Membranes
Lipid bilayer structure

Importance of membrane proteins

- The human genome contains around 25,000 genes
- ~20% of genes are predicted to encode membrane proteins
- Many membrane proteins are at the interface of the cell and its external environment (others are in organelle membranes)
- They dictate how the cell interacts with its environment, hence they are crucial for the correct functioning of cells
- Membrane proteins are important target for pharmaceutical drugs and therefore of medical (and economic) importance

TOP 10 PRESCRIPTION DRUGS BY SALES (USA)

<table>
<thead>
<tr>
<th>RANK</th>
<th>GENERIC NAME</th>
<th>COMPANY</th>
<th>DISEASE / TARGET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atorvastin</td>
<td>Pfizer</td>
<td>Cholesterol / HMGCoA inhibitor</td>
</tr>
<tr>
<td>2</td>
<td>Simvastin</td>
<td>Merck &amp; Co</td>
<td>Cholesterol / HMGCoA inhibitor</td>
</tr>
<tr>
<td>3</td>
<td>Fluticasone/salmeterol</td>
<td>GlaxoSmithKlein</td>
<td>Asthma / steroid with β2 adrenoceptor stimulant</td>
</tr>
<tr>
<td>4</td>
<td>Amlodipine</td>
<td>Pfizer</td>
<td>Hypertension / calcium channel blocker</td>
</tr>
<tr>
<td>5</td>
<td>Olanzapine</td>
<td>Eli Lilly</td>
<td>Schizophrenia / 5-HT receptor blocker</td>
</tr>
<tr>
<td>6</td>
<td>Esomeprazole</td>
<td>AstraZeneca</td>
<td>Gastric ulcer / proton transport protein inhibitor</td>
</tr>
<tr>
<td>7</td>
<td>Epoetin alfa</td>
<td>Johnson &amp; Johnson</td>
<td>Anaemia / synthetic erythropoietin</td>
</tr>
<tr>
<td>8</td>
<td>Sertaline</td>
<td>Pfizer</td>
<td>Depression / blocks 5-HT transporter</td>
</tr>
<tr>
<td>9</td>
<td>Venlafaxine</td>
<td>Wyeth</td>
<td>Depression / blocks 5-HT and noradrenalin transporters</td>
</tr>
<tr>
<td>10</td>
<td>Clopidogrel</td>
<td>Bristol-Meyers Squibb</td>
<td>Thrombosis / ADP receptor blocker</td>
</tr>
</tbody>
</table>

~60% of drugs target a membrane protein:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448992/
Diseases caused by mutations in membrane proteins:

- Cystic fibrosis (epithelial Cl⁻ channel)
- Malignant hyperthermia (sarcoplasmic reticulum Ca²⁺ channel)
- Long-QT syndrome (cardiac K⁺ channel)
- Darier disease (Ca²⁺ pump)
- Becker’s myotonia (skeletal muscle Cl⁻ channel)
- Congenital myasthenic syndrome (acetylcholine receptor)

Eukaryotic cells and their membranes

- All cells are bounded by a membrane
- For eukaryotic cells, this cell membrane is called the plasma membrane
- Except for the most primitive organisms (prokaryotes), cells also have internal membranes
- Internal membranes delineate sub-cellular compartments with specific functions (organelles): nucleus, mitochondria, etc.

Gene Mutations in Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder, a disease that results from mutations, or errors, in genes.

- Cystic fibrosis transmembrane conductance regulator (CFTR)
  - membrane protein that functions as a chloride ion channel
  - consists of 1480 amino acids
  - F508del: amino acid 508 (Phe) is missing
  - G551D: amino acid 551 is Asp instead of Gly (e.g. DNA codon is GAU instead of GGU)

Generalized structure of an animal cell

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The majority of the cell’s membranes are internal membranes.

Transmission electron microscopy (TEM) image of a thin slice of a cell, after staining of membranes with heavy metal ions.

Major components of membranes

- **Lipids**
  - small amphipathic molecules
  - consist of polar ‘headgroup’ and hydrophobic ‘tails’
  - hydrophobic tails provide a permeability barrier to polar/hydrophilic molecules

- **Proteins**
  - functional elements of membranes
  - roles in signalling, transport, adhesion, etc.
Membrane lipids

- generic lipid structure
  - Polar or hydrophilic head group
  - Nonpolar or hydrophobic tails

- structure of a specific lipid

Major types of lipids
- glycerophospholipids (glycerol backbone)
- sphingolipids (sphingosine backbone)
- sterols – e.g. cholesterol

Glycerophospholipids
- glycerol backbone
- phosphate with attached polar group (e.g. choline)
- two hydrocarbon chains (e.g. octadecanoic acid attached)

Sphingolipids
- sphingosine backbone
- attached polar group (can contain phosphate)
- one hydrocarbon chain (e.g. octadecanoic acid attached)

1-octadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine = 18:0-18:1-PC (1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine = SOPC)

Structure of sphingomyelin:
Membrane lipids are amphipathic

- Membrane lipids contain polar (hydrophilic) and non-polar (hydrophobic) groups, i.e. they are amphipathic.
- In an aqueous environment the lipids organise themselves to minimise the interaction of the hydrophobic groups with water, while maximising the interactions of the polar head-groups with the aqueous phase.

Lipid bilayers and membranes

- Phosphatidylcholine and similar lipids will spontaneously form lipid bilayers in water.
- Lipid bilayers constitute permeability barriers: the hydrophobic bilayer core is impermeable to polar and to large molecules.
- Membranes consist of many different lipids (different chains and different headgroups) and also contain proteins.
- The lipid composition of the inner and outer leaflets of the membrane is always different.

The liquid crystalline phase

- Biological membranes contain large amounts of lipids with acyl chains (mainly C₁₆-C₁₈ long) containing cis double bonds.
- Cis bonds prevent the close packing of acyl (glycerol-linked fatty acid) chains, resulting in a bilayer where these chains are mobile.
- In this phase (called the liquid crystalline phase) the lipids can move around in the plane of the bilayer.
The liquid crystalline phase is essential for membrane function

- At low temperatures the liquid crystalline lipid turns into a gel phase, in which the acyl chains are effectively frozen.
- The liquid crystalline phase is essential for the function of the membrane proteins, which require a fluid environment in which to operate.
- The fluid lipid environment is flexible and allows proteins embedded in the bilayer to undergo the conformational changes that are essential to their function.
- Membrane proteins sometimes need to interact with adjacent membrane proteins; the fluid membrane allows them to move in the plane of the bilayer.

Summary

- Lipids based on glycerol and sphingosine, as well as sterols, form the major lipid components of biological membranes.
- Lipids such as phosphatidylcholine form bilayers in water – lipid self-assembly as a bilayer structure is driven by the hydrophobic effect.
- Membrane formation also involves protein insertion, which is an active process (i.e. not self-assembly).
- The fluid nature of the bilayer, where lipids and proteins are free to move in the plane of the bilayer, is essential for membrane protein function.