phospholipid molecules are manufactured in only one monolayer of a membrane, mainly in the cytosolic monolayer of the endoplasmic reticulum membrane. If none of these newly made molecules could migrate reasonably promptly to the noncytosolic monolayer, new lipid bilayer could not be made. The problem is solved by a special class of transmembrane enzymes called *phospholipid translocators*, which catalyze the rapid flip-flop of phospholipids from one monolayer to the other, as discussed in Chapter 12.

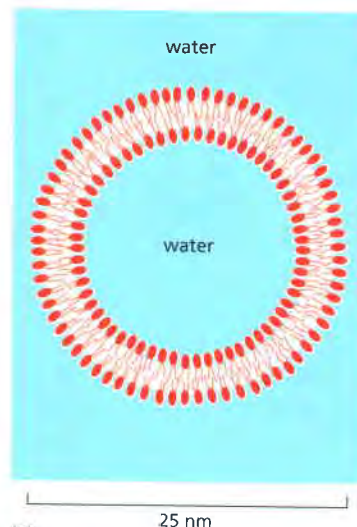
The Fluidity of a Lipid Bilayer Depends on Its Composition

The fluidity of cell membranes has to be precisely regulated. Certain membrane transport processes and enzyme activities, for example, cease when the bilayer viscosity is experimentally increased beyond a threshold level.

The fluidity of a lipid bilayer depends on both its composition and its temperature, as is readily demonstrated in studies of synthetic bilayers. A synthetic bilayer made from a single type of phospholipid changes from a liquid state to a

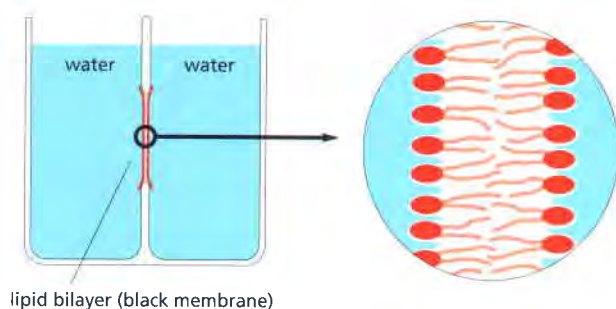


(A)



(B)

Figure 10–9 Liposomes. (A) An electron micrograph of unfixed, unstained phospholipid vesicles—liposomes—in water rapidly frozen to liquid nitrogen temperature. (B) A drawing of a small spherical liposome seen in cross section. Liposomes are commonly used as model membranes in experimental studies. (A, from P. Frederik and W. Hubert, *Meth. Enzymol.* 391:431, 2005. With permission from Elsevier.)



lipid bilayer (black membrane)

Figure 10–10 A cross-sectional view of a black membrane, a synthetic lipid bilayer. This planar bilayer appears black when it forms across a small hole in a partition separating two aqueous compartments. Black membranes are used to measure the permeability properties of synthetic membranes.

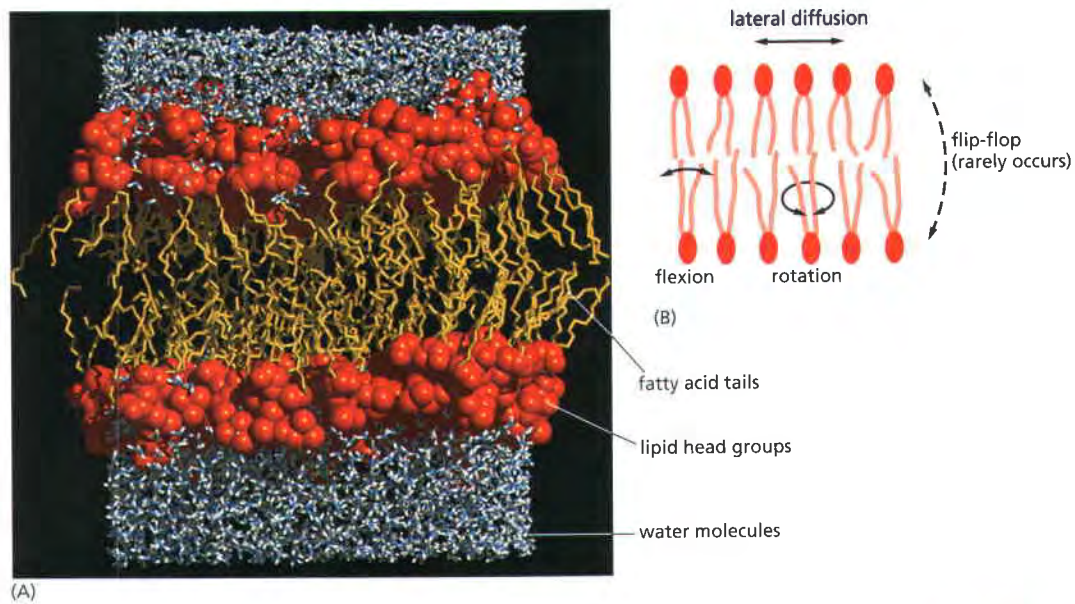


Figure 10-11 The mobility of phospholipid molecules in an artificial lipid bilayer. <CACA> Starting with a model of 100 phosphatidylcholine molecules arranged in a regular bilayer, a computer calculated the position of every atom after 300 picoseconds of simulated time. From these theoretical calculations (taking weeks of processor time in 1995), a model of the lipid bilayer emerges that accounts for almost all of the measurable properties of a synthetic lipid bilayer, such as its thickness, number of lipid molecules per membrane area, depth of water penetration, and unevenness of the two surfaces. Note that the tails in one monolayer can interact with those in the other monolayer, if the tails are long enough. (B) The different motions of a lipid molecule in a bilayer. (A, based on S.W. Chiu et al., *Biophys. J.* 69:1230–1245, 1995. With permission from the Biophysical Society.)

two-dimensional rigid crystalline (or gel) state at a characteristic freezing point. This change of state is called a *phase transition*, and the temperature at which it occurs is lower (that is, the membrane becomes more difficult to freeze) if the hydrocarbon chains are short or have double bonds. A shorter chain length reduces the tendency of the hydrocarbon tails to interact with one another, in both the same and opposite monolayer, and *cis*-double bonds produce kinks in the hydrocarbon chains that make them more difficult to pack together, so that the membrane remains fluid at lower temperatures (Figure 10-12). Bacteria, yeasts, and other organisms whose temperature fluctuates with that of their environment adjust the fatty acid composition of their membrane lipids to maintain a relatively constant fluidity. As the temperature falls, for instance, the cells of those organisms synthesize fatty acids with more *cis*-double bonds, and they avoid the decrease in bilayer fluidity that would otherwise result from the temperature drop.

Cholesterol modulates the properties of lipid bilayers. When mixed with phospholipids, it enhances the permeability-barrier properties of the lipid bilayer. It inserts into the bilayer with its hydroxyl group close to the polar head groups of the phospholipids, so that its rigid, platelike steroid rings interact with—and partly immobilize—those regions of the hydrocarbon chains closest to the polar head groups (see Figure 10-5). By decreasing the mobility of the first

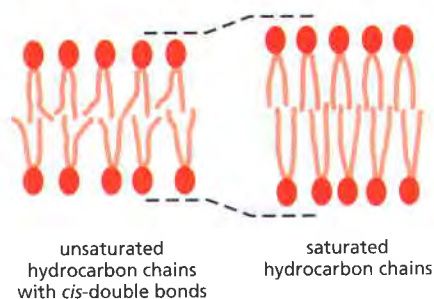


Figure 10-12 The influence of *cis*-double bonds in hydrocarbon chains. The double bonds make it more difficult to pack the chains together, thereby making the lipid bilayer more difficult to freeze. In addition, because the hydrocarbon chains of unsaturated lipids are more spread apart, lipid bilayers containing them are thinner than bilayers formed exclusively from saturated lipids.

Table 10–1 Approximate Lipid Compositions of Different Cell Membranes

LIPID	PERCENTAGE OF TOTAL LIPID BY WEIGHT					
	LIVER CELL PLASMA MEMBRANE	RED BLOOD CELL PLASMA MEMBRANE	MYELIN	MITOCHONDRION (INNER AND OUTER MEMBRANES)	ENDOPLASMIC RETICULUM	<i>E. COLI</i> BACTERIUM
Cholesterol	17	23	22	3	6	0
Phosphatidylethanolamine	7	18	15	28	17	70
Phosphatidylserine	4	7	9	2	5	trace
Phosphatidylcholine	24	17	10	44	40	0
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	14	8	23	27	30

few CH₂ groups of the hydrocarbon chains of the phospholipid molecules, cholesterol makes the lipid bilayer less deformable in this region and thereby decreases the permeability of the bilayer to small water-soluble molecules. Although cholesterol tightens the packing of the lipids in a bilayer, it does not make membranes any less fluid. At the high concentrations found in most eucaryotic plasma membranes, cholesterol also prevents the hydrocarbon chains from coming together and crystallizing.

Table 10–1 compares the lipid compositions of several biological membranes. Note that bacterial plasma membranes are often composed of one main type of phospholipid and contain no cholesterol; their mechanical stability is enhanced by an overlying cell wall (see Figure 11–18). In archaea, lipids usually contain 20–25-carbon-long prenyl chains instead of fatty acids, prenyl and fatty acid chains are similarly hydrophobic and flexible (see Figure 10–20F). Thus, lipid bilayers can be built from molecules with similar features but different molecular designs. The plasma membranes of most eucaryotic cells are more varied than those of procaryotes and archaea, not only in containing large amounts of cholesterol but also in containing a mixture of different phospholipids.

Analysis of membrane lipids by mass spectrometry has revealed that the lipid composition of a typical cell membrane is much more complex than originally thought. According to these studies, membranes are composed of a bewildering variety of 500–1000 different lipid species. While some of this complexity reflects the combinatorial variation in head groups, hydrocarbon chain lengths, and desaturation of the major phospholipid classes, membranes also contain many structurally distinct minor lipids, at least some of which have important functions. The *inositol phospholipids*, for example, are present in small quantities but have crucial functions in guiding membrane traffic and in cell signaling (discussed in Chapters 13 and 15, respectively). Their local synthesis and destruction are regulated by a large number of enzymes, which create both small intracellular signaling molecules and lipid docking sites on membranes that recruit specific proteins from the cytosol, as we discuss later.

Despite Their Fluidity, Lipid Bilayers Can Form Domains of Different Compositions

Because a lipid bilayer is a two-dimensional fluid, we might expect most types of lipid molecules in it to be randomly distributed in their own monolayer. The van der Waals attractive forces between neighboring hydrocarbon tails are not selective enough to hold groups of phospholipid molecules together. With certain lipid mixtures, however, different lipids can come together transiently, creating a dynamic patchwork of different domains. In synthetic lipid bilayers composed of phosphatidylcholine, sphingomyelin, and cholesterol, van der Waals forces between the long and saturated hydrocarbon chains of the sphingomyelin molecules can be just strong enough to hold the adjacent molecules together transiently (**Figure 10–13**).

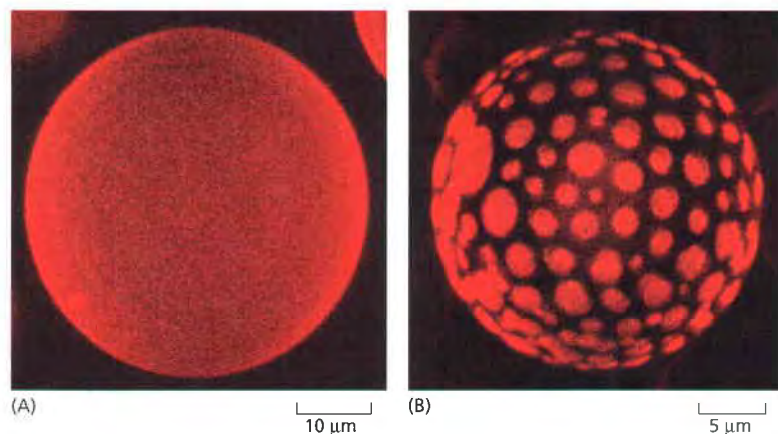


Figure 10-13 Lateral phase separation in artificial lipid bilayers. (A) Giant liposomes produced from a 1:1 mixture of phosphatidylcholine and sphingomyelin form uniform bilayers, whereas (B) liposomes produced from a 1:1:1 mixture of phosphatidylcholine, sphingomyelin, and cholesterol form bilayers with two immiscible phases. The liposomes are stained with trace concentrations of a fluorescent dye that preferentially partitions into one of the phases. The average size of the domains formed in these giant artificial liposomes is much larger than that expected in biological membranes, where rafts may be as small as a few nanometers in diameter. (A, from N. Kahya et al., *J. Struct. Biol.* 147:77–89, 2004. With permission from Elsevier; B, courtesy of Petra Schwille.)

There has been a long debate among scientists whether the lipid molecules in the plasma membrane of animal cells can transiently assemble into specialized domains, called **lipid rafts**. Certain specialized regions of the plasma membrane, such as the *caveolae* involved in endocytosis (discussed in Chapter 13), are enriched in sphingolipids and cholesterol, and it is thought that the specific proteins that assemble there help stabilize these rafts. Because the hydrocarbon chains of sphingolipids are longer and straighter than those of other membrane lipids, raft domains are thicker than other parts of the bilayer (see Figure 10-12) and better accommodate certain membrane proteins (Figure 10-14). Thus, the lateral segregation of proteins and of lipids into raft domains would, in principle, be a mutually stabilizing process. In this way, lipid rafts could help organize membrane proteins—concentrating them either for transport in membrane vesicles (discussed in Chapter 13) or for working together in protein assemblies, as when they convert extracellular signals into intracellular ones (discussed in Chapter 15).

Lipid Droplets Are Surrounded by a Phospholipid Monolayer

Most cells store an excess of lipids in **lipid droplets**, from where they can be retrieved as building blocks for membrane synthesis or as a food source. Fat cells, also called adipocytes, are specialized for lipid storage (see Figure 14-34). They contain vast numbers of large lipid droplets, from which fatty acids can be liberated on demand and exported to other cells through the bloodstream. Lipid droplets store neutral lipids, such as triacylglycerides and cholesterol esters, which are synthesized from fatty acids and cholesterol by enzymes in the

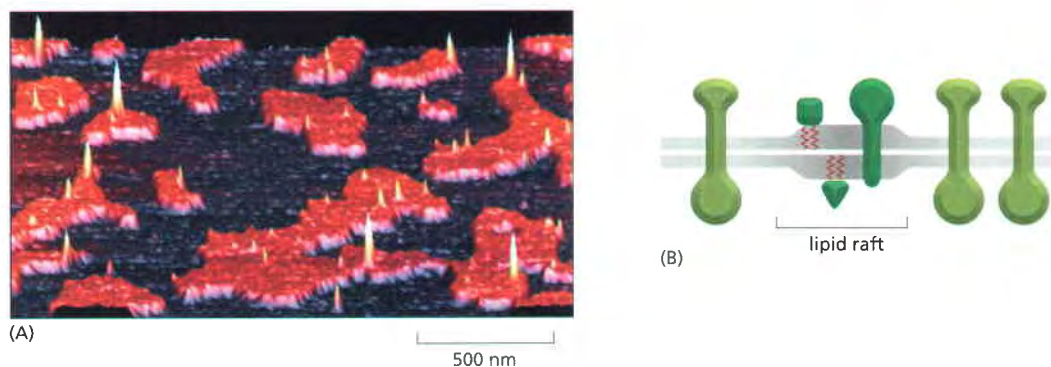


Figure 10-14 The effects of lipid rafts in artificial lipid bilayers. (A) The surface contours of a synthetic bilayer containing lipid rafts, analyzed by atomic force microscopy. Note that the raft areas, shown in orange, are thicker than the rest of the bilayer; as in Figure 10-13, the rafts primarily contain sphingomyelin and cholesterol. The sharp, yellow spikes are incorporated protein molecules, which are attached to the bilayer by a glycosylphosphatidylinositol (GPI) anchor (illustrated in Figure 10-19, example 6), and preferentially partition into the raft domains. (B) Because of both their increased thickness and lipid composition, rafts are thought to concentrate specific membrane proteins (dark green). (A, from D.E. Saslow et al., *J. Biol. Chem.* 277:26966–26970, 2002. With permission from the American Society for Biochemistry and Molecular Biology.)

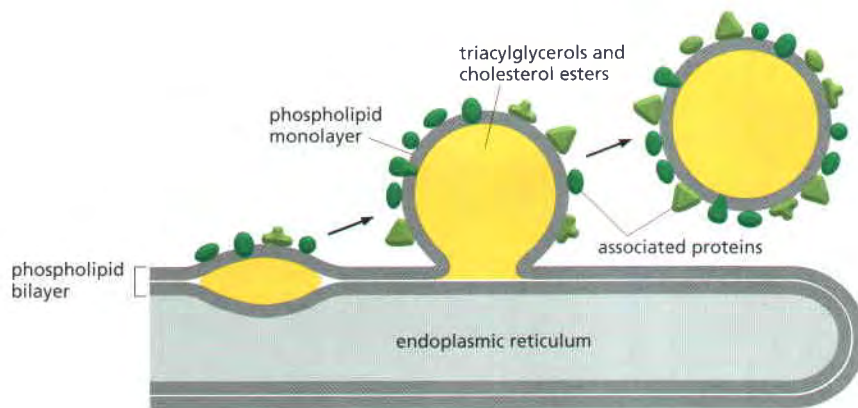


Figure 10-15 A model for the formation of lipid droplets. Neutral lipids are deposited between the two monolayers of the endoplasmic reticulum membrane. There, they aggregate into a three-dimensional droplet, which buds and pinches off from the endoplasmic reticulum membrane as a unique organelle, surrounded by a single monolayer of phospholipids and associated proteins. (Adapted from S. Martin and R.G. Parton, *Nat. Rev. Mol. Cell Biol.* 7:373–378, 2006. With permission from Macmillan Publishers Ltd.)

endoplasmic reticulum membrane. Because these lipids do not contain hydrophilic head groups, they are exclusively hydrophobic molecules, which aggregate into three-dimensional droplets rather than into bilayers.

Lipid droplets are unique organelles because they are surrounded by a single monolayer of phospholipids, which contains a large variety of proteins. Some of the proteins are enzymes involved in lipid metabolism, but the functions of most are unknown. Lipid droplets form rapidly when cells are exposed to high concentrations of fatty acids. They form from discrete regions of the endoplasmic reticulum membrane where many enzymes of lipid metabolism are concentrated. **Figure 10-15** shows one model of how lipid droplets may form and acquire their surrounding monolayer of phospholipids and proteins.

The Asymmetry of the Lipid Bilayer Is Functionally Important

The lipid compositions of the two monolayers of the lipid bilayer in many membranes are strikingly different. In the human red blood cell membrane, for example, almost all of the phospholipid molecules that have choline— $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OH}$ —in their head group (phosphatidylcholine and sphingomyelin) are in the outer monolayer, whereas almost all that contain a terminal primary amino group (phosphatidylethanolamine and phosphatidylserine) are in the inner monolayer (**Figure 10-16**). Because the negatively charged phosphatidylserine is located in the inner monolayer, there is a significant difference in charge between the two halves of the bilayer. We discuss in Chapter 12 how membrane-bound phospholipid translocators generate and maintain lipid asymmetry.

Lipid asymmetry is functionally important, especially in converting extracellular signals into intracellular ones (discussed in Chapter 15). Many cytosolic proteins bind to specific lipid head groups found in the cytosolic monolayer of the lipid bilayer. The enzyme *protein kinase C* (PKC), for example, is activated in response to various extracellular signals. It binds to the cytosolic face of the plasma membrane, where phosphatidylserine is concentrated, and requires this negatively charged phospholipid for its activity.

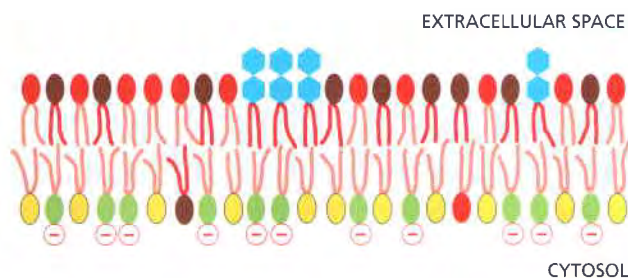


Figure 10-16 The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells. The colors used for the phospholipid head groups are those introduced in Figure 10-3. In addition, glycolipids are drawn with hexagonal polar head groups (blue). Cholesterol (not shown) is thought to be distributed roughly equally in both monolayers.

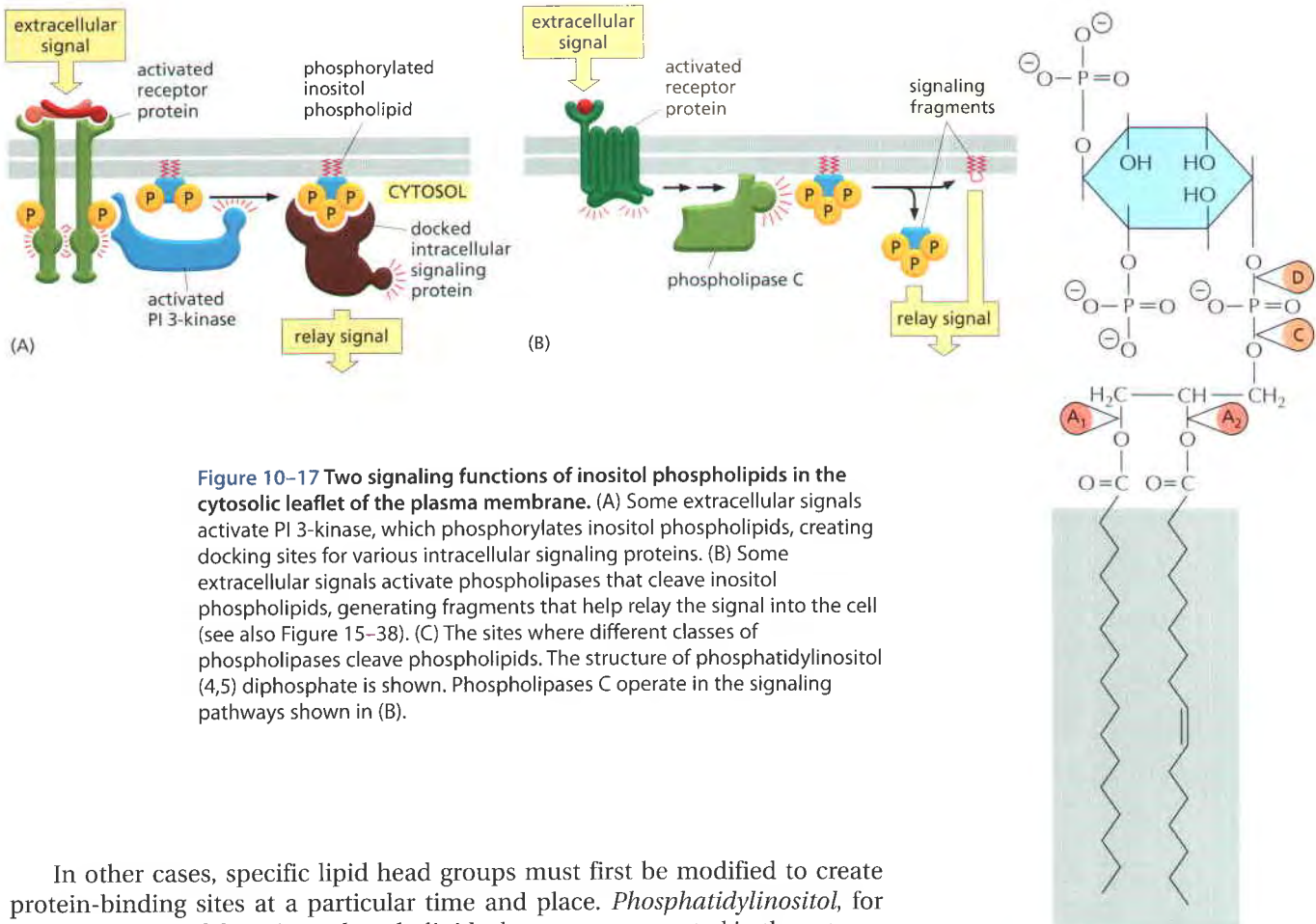


Figure 10-17 Two signaling functions of inositol phospholipids in the cytosolic leaflet of the plasma membrane. (A) Some extracellular signals activate PI 3-kinase, which phosphorylates inositol phospholipids, creating docking sites for various intracellular signaling proteins. (B) Some extracellular signals activate phospholipases that cleave inositol phospholipids, generating fragments that help relay the signal into the cell (see also Figure 15-38). (C) The sites where different classes of phospholipases cleave phospholipids. The structure of phosphatidylinositol (4,5) diphosphate is shown. Phospholipases C operate in the signaling pathways shown in (B).

In other cases, specific lipid head groups must first be modified to create protein-binding sites at a particular time and place. *Phosphatidylinositol*, for instance, is one of the minor phospholipids that are concentrated in the cytosolic monolayer of cell membranes. Various lipid kinases can add phosphate groups at distinct positions in the inositol ring, creating binding sites that recruit specific proteins from the cytosol to the membrane. An important example of such a lipid kinase is *phosphoinositide 3-kinase (PI 3-kinase)*, which is activated in response to extracellular signals and helps to recruit specific intracellular signaling proteins to the cytosolic face of the plasma membrane (Figure 10-17A). Similar lipid kinases phosphorylate inositol phospholipids in intracellular membranes and thereby help to recruit proteins that guide membrane transport.

Phospholipids in the plasma membrane are used in yet another way to convert extracellular signals into intracellular ones. The plasma membrane contains various *phospholipases* that are activated by extracellular signals to cleave specific phospholipid molecules, generating fragments of these molecules that act as short-lived intracellular mediators. *Phospholipase C*, for example, cleaves an inositol phospholipid in the cytosolic monolayer of the plasma membrane to generate two fragments, one of which remains in the membrane and helps activate protein kinase C, while the other is released into the cytosol and stimulates the release of Ca^{2+} from the endoplasmic reticulum (Figure 10-17B-C).

Animals exploit the phospholipid asymmetry of their plasma membranes to distinguish between live and dead cells. When animal cells undergo apoptosis (a form of programmed cell death, discussed in Chapter 18), phosphatidylserine, which is normally confined to the cytosolic monolayer of the plasma membrane lipid bilayer, rapidly translocates to the extracellular monolayer. The phosphatidylserine exposed on the cell surface signals neighboring cells, such as macrophages, to phagocytose the dead cell and digest it. The translocation of the phosphatidylserine in apoptotic cells is thought to occur by two mechanisms:

1. The phospholipid translocator that normally transports this lipid from the noncytosolic monolayer to the cytosolic monolayer is inactivated.
2. A “scramblase” that transfers phospholipids nonspecifically in both directions between the two monolayers is activated.

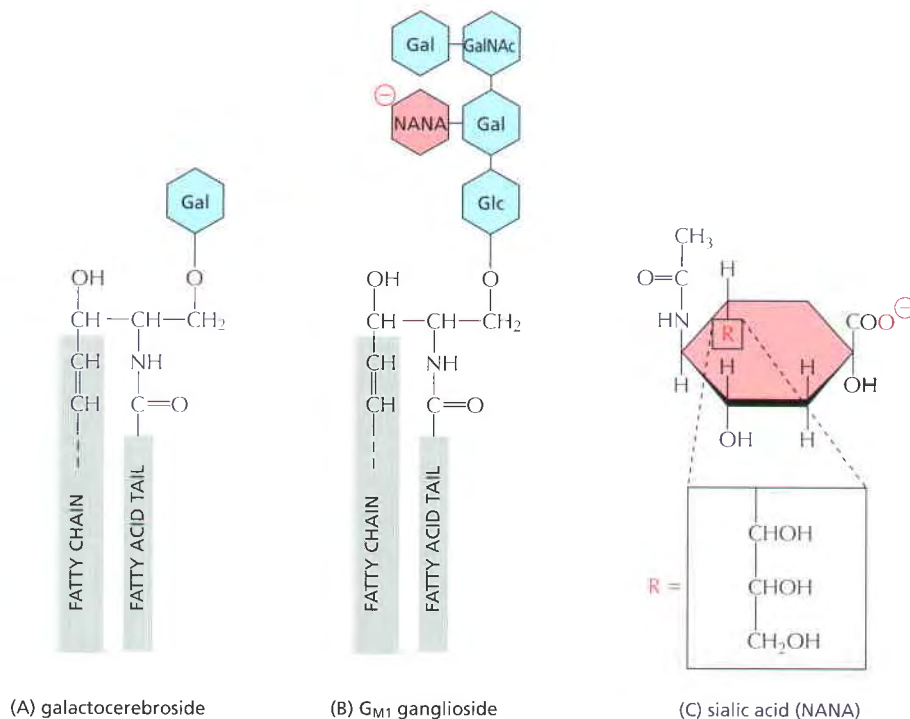


Figure 10-18 Glycolipid molecules.

(A) Galactocerebroside is called a *neutral glycolipid* because the sugar that forms its head group is uncharged. (B) A ganglioside always contains one or more negatively charged sialic acid residues (also called *N*-acetylneuraminic acid, or NANA), whose structure is shown in (C). Whereas in bacteria and plants almost all glycolipids are derived from glycerol, as are most phospholipids, in animal cells almost all glycolipids are based on sphingosine, as is the case for sphingomyelin (see Figure 10-3). Gal = galactose; Glc = glucose, GalNAc = *N*-acetylgalactosamine; these three sugars are uncharged.

Glycolipids Are Found on the Surface of All Plasma Membranes

Sugar-containing lipid molecules called **glycolipids**, found exclusively in the noncytosolic monolayer of the lipid bilayer, have the most extreme asymmetry in their membrane distribution. In animal cells they are made from sphingosine, just like sphingomyelin. These intriguing molecules tend to self-associate, partly through hydrogen bonds between their sugars and partly through van der Waals forces between their long and straight hydrocarbon chains, and they may preferentially partition into lipid rafts. The asymmetric distribution of glycolipids in the bilayer results from the addition of sugar groups to the lipid molecules in the lumen of the Golgi apparatus. Thus, the compartment in which they are manufactured is topologically equivalent to the exterior of the cell (discussed in Chapter 12). As they are delivered to the plasma membrane, the sugar groups are exposed at the cell surface (see Figure 10-16), where they have important roles in interactions of the cell with its surroundings.

Glycolipids probably occur in all animal cell plasma membranes, where they generally constitute about 5% of the lipid molecules in the outer monolayer. They are also found in some intracellular membranes. The most complex of the glycolipids, the **gangliosides**, contain oligosaccharides with one or more sialic acid residues, which give gangliosides a net negative charge (Figure 10-18). The most abundant of the more than 40 different gangliosides that have been identified are in the plasma membrane of nerve cells, where gangliosides constitute 5–10% of the total lipid mass; they are also found in much smaller quantities in other cell types.

Hints as to the functions of glycolipids come from their localization. In the plasma membrane of epithelial cells, for example, glycolipids are confined to the exposed apical surface, where they may help to protect the membrane against the harsh conditions frequently found there (such as low pH and high concentrations of degradative enzymes). Charged glycolipids, such as gangliosides, may be important because of their electrical effects: their presence alters the electrical field across the membrane and the concentrations of ions—especially Ca^{2+} —at the membrane surface. Glycolipids are also thought to function in cell-recognition processes, in which membrane-bound carbohydrate-binding proteins (*lectins*) bind to the sugar groups on both glycolipids and glycoproteins in the process of cell–cell adhesion (discussed in Chapter 19). Surprisingly, however, mutant mice that are deficient in all of their complex gangliosides

show no obvious abnormalities, although the males cannot transport testosterone normally in the testes and are consequently sterile.

Whatever their normal function, some glycolipids provide entry points for certain bacterial toxins. The ganglioside G_{M1} (see Figure 10–18), for example, acts as a cell-surface receptor for the bacterial toxin that causes the debilitating diarrhea of cholera. Cholera toxin binds to and enters only those cells that have G_{M1} on their surface, including intestinal epithelial cells. Its entry into a cell leads to a prolonged increase in the concentration of intracellular cyclic AMP (discussed in Chapter 15), which in turn causes a large efflux of Na^+ and water into the intestine.

Summary

Biological membranes consist of a continuous double layer of lipid molecules in which membrane proteins are embedded. This lipid bilayer is fluid, with individual lipid molecules able to diffuse rapidly within their own monolayer. The membrane lipid molecules are amphiphilic. When placed in water they assemble spontaneously into bilayers, which form sealed compartments.

Cells contain 500–1000 different lipid species. There are three major classes of membrane lipids—phospholipids, cholesterol, and glycolipids—and hundreds of minor classes. The lipid compositions of the inner and outer monolayers are different, reflecting the different functions of the two faces of a cell membrane. Different mixtures of lipids are found in the membranes of cells of different types, as well as in the various membranes of a single eucaryotic cell. Inositol phospholipids are a minor class of phospholipids, which in the cytosolic leaflet of the plasma membrane lipid bilayer play an important part in cell signaling: in response to extracellular signals, specific lipid kinases phosphorylate the head groups of these lipids to form docking sites for cytosolic signaling proteins, whereas specific phospholipases cleave certain inositol phospholipids to generate small intracellular signaling molecules.

MEMBRANE PROTEINS

Although the lipid bilayer provides the basic structure of biological membranes, the membrane proteins perform most of the membrane's specific tasks and therefore give each type of cell membrane its characteristic functional properties. Accordingly, the amounts and types of proteins in a membrane are highly variable. In the myelin membrane, which serves mainly as electrical insulation for nerve cell axons, less than 25% of the membrane mass is protein. By contrast, in the membranes involved in ATP production (such as the internal membranes of mitochondria and chloroplasts), approximately 75% is protein. A typical plasma membrane is somewhere in between, with protein accounting for about half of its mass. Because lipid molecules are small compared with protein molecules, there are always many more lipid molecules than protein molecules in cell membranes—about 50 lipid molecules for each protein molecule in cell membranes that are 50% protein by mass. Membrane proteins vary widely in structure and in the way they associate with the lipid bilayer, which reflects their diverse functions.

Membrane Proteins Can Be Associated with the Lipid Bilayer in Various Ways

Figure 10–19 shows the different ways in which membrane proteins can associate with the membrane. Many extend through the lipid bilayer, with part of their mass on either side (Figure 10–19, examples 1, 2, and 3). Like their lipid neighbors, these **transmembrane proteins** are amphiphilic, having hydrophobic and hydrophilic regions. Their hydrophobic regions pass through the membrane and interact with the hydrophobic tails of the lipid molecules in the interior of the bilayer, where they are sequestered away from water. Their hydrophilic regions are exposed to water on either side of the membrane. The covalent attachment of a fatty acid chain that inserts into the cytosolic monolayer of the