Alberts • Johnson • Lewis • Raff • Roberts • Walter

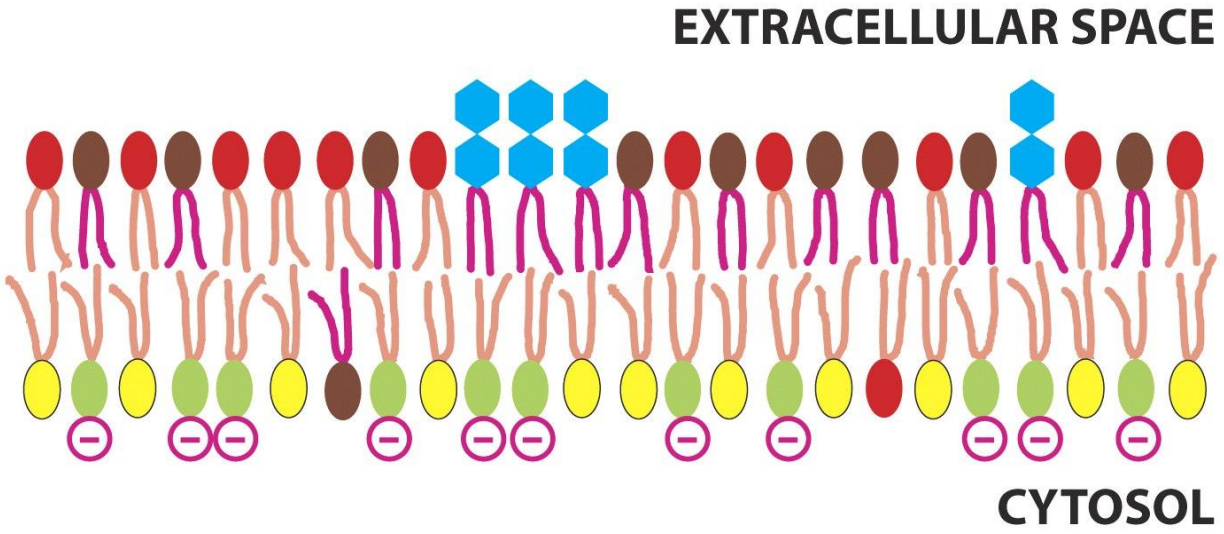
Molecular Biology of the Cell

Fifth Edition

Chapter 10

Membrane Structure

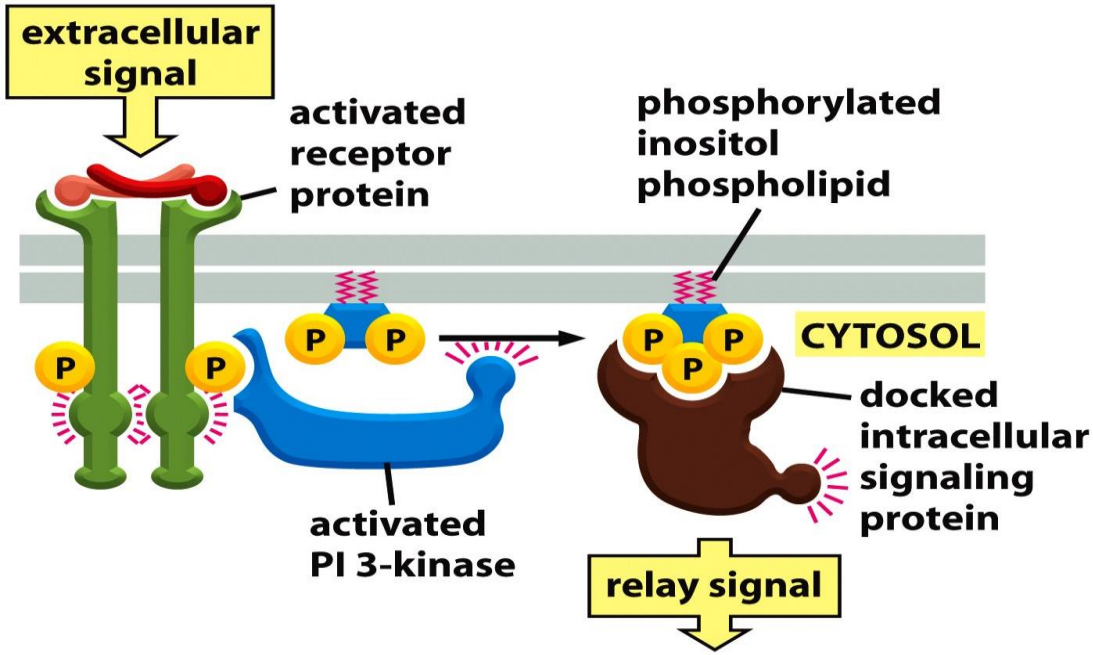
The Asymmetry of the Lipid Bilayer Is Functionally Important



The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells

Lipid asymmetry is functionally important, especially in **converting extracellular signals into intracellular ones**:
The enzyme **protein kinase C (PKC),** which is activated in response to various extracellular signals, binds to the cytosolic face of the plasma membrane, where **phosphatidylserine** is concentrated, and requires this negatively charged phospholipid for its activity

The Asymmetry of the Lipid Bilayer Is Functionally Important



specific lipid head groups must first be modified to create **protein-binding sites** at a particular time and place. One example is **phosphatidylinositol (PI),** one of the minor phospholipids that are concentrated in the cytosolic **monolayer** of cell membranes. Various **lipid kinases** can add phosphate groups at distinct positions on the **inositol ring**, creating binding sites that recruit specific proteins from the cytosol to the membrane. An important example of such a lipid kinase is **phosphoinositide 3-kinase (PI 3-kinase),** which is activated in response to extracellular signals and helps to recruit specific intracellular signaling proteins to the cytosolic face of the plasma membrane.

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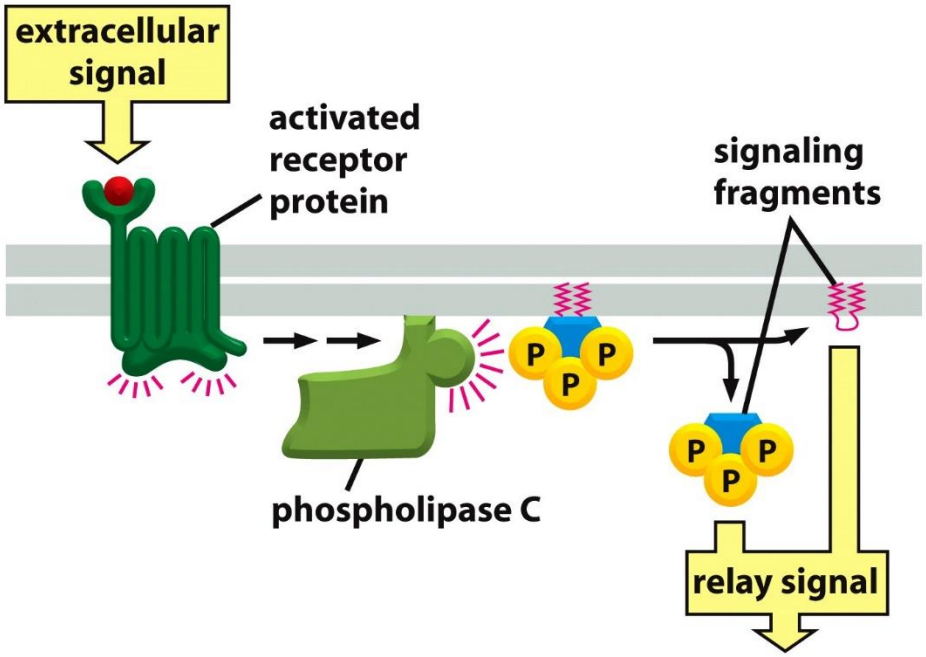


The plasma membrane contains various **phospholipases** that are activated by extracellular signals to cleave specific phospholipid molecules, generating fragments of these molecules that act as **short-lived intracellular mediators**. **Phospholipase C**, for example, cleaves an inositol phospholipid in the cytosolic monolayer of the plasma membrane to generate two fragments, one of which remains in the membrane and helps activate protein kinase C, while the other is released into the cytosol and stimulates the release of Ca2+ from the endoplasmic reticulum

The Asymmetry of the Lipid Bilayer Is Functionally Important

Animals exploit the phospholipid asymmetry of their plasma membranes to distinguish between live and dead cells.

The translocation of the phosphatidylserine in apoptotic cells is thought to occur by two mechanisms:

1. The **phospholipid translocator** that normally transports this lipid from the outer monolayer to the inner monolayer is inactivated.

2. A "**scramblase**" that transfers phospholipids nonspecifically in both directions between the two monolayers is activated.

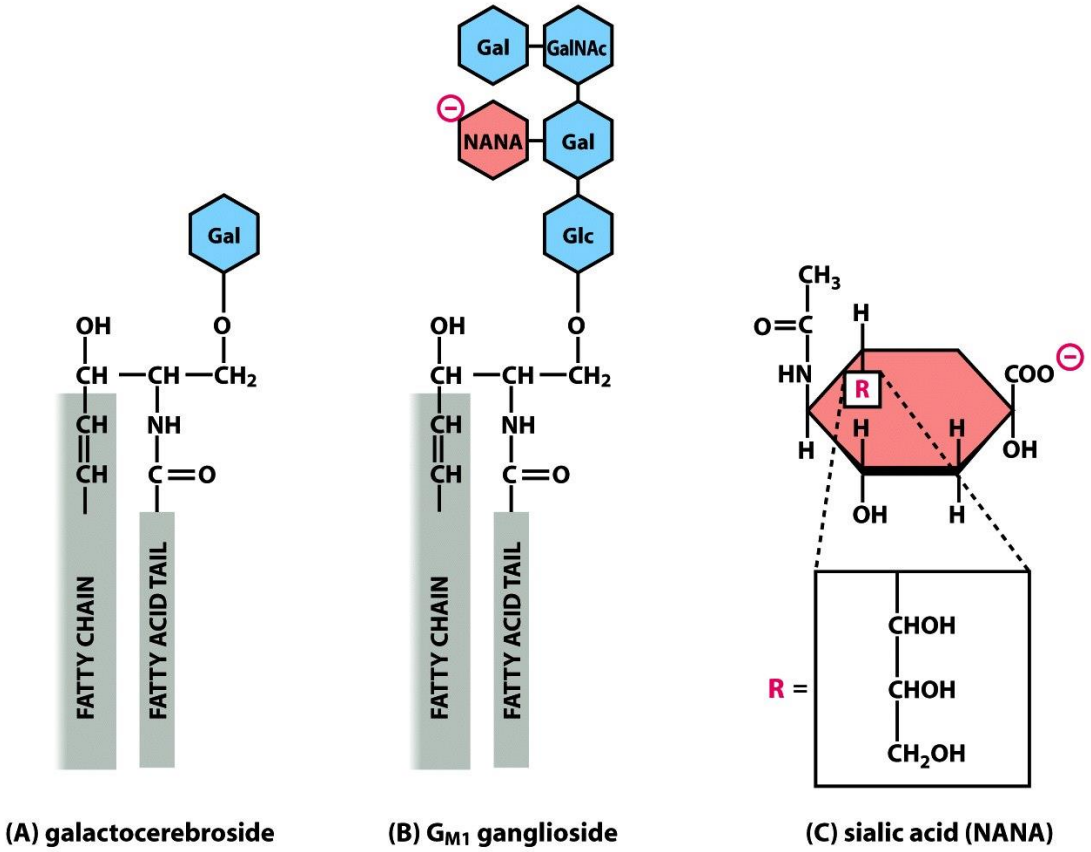
Glycolipids Are Found on the Surface of All Eukaryotic Plasma Membranes

- Sugar-containing lipid molecules called glycolipids.
- Most extreme asymmetry in their membrane distribution: They are found exclusively in the monolayer facing away from the cytosol.
- In animal cells, they are made from sphingosine.
- These intriguing molecules tend to self-associate, partly through hydrogen bonds between their sugars and partly through van der Waals forces between their long and straight hydrocarbon chains, which causes them to partition preferentially into lipid raft phases.
- The asymmetric distribution of glycolipids in the bilayer results from the addition of sugar groups to the lipid molecules in the lumen of the Golgi apparatus.
- As they are delivered to the plasma membrane, the sugar groups are exposed at the cell surface, where they have important roles in interactions of the cell with its surroundings
- they generally constitute about 5% of the lipid molecules in the outer monolayer.

Glycolipids Are Found on the Surface of All Eukaryotic Plasma Membranes

- gangliosides, contain oligosaccharides with one or more sialic acid moieties, which give gangliosides a net negative charge.

- More than 40 different gangliosides that have been identified are in the plasma membrane of nerve cells, where gangliosides constitute 5–10% of the total lipid mass; they are also found in much smaller quantities in other cell types.



(A) galactocerebroside (B) G_{M1} ganglioside (C) sialic acid (NANA)

Glycolipids Are Found on the Surface of All Eukaryotic Plasma Membranes

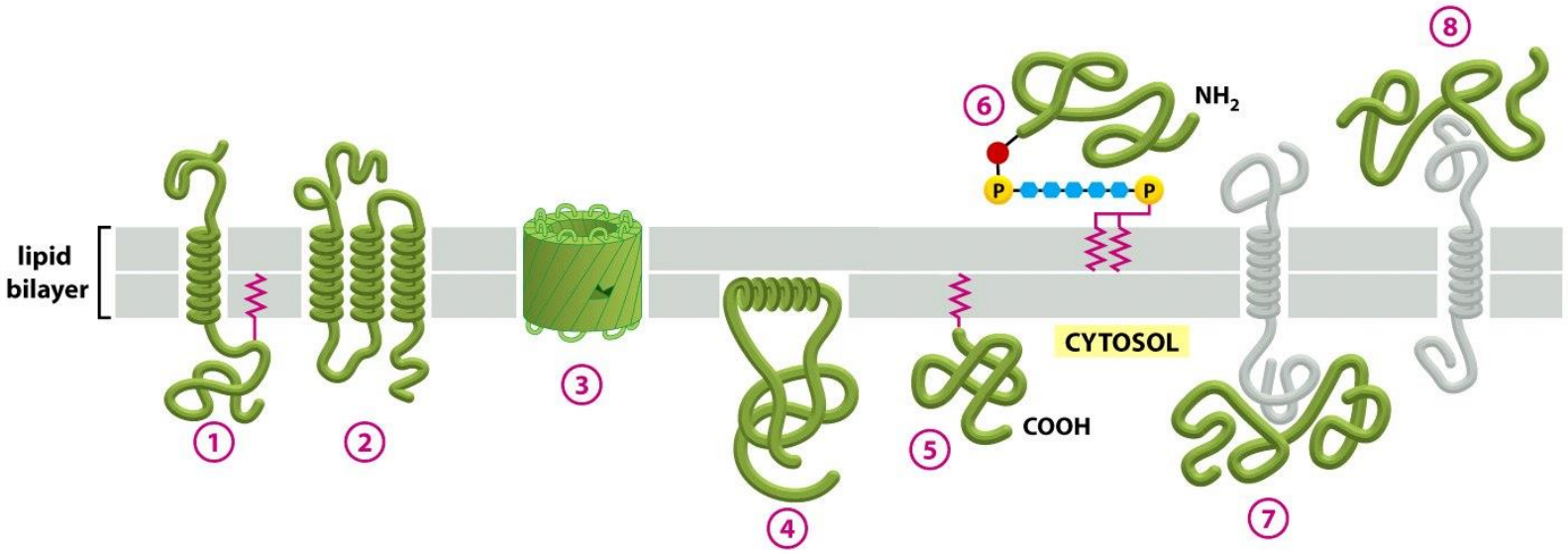
- In the plasma membrane of epithelial cells, glycolipids are confined to the exposed apical surface, where they may help to protect the membrane against the harsh conditions such as low pH and high concentrations of degradative enzymes.

- Charged glycolipids, such as gangliosides, may be important because of their electrical effects: their presence alters the electrical field across the membrane and the concentrations of ions—especially Ca^{2+}—at the membrane surface. Mutant mice that are deficient in all of their complex gangliosides show abnormalities in the nervous system, including **axonal degeneration and reduced myelination**.

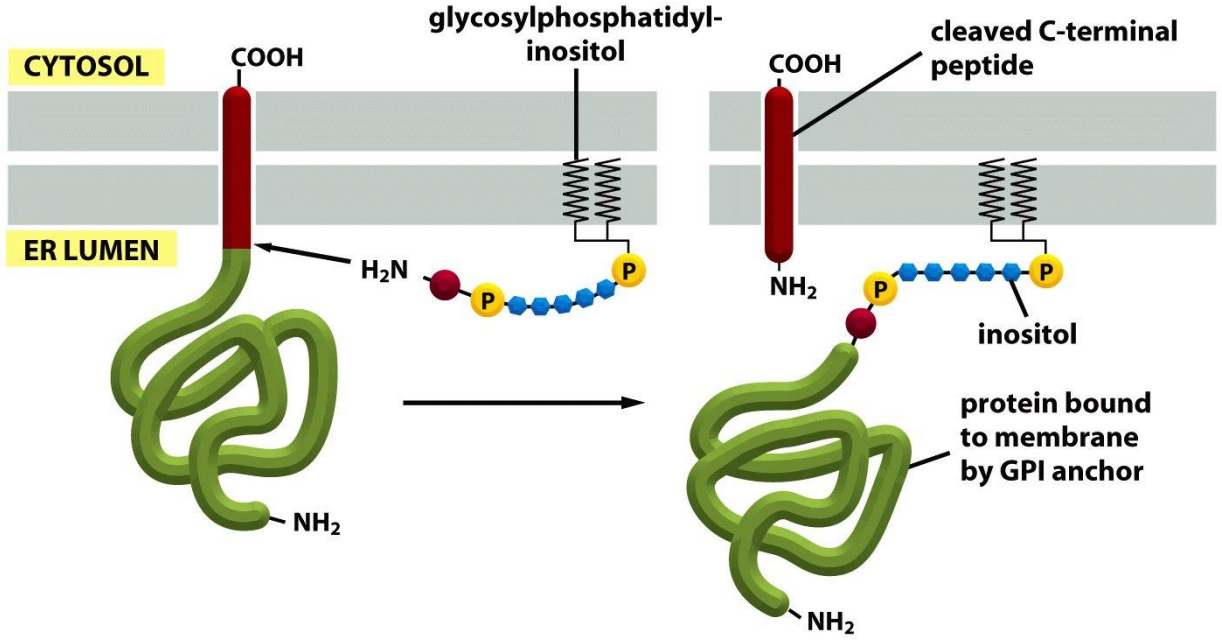
- Glycolipids function in cell-recognition processes, in which membrane-bound carbohydrate-binding proteins (lectins) bind to the sugar groups on both glycolipids and glycoproteins in the process of cell–cell adhesion

- The ganglioside GM1 for example, acts as a cell-surface receptor for the bacterial toxin that causes the debilitating diarrhea of cholera. Cholera toxin binds to and enters only those cells that have GM1 on their surface, including intestinal epithelial cells. Its entry into a cell leads to a prolonged increase in the concentration of intracellular cyclic AMP, which in turn causes a large efflux of Cl^-, leading to the secretion of Na^+, K^+, HCO_3^-, and water into the intestine.
- Polyomaviruses also enter the cell after binding initially to gangliosides.

Membrane Proteins



(1) a single α helix: "**single-pass transmembrane protein**".
(2) as multiple α helices: "**multipass transmembrane protein**".
(3) as a rolled-up β sheet (a β barrel): "**multipass transmembrane protein**".
Some of these "single-pass transmembrane protein" and "multipass" proteins have a covalently attached fatty acid chain inserted in the cytosolic lipid monolayer (1).
(4) Some of these are anchored to the cytosolic surface by an amphiphilic α helix that partitions into the cytosolic monolayer of the lipid bilayer through the hydrophobic face of the helix.
(5) Others are attached to the bilayer solely by a covalently bound lipid chain—either a fatty acid chain or a prenyl group —in the cytosolic monolayer: **Src kinase, Ras GTPase**
(6) via an oligosaccharide linker, to phosphatidylinositol in the noncytosolic monolayer—called a **GPI anchor**.
(7, 8) Finally, membrane-associated proteins are attached to the membrane only by noncovalent interactions with other membrane proteins: **peripheral membrane proteins**



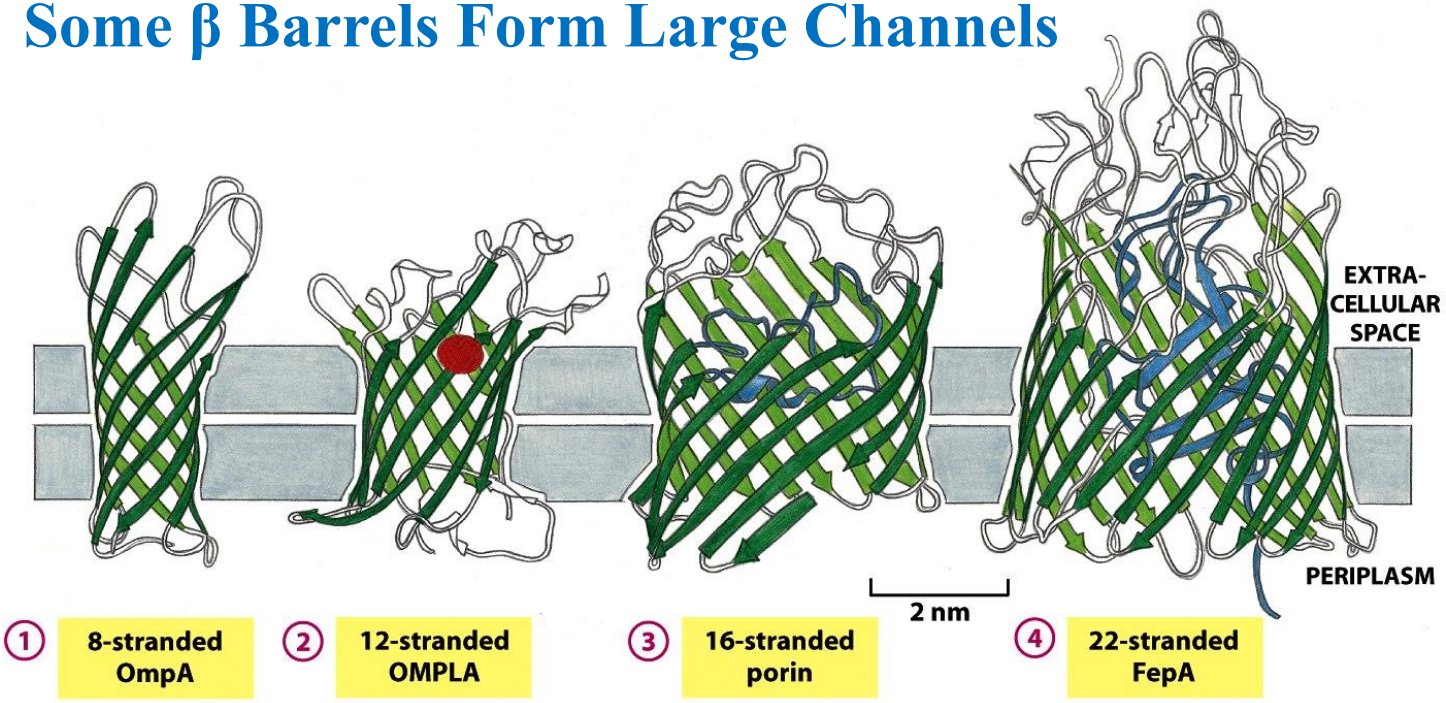
The sugar chain contains an inositol attached to the lipid. It is followed by a glucosamine and three mannoses. The terminal mannose links to a phosphoethanolamine that provides the amino group to attach the protein.

The signal that specifies this modification is contained within the hydrophobic C-terminal sequence and a few amino acids adjacent to it on the lumenal side of the ER membrane. Because of the **covalently** linked lipid anchor, the protein remains membrane-bound, with all of its amino acids exposed initially on the lumenal side of the ER and eventually on the exterior of the plasma membrane.

they can in principle be released from cells in soluble form in response to signals that activate a specific phospholipase in the plasma membrane.

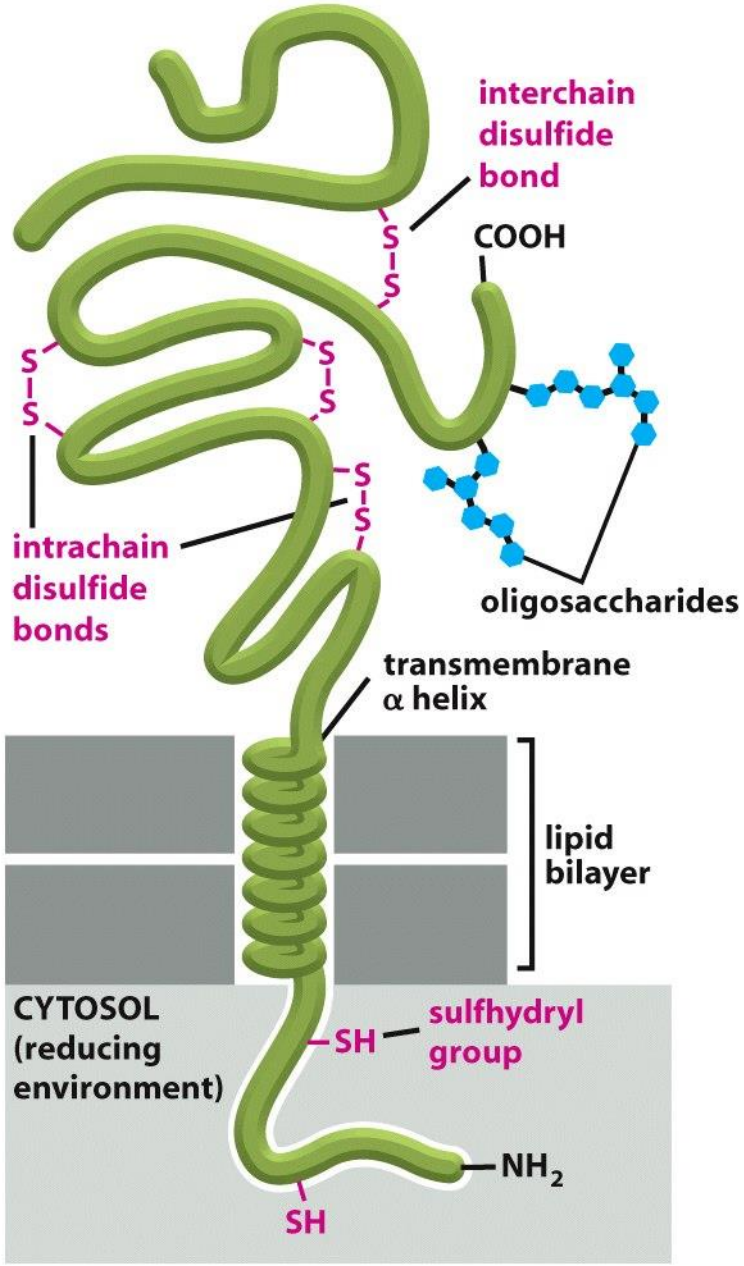
GPI anchors may be used to direct plasma membrane proteins into lipid rafts and thus segregate the proteins from other membrane proteins.

Some β Barrels Form Large Channels



(A) The E. coli OmpA protein serves as a receptor for a bacterial virus.
(B) The E. coli OMPLA protein is an enzyme (a lipase) that hydrolyzes lipid molecules. The amino acids that catalyze the enzymatic reaction (shown in red) protrude from the outside surface of the barrel.
(C) A porin from the bacterium *Rhodobacter capsulatus* forms a waterfilled pore across the outer membrane. The diameter of the channel is restricted by loops (shown in blue) that protrude into the channel.
(D) The E. coli FepA protein transports iron ions. The inside of the barrel is completely filled by a globular protein domain (shown in blue) that contains an iron-binding site.

Many Membrane Proteins Are Glycosylated



A single-pass transmembrane protein. The **oligosaccharide chains** and **disulfide bonds** are all on the noncytosolic surface of the membrane. The sulfhydryl groups in the cytosolic domain of the protein do not normally form disulfide bonds because **the reducing environment in the cytosol** maintains these groups in their reduced (–SH) form. These bonds form on the noncytosolic side, where they can help stabilize either the folded structure of the polypeptide chain or its association with other polypeptide chains.

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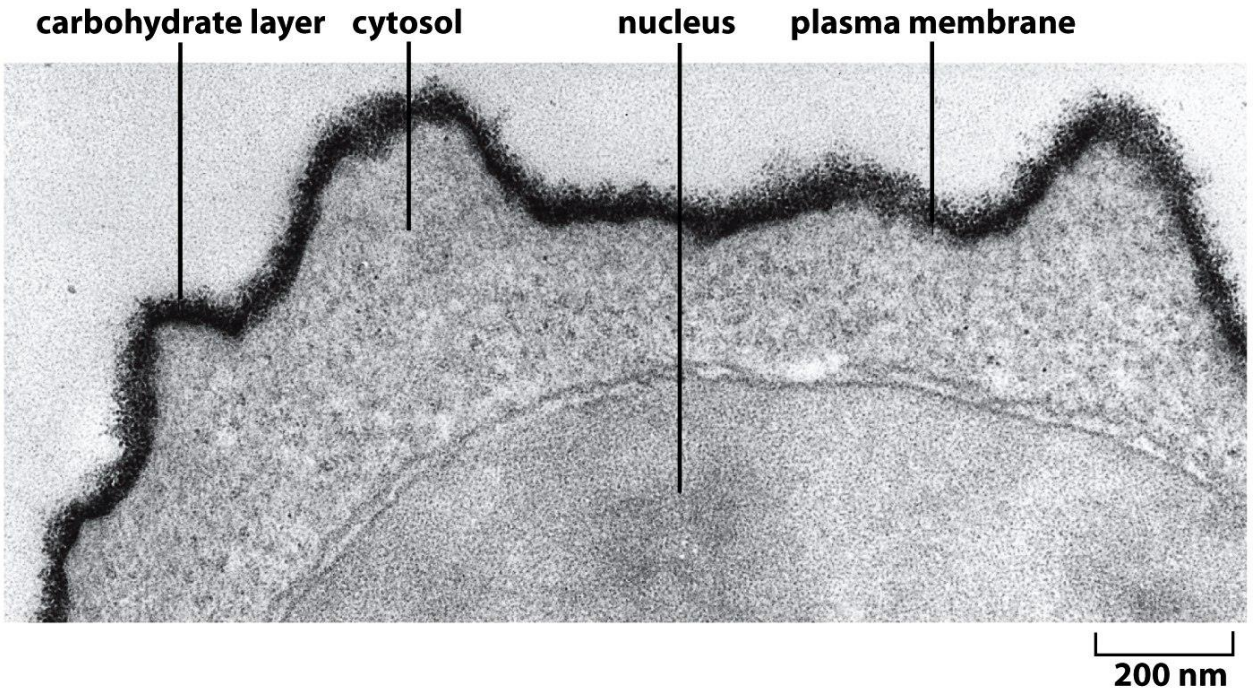
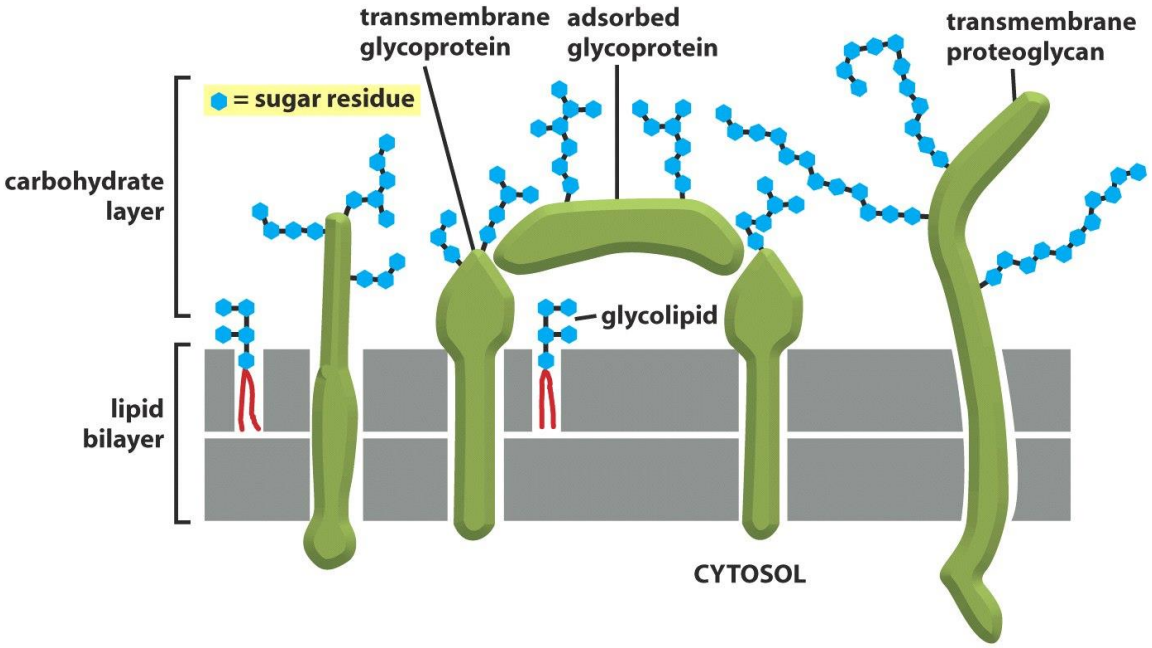


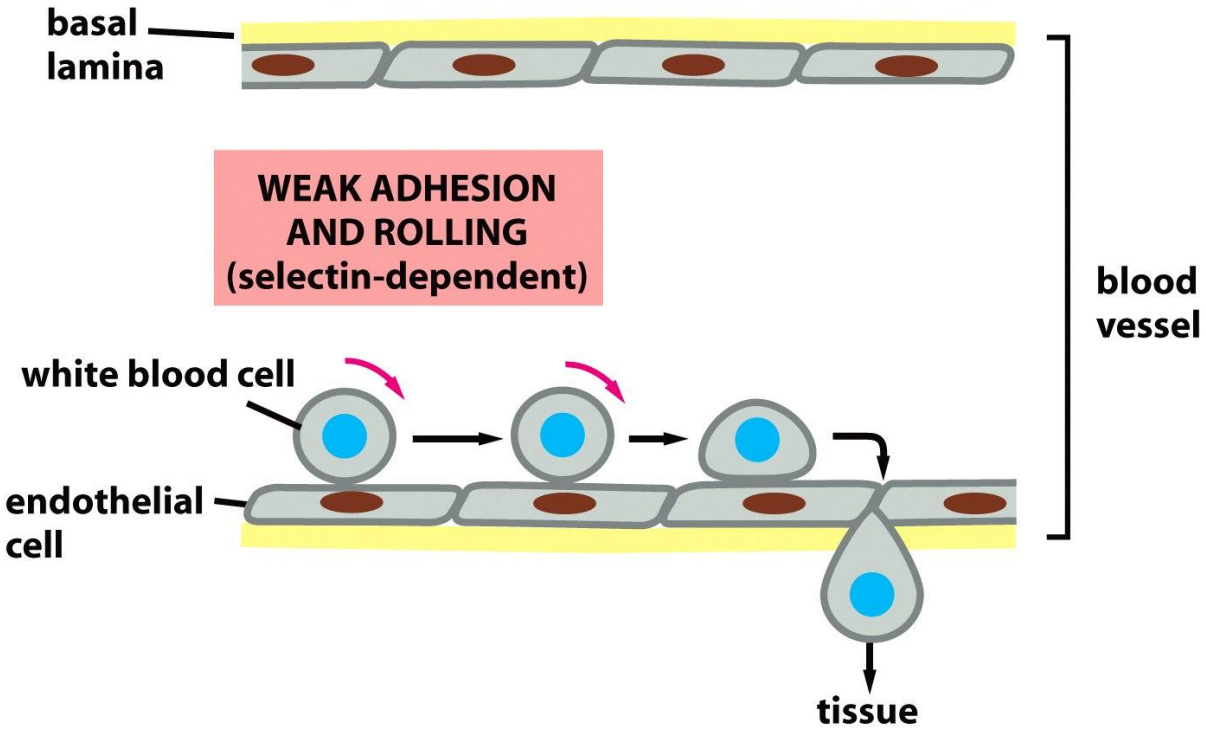
Carbohydrates extensively coat the surface of all eukaryotic cells.
These carbohydrates occur as oligosaccharide chains covalently bound to membrane proteins (**glycoproteins**) and lipids (**glycolipids**). They also occur as the polysaccharide chains of integral membrane **proteoglycan** molecules. Proteoglycans, which consist of long polysaccharide chains linked covalently to a protein core, are found mainly outside the cell, as part of the extracellular matrix. But, for some proteoglycans, the protein core either extends across the lipid bilayer or is attached to the bilayer by a glycosylphosphatidylinositol (GPI) anchor.

Many Membrane Proteins Are Glycosylated



- The terms cell coat or **glycocalyx** are used to describe the carbohydrate-rich zone on the cell surface.
- protect cells against mechanical and chemical damage.
- It keeps various other cells at a distance, preventing unwanted cell–cell interactions.
- they usually contain fewer than 15 sugars, the chains are often branched, and the sugars can be bonded together by various kinds of covalent linkages.
- Both the diversity and the exposed position of the oligosaccharides on the cell surface make them especially well suited to function in specific **cell-recognition processes.** plasma-membrane-bound lectins that recognize specific oligosaccharides on cell-surface glycolipids and glycoproteins mediate a variety of transient cell–cell adhesion processes, including those occurring in lymphocyte recirculation and inflammatory responses.

Selectins Mediate Transient Cell–Cell Adhesions in the Bloodstream



Selectins are cell-surface carbohydrate-binding proteins (lectins) that mediate a variety of transient cell–cell adhesion interactions in the bloodstream**. The selectins control the binding of white blood cells to the endothelial cells lining blood vessels, thereby enabling the blood cells to migrate out of the bloodstream into a tissue.**