

Phospholipids and Membrane Structure

- 4.1** The Big Picture
- 4.2** Phospholipids Are the Basic Building Blocks of Cellular Membranes
- 4.3** The Fluid–Mosaic Model Explains How Phospholipids and Proteins Interact within a Cellular Membrane
- 4.4** The Smooth Endoplasmic Reticulum and Golgi Apparatus Build Most Eukaryotic Cellular Membrane Components
- 4.5** Chapter Summary

4.1 The Big Picture

The purpose of this chapter is to introduce the general structure and assembly of membranes. The presence of at least one membrane is required for any organism to be considered alive, but this does not mean that all membranes are alike. Recall from Chapter 1 that, despite its relatively simple structure, the carbon atom is capable of forming a multitude of different molecules; this is especially evident when one considers the molecules that compose a membrane. Unlike nucleic acids and proteins, which are built from simple nucleotide and amino acid subunits, membranes are much larger structures composed of a tremendous variety of molecules. Phospholipids are some of the most abundant molecules in membranes, so in this chapter we will focus on them; our goal is to discuss the common features shared by *all* membranes, and thus complete our survey of the building blocks of cells. We will reserve the details concerning membrane specialization for later chapters.

This chapter contains three major sections:

- Unlike nucleic acids and proteins, phospholipids are not composed of linear polymers of a small group of subunits; instead, they are branched molecules, and each branch is often unique, making it nearly impossible to memorize them all. Because of this, our strategy for learning phospholipid structure will rely heavily on generalizations, such that we can more easily understand the structural details of specific phospholipids in later chapters.
- The fluid–mosaic model explains how phospholipids and other molecules are arranged to yield a biologically functional membrane. Our focus will be on the general concepts that apply to all membranes. Understanding the implications of these concepts will be crucial when we begin discussing specific membranes in later chapters, so this idea will likely require more attention than the first.
- Phospholipid synthesis and membrane formation occur in an assembly-line-like fashion. This concerns the molecular mechanisms cells use to build phospholipids and organize them into functional membranes. Notice that the first two ideas are focused on *what* these structures are, while this idea addresses *how* they are made. It is important to understand the sequence of events, and the reasons why each step is necessary. Fully understanding this information will require solid comprehension of the basic chemistry we discussed in Chapter 1, because we will be discussing enzymatic reactions that give rise to the structurally complex molecules, including phospholipids, that compose membranes.

4.2 Phospholipids Are the Basic Building Blocks of Cellular Membranes

KEY CONCEPTS

- ▶ Of the four major classes of molecules that serve as the building blocks for cells (sugars, nucleic acids, proteins, phospholipids), phospholipids are the most structurally complex.
- ▶ Phosphoglycerides are the most common phospholipids; they are composed of two fatty acyl groups and a polar head group attached to a glycerol backbone.
- ▶ The length and degree of saturation of the fatty acyl tails can vary between different phospholipids.
- ▶ The primary function of phospholipids is to form the lipid bilayer that is characteristic of all cellular membranes.
- ▶ Phospholipid bilayers are selectively permeable to solutes.

Phospholipids are structurally and functionally different from the other cellular building blocks we have discussed in Chapters 1, 2, and 3. Before we begin our detailed examination of phospholipids, let's compare their structural properties to these other basic building blocks. In Chapter 2, we learned that nucleic acids are, structurally, some of the simplest biomolecules in cells; they are composed of only four different nucleotide subunits, joined into linear polymers by one type of chemical bond (the phosphoester bond), and stabilized as linear pairs by hydrogen bonds. The complexity of nucleic acids arises not from their basic structure, but from their *tremendous size*—the average lengths of prokaryotic and eukaryotic genes are approximately 900 and 1,300 base pairs, respectively. Structures of this size can adopt a wide variety of shapes, giving rise to the different folded forms of nucleoid and chromatin (see Chapter 2, *DNA Packaging Is Hierarchical*).

The same pattern is evident in proteins. Polypeptides are composed of 20 different amino acids, joined into linear polymers by one type of chemical bond (the peptide bond), and stabilized by five different types of chemical bonds (see Chapter 3, *Five Classes of Chemical Bonds Stabilize Protein Structure*). The average length of a protein ranges from ~250 to ~300 to ~470 amino acids in archaea, prokaryotes, and eukaryotes, respectively. Notice that over the course of evolution from archaea to eukaryotes, the length of an average protein nearly doubled.

The pattern continues for sugars. Oligosaccharides and polysaccharides are some of the most diverse types of biomolecules, yet most of them are composed of fewer than 20 monosaccharide subunits joined by a small number of bonds (principally the glycosidic bond, a form of ether bond). But size alone does not account for the tremendous diversity of oligosaccharides and polysaccharides. Cells employ *two additional strategies* for increasing variation in these structures: branching and chemical modification. In branching, sugar subunits in these polymers form polygonal, ring-like structures, and the carbon atoms that form most of the vertices in these polygons contain functional groups capable of forming covalent bonds with similar groups on other sugars. This means that a single sugar subunit (a monosaccharide) can form bonds with two or more neighboring sugars, forming a branched network (see Figure 1-14). This way, the same number of monosaccharides can be combined into multiple combinations, increasing the structural variation. This strategy does not apply to nucleic acids, and appears only rarely in proteins (in the form of disulfide bonds formed between cysteine amino acids in two different polypeptides).

The second additional strategy involves modifying the functional groups attached to carbon atoms in sugars (e.g., hydroxyl groups) by adding or substituting different functional groups (e.g., acetyl groups, phosphate groups). Each modification results in the formation of a different type of sugar subunit, greatly increasing the potential diversity of sugar polymers. We have seen this strategy employed before, in both nucleic acids (e.g., methylation, see Figure 2-18) and proteins (e.g., acetylation and phosphorylation, see Figure 3-15). This strategy is commonly used in cells.

Phospholipids also acquire their structural diversity through branching and chemical modification. Branching is so important for phospholipids that *all* phospholipids are branched (hence the complexity), and phospholipids use a special kind of chemical modification not seen in any other classes of cellular building blocks (unsaturation of hydrocarbons); this is where the bulk of the structural variation arises. Unlike oligo/polysaccharides, nucleic acids, and proteins, phospholipids are not polymers of a simple structure, and are considerably less diverse as a result. Of these four major classes of molecules, phospholipids are by far the smallest in size. The molecular weight of most phospholipids is less than 1,000 daltons, while most DNA and proteins are at least 10 to 20 times this size. The size of sugar polymers in cells varies considerably, from disaccharides (<500 daltons) to enormous polysaccharide complexes (>1 million daltons).

It is estimated that eukaryotic cells contain ~1000 different lipids (approximately one-tenth the number of different genes and proteins), including only about 20 different phospholipids. The reason for this relatively small number is that phospholipids perform far fewer unique functions than the other cellular building blocks. This does not mean that these functions are less important: phospholipids are absolutely essential ingredients in any cellular membrane. Instead of focusing on the tremendous number of possible different structures (as we did for proteins in Chapter 3), let's pay attention to the subtle changes we find between different phospholipids. The reason these changes are important is that they ultimately impact the overall structure of the membrane that contains them. And recall from Chapter 1 that the structure–function relationship predicts that when these structures adopt different shapes, they perform different functions in cells.

■ ■ Phospholipids Contain Four Structural Elements

Like nucleic acids and proteins, phospholipids have a backbone, which serves as an attachment site for different functional groups, as shown in **FIGURE 4-1**. What makes this backbone different, however, is that it does not form covalent bonds with other phospholipid molecules (i.e., make polymers). Each phospholipid is a separate molecule in a membrane.

■ ■ Glycerol Is a Three-Carbon Sugar-Alcohol

Two molecules serve as backbones for phospholipids (**BOX 4-1**). The more common backbone is a three-carbon sugar-alcohol known as **glycerol**. Glycerol contains three carbon atoms linked together by single bonds, and each carbon atom is also attached to two hydrogen atoms and a hydroxyl group, allowing each carbon atom to arrange the four bonds in a tetrahedral arrangement (see Figure 1-9). Phospholipids constructed from a glycerol backbone are called **phosphoglycerides**, to distinguish them from a phospholipid called **sphingomyelin**, which contains a different backbone molecule. Because they are the most abundant type of phospholipids, we will first focus our attention on the phosphoglycerides.

■ ■ The Lipid Portion of a Phospholipid Can Vary Widely in Structure

Phospholipids are named as such because they contain lipids. Recall from Chapter 1 that lipids are long, linear polymers made up almost entirely of carbon and hydrogen, which makes them very hydrophobic. Phospholipids contain two lipids called **fatty acids** because they contain a carboxylic acid group at one end. (The remaining portion of the fatty acid is often called the tail.) The ester bond is formed by a dehydration reaction involving a hydroxyl group on glycerol and the hydroxyl group on the carboxylic acid of a fatty acid. The formation of these bonds is never random: one fatty acid attaches to a terminal carbon of glycerol, and the second attaches to the middle carbon atom, as shown in Figure 4-1. The two fatty acids that attach to a glycerol backbone do not need to be identical.

Because there are two fatty acids in each phospholipid, the number of combinations found in different phospholipids is simply twice the number of different fatty acids found in cells. Most cells contain about 10 fatty acids, and they are classified into 2 structural groups, shown in **FIGURE 4-2**. One group contains fatty acids with only single covalent

BOX 4-1 TIP

Beware of falling into the jargon trap. The rest of this chapter introduces a lot of words that may be new to most beginning cell biology students, especially the names of specific molecules. This can sometimes give the illusion that the concepts behind these names are terribly complicated, but that is typically not true. If the name of a molecule causes confusion, rename it and move on. After getting comfortable with how these molecules function, go back and learn their proper names.

Phospholipids are often abbreviated in this style.

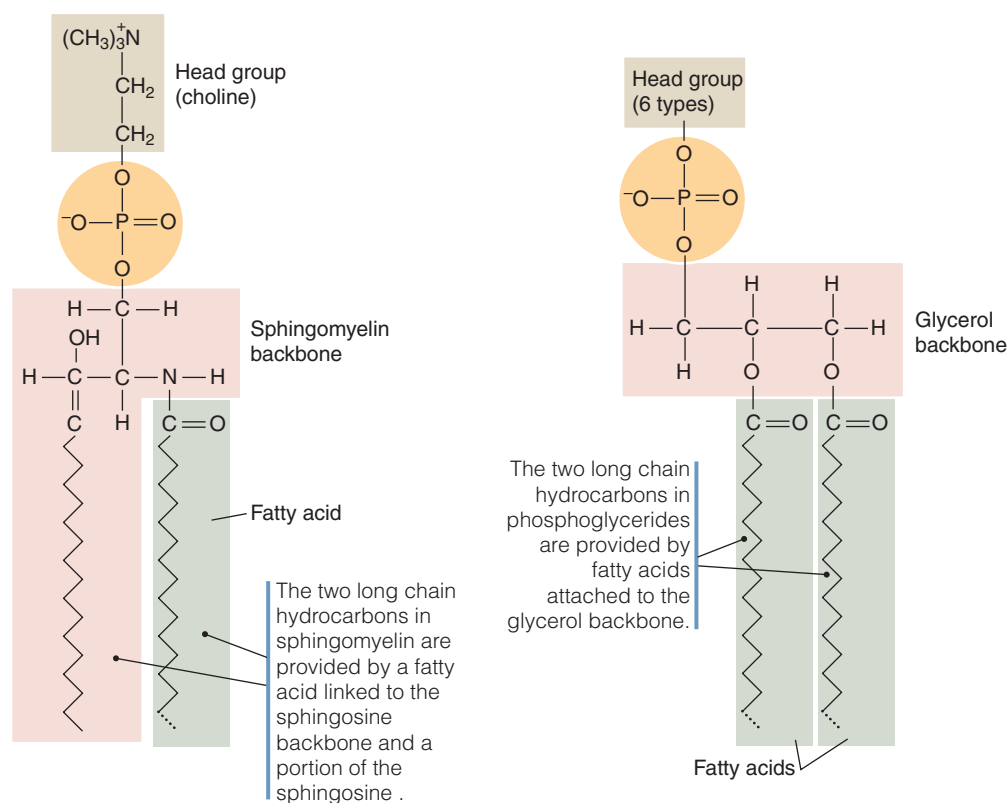
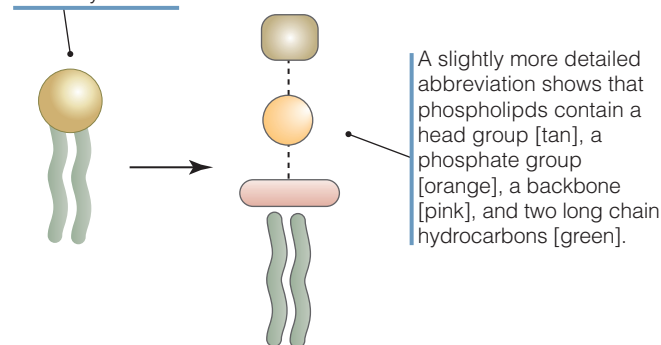


FIGURE 4-1 Phospholipid structure.

bonds (no double bonds) between the carbons in the tail; this means that as many hydrogen atoms as possible have been attached to the carbon atoms. A common name for members of this group is **saturated** (i.e., they are “fully stocked” with hydrogens). Saturated fatty acids only differ with respect to how many alkyl ($-\text{CH}_2-$) groups they contain in their tails. Due to the nature of the chemical reactions cells used to synthesize them, these fatty acids nearly always have an even number of carbons, and the three most common saturated fatty acids used to make phospholipids contain 16, 18, or 20 carbons. The tail end always contains a methyl group ($-\text{CH}_3$), and the opposite end contains the carboxylic acid group we discussed previously.

The second, more numerous class of fatty acids *does* contain double bonds between the carbon atoms in the tail. These also usually contain even numbers (16–20) of carbon atoms, but due to the varied placement of the double bonds, many more structures can be made from any given number of carbon atoms in the tail. Because of the double bonds,

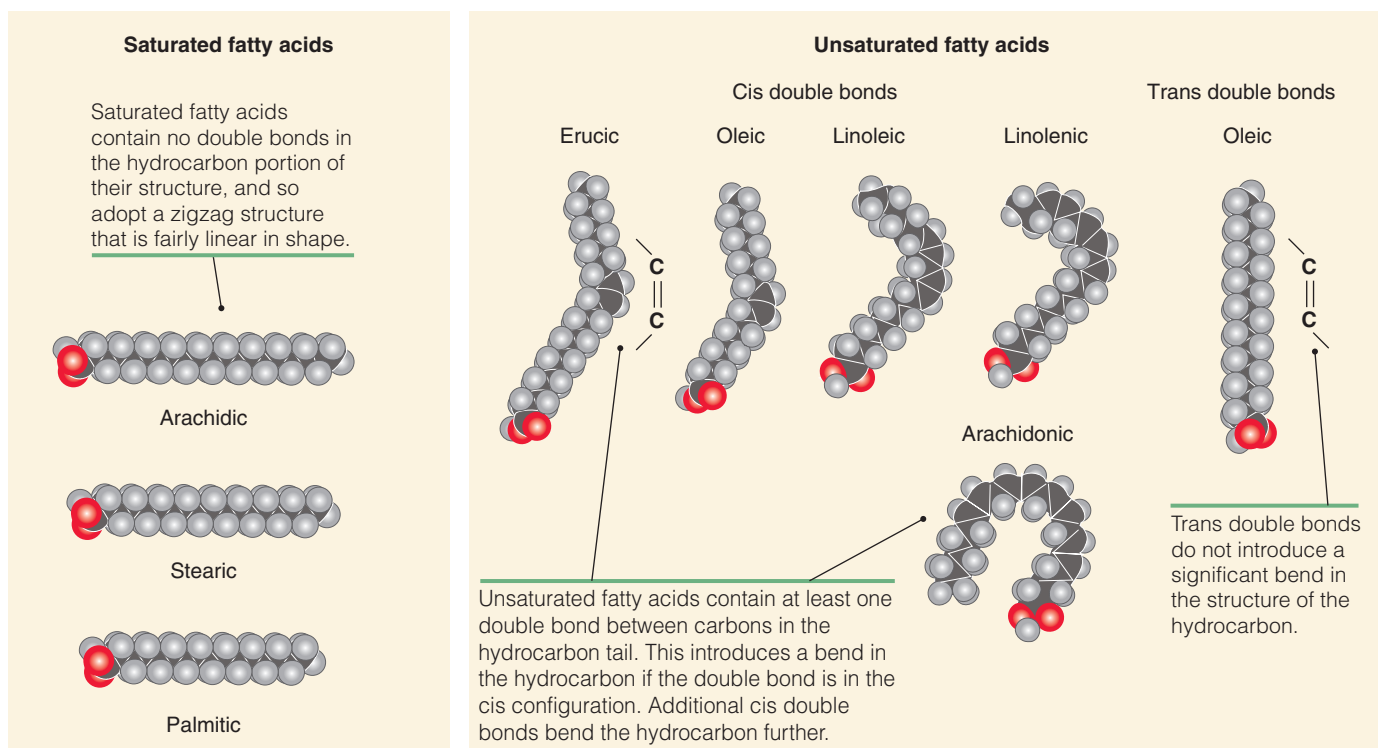


FIGURE 4-2 Two classes of fatty acids in cells.

these molecules have fewer hydrogen atoms per carbon than the saturated fatty acids, and so are called **unsaturated** fatty acids. They are further classified according to how many double bonds they contain (monounsaturated vs. polyunsaturated). Most unsaturated fatty acids in membranes contain one or two double bonds.

These double bonds are very important. Recall from Chapter 1 (see Figure 1-9) that when carbon forms four covalent bonds, these bonds are arranged as a tetrahedron around the atomic nucleus, but when it forms three bonds (i.e., combining two single bonds to form one double bond), the bonds adopt a planar, triangular orientation. This switch from a tetrahedral shape to a flat triangular one has a significant impact on the overall structure of the fatty acid tail. Whereas saturated fatty acids have zigzag tails because of the tetrahedral orientation at each carbon, two different orientations are possible for each double bond in an unsaturated fatty acid. If the upstream and downstream carbon atoms that lie on either side of the double bond are positioned on *opposite* sides of the double bond, this is called a **trans configuration**, and the fatty acid is called a **trans fatty acid**. Notice in Figure 4-2 that a fatty acid tail containing one or more trans bonds assumes a somewhat linear configuration, fairly similar to that for a saturated fatty acid. But, if the upstream and downstream carbon atoms lie on the *same* side of the double bond (called the **cis configuration**), the fatty acid assumes a very different shape. These **cis fatty acids** have “kinks,” or bends, in their tails. As the number of cis double bonds increases, so does the degree of bending; note that arachidonic acid, which contains four cis double bonds, actually forms a U shape.

■ Polar Head Groups Confer Additional Specificity on the Structure of Phospholipids

The third structural element in phospholipids is known as the **head group**. The six head groups attached to phosphoglycerides in eukaryotic cells are shown in **FIGURE 4-3**. Note that three of these are ionic (PC, PE, PS), and three (PI, PG, the *bis*-glycerol portion

of CL) are clearly polar, due to the high number of hydroxyl groups they contain. All six are linked to the glycerol backbone by a **phosphate group**. The presence of a polar (charged) head group makes this portion of the phospholipid hydrophilic; as a result, these head groups attract water, while the hydrophobic lipid tails repel water.

Because phosphoglycerides are composed of three different functional groups in addition to the glycerol backbone, their formal names are often quite long. For example, a phosphoglyceride built from one stearic acid, one oleic acid, a choline head group, a phosphate group, and a glycerol backbone is called 1-stearoyl-2-oleoyl-phosphatidylcholine. (Note that even a name this long does not mention how many double bonds the oleic acid has, or whether the double bonds are arranged in a cis or trans configuration.) To avoid being bogged down by these long names, most scientists use only the latter portion of the name (e.g., phosphatidylcholine), or even just a simple acronym (e.g., phosphatidylinositol is often abbreviated PI, as shown in Figure 4-3). As a result, the precise lipid composition of individual phospholipids is often not considered in discussions of membrane structure.

The combination of six different head groups and variations in fatty acid structures gives rise to about 1,000 distinct phosphoglycerides in eukaryotic membranes.

■ The Amphipathic Nature of Phospholipids Allows Them to Form Lipid Bilayers in Aqueous Solution

Molecules like phospholipids that both attract and repel water are called **amphipathic**. Amphipathic molecules have characteristic properties when they are added to water, the most noticeable being that they spontaneously aggregate into groups or clusters; this occurs because clustering is energetically favorable. All molecules added to liquid water, regardless of their chemical makeup, have to interact with the nearest water molecules, and this interaction imparts some degree of structural organization on these water molecules (this is sometimes referred to as the **water shell** or **hydration shell**). Recall from Chapter 3 that the laws of thermodynamics state that all molecules, including water, seek an energy state with the highest degree of entropy. The water molecules in the hydration shell have low entropy, so the fewer water molecules necessary to form a hydration shell, the better. The hydrophobic portions of phospholipids aggregate because this reduces the number of water molecules in the hydration shell surrounding them.

When purified phospholipids are added to liquid water, they form three characteristic structures, as shown in **FIGURE 4-4**. The smallest of these is simply a ball, called a **micelle**. The hydrophobic tails of the phospholipids aggregate in the center of the micelle, and the hydrophilic head groups spread out to form the surface facing the water. The next larger structure is called a **liposome**; it resembles a micelle that has formed a shell around an inner compartment of water. Because the phospholipids interact with water at both the

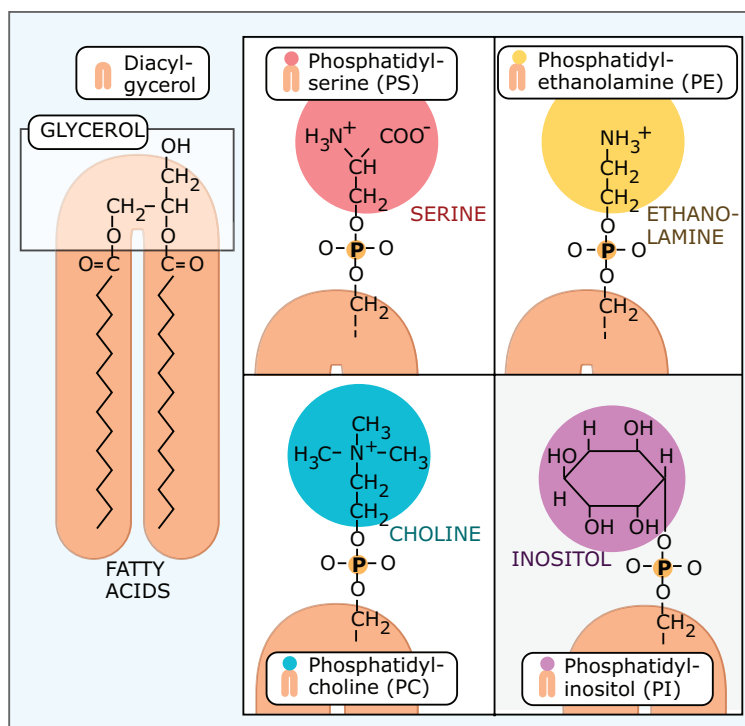


FIGURE 4-3 Six phosphoglycerides in eukaryotes. Each of the four components is indicated in color.

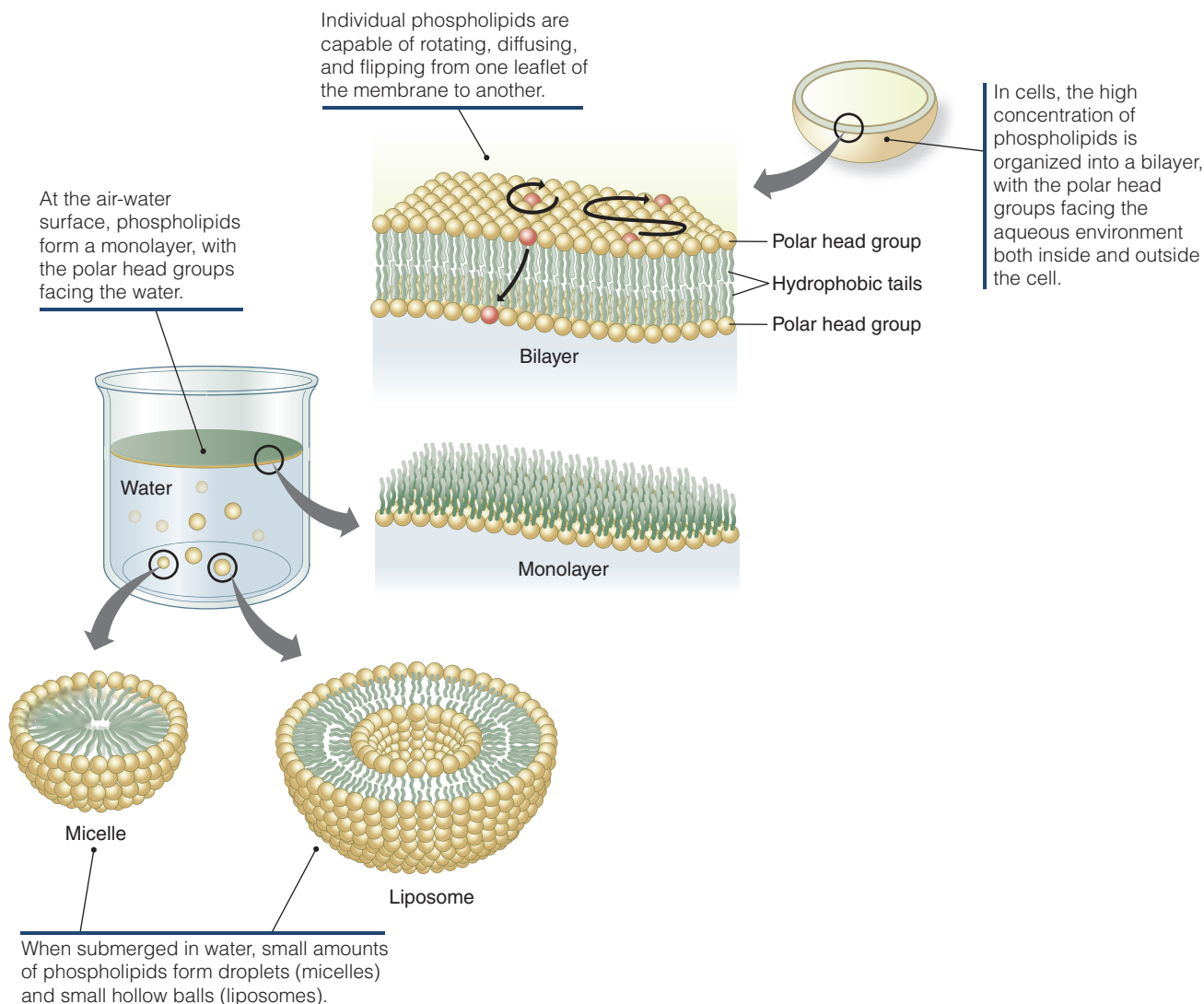


FIGURE 4-4 Four forms of phospholipid clusters.

inner and outer surfaces, they reorganize to form two layers. Notice that the hydrophobic tails of both layers cluster together, away from the water.

Micelles and liposomes do not typically form in most cells. However, because cellular membranes enclose aqueous compartments just as liposomes do, the phospholipids in membranes are oriented in essentially the same fashion. The largest structure formed by phospholipids interacting with water is a **monolayer**, formed at the air-water surface. Cells contain water on both sides of their membranes, so every cellular membrane contains phospholipids oriented in a **bilayer** (composed of two **leaflets**), with a single hydrophobic interior and two hydrophilic surfaces that interact with water, shown in Figure 4-4. This bilayer forms spontaneously, requiring no energy input or assistance from cells.

■ Individual Phospholipids Can Diffuse Freely within a Single Layer

Because phospholipids are not covalently attached to one another, they can diffuse within each leaflet, as seen in Figure 4-4. Note that the hydrophobic tails in the membrane interior repel the polar head groups, discouraging spontaneous flipping of phospholipids from one leaflet to the other. In effect, membranes serve as diffusion barriers for their own

BOX 4-2

The soap bubble demonstration. One easy way to observe the fluidity in a membrane is to blow a soap bubble in a well-lit area and watch as the surface of the bubble changes color. This change in color is caused by variation in the thickness of the bubble surface. The detergent molecules that form the bubble exhibit the same kind of fluidity that phospholipids have in a bilayer. When the bubble finally pops, notice that it leaves a wet spot where it lands, indicating that a membrane is a fluid.

phospholipids, making it difficult for them to flip from one side of the hydrophobic interior to the other. Phospholipid bilayers are sometimes described as two-dimensional fluids because of this restricted diffusion (**BOX 4-2**).

■ Lipid Bilayers Are Asymmetrical

Because phospholipids do not typically spontaneously flip from one side of a membrane bilayer to the other, the relative concentration of individual phospholipids on two sides of the same membrane can differ. For example, phosphatidylcholine (PC) is concentrated in the external leaflet of the plasma membrane, and phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylinositol (PI) in the cytoplasmic leaflet. The functional consequences of this asymmetry are not well understood, but the loss of asymmetry is usually a property of a damaged or dying cell. The distribution of phospholipids in the two leaflets of a membrane is regulated by three classes of proteins that we will discuss later in this chapter.

■ Phospholipid Bilayers Are Semipermeable Barriers

Because the hydrophobic tails of phospholipids are concentrated in the interior of a membrane, they repel most hydrophilic molecules and form a barrier to diffusion from one side of the membranes to the other. This is the structural foundation for the selective barrier we discussed at the beginning of Chapter 1. Using artificial membranes composed entirely of phospholipids (i.e., no proteins or other cellular materials), scientists have measured the permeability of phospholipid bilayers to a variety of chemicals that cells commonly encounter, and they observe three simple trends, illustrated in **FIGURE 4-5**:

- **Small molecules are more permeable than large molecules.** Water (molecular weight: 10 daltons), molecular oxygen (O_2 ; 16 daltons), and carbon monoxide (CO; 14 daltons) are among the smallest molecules in cells, and they diffuse through lipid bilayers quite easily. Larger molecules (sugars, amino acids, nucleotides) cannot diffuse through lipid bilayers.
- **Nonpolar molecules are more permeable than polar molecules.** Remember that the hydrophobic tails of the phospholipids are the primary barriers to diffusion. Therefore, the more nonpolar a molecule is, the more easily it can pass through a membrane. Nitrous oxide (NO), O_2 , and CO_2 have little to no electrical polarity and diffuse quite easily. Methane (CH_4), ethanol (CH_3-CH_2-OH), and propane (C_3H_8) are very hydrophobic, and therefore also readily diffuse through the hydrophobic region of a phospholipid bilayer.

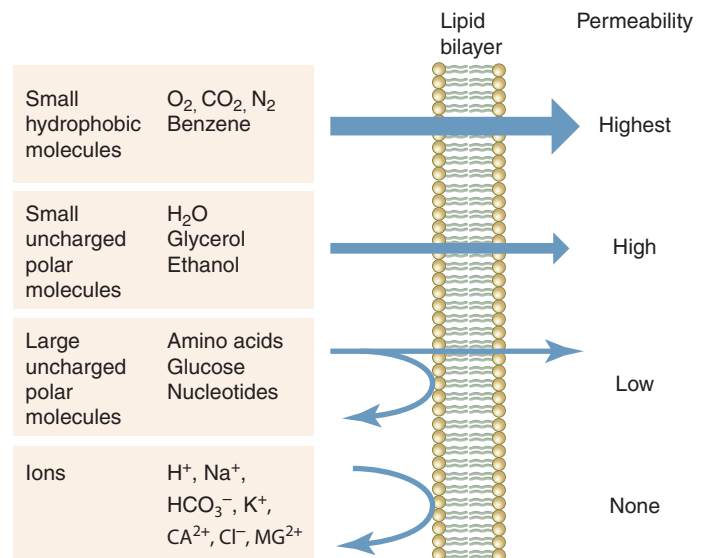


FIGURE 4-5 Phospholipid bilayers have varying permeability to solutes.

- **Charged molecules do not diffuse.** Any charged molecule, regardless of size, is repelled by the hydrophobic portion of a lipid bilayer and therefore cannot diffuse. This includes ions (H^+ , Ca^{+2} , Na^+ , K^+ , Cl^- , HCO_3^- , PO_4^{-2} , etc.). This is one of the most useful properties of phospholipid bilayers, because it allows cells to build gradients of ions and other charged molecules on one side of a membrane, a topic we will cover in Chapter 10.

One shorthand means of estimating the membrane permeability of a given molecule is called the partition coefficient (abbreviated D). The formal definition of this value is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium. In organic chemistry, the value reflects the relative solubility of a molecule in a hydrophobic solvent (e.g., a liquid hydrocarbon such as octanol) versus its solubility in liquid water. In general, the higher the D value, the more membrane permeable a compound is.

■ Maintaining a Chemical Imbalance across a Membrane Is Essential for Life

Recall from Chapter 1 that for a cell to remain alive, it must *never* be in chemical equilibrium with its surrounding environment. One of the easiest ways to remain out of equilibrium is to build a gradient of impermeable molecules on one side of the plasma membrane. All cells do this routinely by pumping ions from one side of the plasma membrane to the other. Prokaryotes use specialized proteins to pump H^+ or Na^+ ions from their cytosol into the extracellular environment, while eukaryotes use a protein that creates two gradients simultaneously: it pumps K^+ ions into the cytosol while pumping Na^+ ions out of the cytosol. We will have a much closer look at ion pump proteins in Chapters 10 and 11.

CONCEPT CHECK #1

Nonpolar amino acids contain a hydrophobic side chain attached to a polar backbone, similar to the structure of phospholipids. Why do polymers of amino acids (i.e., proteins) form such a wide variety of shapes, while clusters of phospholipids do not?

4.3 The Fluid–Mosaic Model Explains How Phospholipids and Proteins Interact within a Cellular Membrane

KEY CONCEPTS

- ▶ The fluid–mosiac model of membrane structure, proposed in the 1970s, forms the foundation for our current model of membrane structure.
- ▶ The updated version of the fluid–mosaic model emphasizes the mosaic property of membranes by introducing clusters of phospholipids, proteins, and cholesterol called lipid rafts.
- ▶ Proteins associate with membranes in three different ways.
- ▶ The transmembrane portion of most membrane-spanning proteins form an α -helix.
- ▶ The fluidity of membranes is dynamic and sensitive to four different variables.
- ▶ Some membranes contain immobilized protein complexes that permit stable attachment of the membrane to surfaces such as other cells or extracellular molecules.

All membranes are made up of three principal ingredients: *phospholipids* (phosphoglycerides and others), *other lipids* (primarily cholesterol and compounds called glycolipids), and *proteins* (BOX 4-3). Even in the early 20th century, identifying these ingredients was fairly straightforward, but assembling this information to create an accurate picture of a membrane was quite challenging. A good example is the bilayer organization of phospholipids: virtually nothing else in nature is arranged as a bilayer, so it was not at all obvious that membrane

BOX 4-3 TIP

Refer to Figure 1-10 for an illustration of lipid structures, including cholesterol.

phospholipids are arranged in this fashion. In 1972, Drs. S. Jonathan Singer and Garth Nicholson assembled the findings of decades of studies and proposed the **fluid–mosaic model** for membrane organization, shown at the top of **FIGURE 4-6**, which represented a tremendous advance in our understanding of how cells are built. The central tenet of this model is that a membrane resembles a mosaic pattern, wherein the phospholipid bilayer acts like a planar fluid, with membrane proteins floating randomly within it, supported by hydrophobic interactions between phospholipid tails and hydrophobic amino acids. (Cholesterol molecules were proposed to float in the phospholipid fluid, acting as “spacers” to maintain proper fluidity of the phospholipids.) Initially, the proteins were thought to be relatively scarce relative to the phospholipids, and have minimal interactions with them.

Recent evidence suggests that the picture is far more complicated, so changes have been made to the model, as shown at the bottom of Figure 4-6:

- We now know that most membrane proteins are extremely large, dwarfing the surrounding phospholipids, and that they can cluster to form large patches (sometimes called **lipid rafts**) that are chemically and physically distinct from the surrounding membrane. These patches contain proteins, phospholipids, and other lipids (especially cholesterol) bound together tightly enough to resist chemical disruption, though they are not covalently linked. One scientist, David M. Engelman, summarized this finding as, “membranes are more mosaic than fluid.”²

Original fluid–mosaic model

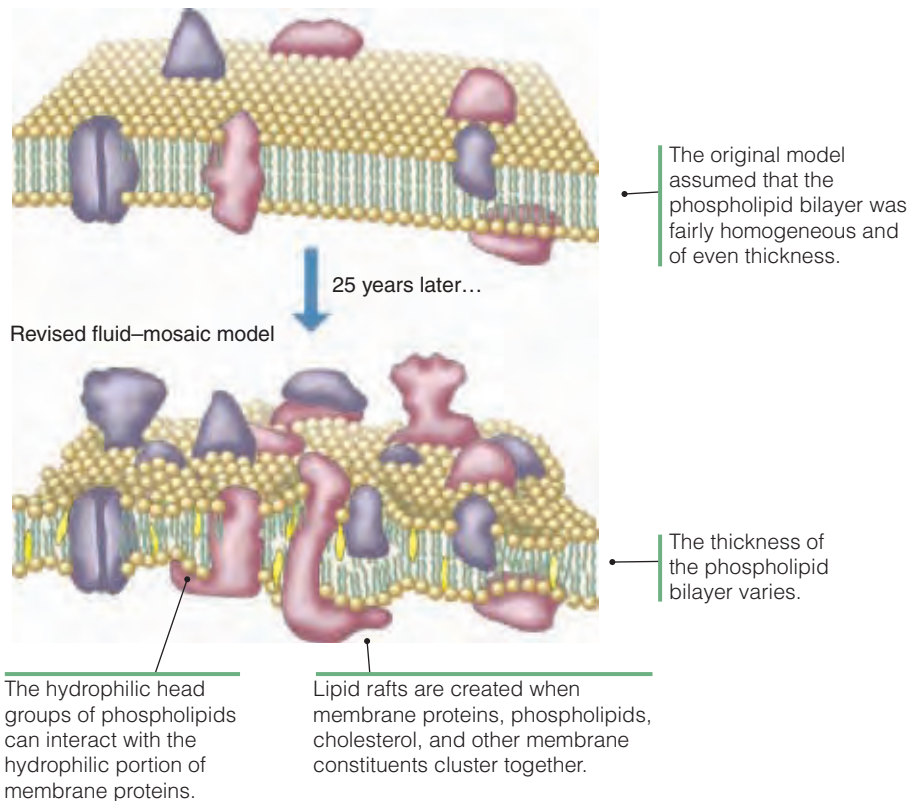


FIGURE 4-6 The evolution of the fluid–mosaic model.

² Membranes are more mosaic than fluid. *Nature* 438, 578–580 (1 December 2005) | doi:10.1038/nature04394.

- Hydrophilic portions of phospholipids also associate with membrane proteins. Due to their relatively large size, membrane proteins can spread out over the surface of a membrane, allowing the hydrophilic head groups of phospholipids to form noncovalent bonds with hydrophilic regions of the proteins. This may be one means for stabilizing lipid rafts.
- The interaction of both hydrophilic and hydrophobic portions of phospholipids with membrane proteins distorts phospholipids from the idealized planar arrangement suggested by the original fluid–mosaic model. The implication of this is that due to these differences in phospholipid arrangement, there are variations in the thickness of a membrane.
- The formation of lipid rafts and distortions of the phospholipid bilayer by membrane proteins change over time—a membrane is *dynamic*. How cells control membrane fluidity and the formation or dissolution of lipid rafts is still not very clear (BOX 4-4).

Membrane Proteins Associate with Membranes in Three Different Ways

Membrane proteins are organized into three classes, according to how they associate with the lipid bilayer, as shown in **FIGURE 4-7**:

1. **Integral membrane proteins** are embedded into the lipid bilayer. They can either bend a portion of their structure into the bilayer (these are called **monotonic proteins**), or span the bilayer entirely (these are called **membrane-spanning**, or

BOX 4-4

The pool analogy. One way to visualize the *traditional* fluid–mosaic model is to imagine pouring enough ping-pong balls into a swimming pool to cover almost the entire surface. If we watched them long enough, we'd see that the balls do not stay in one place. They jostle about and appear to flow over the water surface. This is a good approximation of how the head groups of phospholipids move in a fluid membrane (the fatty acid tails would be underneath the balls, in the water). To represent proteins in the membrane, we could throw in some buoyant objects (rubber ducks, beach balls, empty soda bottles, etc.). They too would flow over the surface, but not as quickly. Cholesterol molecules could be represented by blocks of wood: they float on the surface of the pool, but don't project above the ping-pong balls (i.e., they would be mostly submerged).

To incorporate the recent modifications of the fluid–mosaic model, we could make the following changes: (1) our protein objects would have to be much larger—imagine replacing some of the rubber ducks, and beach balls with much larger objects, such as air mattresses or floating pool lounge chairs, and increasing their numbers so they become a much greater percentage of the objects in the pool; and (2) we'd have to add some sort of sticky substance to the protein objects that could capture some of the ping-pong balls and wood blocks and permit the proteins to stick together, even if for a short time. If a group of floating chairs, ping-pong balls, and wood blocks clustered together because of the sticky tape, that complex would represent a lipid raft.

Note that our revised pool surface would be much less uniform than the one we began with. Floating complexes / lipid rafts would be mostly immobile, while individual balls, blocks, and protein objects would flow around them. And, because the proteins have such diverse shapes and are moving, the ping-pong balls and wood blocks around them would not be arranged in an even, flat plane. Some might be slightly submerged for a while, and others could be projecting out of the pool by a small amount. Finally, imagine that if we waited long enough, we would see these clusters would break up and reform; no single “picture” of this pool would represent what is happening, because everything is moving.

Also, don't forget that a membrane is a bilayer, so this scene plays out on both sides of the membrane.

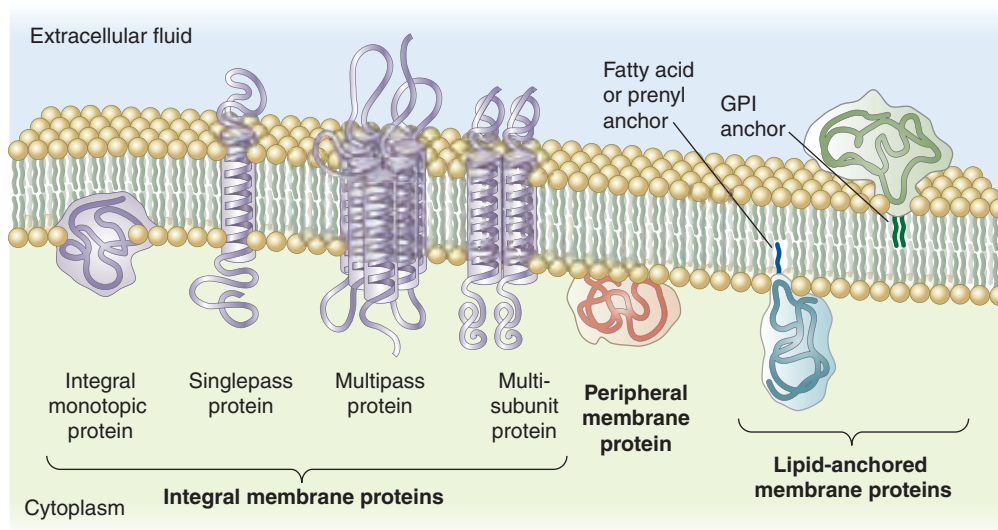


FIGURE 4-7 Three classes of membrane proteins. Each class is represented by a different color protein.

transmembrane proteins). The portion of these proteins that lies within the plane of the bilayer must contain enough hydrophobic amino acids to stabilize its interactions with the phospholipid tails. Membrane-spanning proteins may have one (called **singlepass**) or more (**multipass**) regions that extend entirely through the membrane bilayer. We will discuss how transmembrane proteins achieve these orientations in Chapter 8. In some cases, two or more transmembrane polypeptides bind together to form a multi-subunit transmembrane protein (**BOX 4-5**).

2. **Lipid-anchored membrane proteins** do not actually penetrate the lipid bilayer at all. Instead, they have a lipid covalently attached to the end of a cysteine amino acid (see Chapter 3, *Covalent Modifications Are Relatively Long Lasting*). Two types of lipids, called **prenyl groups**, are attached to the cysteine amino acids of some proteins. Notice that both the farnesyl and geranylgeranyl lipids contain long, trans-polyunsaturated regions that project outward from the cysteine side chain. Similarly, a modified phospholipid called **glycophosphatidylinositol** (GPI) can be attached to the carboxy terminus of some membrane proteins. These long hydrocarbon chains penetrate the lipid bilayer to associate with the hydrophobic interior of a membrane, thus serving as anchors to keep a protein associated with a membrane.
3. Some proteins are classified as membrane proteins even if they do not come into direct contact with the lipid bilayer. These **peripheral membrane proteins** bind to integral membrane proteins, and this binding is stable enough to effectively immobilize them at or near the surface of a membrane. These proteins are classified as membrane proteins because they typically remain associated with isolated membranes and/or membrane proteins when a cell is lysed (broken apart).

BOX 4-5 TIP

For an example of a dimeric membrane spanning protein, see Figure 6-18, (an integrin).

■ Transmembrane Proteins Typically Use Alpha Helices to Cross the Lipid Bilayer

Despite the multitude of possible shapes that proteins can adopt, virtually all of those that are known to completely span a membrane use the same types of secondary structures in their membrane-spanning regions. As we discussed in Chapter 3 (see *Secondary Structure Is Defined by Regions of Repetitive, Predictable Organization in the Primary Structure*), α -helices and β -sheets are two of the most common secondary structures found in proteins. Of those transmembrane proteins whose secondary structures are known, the most common secondary structure formed by the amino acids in the interior of a membrane is an α -helix.

By taking a look at the orientation of an α -helix within a phospholipid bilayer (**FIGURE 4-8**), we can see why this is true. Remember that the polypeptide backbone for all proteins is polar, due to the presence of the oxygen and nitrogen atoms. These two atoms stabilize secondary structures by forming hydrogen bonds. But the hydrophobic region created by

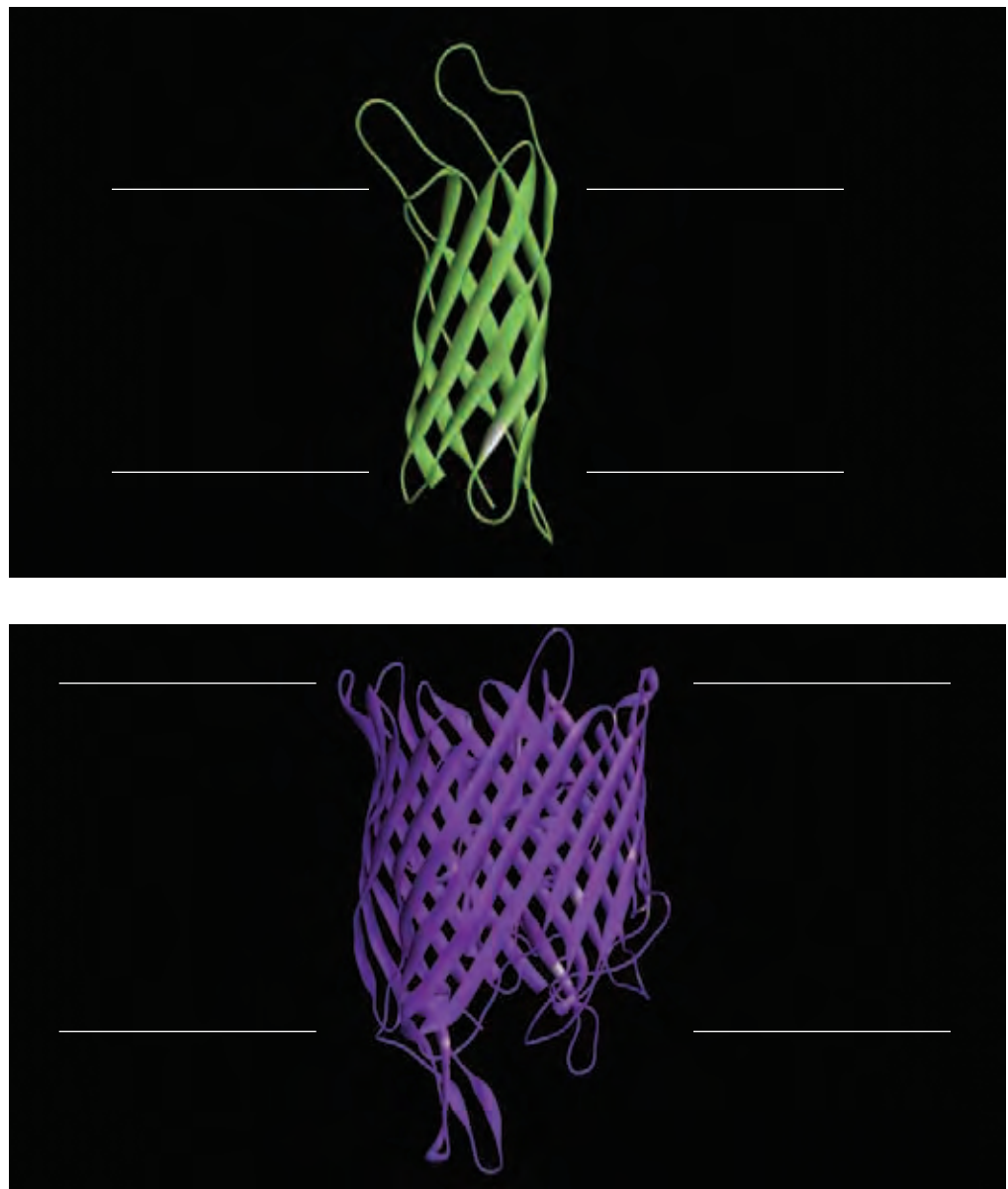


FIGURE 4-8 The orientation of alpha helices and beta sheets in transmembrane portions of integral membrane proteins.

phospholipid tails in a membrane is nonpolar, and discourages hydrogen bond formation. We therefore encounter a problem: how can a protein, which always has polar atoms in its backbone, remain stable in the hydrophobic interior of a membrane? The answer is elegantly simple. By forming an α -helix, a protein is able to completely surround the polypeptide backbone with hydrophobic amino acid side chains while preserving the hydrogen bonds formed along the backbone. Because the side chains always project outward from an α -helix (see Figure 3-6), these side chains can interact with the phospholipid tails, effectively stabilizing the amino acids forming the α -helix in the membrane interior. This results in two forms of complementary stabilization: the hydrogen bonds in the backbone stabilize the α -helix, while the hydrophobic side chains anchor the helix in the lipid portion of the membrane.

Therefore, the membrane-spanning region of a singlepass membrane protein is typically a single α -helix composed of mostly hydrophobic amino acids. If an integral membrane protein contains more than one transmembrane region, they may cluster together; in this case, the portion of each α -helix that remains in contact with the phospholipid tails must be hydrophobic, but the side that binds to the other α -helices can vary considerably, and may even contain a large number of polar and/or ionic amino acids, as illustrated in Figure 4-8. We will see examples of multispanning proteins like these in Chapters 10, 11, and 14.

Beta sheets, usually arranged in an antiparallel fashion, are also found in membrane-spanning regions of integral membrane proteins, though they are less common. When these sheets are large enough, they bend to create a cylindrical structure called a β -barrel, as shown in Figure 4-8. Some of these barrels serve as membrane channels. Many channel-like barrels have alternating hydrophobic and hydrophilic amino acids in each strand. This distribution of amino acids creates both a hydrophobic face and a hydrophilic face on the β -sheets. The hydrophobic face projects outward into the phospholipid tails, while the hydrophilic side of the barrel faces inward, facilitating transport of hydrophilic solutes and water through the membrane.

■ Cellular Membranes Are Both Fluid and Static

Every membrane in a cell has its own distinct structure and function. Some are quite porous, such as the outer membrane of gram-negative bacteria, while others, such as the inner membrane of mitochondria and chloroplasts, are permeable to only a small number of molecules. Likewise, membranes can vary in their degree of fluidity: the endoplasmic reticulum and Golgi membranes in eukaryotic cells permit a great deal of diffusion of phospholipids and membrane proteins, whereas in most cells, some regions of the plasma membrane are much more static and heterogeneous. Because each membrane is composed of a unique combination of different phospholipids and proteins, plus varying amounts of other lipids, cells can customize their membranes to optimize the functions they perform. We will see numerous examples of specialized membranes in later chapters.

■ Membrane Fluidity Is Sensitive to at Least Four Different Variables

The balance point between membrane fluidity and structural stability is determined by a number of different factors. In most experiments concerning membrane fluidity, small probe molecules are added to a membrane, and then their movements are tracked over time with a microscope (note that the fluidity of the phospholipids themselves is not typically measured). The farther the probes move over time, the greater the fluidity of the membrane. Because membrane phospholipids are smaller than membrane proteins and act independently from one another, their chemical composition contributes a great deal to the overall fluidity of most membranes. Specifically, the length and saturation of lipid tails affects membrane fluidity, according to two very simple trends:

- Phospholipids containing short (≤ 16 carbon atoms) lipid tails increase membrane fluidity, relative to those containing long lipid tails (> 16 carbon atoms).
- Cis unsaturated fatty acid tails have kinks induced by the cis double bonds, and therefore occupy a greater volume of space in a membrane than a saturated fatty acid tail of the same length. This increased volume decreases the density of phospholipids in a membrane, and ultimately leads to an increase in membrane fluidity.

Other variables also impact membrane fluidity:

- The amount of cholesterol, a common lipid component of most membranes, present makes a big difference. Other than a single hydroxyl group that interacts with water, cholesterol is composed entirely of carbon and hydrogen, and is therefore very hydrophobic. It inserts spontaneously into membranes, and interacts primarily with the tails of membrane phospholipids. The concentration of cholesterol varies considerably in different cellular membranes (**TABLE 4-1**). At low concentrations (approximately 10–30% of the total number of molecules in a membrane), its rigid, planar structure allows it to act as a spacer between phospholipids, thereby increasing their motion and the associated fluidity of a membrane. At higher concentrations (around 50%, as in most eukaryotic plasma membranes), cholesterol can actually have the opposite effect, making a membrane more rigid (**BOX 4-6**).
- Temperature and atmospheric pressure affect the motion of membrane constituents. A rise in temperature increases the Brownian motion (random movement) of every component of a membrane, and this increased motion translates to increased fluidity. In addition, significant changes in pressure, such as when a marine mammal such as a whale dives thousands of meters below the ocean surface, will literally compress the constituents of cellular membranes into smaller volumes, thereby hindering diffusion and decreasing fluidity.

■ Membrane Components Can Form Large Molecular Complexes with Little or No Mobility

Membranes or membrane patches do not always need to move to be useful. For example, multicellular organisms use proteins embedded in their plasma membrane to adhere to one another, as shown in **FIGURE 4-9**. To be stable, these so-called **cell–cell junctions** have to be held in place by clusters of proteins in the cell interior. All of this binding between cytosolic

TABLE 4-1 Major lipid components of selected biomembranes.

Source/Location	COMPOSITION (MOL %)			
	PC	PE + PS	SM	Cholesterol
Plasma membrane (human erythrocytes)	21	29	21	26
Myelin membrane (human neurons)	16	37	13	34
Plasma membrane (E. coli)	0	85	0	0
Endoplasmic reticulum membrane (rat)	54	26	5	7
Golgi membrane (rat)	45	20	13	13
Inner mitochondrial membrane (rat)	45	45	2	7
Outer mitochondrial membrane (rat)	34	46	2	11
Primary leaflet location	Exoplasmic	Cytosolic	Exoplasmic	Both

PC = phosphatidylcholine; PE = phosphatidylethanolamine; PS = phosphatidylserine; SM = sphingomyelin.

BOX 4-6

The dance floor analogy. To visualize the relationship between fatty acid saturation, cholesterol concentration, and membrane fluidity, let's imagine the dynamics on a crowded dance floor, with the dancers playing the role of the phospholipids. If everyone dances with their arms flat against their side and their legs almost perfectly straight (i.e., mostly jumping up and down), they take up relatively little space, so more dancers can fit on the floor. This is analogous to a membrane composed entirely of fully saturated phospholipids. To create more room for the dancers, one can add a cholesterol analog: nondancing elements, such as security staff (bouncers). The dancers have to make room for the bouncers, so they increase their movement (fluidity) as the bouncers walk across the floor (i.e., moving bouncers always leave a wake). This is how a low concentration of cholesterol can *increase* membrane fluidity—the cholesterol disrupts the packing of the phospholipids, and creates spaces where more movement can take place. If one had approximately equal numbers of dancers and bouncers on the floor (a 1:1 ratio, as in some regions of the plasma membrane), the dancers would have a much harder time moving about; they might even be boxed in by some of the bouncers. This is why high concentrations of cholesterol *decrease* membrane fluidity.

Now, imagine the same scenario, except we will introduce unsaturated fatty acids. Let the legs of the dancers represent the fatty acyl tails of the fatty acids. Saturated and trans unsaturated fatty acids are relatively straight, but cis unsaturated fatty acids are bent. So, if we imagine that one of the two fatty acids on the phospholipids is cis unsaturated, this is represented by having some of the dancers bend one of their legs at the knee. Now, when these “cis unsaturated” dancers move, they occupy much more space, due to their lower legs sticking outward. A dance floor containing a combination of saturated and cis unsaturated dancers is more fluid than one containing only saturated dancers; cis unsaturated phospholipids increase membrane fluidity, by creating space to move.

and membrane proteins results in the formation of some very large molecular complexes. Similar clustering of proteins in the plasma membrane occurs when cells bind to elements of the extracellular matrix, forming **cell–matrix junctions**. Regardless of the type of fatty acid chains in the phospholipids, or the amount of cholesterol in a membrane, large molecular complexes like these cannot diffuse easily. In fact, it is rather useful for these complexes to remain immobile, because they can partition a membrane into regions. We will see several examples of these types of membrane complexes in Chapters 5 and 6.

CONCEPT CHECK #2

One of the most significant additions to the original fluid–mosaic model is the concept of variation in phospholipid distribution in membranes. Based on our discussion of molecular teamwork in Chapter 1, what impact would you expect organized clusters of phospholipids to have on the function of membranes?

4.4 The Smooth Endoplasmic Reticulum and Golgi Apparatus Build Most Eukaryotic Cellular Membrane Components

KEY CONCEPTS

- ▶ The lipid components of membranes are built from precursor molecules in the cytosol.
- ▶ In humans, most cells receive lipids, including cholesterol, by engulfing lipoprotein complexes that are synthesized by the liver and circulate in the bloodstream.
- ▶ Phosphoglycerides are assembled in the smooth endoplasmic reticulum.
- ▶ Six different phosphoglycerides, each containing a different head group, are synthesized from a common precursor, phosphatidic acid.

- ▶ Most sphingolipids are assembled in the Golgi apparatus from precursors made in the endoplasmic reticulum.
- ▶ Proper assembly and delivery of complete membranes requires at least nine distinct steps following the synthesis of membrane components.
- ▶ Flippases, floppases, and scramblases are enzymes that move phospholipids from one leaflet of a membrane to the other, thereby generating an asymmetrical distribution of membrane components that is necessary for proper membrane function.
- ▶ Lipid carrier proteins are capable of transporting lipids from one membrane to another in a cell.

The final major topic of this chapter explores how biological membranes are assembled. Historically, our understanding of the biochemistry responsible for membrane synthesis, especially for phospholipids, has lagged far behind that for the other basic cellular building blocks (sugars, nucleic acids, and proteins). But considerable progress has been made in the last 15 years, such that we can now examine the mechanisms responsible for membrane synthesis with a level of detail comparable to that for DNA and protein synthesis. Our first step is to examine how and where each of the major membrane components are built, and then we will examine how they are organized to form functional membranes.

■ Glycerol and Fatty Acids Are Synthesized in the Cytosol

Glycerol, which forms the backbone of all phosphoglycerides, is synthesized in the cytosol. For most cells, the precursor to glycerol is a closely related molecule called **glycerol-3**

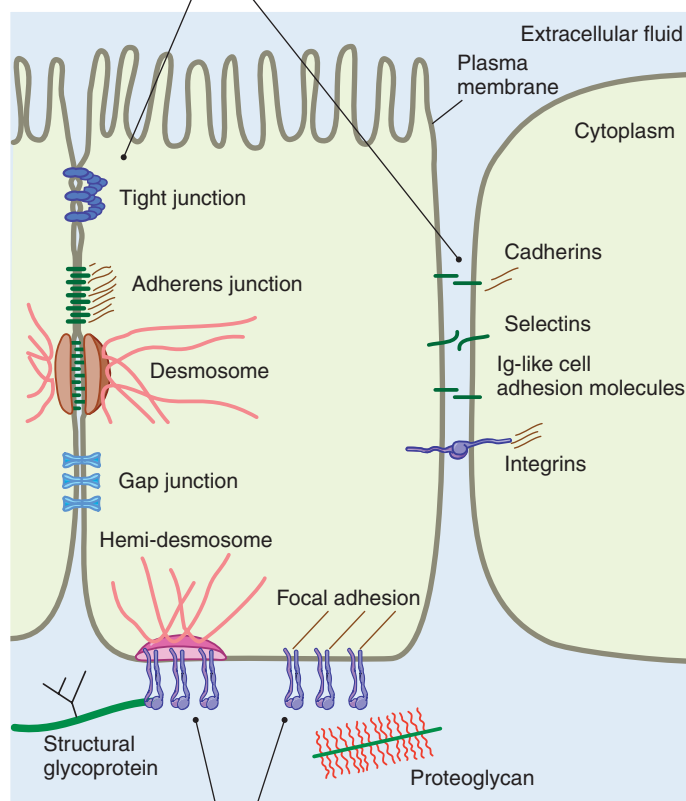
phosphate. Glycerol-3 phosphate is typically quite abundant in cells because it is an intermediate molecule formed during the digestion of food molecules (sugars, fats, proteins) to make ATP. We will visit this topic again in much more detail in Chapter 10.

The fatty acids used to build the tails of phosphoglycerides and other lipids are synthesized in the cytosol by an enzyme called **fatty acid synthase**. In humans, most cells don't have to synthesize their own fatty acids; instead, they absorb fatty acids from molecular complexes called **lipoproteins**. Lipoproteins are made by cells in the liver that secrete them into the bloodstream, which carries them to the remainder of the cells in the body. The remaining ingredients needed to synthesize membranes (phosphate groups, water, etc.) are in such great abundance in cells that we can take them for granted.

■ The Synthesis of Phosphoglycerides Begins at the Cytosolic Face of the SER Membrane

All phosphoglyceride synthesis begins with the covalent attachment of two fatty acids to glycerol by transmembrane enzymes called **acyl transferases** in the smooth endoplasmic reticulum (SER). The resulting product, called phosphatidic acid, spontaneously inserts itself into the cytoplasmic leaflet of the smooth endoplasmic reticulum membrane. Six different molecules, called head

Some proteins bind to other cells, allowing cells to form clusters.



Some proteins bind to molecules in the extracellular space, permitting cells to attach and crawl on these molecules.

FIGURE 4-9 Plasma membrane proteins form clusters that permit cell adhesion.

groups, are added to the phosphate group to generate six different phospholipids. The standard convention for naming most phospholipids is “Phosphatidyl-X” where X is the name of the head group. Often, we simply abbreviate them as PC, PS, PE, PI, PG, and bisPG (a derivative of PG also called cardiolipin, or CL).

Each of these phospholipids plays an important role in regulating cellular activities. They are far more than space-filling molecules in the “fluid” portion of a membrane. For example, when PI is modified by the addition of two more sugars to the inositol head group, the resulting glycosylphosphatidylinositol (GPI) can act as the anchor for some lipid-anchored membrane proteins. GPI synthesis begins on the cytosolic face of the endoplasmic reticulum (ER), and is completed in the ER interior, as shown in **FIGURE 4-10**. The relative concentrations of these phospholipids can vary considerably between different cell types and among different membranes in the same cell. In later chapters, we will refer back to these phospholipids to help explain how specific cellular functions are performed.

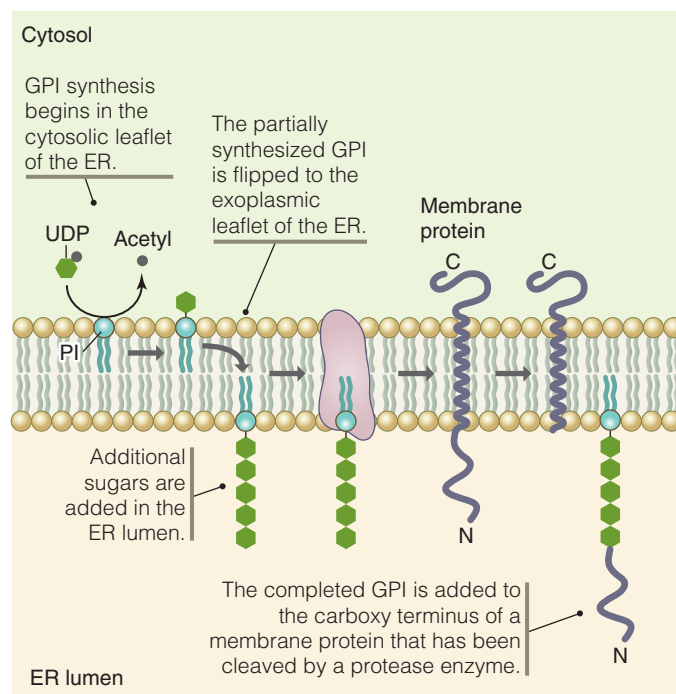


FIGURE 4-10 GPI is synthesized and attached to membrane proteins in the ER.

Additional Membrane Lipids Are Synthesized in the Endoplasmic Reticulum and Golgi Apparatus

Phosphoglycerides are by far the most abundant lipids found in membranes, but other membrane lipids are also noteworthy. For example, the **farnesyl** and **geranylgeranyl lipids** that are attached to lipid-anchored membrane proteins are precursors of cholesterol, and are synthesized in the ER membrane from the same building blocks used to make fatty acids. The enzymatic steps for synthesizing cholesterol are different than those used to make fatty acids, and are so complicated that elucidation of the entire synthesis pathway took over two decades to complete and led to the Nobel Prize in 1964. As with fatty acids, most cholesterol synthesis in humans takes place in the liver.

Most Membrane Assembly Begins in the SER and Is Completed in the Target Organelle

Once the phosphoglycerides and other lipids have been synthesized at the cytosolic face of the SER, they are joined by additional membrane proteins synthesized in the rough endoplasmic reticulum (RER) to form a fluid-mosaic structure that closely resembles a mature cellular membrane. Simply collecting all of these molecules in the same location (the ER), however, is not enough to ensure the functional stability of all cellular membranes. Eight tasks remain before membrane synthesis is complete. These tasks, in rough chronological order (some occur simultaneously, or at multiple times in multiple locations), are:

1. **Membrane proteins in the endomembrane system are inserted in the ER.** All cellular membranes contain proteins. Recall from Chapter 1 (see *The Plasma Membrane, Endoplasmic Reticulum, Golgi Apparatus, Endosomes, Lysosomes, and Peroxisomes Form a Protein-Trafficking Network Called the Endomembrane System*) that the ER is linked to many other organelles by a vesicle-shuttling system. These vesicles are membrane-bound compartments that bud from one organelle and fuse

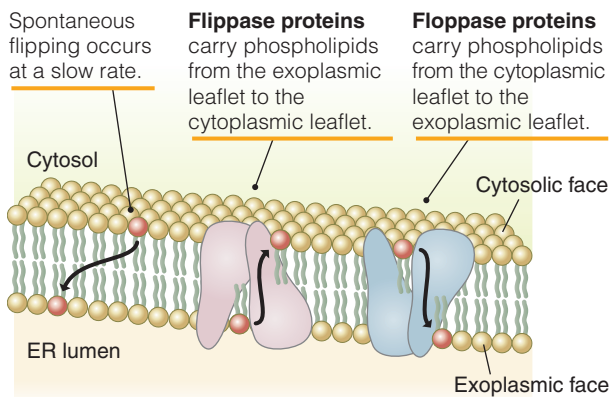


FIGURE 4-11 Three mechanisms for translocation of phospholipids from one leaflet of the ER membrane to the other.

with another. The membrane proteins in the endomembrane system originate in the endoplasmic reticulum.

2. **Nonspecific flippases and floppases transport phosphoglycerides from one membrane leaflet to the other in the ER.** Earlier in this chapter we mentioned that membrane phosphoglycerides are not equally distributed in both layers of a membrane. For example, PC is enriched in the external face of the plasma membrane, sometimes called the **exoplasmic** or **ectoplasmic leaflet**, relative to the internal face, called the **cytoplasmic leaflet**. Some of this asymmetry actually originates in the ER. All phosphoglycerides are synthesized on the cytoplasmic leaflet of the ER, but a membrane consists of *two* leaflets: How do the phosphoglycerides get to the other side of the phospholipid bilayer? There are two mechanisms, shown in **FIGURE 4-11**. First, phospho-

glycerides have the ability to spontaneously flip-flop from one side of a membrane to the other. This is not a rapid process—the half-life for this flip-flopping (i.e., time it takes for half of them to flip sides at least once) ranges from several hours to days. The second mechanism is much more rapid: a group of transmembrane proteins called **floppases** use ATP energy to carry phospholipids, including phosphoglycerides, to the exoplasmic leaflet of the ER. Note that this is a one-way ride; floppases do *not* move phospholipids back to the cytoplasmic leaflet. The return journey takes place on proteins conveniently named **flippases**, which also use ATP to selectively power the transport in the reverse direction only. The half-life for transport by both types of enzymes is less than one minute.

3. **Membrane vesicles transport new phosphoglycerides and membrane proteins from the endoplasmic reticulum to other organelles in the endomembrane system.** Despite both spontaneous and enzyme-assisted flipping and flopping, the absolute number and relative concentration of phosphoglycerides in both leaflets of the ER are *not* identical. When membrane-bound vesicles shuttle between organelles in the endomembrane system, they preserve the membrane asymmetry of their parent organelles; a vesicle budding from the ER and fusing with the Golgi apparatus will, in effect, donate a piece of ER membrane to the Golgi apparatus, such that whatever asymmetry was present in the ER is passed to the Golgi. Vesicles budding from the Golgi apparatus and fusing with the plasma membrane will likewise preserve the asymmetry of the Golgi, thereby replicating the unequal distribution of membrane components that began in the ER. (Note that these vesicles also contain the proteins synthesized in the ER. We will discuss these proteins in the next section.) This membrane trafficking will be covered in much greater detail in Chapter 9.
4. **Glycolipid synthesis is completed on the exoplasmic face of the Golgi apparatus.** Some lipid precursors synthesized in the ER arrive in the Golgi and are converted into glycolipids by enzymes in the lumen of the Golgi apparatus. Because all of the completed glycolipids are present in the *exoplasmic* face of the Golgi membranes, this adds to the overall membrane asymmetry. This is the final stage of membrane component synthesis. All subsequent steps involve modifying and/or moving components to their proper destination(s). The mechanisms governing proper sorting of membrane components to different destinations are quite complex, and are discussed in detail in Chapter 9.

5. **Final orientation of plasma membrane lipids occurs *in situ*.**

Aside from the ER, most attention on membrane asymmetry has focused on the plasma membrane, which is probably the most asymmetric membrane in most cells. The plasma membrane of most cells contains a variety of phospholipid transport proteins, including specialized flippases and floppases that are much more selective for specific phospholipids than their ER counterparts. As a result, one (PC) is highly enriched in the exoplasmic leaflet, while the remainder of the phosphoglycerides are relatively enriched in the cytoplasmic leaflet, as shown in **FIGURE 4-12**. Because this reorganization takes place directly in the plasma membrane, rather than in the ER or Golgi compartments previously traversed by these molecules, it is said to occur *in situ* (from Latin, literally meaning “in place”).

The asymmetric organization of the plasma membrane plays an important role in many cellular functions, such as controlled cell death (also called **apoptosis**) and cell signaling, which we will discuss in Chapters 11 and 13. It is perhaps not surprising, then, that a third class of phospholipid transporters, called **scramblases**, can have a profound impact on cellular function. These enzymes are capable of both flipping *and* flopping phospholipids in the plasma membrane, and require no metabolic energy (e.g., ATP) to do so. Short-term activation of scramblases triggers cellular signaling pathways, but promotes apoptosis if the scrambling is not repaired.

6. **Membrane proteins in other organelles are inserted *in situ*.**

Most proteins synthesized by free ribosomes in the cytosol (i.e., those not attached to the RER) remain in the cytosol for the duration of their existence. A subset of these, however, contain amino acid sequences (tags) that target them to specific organelles, shown in **FIGURE 4-13**. In addition, cytosolic proteins containing the proper sequences can attach to, or insert themselves into, the membranes of mitochondria, chloroplasts, and peroxisomes. There is some evidence that vesicles from the ER can fuse with and donate membrane components to these organelles in at least some cells, but most membrane proteins in these organelles do not arrive via this route. The mechanisms governing targeting of cytosolic proteins to these organelles will be discussed in Chapter 8.

7. **Fatty acid binding proteins carry phospholipids to peroxisomes, mitochondria, and chloroplasts.**

Because most phospholipid synthesis occurs in the ER, those organelles that receive little or no

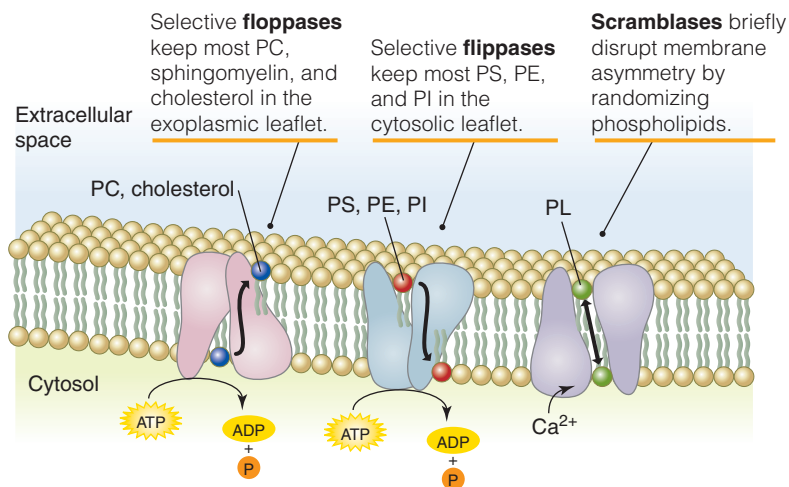


FIGURE 4-12 Establishment and maintenance of lipid asymmetry in the plasma membrane.

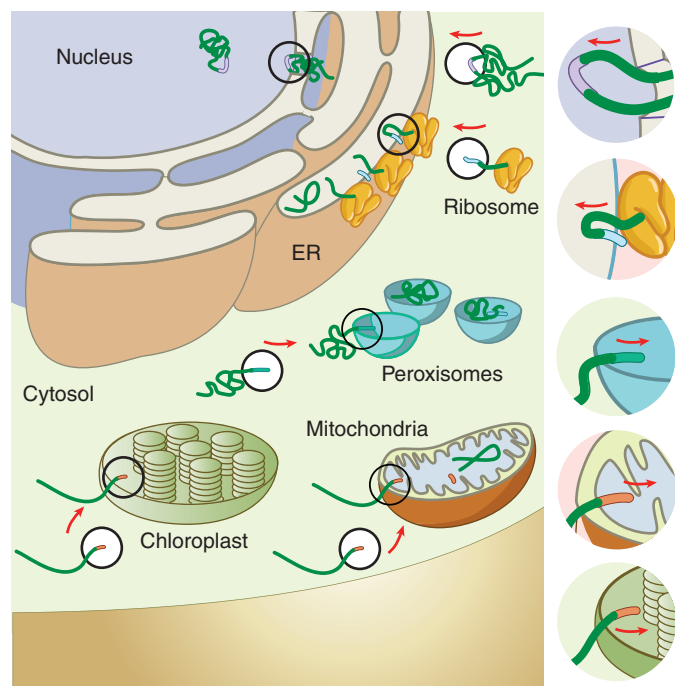


FIGURE 4-13 Protein “tags” direct some cytosolic proteins to enter organelles.

BOX 4-7 FAQ

What is a “protein family”? Protein families are groups of proteins with similar structure and function that are thought to have arisen from a common ancestral gene. There is no formal definition for what constitutes a family, just as there is no strict universal definition for motif or domain (see Chapter 3, *Motifs Are Specific Combinations of Secondary Structures*, and *A Domain Is a Portion of a Protein That Adopts a Characteristic Shape*). When a group of proteins are called a *family*, this simply represents a consensus among those who study the proteins that they share enough common features to warrant a group name.

vesicle traffic from the ER must have an alternative means for building their own phospholipids. While the details of this type of transport have yet to be uncovered, at least five families of proteins are involved (**BOX 4-7**); collectively, they are known as **lipid-binding proteins**. The best characterized of these is sterol carrier protein-2, which delivers both fatty acids and cholesterol to peroxisomes, mitochondria, and chloroplasts, as shown in **FIGURE 4-14**.

8. **Cholesterol is delivered to target membranes.** Cholesterol is synthesized in the ER, but most of it is not carried to the plasma membrane via ER-derived vesicles, as is true for nearly all other components of the plasma membrane. Direct observation of cholesterol transport with a microscope shows that it can make the journey from the ER to the plasma membrane much faster than any membrane protein. This observation helps explain why the concentration of cholesterol in the ER and Golgi apparatus is much lower than that found in the plasma membrane.

Collectively, all of these steps are required to build and maintain healthy membranes in cells, as summarized in **FIGURE 4-15**. Most of the molecular details of the mechanisms governing such a complicated web of activities have yet to be discovered; nonetheless, we now understand enough about how the membrane constituents interact to accomplish a wide range of cellular functions, and these subjects will be addressed in much greater detail in Chapters 5–14.



FIGURE 4-14 Sterol carrier protein-2 structure. Note the fatty acid bound to it.

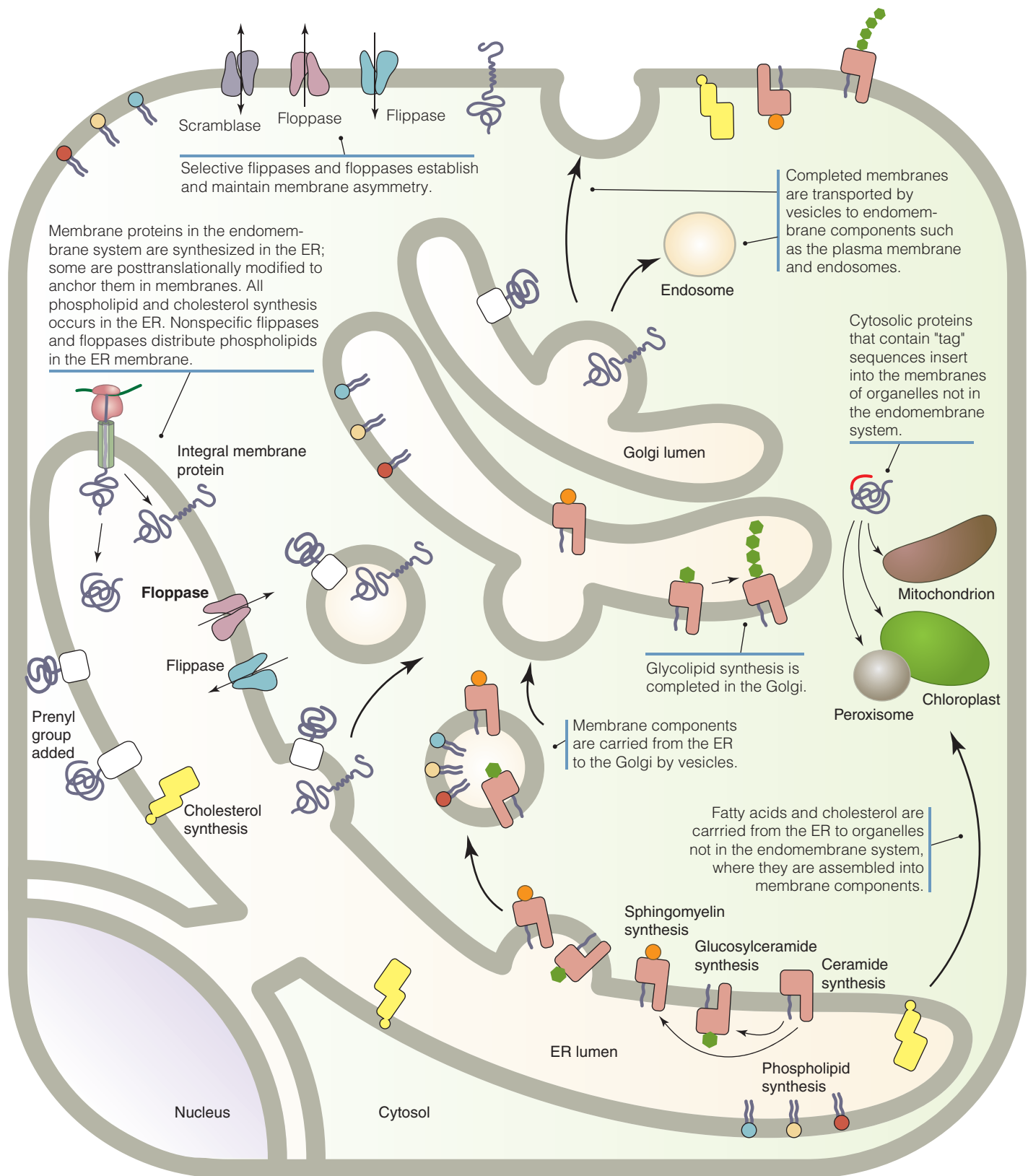


FIGURE 4-15 Summary of membrane synthesis mechanisms in eukaryotes.

CONCEPT CHECK #3

The steps outlined in this section describe a mechanism for manufacturing specialized membranes in a cell. This is an excellent example of how cellular information is put to work. In our everyday lives, we are familiar with numerous manufacturing strategies for converting information into tangible products. For example, an assembly line uses a linear sequence of processes to change starting materials into a single finished product, generally in a single location; a centralized network is capable of generating multiple finished products in a single location, then sorting and delivering the products to their proper destinations; and a distributed network sorts the starting materials into multiple, specialized sites, then manufactures different products at each site. Apply your understanding of membrane synthesis to compare it to each of these manufacturing strategies. What similarities are there between each of these strategies and the mechanisms cells use to build membranes?

4.5 Chapter Summary

Phospholipids are the smallest of the four cellular building blocks, yet they assemble to form membranes, the largest structures in cells. Phospholipids are complex structures, composed of three distinct elements, that combine to form about 1,000 different molecules in eukaryotic cells. The greatest variation in phospholipid structure occurs in the fatty acid tails, which can vary in length and the number of double bonds they contain. All phospholipids are amphipathic, and therefore spontaneously organize as a bilayer. The hydrophobic interior of a phospholipid bilayer serves as a selective barrier to diffusion, limiting the movement of solutes between compartments in a cell. Cell membranes are composed of at least four types of molecules: phospholipids arranged as a bilayer, membrane proteins, glycolipids, and cholesterol. The fluid–mosaic model, recently updated, provides the foundation for our understanding of membrane structure; the fluid portion of the membrane is composed of phospholipids and glycolipids, and the mosaic portion contains membrane proteins and their associated molecules. Cholesterol has opposing effects on membrane fluidity depending on its relative concentration in a membrane. It is most abundant in the plasma membrane, where it decreases fluidity and stabilizes the membrane.

Membranes are synthesized by a complex set of chemical reactions and molecular trafficking. The precursors of membrane molecules are synthesized in the cytosol and endoplasmic reticulum, then combined in a multipart process that requires at least eight distinct steps. The endomembrane system, which links several organelles via transport vesicles, synthesizes most membrane components in a stepwise fashion, beginning in the endoplasmic reticulum, progressing to the Golgi apparatus, then concluding at the target organelle. Membranes not included in the endomembrane system receive proteins directly from the cytosol, and phospholipids are carried from the endoplasmic reticulum to these membranes by cytosolic lipid carrier proteins; the lipid carrier proteins also deliver cholesterol to membranes from the endoplasmic reticulum. Finally, flippase and floppase proteins redistribute the phospholipids in the two leaflets of a membrane, generating membrane asymmetry.

CONCEPT CHECK ANSWERS #1

The key difference between polypeptides and membranes is that the amino acids in polypeptides are covalently linked to one another, such that a change in shape of one portion of a polypeptide can impact the structure of the entire polypeptide. In contrast, phospholipids are never covalently linked to one another, so each acts independently. If one region of the membrane changes shape (e.g., forms a lipid raft), the phospholipids surrounding this region are largely unaffected.

CONCEPT CHECK ANSWERS #2

Variations in membrane fluidity allow for the formation of clustered teams of molecules in phospholipids. This selective clustering permits greater specialization of membranes, enhancing the division of labor that is key to cell survival. For example, clusters of molecules in a membrane can subdivide the membrane into distinct compartments that perform different functions. In general, the more heterogeneous a membrane is, the greater the number of distinct tasks it can perform.

CONCEPT CHECK ANSWERS #3

Assembly line: Cells use enzymes to manufacture the precursor molecules of membrane components in one location, somewhat like assembly lines. For example, glycerol and fatty acids are synthesized via a sequence of steps in the cytosol, while cholesterol and ceramide are likewise synthesized in the ER. Another assembly-line-like strategy is the modification of phospholipids (e.g., addition of sugars to glycolipids) and membrane proteins (e.g., addition of GPI) that takes place in the Golgi apparatus after their synthesis in the ER.

Centralized network: The ER resembles a central assembly point in a centralized network, in that both phosphoglyceride and sphingomyelin synthesis is completed in the ER before these molecules are sent to the Golgi apparatus for sorting to their final destinations in the endomembrane system.

Distributed network: The final orientation of phospholipids in a membrane is determined *in situ* by the flippases and floppases for each membrane. Similarly, cholesterol and other lipids are delivered by lipid-binding proteins to organelles without having to pass through the Golgi apparatus.

DESIGN QUERY:

1. Please check if is this the updated art? Thanks.