Chapter 1

Membrane Structure and Function

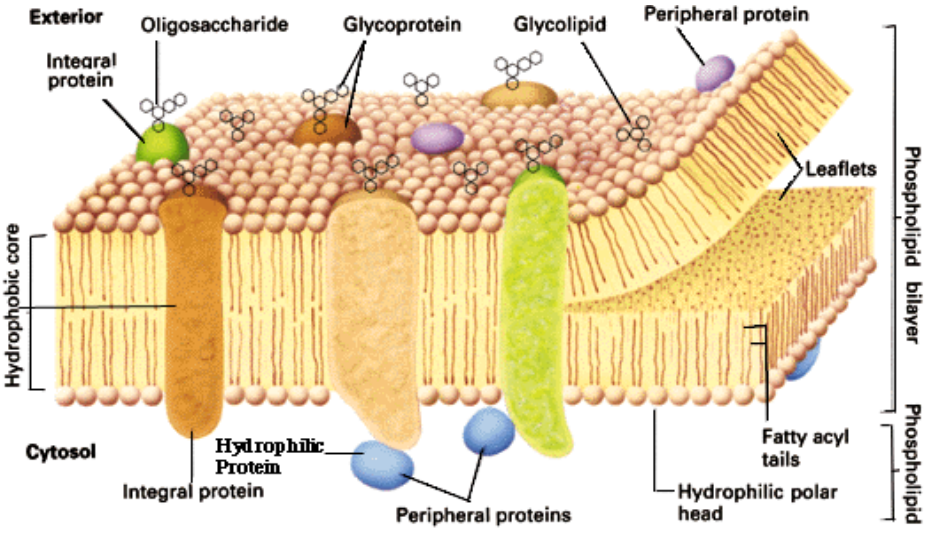
Architecture of Membranes

Subcellular fractionation techniques can partially separate and purify several important biological membranes, including the plasma and mitochondrial membranes, from many kinds of cells. These preparations are often contaminated with membranes from other organelles. However, the plasma membranes from human erythrocytes can be isolated in near purity because these cells contain no internal membranes.

All membranes contain phospholipids and proteins. The protein:lipid ratio varies greatly:

- The inner mitochondria membrane is 76% protein.
- The myelin membrane is only 18% protein.

Because of its high phospholipid content, myelin can electrically insulate the nerve cell from its environment. The lipid composition varies among different membranes. All membranes contain a substantial proportion of phospholipids, predominantly phosphoglycerides, which have a glycerol backbone. All membrane phospholipids are amphipathic, having both hydrophilic and hydrophobic portions. Sphingomyelin, phospholipid that lacks a glycerol backbone, also is commonly found in plasma membranes. Instead of a glycerol backbone it contains sphingosine, an amino alcohol with a long unsaturated hydrocarbon chain. A fatty acyl side chain is linked to the amino group of sphingosine by an amide bond to for a ceramide. The terminal hydroxyl group of sphingosine is esterified to phosphocholine, thus the hydrophilic head of sphingomyelin is similar to that of phosphatidylcholine.



Nearly all fatty acyl chains found in the membranes of eukaryotic cells have:

- an even number of carbon atoms (usually 16, 18, or 20).
- Unsaturated fatty acyl chains normally have one double bond
- but some have two, three ore four. In general, all such double bonds are of the cis configuration:

A cis double bond introduces a rigid kink in the otherwise flexible straight chain of a fatty acid.

A minor difference among phospholipids concerns the charge carried by the polar head groups at neutral pH. Some phosphoglycerides (phospatidylcholine, phosphatidylethanolamine) have no net electric charge; others (9 phosphatidylglycerol, cardiolipin, phosphatidyserine) have a net negative charge. A few rare phospholipids carry a net positive charge at neutral pH. Nonetheless, the polar head groups in all phospholipids can pack together into the characteristic bilayer structure. Sphingomyelin and glycolipids are similar in shape to phosphoglycerides and can form mined bilayer with them.

Cholesterol and its derivatives constitute another important class of membrane lipids, the steroids. The basic structure of steroids is the four-ring hydrocarbon shown. Cholesterol is the major steroid constituent of animal tissues; other steroids play more important roles in plants. Although cholesterol is almost entirely hydrocarbon in composition, it is amphipathic because it contains a hydroxyl group that interacts with water. Cholesterol is especially abundant in plasma membrane of mammalian cells but is absent fro most prokaryotic cells.

Phospholipid Bilayer the Basic Structural Unit of membranes

Despite the variable compositions of biological membranes, the basic structural unit of virtually all biomembranes is the phospholipid bilayer. This bilayer is a sheet like structure composed of two layers of phospholipid molecules whose polar head groups face the surrounding water and whose fatty acyl chains form a continuos hydrophobic interior and 3 nm thick. Each phospholipid layer in this lamellar structure is called a leaflet. The major driving force for the formation of phospholipid bilayers is hydrophobic interaction between the fatty acyl chains of glycolipid and phospholipid molecules. Van der Waals interactions among the hydrocarbon chains favor close packing of these hydrophobic tails. Hydrogen bonding and electrostatic interactions between the polar head groups and water molecules also stabilize the bilayer. Micelles are generally not formed by phospholipids in aqueous solutions, since the fatty acyl chains in sphingomyelins, glycolipids, and all phosphgyceriders are too large to fit into the interior of a micelle.

Two dimensional movement of molecules in a membrane

In both pure phospholipid bilayers and in natural membranes, thermal motion permits phospholipid and gycolipid molecules to rotate freely around their long axes and to diffuse laterally within the membrane leaflet. Because such movements are lateral or rotational, the fatty acyl chains remain in the hydrophobic interior of the membrane. In both natural and artificial membranes, a typical lipid molecule exchanges places with its neighbors in a leaflet about 10^7 times per second and diffuses several micrometers per second at 37^{o}C. Thus a lipid could diffuse 1 □ in a bacterial cell membrane in only 1 s and of an animal cell in about 20 s.

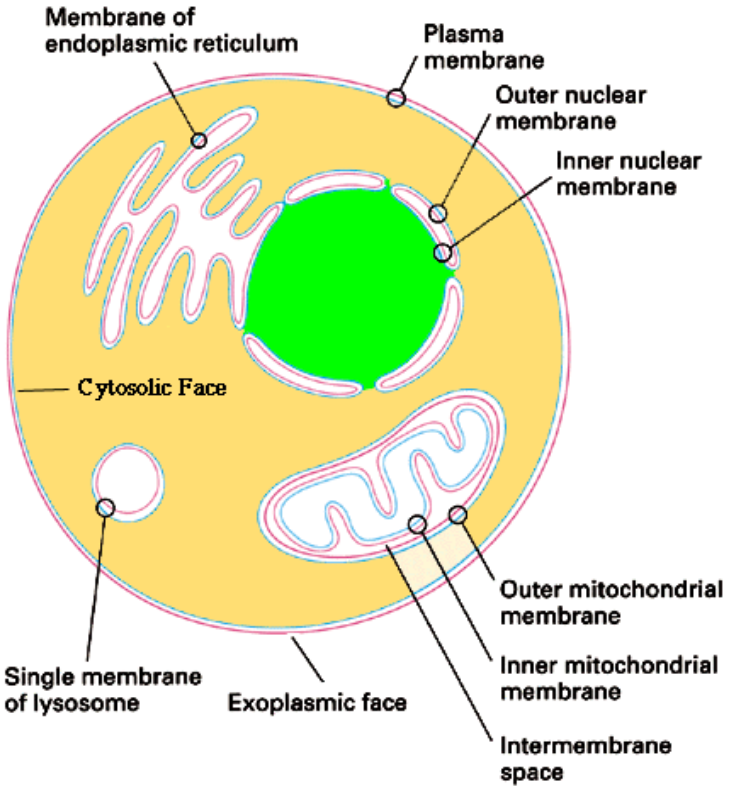
In pure phospholipid bilayers, phospholipids do not migrate, or flip-flop, from one leaflet of the membrane to the other. In some natural membranes, however, they occasionally do so, catalyzed somehow by one or more membrane proteins. Energetically, such movements are extremely unfavorable, because the polar head of a phospholipid must be transported through the hydrophobic interior of the membrane.

The mobility of membrane lipids can be measure by electron-spin resonance spectroscopy. In this technique, synthetic phospholipids containing a nitroxide group attached to a fatty acyl chain are introduced into otherwise normal phospholipid membranes.

Two systems of pure phospholipid bilayer are liposomes and planar bilayers. Liposomes are spherical vesicles up to 1 □ in diameter consisting of a phospholipid bilayer that encloses a central aqueous compartment. They are formed by mechanically dispersing phospholipids in water.

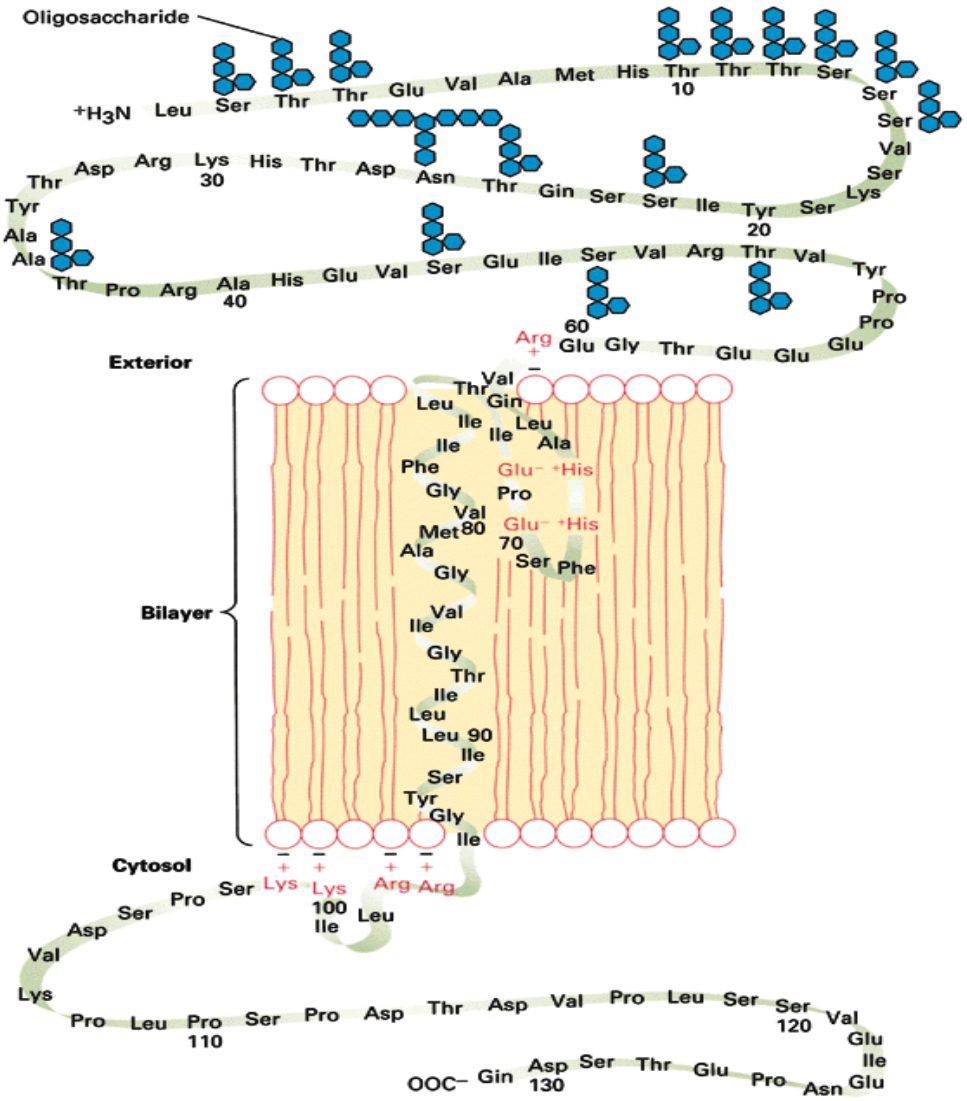
Planar bilayer are formed across a hole in a partition that separates two aqueous solutions. When a suspension of liposomes or a planar bilayer composed of a single type of phospholipid is heated, it undergoes an abrupt change in physical properties over a very narrow temperature range. This phase transition is due to increased motion about the C-C bonds of the fatty acyl chains, which pass from a highly ordered, gel-like state to a more mobile fluid state. During the gel-to fluid transition, a relatively large amount of heat is absorbed over a narrow temperature range which is the melting temperature of the bilayer.

In general, lipids with short or unsaturated fatty acyl chains undergo phase transition at lower temperatures than lipids with long or saturate chains.



One piece of evidence that the phospholipid bilayer structure is common to all biomembranes is that, as detailed above, many of the physical properties of pure phospholipid bilayers are similar to those of natural cellular membranes. Another is that either a single species of phospholipid, or a mixture of phospholipids with a composition approximating that found in natural membranes, spontaneously forms either planar bilayers or liposomes when dispersed in aqueous solutions.

Some of the earliest direct experimental



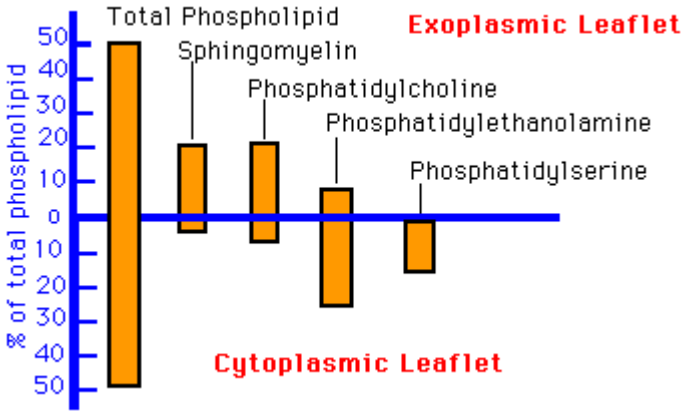
All Integral Proteins Bind Asymmetrically to the Lipid Bilayer Each type of integral membrane protein has a single, specific orientation with respect to the cytosolic and exoplasmic faces of a cellular membrane. All molecules of any particular integral membrane protein, such as glycphorin, lie in the same direction. This absolute asymmetry in protein orientation give the two membrane faces their different characteristics. In contrast to phospholipids, proteins have never been observed to flip-flop across a membrane. Such movement would be energetically unfavorable; it would require a transient movement of hydrophilic amino acid and sugar residues through the hydrophobic interior of the membrane. The asymmetry of membrane proteins is established during their biosynthesis and maintained throughout the proteins lifetime.

Membrane asymmetry is most obvious in the case of membrane glycoproteins and glycolipids. In the plasma membrane, all the O- and N-lined oligosacharides in glycoproteins and all of the oligosaccharides in glycolipids are on the exoplasmic surface. In the endoplasmic reticulum, they are found on the interior, or lumenal, membrane surface.

Membrane Leaflets Have Different Lipid Compositions

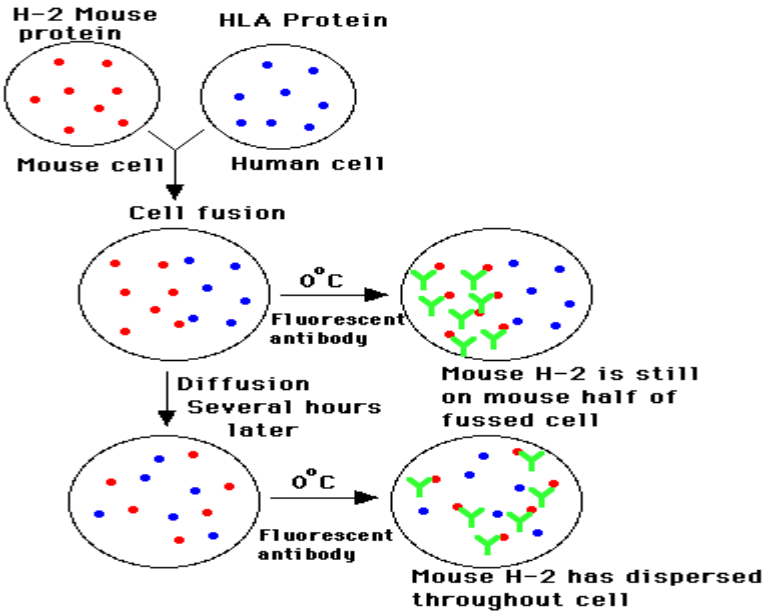
The lipid compositions of the two membrane leaflets are quite different in all the plasma membranes analyzed thus far. In the human erythrocyte and in a line of canine kidney cells grown in culture, all of the glycolipids, and almost all of

sphingomyelin and phosphatidycholine are found in the exoplasmic leaflet. In contrast, lipids with neutral or negative polar head groups, such as phosphatidylethanolamine and phospatidylserine are preferentially located in the cytosolic leafet. The relative abundance of a particular phospholipid in the two leaflets of a plasma membrane can be determined based on its susceptibility to hydrolysis by phospholipases added to the cell exterior. Phospholipases cannot penetrate the cytosolic face of the plasma membrane.



Most Integral Proteins and Lipids Are Laterally Mobile in Biomembranes

Proteins and lipids are laterally mobile within one leaflet. Two different cell can be fused for the purpose of observing the movement of their distinct surface proteins within the membrane. Immediately after fusion, the mouse and human antigens are grouped in separate areas, but they quickly diffuse throughout the cell. Soon after fusion both halves are equally fluorescent, demonstrating the most of the surface proteins were not rigidly held in place on the original mouse and human cells. According to this concept, a fluid mosaic model of the membrane has been developed.



Electron micrographs revealing mobility of protein particles in Freeze-fractured vesicles prepared from the inner mitochondrial membrane. Integral protein particles are visible as protuberances that are randomly distributed in the surface of a free-fractured vesicle. After the vesicle was subjected to a strong electric field and the rapidly frozen, all the particles clustered at one end, showing that the particles can move laterally within the membrane plane in response to a voltage gradient. Their rate of movement is similar to that of many other integral membrane proteins.