The Components and Properties of Cell Membranes

(Independent Learning Module)

OBJECTIVES

- Describe the structure of a biological membrane, and discuss the interactions that hold the parts of a membrane together.
- Name the major classes of membrane lipids.
- List the parts of a phospholipid.
- Explain how saturated versus unsaturated fatty acids can affect the properties of membranes.
- Describe the role of cholesterol in eukaryotic membranes.
- Explain how a lipid bilayer can be a fluid, yet maintain asymmetry.
- Suggest why 'flipping' from one side of a membrane to the other is a rare event for lipids, and an even more rare event for integral membrane proteins.

KEY WORDS

amphipathic
biological membrane
cholesterol
glycolipid
integral membrane protein
lipid bilayer
lipid raft
membrane fluidity
phospholipid
transmembrane protein

SUPPLEMENTAL READING:

Boron and Boulpaep, Medical Physiology, Saunders, 2003, pp. 9-17.
Alberts et al. Essential Cell Biology, Garland Publishing,1998, pp. 347-369.

WEB-BASED TUTORIAL:

http://cit.ucsf.edu/ext/membranes/
This module presents the same text as in this ILM, but also includes interactive figures, self-assessment questions and pop-up definitions to key words. The tutorial contains slightly more detail than this ILM; you will not be held responsible for those additional details on the exam. To view the tutorial, you must have Flash Player 6. To install, go to: www.macromedia.com/shockwave/dowload/dowload.cgi?P1_Prod_Version=ShockwaveFlash

I. INTRODUCTION

Biological membranes, sheet-like structures composed of lipids and proteins, can be found surrounding cells (the plasma membrane) and inside of cells (forming the boundaries of organelles such as the ER, nucleus, Golgi apparatus, mitochondria, and lysosomes in eukaryotic cells). In either case, membranes serve as barriers, separating the contents within the membrane from the outside environment. The plasma membrane keeps a cell intact by holding all of the cellular components inside, and also keeps many unwanted molecules outside of the cell. Internal membranes are crucial for creating micro-environments

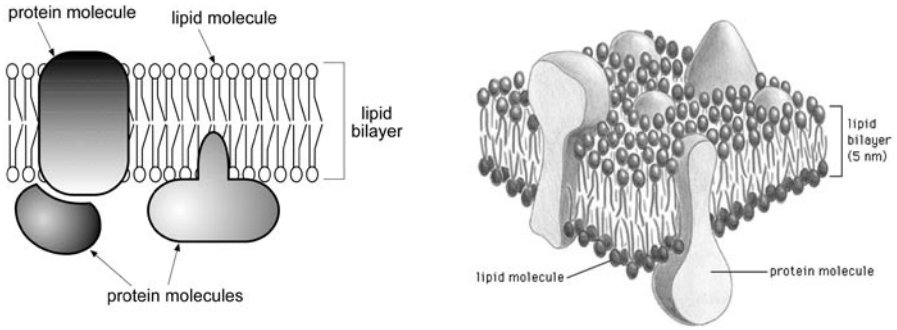

Figure 1. *Two views of a cellular membrane. These show 2D and 3D depictions of a cell membrane. (3D drawing from Alberts et. al., Essential Cell Biology, 1998, Garland Publ, Fig 11-4, p. 348.)*

containing sequestered enzymes or high concentrations of hydrogen ions (low pH).

All biological membranes have a similar general structure (Fig. 1). The membrane lipids are organized in a bilayer (two sheets of lipid make a single membrane) approximately 50 to 100 Å thick. Embedded in and associated with the lipid portion of the membrane are proteins, which stabilize the membrane and carry out membrane functions. We will first focus on the classes of membrane lipids, their properties, and their role in the formation of membranes.

II. MEMBRANE LIPIDS ARE AMPHIPATHIC MOLECULES

In general, lipids are water-insoluble molecules that serve as fuel molecules, are stored as concentrated sources of energy, act as signal molecules, and are components of biological membranes. We will be focusing on the latter function. Lipids that make up biological membranes are amphipathic; they contain both hydrophilic and hydrophobic groups. The **amphipathic** nature of lipids is of key importance to the structure of membrane bilayers, as will be discussed below. There are three classes of membrane lipids: phospholipids, glycolipids, and cholesterol. Phospholipids and glycolipids have a similar structure (Fig. 2). (The structure of cholesterol is a bit different, and is presented later.) They contain a hydrophilic or polar 'head' and one or two hydrophobic hydrocarbon 'tails' derived from fatty acids. The fatty acids in phospholipids usually have an even number of carbon atoms, averaging 14 to 24, with 16 and 18 being the most common

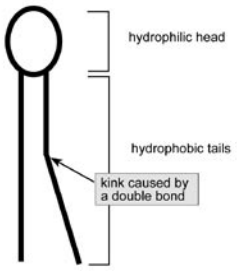

Figure 2. *Schematic of a membrane lipid. This cartoon will be used to represent lipids throughout the syllabus.*

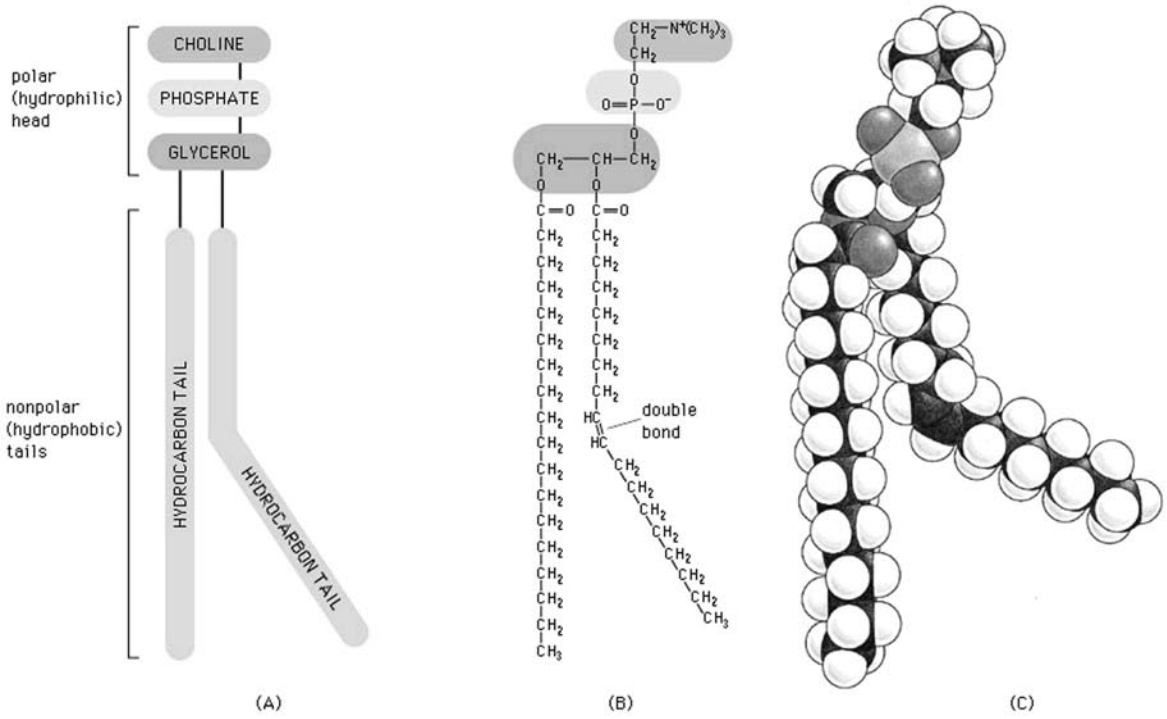

Figure 3. *Three representations of a phosphoglyceride. Here, phosphatidylcholine is represented (A) schematically, (B) as its chemical formula, and (C) as a space-filling model. Choline is linked via a phosphate to glycerol, forming the hydrophilic head. Glycerol is in turn linked to two hydrocarbon chains, forming the hydrophobic tail. The two hydrocarbon chains originate as fatty acids - that is, hydrocarbon chains with a carboxyl group (-COOH) at one end which become attached to glycerol via their carboxyl groups. (From Alberts et al., Essential Cell Biology, 1998, Garland Publ, Fig 11-6, p. 349.)*

numbers. The fatty acids may be saturated (no double bonds between carbons) or unsaturated (contains double bonds). Usually, one of the two fatty acid chains has at least one double bond. A double bond in a fatty acid chain creates a 'kink,' which is represented as a bend in the chain in Figure 2. We will come back to this important property when discussing membrane fluidity.

Phospholipids are the major class of membrane lipids—they are abundant in all biological membranes. Phospholipids are derived from either glycerol (a three-carbon alcohol) or sphingosine (a more complex alcohol). Most membrane phospholipids have a phosphate or a phosphorylated alcohol, which is esterified to glycerol, which in turn is esterified to two fatty acid chains. The most abundant membrane phospohlipids contain one of several alcohols, including serine, ethanolamine, choline or inositol. Phosphatidylcholine (Fig. 3) is the most common type of phospholipid in most cell membranes. Phosphatidylserine, phosphatidylethanolamine, and another phospholipid called sphingomyelin (derived from the alcohol sphingosine, as mentioned above) are also abundant in the plasma membrane of many mammalian cells. Another important phospholipid, phosphatidylinositol, is present in only small quantities, but is

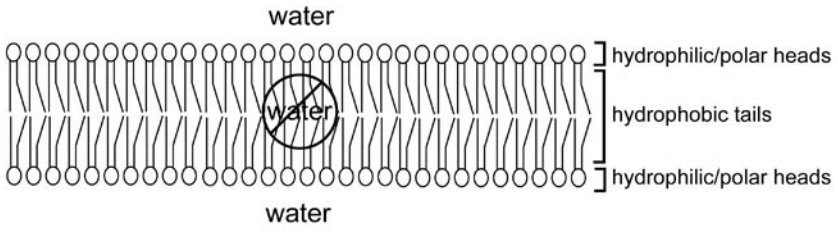

Figure 4. *Section of a phospholipid bilayer. Water is excluded from the hydrophobic interior.*

extremely important for cell signaling (and will be discussed in the Signaling lecture).

Cholesterol is also abundant in eukaryotic cell membranes (up to one molecule for every phospholipid in most eukaryotic cells). The structure and function of cholesterol will be discussed below. **Glycolipids** are similar to phospholipids in structure, but have sugars as part of their head groups. Glycolipids are significantly less abundant, and will only briefly be discussed further here.

III. SELF-ASSEMBLY OF MEMBRANE LIPIDS: FORMATION OF A LIPID BILAYER

You have learned that protein folding is driven by the clustering of hydrophobic residues in the core of the protein, such that they do not contact water. The same phenomenon drives the formation and stabilization of membranes. Membrane lipids overcome the conflict between the chemical properties of their head and tail groups by forming a sheet composed of two layers of lipid, also called a **lipid bilayer** (Fig. 4). The hydrophilic heads face out, interacting with water molecules. The hydrophobic tails are oriented inside of the bilayer, where they are shielded from water. Note that the hydrophobic tails cluster not because of any strong attraction. Instead, hydrophobic tails are driven together because they are repelled from water. Thus, when lipids are added to water, lipid bilayer sheets self-assemble rapidly and spontaneously. The bilayer sheets self-seal to complete the sequestration of the hydrophobic interior of the bilayer from water (Fig. 5). Once lipid bilayers have formed, the membrane lipids are held together by weak noncovalent forces: van der Waals attractive forces are at work among the hydrocarbon tails, and ionic and hydrogen bonds form between the head groups and water.

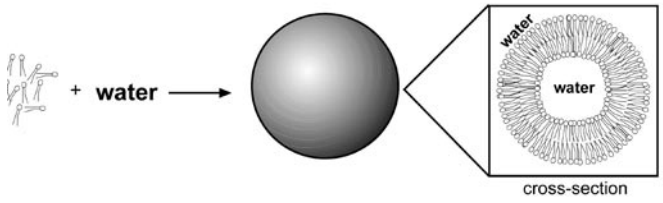

Figure 5. *Formation of a sealed lipid bilayer. A lipid bilayer will self-seal to avoid exposing the hydrophobic interior to water. The polar head groups of the outer portion of the bilayer compose the surface. Water (and anything else in the medium) is trapped in the center of the orb.*

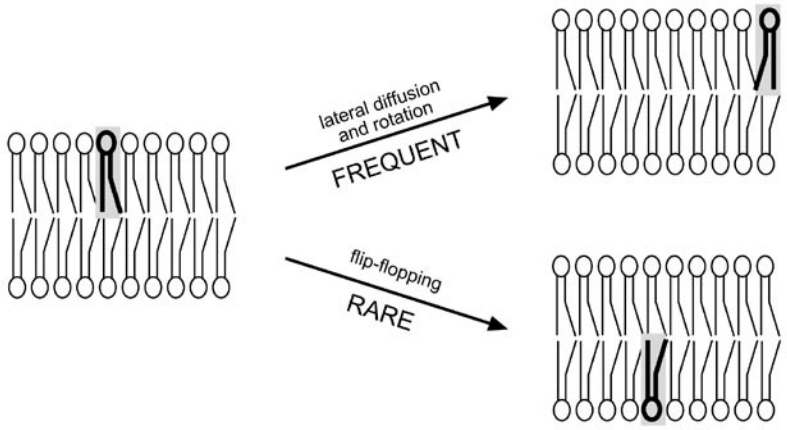

Figure 6. *Membrane fluidity. Membrane components can readily diffuse laterally. Here the highlighted lipid diffuses and rotates within the plane of the membrane. Proteins can also easily do the same. Flip-flopping is a rare event for lipids and is never exhibited by proteins.*

IV. THE LIPID BILAYER IS A TWO-DIMENSIONAL FLUID

Since the forces holding the bilayer together are weak noncovalent interactions, lipids and many associated proteins in the membrane bilayer are not rigidly held in place. In fact, membrane constituents can move about and change places with one another quite easily within the plane of the bilayer. Membrane lipids and many membrane proteins undergo constant lateral diffusion (Fig. 6). To imagine this, picture yourself navigating through a large mass of helium balloons on strings attached to the ground—since the balloons are not held together by any strong forces, they can trade places with one another and rotate freely within the plane that the balloons are in. This is referred to as **membrane fluidity**. As you will see later, lipids and proteins must to move around within the membrane to interact with one another and carry out important membrane functions. There are no barriers against lateral diffusion. However transverse movement, or flipping from one side of the bilayer to the other, is energetically unfavorable and therefore rare for lipids. Thus, the fluidity of cell membranes is confined to two dimensions. The degree of a membrane's fluidity must be maintained within certain limits. For example, membrane functions are significantly impaired when fluidity is experimentally increased beyond a certain level. A membrane should have some stability, or it will not serve as an adequate barrier.

Cholesterol regulates membrane fluidity in eukaryotes, with the exception of yeast and plants. Like other membrane lipids, cholesterol has a polar head and a hydrophobic tail (Fig. 7). The polar part of cholesterol is simply a hydroxyl group, which interacts with the heads of other membrane lipids and water. The hydrophobic tail of cholesterol is embedded in the hydrophobic interior of the membrane. Cholesterol can either increase or decrease membrane fluidity, depending on its concentration. At moderate concentrations, cholesterol fits into gaps between phospholipid molecules (Fig. 8). The rigid sterol ring interacts with the hydrocarbon tails of phospholipids nearest the polar head. By forming van der Waals interactions with lipid tails, cholesterol decreases

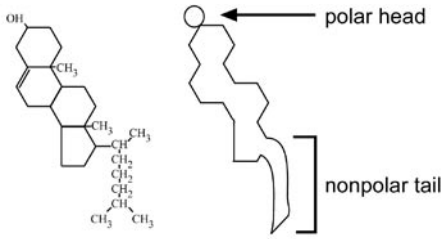

Figure 7. *Structure of cholesterol. Like other lipids, cholesterol has a polar head group and a hydrophobic tail. On the right is a schematic of the structure.*

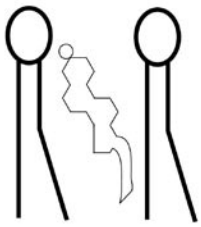

Figure 8. *Positioning of cholesterol in a membrane. Cholesterol fits between lipids containing double bonds, adding stability.*

their mobility and therefore makes membranes more rigid and less permeable. At high concentrations, cholesterol can interfere with alignment of fatty acyl chains, increasing fluidity and lowering the temperature at which membrane crystallization occurs. The length and degree of unsaturation of phospholipids also influence membrane fluidity. Longer chains have greater affinity for one another in the interior of the bilayer, and increase the rigidity of the membrane. Likewise, saturated fatty acids, which lack any double bonds or kinks, can pack together and interact more easily than those with double bonds (Fig. 9), which decreases fluidity. Microorganisms can adjust the lipid composition of their membranes to maintain fluidity in response to environmental temperature changes.

For many years, it was thought that lipid molecules in cell membranes are distributed randomly to avoid phase separation (altered viscosity in particular regions of the membrane). However, a growing body of evidence supports the existence of **lipid rafts**, specialized lipid microdomains enriched in cholesterol and sphingolipids (sphingomyelin, mentioned earlier, is one example of a sphingolipid). The tails of sphingolipids tend to be long and saturated, resulting in decreased fluidity within these microdomains. Lipid rafts are thought to play a role in sequestering membrane proteins in specific membrane regions.

V. THE ASYMMETRY OF LIPIDS IN MEMBRANES IS FUNCTIONALLY IMPORTANT

The compositions of the two monolayers of the lipid bilayer in many membranes are strikingly different. For example, in the human red blood cell membrane, the outer monolayer contains a preponderance of phosphatidylcholine. The inner monolayer contains a large amount of phosphatidylserine. Many cytoplasmic proteins bind to specific lipid head groups found in the cytoplasmic monolayer of the lipid bilayer. Also, one particular phospholipid that is concentrated in the cytosolic monolayer of the membrane, phosphatidylinositol, is the precursor for intracellular signaling molecules, and is important in relaying signals from the outside of the membrane to the inside (described in the Signaling lecture). Glycolipids are found exclusively in the noncytoplasmic (outer) monolayer of the lipid bilayer (Fig. 10). The sugar groups are exposed at the cell surface, where they have important roles in interactions of the cell with its surroundings. The asymmetric distribution of lipids in membranes is maintained because lipids rarely "flip" from one leaflet of the bilayer to the other.

V. INTEGRAL MEMBRANE PROTEINS ARE ALSO AMPHIPATHIC

In nature, membranes do not form without proteins. Without proteins to strengthen and stabilize them, membranes would be incredibly flimsy. Membrane proteins are also crucial for transport of substances in and out of cells, communication with other cells and the environm ɛrradically in their

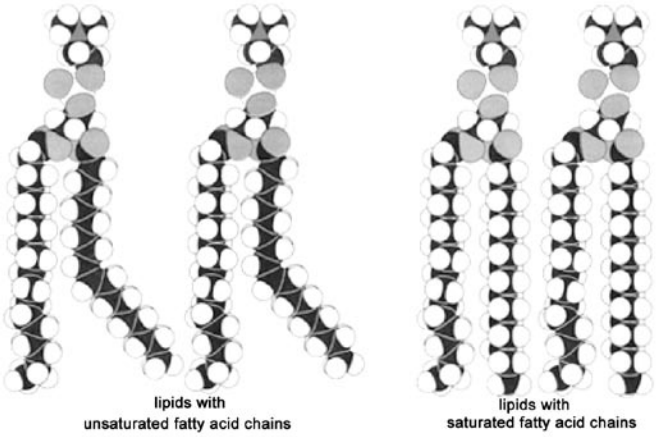

Figure 9. *The influence of double bonds in hydrocarbon chains on lipid packing. In unsaturated lipids, the presence of double bonds makes it more difficult to pack the chains together. A synthetic lipid bilayer containing only lipids with unsaturated fatty acids would be much more fluid than a bilayer containing lipids with saturated fatty acids.*

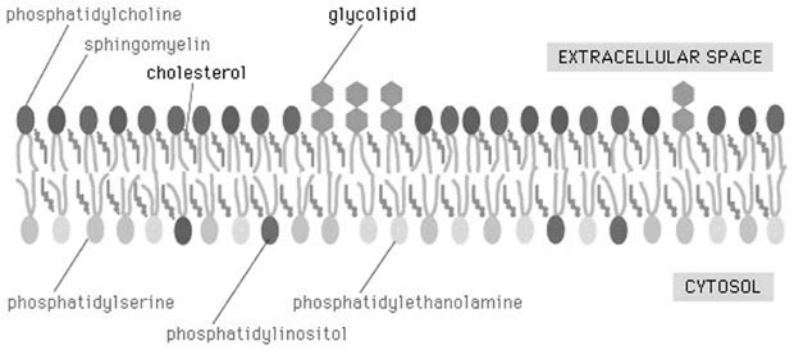

Figure 10. *The asymmetrical distribution of phospholipids and glycolipids in a typical plasma membrane. Five types of phospholipid molecules are shown. The glycolipids, located in the external monolayer of the membrane, are drawn with hexagonal head groups to represent sugars. Cholesterol is distributed almost equally in both monolayers. (From Alberts et al., Essential Cell Biology, 1998, Garland Publ, Fig 11-17, p.355.)*

protein content. For example, the protein content of plasma membranes is typically 50%, while the protein content of organelle membranes involved in energy generation (i.e. the internal membranes of mitochondria and chloroplasts) is upwards of 75%. Proteins can associate with lipid bilayers in many different ways. Membrane proteins are classified experimentally based on how tightly they associate with the lipid bilayer. Proteins that are not released from the lipid bilayer, even upon exposure to extreme changes in pH or ionic conditions, are termed **integral membrane proteins** (Fig. 11). Some integral membrane proteins, called **transmembrane proteins**, pass completely through a membrane, while others insert only a small portion (either a helix or a covalently linked lipid) into the lipid bilayer. Transmembrane proteins typically span the lipid bilayer with either a single helix (often called single-pass transmembrane proteins) or several helices (multipass transmembrane proteins). The membrane-spanning helices, called transmembrane domains, interact with the hydrophobic tails of membrane lipids and anchor the protein in the membrane. The parts of the protein that are exposed to water on either side of the membrane are largely hydrophilic.

In most cases, proteins are asymmetric, and their orientation is critical for their function. For example, a protein that interacts with extracellular substances may have a larger region exposed to the outside of the cell but only a small polypeptide portion exposed to the cytosol. The particular orientation of a protein is established during its synthesis. Due to the extensive polar regions on both sides of the membrane, integral membrane proteins do not flip transversely through the hydrophobic interior of the membrane, which preserves the asymmetry of membranes.

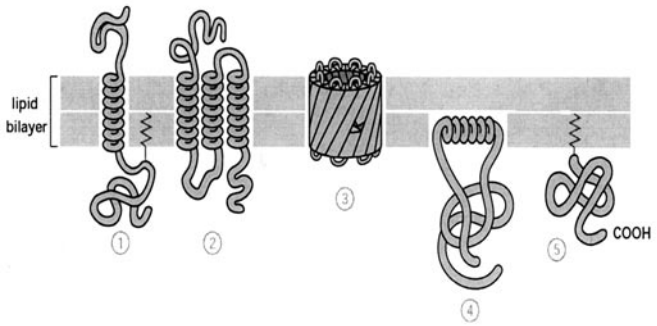

Figure 11. *Various ways in which integral membrane proteins associate with the lipid bilayer. Some integral membrane proteins are transmembrane proteins (1, 2 and 3). Most transmembrane proteins are thought to extend across the bilayer as (1) a single alpha helix, (2) as multiple alpha helices, or (3) as a rolled-up β sheet. Some of these proteins have covalently-attached fatty acid chain inserted in the cytoplasmic lipid monolayer (1). Other integral membrane proteins are exposed only on one side of the membrane (4 and 5). Some of these are anchored to the cytosolic surface by an amphipathic alpha helix that partitions into the cytosolic monolayer of the lipid bilayer (4). Other integral membrane proteins are anchored in the bilayer solely by a covalently attached lipid chain. (Adapted from Alberts et al., Molecular Biology of the Cell, 4th ed, 2002, Garland Publ, Fig 10-17, p.594.)*

VI. CONCLUSION: THE FLUID MOSAIC MODEL

All of the characteristics of membranes that have been discussed are summed up in what is called the fluid mosaic model. The fluid mosaic model was proposed in 1972 by Singer and Nicolson to explain the overall organization of biological membranes, and many aspects of the model have been verified experimentally. Important features of the model are as follows:

- (the "mosaic" part of the model) Membrane lipids are arranged in a bilayer. The lipid bilayer contains proteins, adding functionality and contributing to permeability. The inner and outer layers of a membrane have different lipid and protein compositions and different functions.

- (the "fluid" part of the model) Lipids and proteins are free to diffuse laterally in the membrane unless held in place by specific interactions. However, due to the hydrophobicity of the interior of the membrane, proteins cannot flip from one side of the membrane to the other, and lipids do so only rarely.