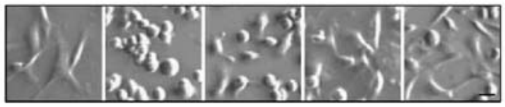

HUMAN CELL BIOLOGY--BIO315HF

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The Human Cell Membrane

Lecture Outline

- Introduction
- The Fluid Mosaic Model of the Cell Membrane
- Structure of Phospholipids - The Amphipathic Nature of Phospholipids
- Asymmetry of Lipid Bilayer
- Micelles: An Alternative Lipid Conformation
- Liposomes
- Cholesterol: Stabilizes the Membrane
- Membrane Protein Functions
- Association of Proteins with the Membrane
- Glycoproteins Sugar Coat the Cell
- Protein Domains in the Cell Membrane
- Lipid Rafts and Caveolae
- Fluidity of the Cell Membrane
- Membrane Fluidity: Early Work
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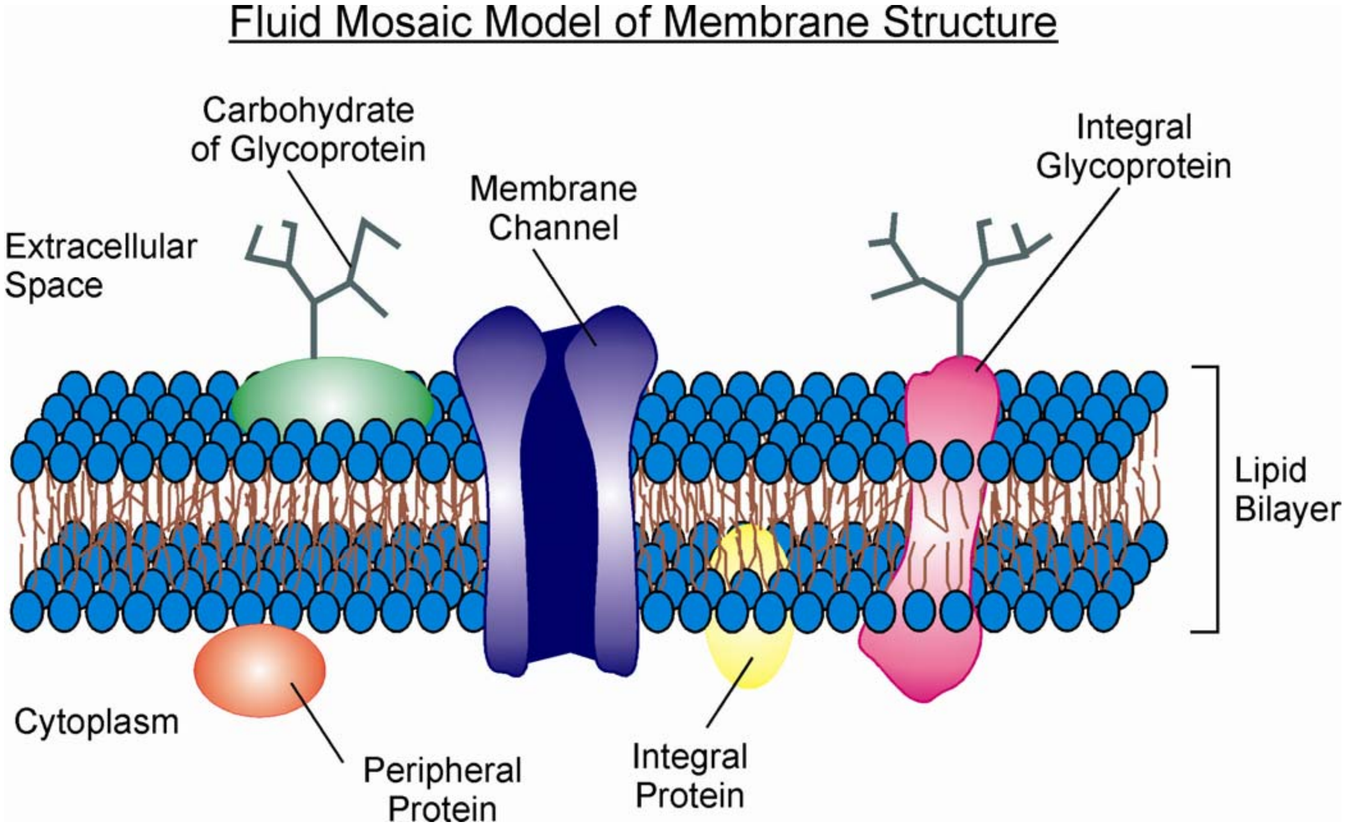
Introduction

All cells are surrounded by a cell membrane (also called the plasma membrane). This is a biological membrane or biomembrane consisting of a double layer of lipids in which proteins are located. The cell membrane keeps the components of the cell isolated from the external environment. It also serves as the communications interface between the cell and its environment. Biological membranes also compartmentalize cellular functions. Inside the cell, endoplasmic reticulum, Golgi, lysosomes, vesicles and vacuoles are surrounded by a single biological membrane. Mitochondria and the nucleus are surrounded by two biomembranes. The cell membrane is involved in regulating the flow of materials into and out of the cell, mediating intercellular communication and adhesion and a multitude of other functions. The structure and functions of the cell membrane have been defined by over a half a century of research using biochemical, physiological, cellular and molecular techniques. In this lecture, our goals are to learn the major constituents of the biomembranes and to understand how they are organized into a functional cell membrane. The information is designed to set the stage for the lectures that follow rather than presenting a complete or historical review.

The Fluid Mosaic Model of the Cell Membrane

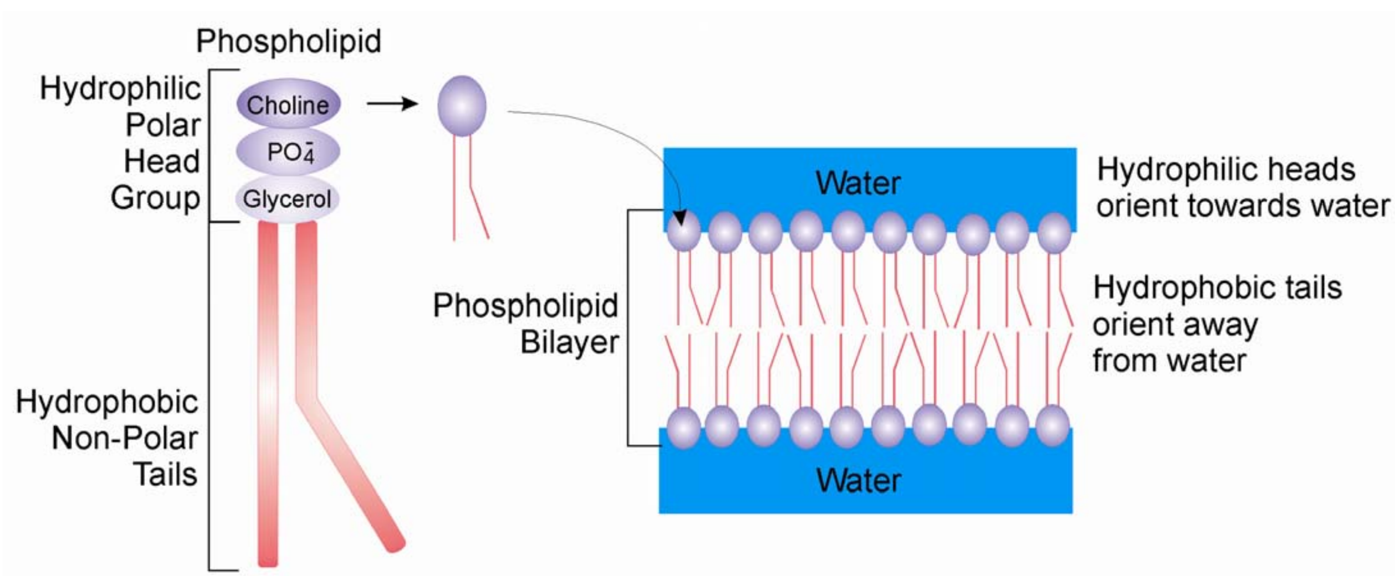
The most widely accepted model of the cell membrane is the "Fluid Mosaic Model". By this concept the cell membrane consists of a continuous, fluid, double layer of phospholipids. Proteins either are embedded in the bilayer or associated with either the cytoplasmic or extracellular face. Carbohydrates are linked to the proteins (glycoproteins) or lipids (glycolipids) only on the extracellular side. The phospholipid profiles of the cytoplasmic and extracellular layers differ. Cholesterol, in varying amounts depending on the cell type, lies within the membrane serving to stabilize it.



Structure of Phospholipids-The Amphipathic Nature of Phospholipids

The basic structure of biomembranes is defined by their continuous components-the phospholipids. These molecules have an important attribute that allows them to form membranes. One part of them associates with water while the other part shuns it. As we see this underlies the basic organization of the biological membrane.

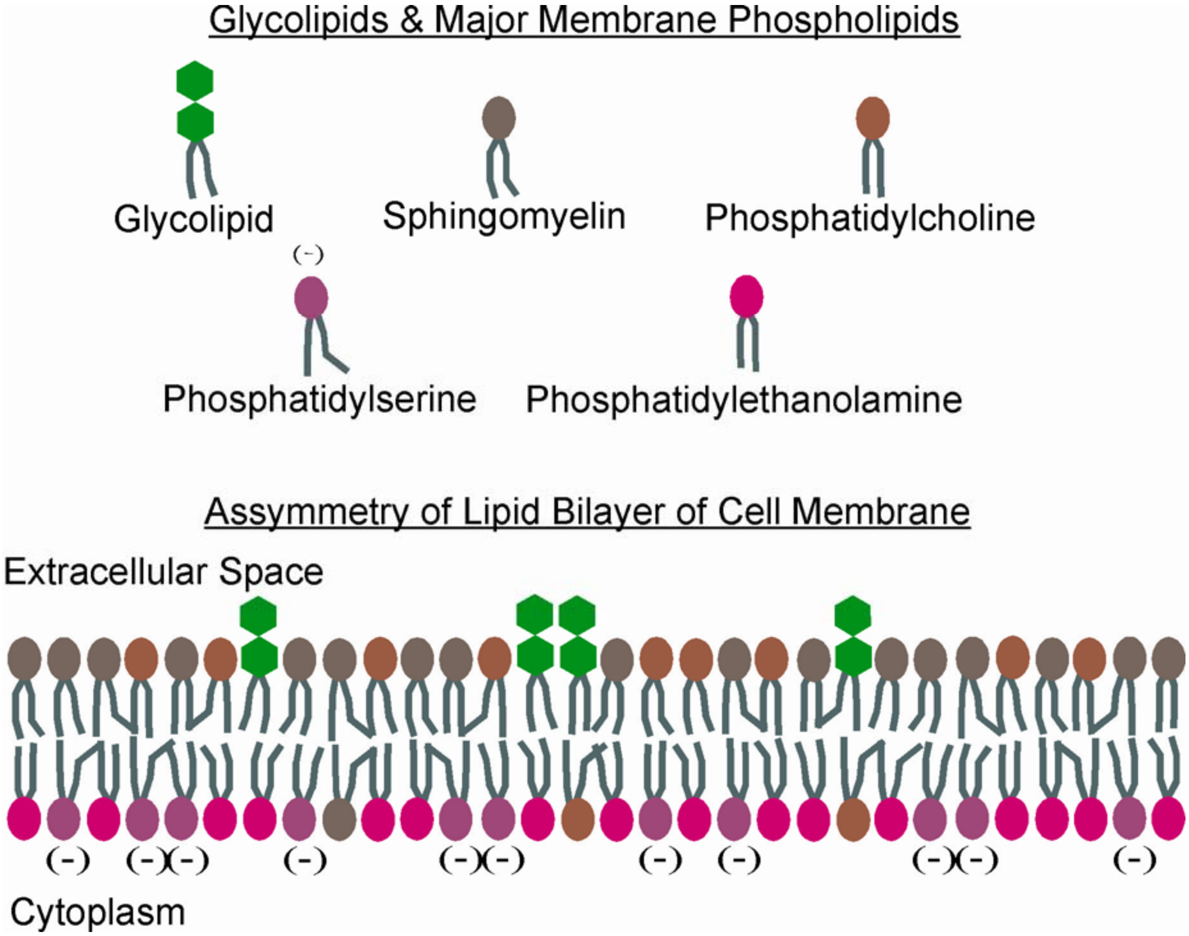
- Hydrophilic head--"likes" water--polar end
- Hydrophobic tail--"hates water"--non-polar chain of fatty acids
- Tail--length & number double bonds differs in different phospholipids



Asymmetry of Lipid Bilayer

The phospholipid bilayer defines many of the physical attributes of the membrane (e.g., how fluid it is at any temperature). It also contains lipids that are involved in cell communication (signal transduction) as discussed in future lectures.

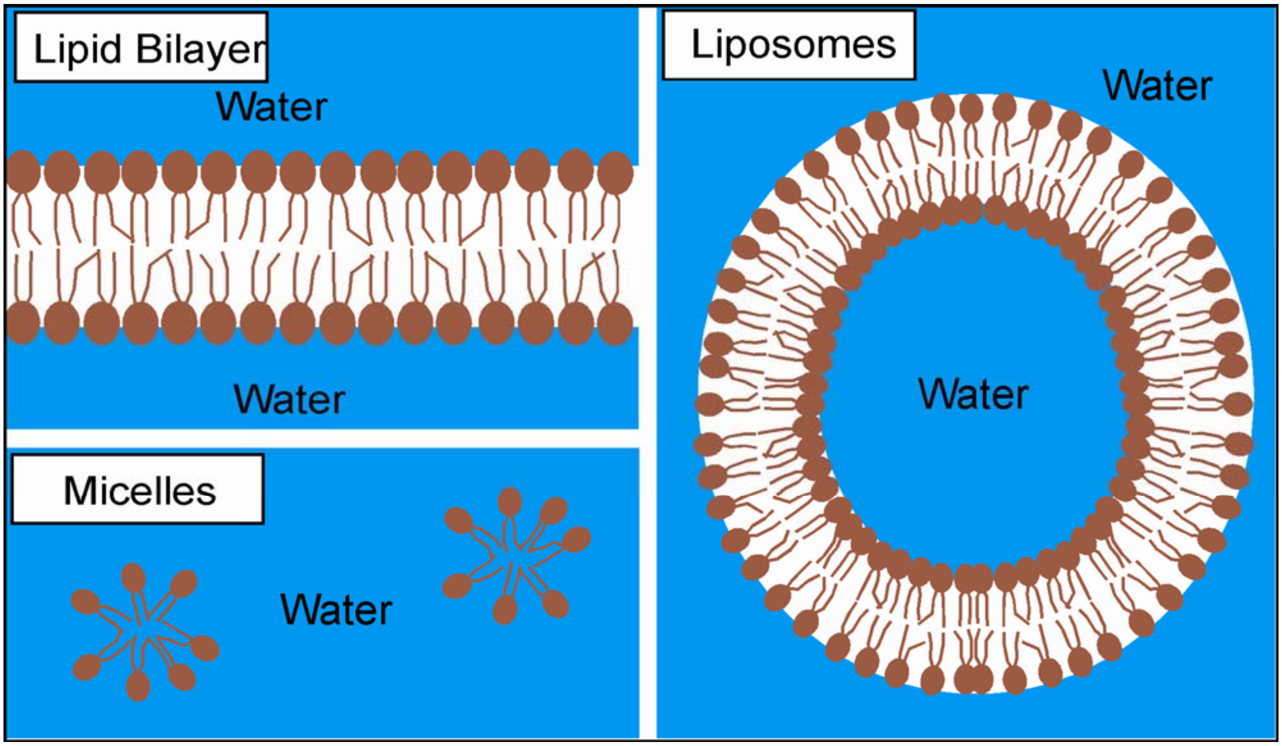
- Outside: more phosphatidylcholine
- Inside: more phosphatidylserine
- Glycolipids: only on outside face



Micelles: An Alternative Lipid Conformation

The structure of phospholipids allows them to form other configurations such as micelles and liposomes. The role of micelles remains open to discussion. Micelles can form when the lipid amount is low relative to water ratio.

- Micelles can form at regions of membrane instability (fusion?)



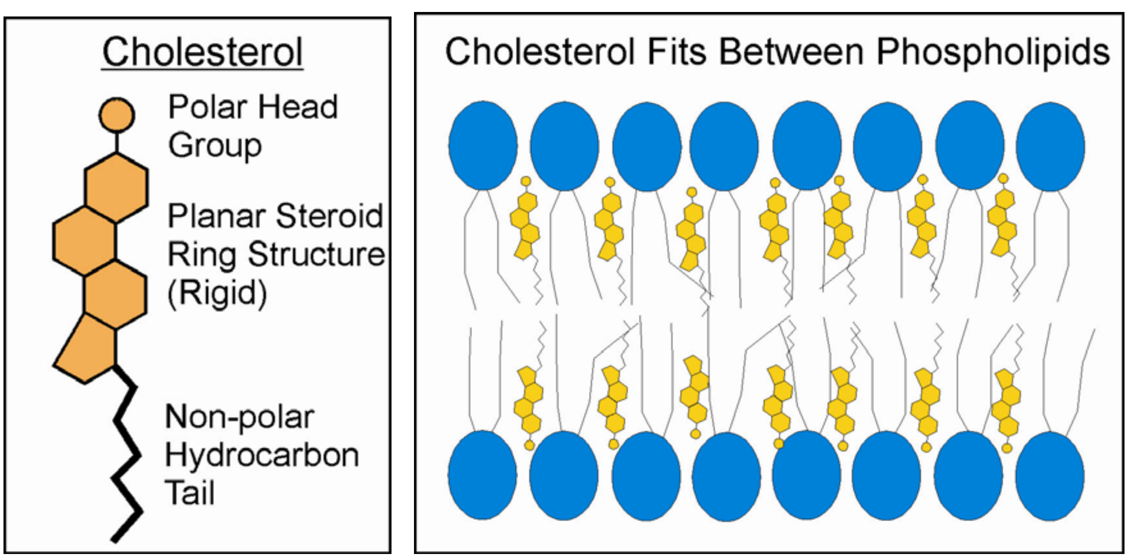
Liposomes

Liposome-like structures underlie such things as LDL-particles and are being used in medicine among other areas.

- Liposomes are bilayered lipid vesicles
- Form by sonicating lipids in aqueous solution
- Vehicles for drug, nucleic acid, Ab delivery
- Used in cosmetics

Cholesterol: Stabilizes the Membrane

- Steroid lipid
- Flat shape: Interdigitates between phospholipids
- Present in animal cell membranes
- Absent in bacteria; most plants--Cell walls provide stability



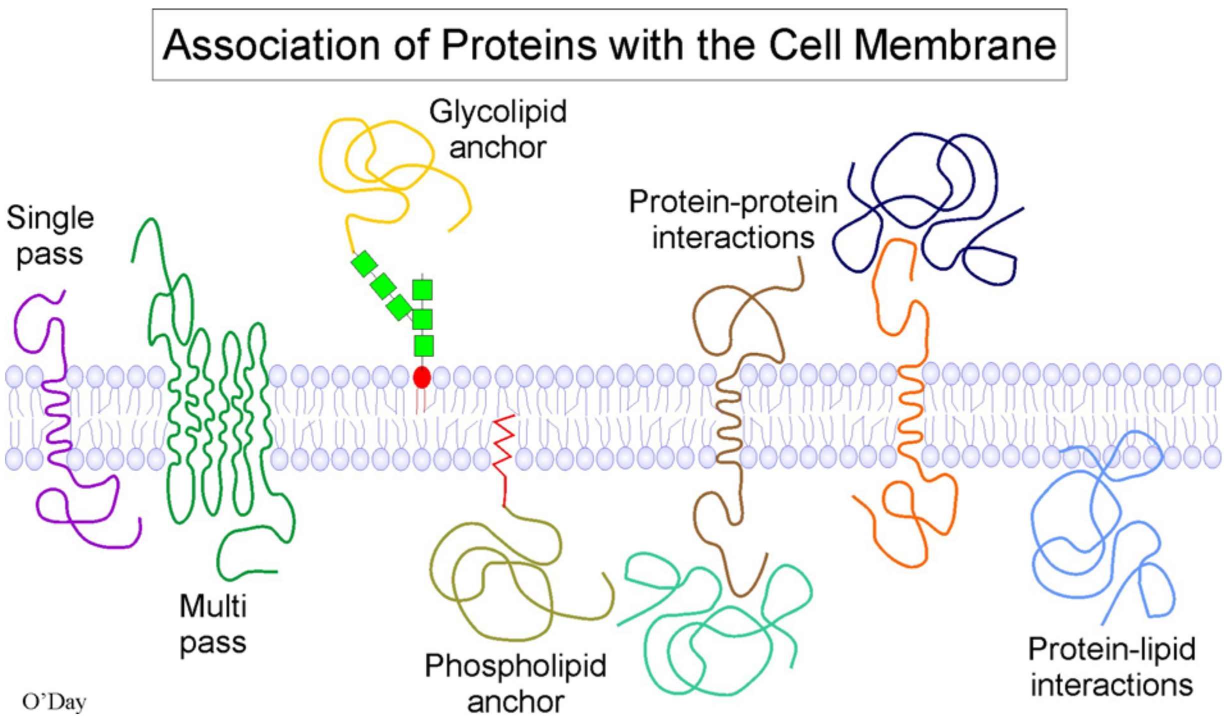
Membrane Protein Functions

As we will begin to realize as this course progresses, there are thousands of different membrane proteins. These points will be elaborated upon in future lectures.

- Define functional characteristics (e.g., membrane transport, cell adhesion, intercellular communication, etc.)
- Various functional types: enzymes, channels, adhesion molecules, etc.
- Some float freely in lipid bilayer
- Many are attached to cytoskeleton
- Types also based upon isolation characteristics: integral or peripheral

Association of Proteins with the Cell Membrane

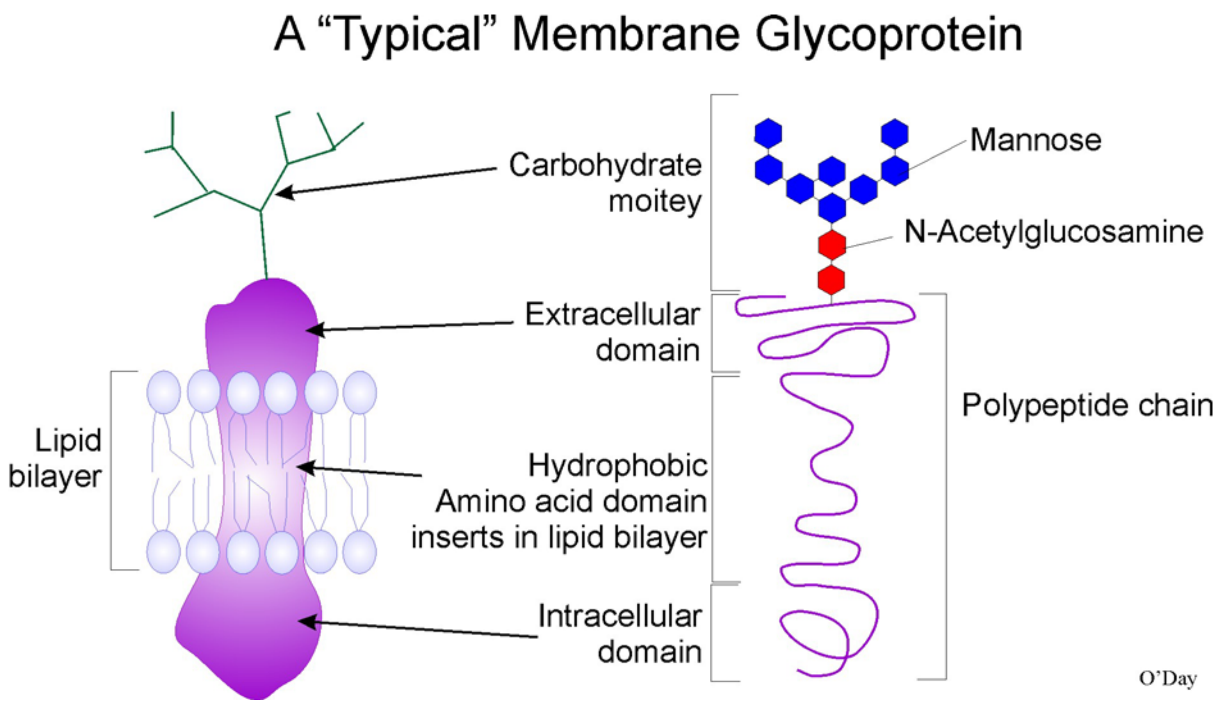
Membrane proteins associate with the lipid bilayer in many different ways. The figure below shows the most common liaisons that occur.



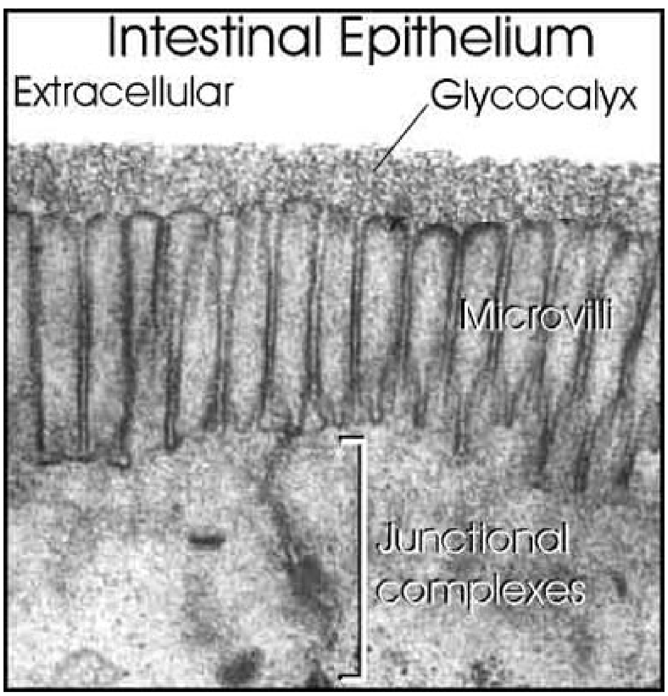
Proteins may contain a single lipid-spanning domain (single pass) or several (multipass). They may be linked to the membrane by a glycolipid or phospholipid anchor. Proteins that are linked to or embedded in the cell membrane may associate with other proteins (protein-protein interactions) either on the inner or outer face of the membrane. Proteins may interact directly with lipids in the bilayer. Each of these associations will be discussed as we progress through the course.

Glycoproteins Sugar Coat the Cell

Many of the membrane proteins are covalently linked to sugar residues. They may consist of a few sugars or extend into long carbohydrate moieties. The sugar groups are always oriented towards the external environment, never the cytoplasm. The following shows an example of an integral membrane glycoprotein.



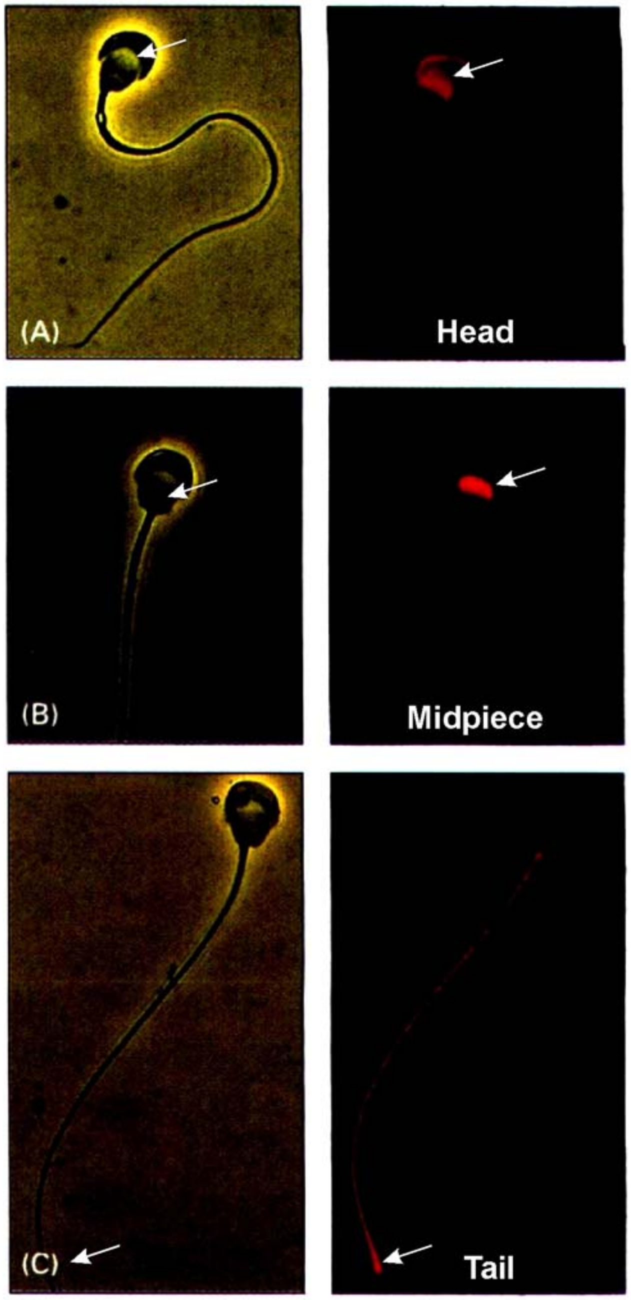
When the carbohydrate component of the glycoprotein is extensive, typically interacting with extracellular matrix components it can be seen in the electron microscope. The extensive "sugar coating" of the intestinal epithelium is called the glycocalyx.



Protein Domains in Cell Membranes

In most cells, the membrane proteins are not randomly localized but exist in complexes that are localized to specific domains. This is an exciting area of cell biology that is growing rapidly. For example, RACK1 (Receptor for Activated C Kinase 1) organizes many constituents involved in cellular signaling as discussed in a future lecture. One of the first cell types where protein membrane domains were identified was the sperm cell as shown in the next figure. Whole sperm were injected into rabbits to induce antibody formation.

Three rabbit antibodies that were produced identified three different regions of the surface (i.e., proteins in the membrane) of the sperm.

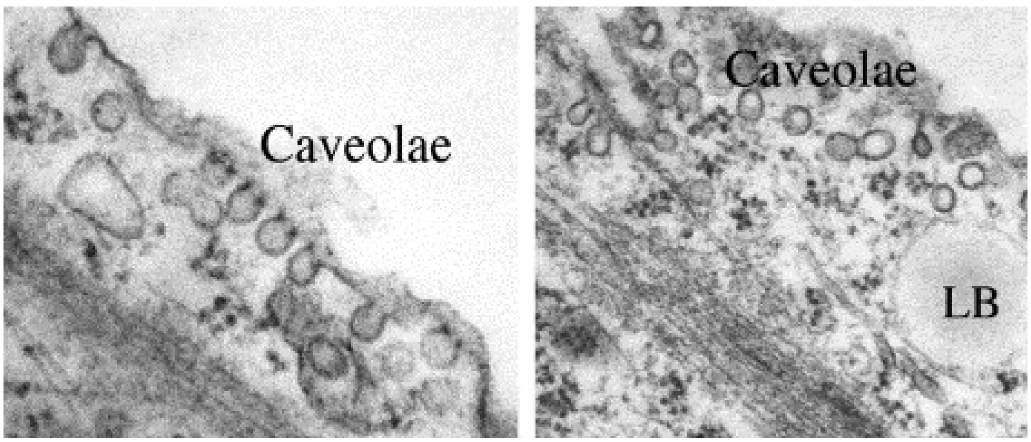


This work showed:

- Some proteins are restricted to certain sites in the membrane
- It's common for specific regions to serve special functions (e.g. sperm's receptor for egg binding & fusion; junctional adhesion molecules)

Lipid Rafts and Caveolae

Thus proteins are known to exist in domains. But the membrane isn't just made up of a continuous bilayer in which proteins and protein domains reside. There are discontinuities within it. lipid domains or "rafts" have been shown to exist which contain difference concentrations of certain lipids such as cholesterol and sphingolipids. These are considered to be sites where other specific molecules group for specific functions. Caveolae ("little caves") first seen in the electron microscope as distinct invaginations (infoldings) of the cell membrane are a special type of lipid raft that have small caveolin protein molecules localized on their cytoplasmic side (Review: Razani & Lisanti, 2001. Exp. Cell Research 271: 36-44). It is likely that the accumulation of many proteins makes the caveolae lipid rafts become evident in the electron microscope. The caveolae have been implicated in the uptake of cholesterol by endocytosis and in the accumulation of signal transduction and other components prior to their endocytosis by receptor mediated endocytosis (see future lectures). While caveolae are known to be stable, cholesterol-rich membrane domains containing the structure-specific protein caveolin, their potentially diverse roles in cell function are under analysis. The membrane components are formed in the golgi and inserted into the cell membrane but much remains to be learned about their biogenesis (Parton et al, 2006. J. Cell Science 119: 787-786). For us, lipid rafts and caveolae reveal that there is much more to be learned about the structure and function of the cell membrane. The following picture shows the ultrastructural appearance of caveolae with the dark areas representing the caveolin protein.



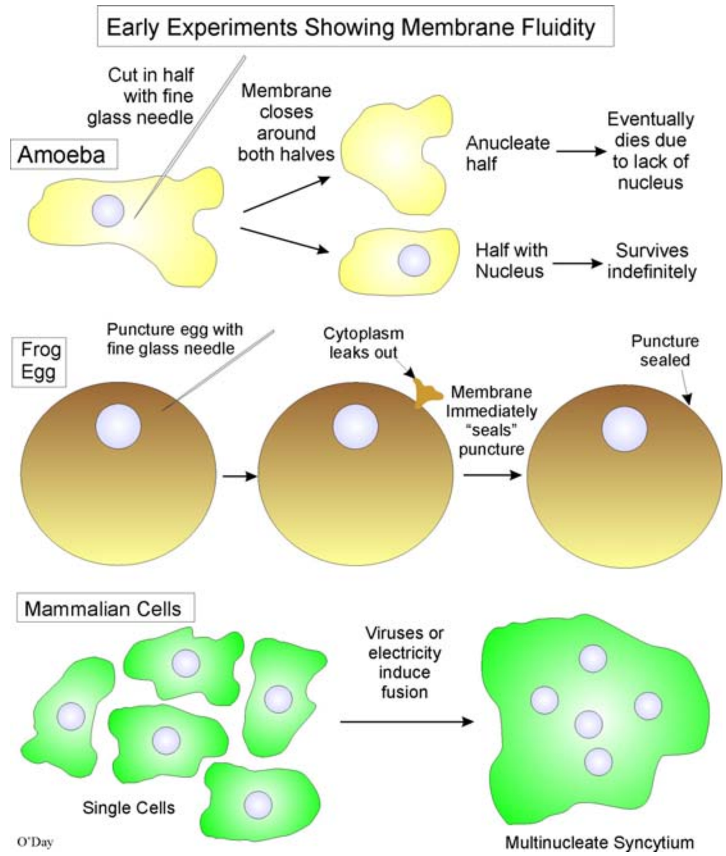
Fluidity of the Cell Membrane

As the "fluid mosaic model" emphasizes the cell membrane is fluid. But this wasn't always appreciated by earlier scientists.

- Lipid phase is fluid
- Fluidity depends upon types of lipids, temperature, etc.
- Membranes fuse during cytokinesis (cell division after mitosis), exocytosis, phagocytosis, etc.
- Some membranes are designed for fusion: e.g., sperm-egg, myoblasts
- Specificity of fusion is defined by protein receptors

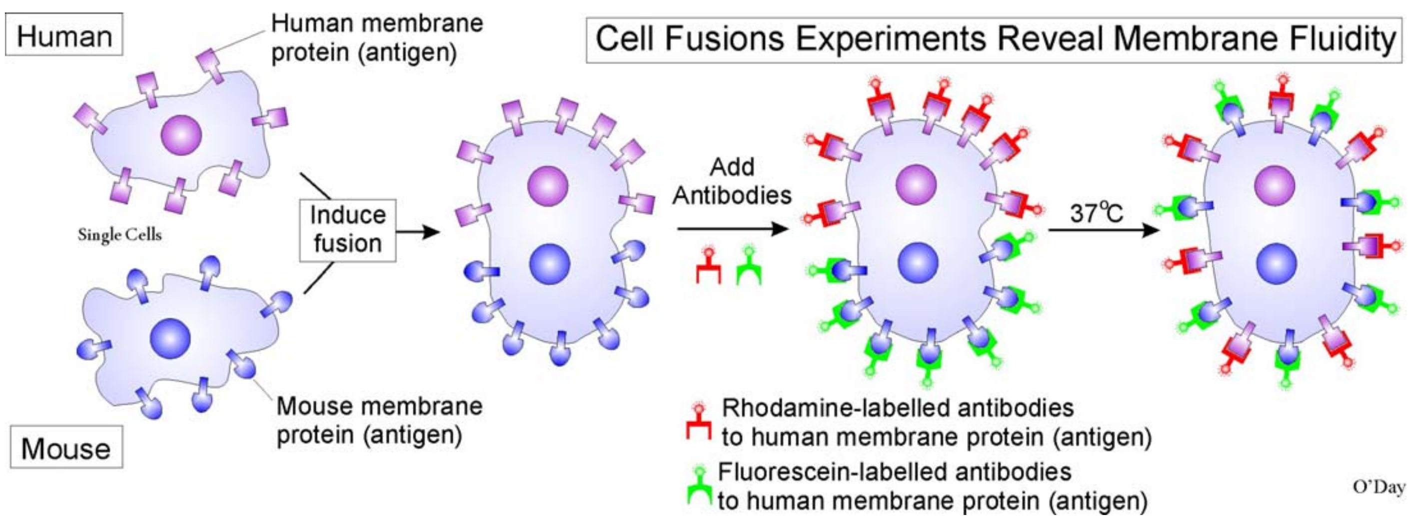
Membrane Fluidity: Early Work

- Cut Amoebae proteus in half with glass needle: both halves crawl away
- Stick glass needle into a frogs egg: it seals up and egg is normal
- Treat cells with certain viruses or electricity: cells that don't normally fuse will fuse together.



Membrane Fluidity: Cell Fusion Experiments

There was a joke going around when I was a kid, "Are you a man or a mouse, squeek up!" That question takes on new meaning when we look at the next experiment where human and mouse cells were induced to fuse to verify the fluidity of the cell membrane.



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