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BIOMEMBRANE STRUCTURE

REVIEW THE CONCEPTS

1. The spontaneous assembly of phospholipid molecules into a lipid bilayer creates a sheetlike structure that is two molecules thick. Each layer is arranged so that the polar head groups of the phospholipids are exposed to the aqueous environment on one side of the bilayer and the hydrocarbon tails associate with the tails of the other layer to create a hydrophobic core. In cross section, the bilayer structure thus consists of a hydrophobic core bordered by polar head groups. When stained with osmium tetroxide, which binds strongly to polar head groups, and viewed in cross section, the bilayer looks like a railroad track with a light center bounded on each side by a thin dark line.

2. The amphipathic nature of phospholipid molecules (a hydrophilic head and hydrophobic tail) allows these molecules to self-assemble into closed bilayer structures when in an aqueous environment. The phospholipid bilayer provides a barrier with selective permeability that restricts the movement of hydrophilic molecules and macromolecules across the bilayer. The different types of proteins present on the two faces of the bilayer contribute to the distinctive functions of each membrane, and control the movement of selected hydrophilic molecules and macromolecules across it.

3. The three main types of lipid molecules in biomembranes are phosphoglycerides, sphingolipids, and steroids. All are amphipathic molecules having a polar head group and a hydrophobic tail, but the three types differ in chemical structure, abundance and function.

4. Lipid bilayers are considered to be two-dimensional fluids because lipid molecules (and proteins if present) are able to rotate along their long axes and move laterally within each leaflet. Such movements are driven by thermal energy, and may be quantified by measuring fluorescence recovery after photobleaching, the FRAP technique. In this technique, specific membrane lipids or proteins are labeled with a fluorescent reagent, and then a laser is used to irreversibly bleach a small area of the membrane surface. The extent and rate at which fluorescence recovers in the bleached area, as fluorescent molecules diffuse back into the bleach zone and bleached molecules diffuse outward, can be measured. The extent of recovery is proportional to the fraction of labeled molecules that are mobile, and the rate of recovery is used to calculate a diffusion coefficient, which is a measure of the molecule's rate of diffusion within the bilayer. The degree of fluidity depends on factors such as temperature, the length and saturation of the fatty acid chain portion of phospholipids, and the presence/absence of specific lipids such as cholesterol.

5. Water-soluble substances are hydrophilic; they are therefore repelled by the hydrophobic core of the bilayer, which is composed of non-polar hydrocarbon tails of the phospholipids. Proteins that span the cell membrane (transmembrane proteins) provide a channel or passageway through which these substances can cross the membrane. The proteins fold such that their non-polar residues are in contact with the phospholipid bilayer and their polar residues line the channel through which the hydrophilic substances travel from one side of the cell membrane to the other.

6. Membrane-associated proteins may be classified as integral membrane proteins, lipid-anchored membrane proteins, or peripheral membrane proteins. Integral membrane proteins pass through the lipid bilayer and are therefore composed, of three domains: a cytosolic domain exposed on the cytosolic face of the bilayer; an exoplasmic domain exposed on the exoplasmic face of the bilayer; and a membrane-spanning domain, which passes through the bilayer and connects the cytosolic and exoplasmic domains. Lipid-anchored membrane proteins have one or more covalently attached lipid molecule, which embeds in one leaflet of the membrane and thereby anchors the protein to one face of the bilayer. Peripheral proteins associate with the lipid bilayer through interactions with either integral membrane proteins or with phospholipid heads on one face of the bilayer.

7. a. aquaporins
   b. porins

8. Cytosolic proteins are anchored to the plasma membrane by acylation or prenylation. In the case of acylation, an N-terminal glycine residue of a protein is covalently attached to the 14-carbon fatty acid myristate (myristoylation) or a cysteine residue in a protein is attached to the 16-carbon fatty acid palmitate (palmitoylation). Prenylation occurs when the –SH group on a cysteine residue at or near the C-terminus of the protein is bound through a thioether bond to either a farnesyl or a geranylgeranyl (prenyl) group. Cell-surface proteins and heavily glycosylated proteoglycans are present on the exoplasmic face of the membrane and are linked there by a glycophosphatidylinositol (GPI) anchor.

9. Since biomembranes form closed compartments, one face of the bilayer is automatically exposed to the interior of the compartment while the other is exposed to the exterior of the compartment. Each face therefore interacts with different environments and performs different functions. The different functions are in turn directly dependent on the specific molecular composition of each face. For example, different types of phospholipids and lipid-anchored membrane proteins are typically present on the two faces. In addition, different domains of integral proteins are exposed on each face of the bilayer. Finally, in the case of the plasma membrane, the lipids and proteins of the exoplasmic face are often modified with carbohydrates.

10. Detergents are amphipathic molecules. The hydrophobic part of a detergent molecule readily interacts with the hydrophobic tails of the phospholipids disrupting their interaction with each other; the hydrophilic part readily associates with water. This breaks up the organization of the lipid bilayer, ultimately leading to formation of micelle droplets, composed of a single phospholipid layer with the polar heads in contact with water and a hydrophobic core excluding water.

    Ionic detergents, like all detergents, bind to both the hydrophilic and hydrophobic regions of membrane proteins that have been exposed after lipid bilayer disruption. Because of their charge, they can also disrupt the ionic and hydrogen bonds holding together the secondary and tertiary structure of a protein and are thus useful for completely denaturing a protein.

    Non-ionic detergents do not denature proteins and are therefore useful for extracting membrane proteins while maintaining their native conformation. At concentrations below the critical micelle concentration, they also prevent the hydrophobic regions of proteins that have been extracted from the cell membrane from interacting with each other and forming insoluble aggregates.

11. a. peripheral
    b. lipid anchored
    c. integral membrane protein. No, a strong ionic detergent like SDS will denature the protein.

12. Lipid raft

13. a. Membrane phospholipids are synthesized at the interface between the cytosolic leaflet of the endoplasmic reticulum (ER) and the cytosol. Water-soluble, small molecules are synthesized and activated in the cytosol. Membrane-bound enzymes of the ER then link these small molecules to create larger, hydrophobic membrane phospholipids.
    b. Membrane phospholipids can be flipped from the cytosolic leaflet of the ER membrane to the exoplasmic leaflet. This process, mediated by flippases, results in the incorporation of newly synthesized phospholipids into both leaflets.
    c. Phospholipids can be moved from their site of synthesis to other membranes (e.g., to the plasma membrane). Some of this transport is by vesicles. Some is due to direct contact between membranes. Small, soluble lipid-transfer proteins also mediate transfer. The mechanism of phospholipid transfer between membranes is not yet well understood.

14. The common fatty-acid chains in phosphoglycerides include myristate, palmitdate, stearate, oleate, linoleate, and arachidonate (see Table 2-4). These fatty acids differ in carbon atom number by multiples of 2 because they are elongated by the addition of 2 carbon units. For example, the acetyl group of acetyl CoA is a 2-carbon moiety.

15. Fatty acids have very low solubility inside an aqueous-rich intracellular environment. Therefore, they associate with fatty-acid binding proteins (FABPs), which are cytosolic proteins that contain a hydrophobic pocket or barrel, lined by β sheets. This pocket provides a haven for the long-chain fatty acid, where it interacts in a noncovalent fashion with the FABP.

16. The key regulated enzyme in cholesterol biosynthesis is HMG (β-hydroxy-β-methylglutaryl)-CoA reductase. This enzyme catalyzes the rate-controlling step in cholesterol biosynthesis. The enzyme is subject to negative feedback regulation by cholesterol. In fact, the cholesterol biosynthetic pathway was the first biosynthetic pathway shown to exhibit this type of end-product regulation. As the cellular cholesterol level rises, the need to synthesize additional cholesterol goes down. The expression and enzymatic activity of HMG-CoA reductase is suppressed. HMG-CoA reductase has eight transmembrane segments and, of these, five compose the sterol-sensing domain. Sterol sensing by this domain triggers the rapid, ubiquitin-dependent proteasomal degradation of HMG-CoA reductase. Homologous domains are found in other proteins such as SCAP (SREBP cleavage activating protein) and Niemann-Pick C1 (NPC1) protein, which take part in cholesterol transport and regulation.

17. Most phospholipids and cholesterol membrane-to-membrane transport in cells is not by Golgi-mediated vesicular transport. One line of evidence for this is the effect of chemical and mutational inhibition of the classical secretory pathway. Either fails to prevent cholesterol or phospholipid transport between membranes, although they do disrupt the transport of proteins and Golgi-derived sphingolipids. Membrane lipids produced in the ER cannot move to the mitochondria by classic secretory transport vesicles. No vesicles budding from the ER have been found to fuse with mitochondria. Other mechanisms are thought to exist. However, presently these are poorly defined. They include direct membrane-membrane contact and small, soluble lipid-transfer proteins.

18. Statins block the conversion β-hydroxy-β-methylglutaryl linked to CoA (HMG-CoA) to mevalonate (an important intermediate in cholesterol synthesis) by competitively binding the enzyme necessary for this conversion (HMG-CoA reductase).