Lecture 15
The Lipid Bilayer: A Dynamic Self-Assembled Structure of Multiple Lipid Classes
**LIPIDS**- Biological molecules with low solubility in water and high solubility in non-polar solvents
-Lipids form biological membranes
-Lipids are the most efficient way to store energy

**EXAMPLES:**
Fats and oils, Vitamins and hormones, membrane components.

Lipids are indispensable to metabolism & cell structure.
Outline:

1) Classification and Properties of Lipids
2) Biological Functions of Lipids
3) Lipids in Bioscience
Classification of Biological Lipids

- Triacylglycerol
  - Storage lipids
- Phospholipid
- Sphingolipid
- Cholesterol

Storage lipids: Triacylglycerol
Membrane lipids: Phospholipid, Sphingolipid, Cholesterol
Lipid Type is Specialized for Biological Function

Storage lipids: Triglycerides, they are the main component of lipid droplets in adipocyte cells.

Membrane Lipids: Phospholipids, Sphingolipids, etc. They are the polar lipids that make up biological membranes.
Composition of Triglycerides

Triglycerides are neutral lipids. They are composed of one glycerol molecule and three long carbon chain acids known as fatty acids.
Fatty Acids

Fatty acids are straight hydrocarbon chain organic acids. The most common number of carbon atoms in the chain is 16-18.
Saturated Fatty Acids

-When fatty acids are saturated, no more hydrogen atoms can be added. All bonds between carbon atoms are single bonds.  
The hydrocarbon chain is straight in saturated fatty acids. As a result, the molecular packing is dense and the melting point is high.
-Example: Butter.
- Unsaturated fatty acids have one or more double bonds between carbon atoms are single bonds. Monounsaturated: one double bond. Polyunsaturated: more than one double bond.
Cis-Unsaturated Fatty Acids

- Most naturally occurring unsaturated fatty acids are in *cis*. Carbon-carbon bonds adjacent to double bonds are on the same side.
- The hydrocarbon chain is bent in cis-un saturated fatty acids, so the molecular packing is less dense and the melting point is lower than saturated fatty acids.
- Example: Olive oil.
Trans Fatty Acids

-Most trans fatty acids are created in an industrial process that adds hydrogen to liquid vegetable oils to make them more solid. The carbon bonds adjacent to double bonds are on the opposite side.

-The hydrocarbon chain is straight in trans fatty acids, so the molecular packing is more dense and the melting point is higher than saturated fatty acids.

-Example: Crisco
The trans fat cookie challenge: GONE!!

The FDA has proposed that trans fats no longer be “generally recognized as safe.”

Trans fats raise your bad (LDL) cholesterol levels and lower your good (HDL) cholesterol levels. Eating trans fats increases your risk of developing heart disease and stroke. It’s also associated with a higher risk of developing type 2 diabetes.

It is estimated that 7,000-20,000 deaths a year could be prevented by eliminating trans fats.
## Chemical Properties of Triglycerides

### FAT SUMMARY

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Saturated</th>
<th>Unsaturated (cis)</th>
<th>Unsaturated (trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Straight</td>
<td>Bent</td>
<td>Straight</td>
</tr>
<tr>
<td>Shape of carbon chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular packing</td>
<td>Dense</td>
<td>Less Dense</td>
<td>Dense</td>
</tr>
<tr>
<td>Melting point</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
Classification of biological lipids

- Hydrophilic group
- Glycerol
- Hydrophobic tails
- Sphingosine
- Sterol ring

Types of lipids:
- Triacylglycerol (Storage lipids)
- Phospholipid
- Sphingolipid
- Cholesterol

Membrane Lipids
Phospholipid Structure

(A) Diagram showing the polar (hydrophilic) head group, consisting of choline, phosphate, and glycerol, and the nonpolar (hydrophobic) tails.

(B) Chemical structure of the phospholipid, highlighting the head group and the hydrocarbon tails.

(C) 3D model of the phospholipid, showing the hydrophilic head and hydrophobic tails.

Figure 10-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Types of Phospholipids

phosphatidyl-ethanolamine (A)
phosphatidyl-serine (B)
phosphatidyl-choline (C)
sphingomyelin (D)
sphingosine (E)

Figure 10-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Shape of the Lipid Dictates its Packing Arrangement

Critical micelle concentration (cmc) is the concentration above which amphiphiles aggregate into micelles.
Phospholipids Form Liposomes

ENERGETICALLY UNFAVORABLE

- planar phospholipid bilayer with edges exposed to water

- sealed compartment formed by phospholipid bilayer

ENERGETICALLY FAVORABLE

Figure 10-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Lateral diffusion is fast: a lipid in a bilayer could diffuse the length of a bacterial cell (1-2 μm) in less than a second. Transverse diffusion (flip-flopping) is slow, when measured half-times are several days.
FRAP Demonstrates Rapid Lateral Diffusion in Membranes

(A) Bleach → (B) Recovery → (C) Recovery

(D) Fluorescence intensity

Biochemistry. 5th edition.
Stryer L. 2002.
**Bilayer Fluidity Varies with Temperature**

Phase transition temperature

Below the phase transition temperature: gel phase

Above the phase transition temperature: liquid crystal phase

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Biochemistry. 5th edition, Stryer

Heller et al., J. Phys. Chem 1993
Classification of biological lipids

Triacylglycerol | Phospholipid | Sphingolipid | Cholesterol
Storage lipids | Membrane Lipids
Eukaryotic Plasma Membranes Contain Cholesterol

Cholesterol makes the plasma membrane less permeable. It’s rigid sterol ring interacts with the hydrocarbon chain closest to the polar head group and thus partially immobilizes it. Cholesterol also broadens the temperature range for the order-disorder phase transition.
Outline:

1) Classification and Properties of Lipids
2) Biological Functions of Lipids
3) Lipids in Bioscience
Why are Membranes Needed?

What would you need to synthesize a cell *de novo*, or how did the first protocell come to be?

Let’s operationally define a living cell as one that can autonomously replicate, and that is subject to Darwinian evolution.

It needs a membrane, to keep everything together, and a biopolymer that can replicate itself (such as RNA) and hopefully also make more membrane.
The protocell evolves

A membrane can separate the protocell from the environment. If each cell needs a molecule to serve as a template and a molecule to serve as an enzyme, then any protocell with a more efficient replicase will outcompete a cell with an inefficient replicase. The membrane vesicle enables this evolution.

Szostack et al., Nature 2001
Vesicle growth and division

The vesicle could fuse with smaller vesicles and obtain fresh nucleotides from the environment. Alternately it could be permeable to small molecules, and lipids could be catalytically generated and incorporated from the inside. Vesicles that grew too big would divide.

Szostack et al., Nature 2001
Cells contain many types of membranes.
Phospholipids, Sphingolipids and Sterols are the Major Lipid Components of Cell Membranes
## Lipid Composition of Different Membranes

### Table 10–1 Approximate Lipid Compositions of Different Cell Membranes

<table>
<thead>
<tr>
<th>LIPID</th>
<th>LIVER CELL PLASMA MEMBRANE</th>
<th>RED BLOOD CELL PLASMA MEMBRANE</th>
<th>MYELIN</th>
<th>MITOCHONDRIUM (INNER AND OUTER MEMBRANES)</th>
<th>ENDOPLASMIC RETICULUM</th>
<th>E. COLI BACTERIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>17</td>
<td>23</td>
<td>22</td>
<td>3</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Phosphatidylethanolamine</td>
<td>7</td>
<td>18</td>
<td>15</td>
<td>28</td>
<td>17</td>
<td>70</td>
</tr>
<tr>
<td>Phosphatidylserine</td>
<td>4</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>trace</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>24</td>
<td>17</td>
<td>10</td>
<td>44</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Sphingomyelin</td>
<td>19</td>
<td>18</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Glycolipids</td>
<td>7</td>
<td>3</td>
<td>28</td>
<td>trace</td>
<td>trace</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>22</td>
<td>13</td>
<td>8</td>
<td>23</td>
<td>27</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 10–1 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Membrane asymmetry is important for signaling, providing binding sites for specific proteins, and exocytosis.
Phospholipid Flipases Speed Transverse Diffusion in the Membrane

Pomorski and Menon Cell.
Example Flippase from Gram-negative Bacteria: MsbA

Thought to help move lipopolysaccharide across bacterial inner membrane, controversial.

King and Sharom, Critical Rev. Biochem. 2012
Biological Membranes are Not Homogeneous: Lipid Rafts

Left: liposomes made from 1:1 phosphatidylcholine and spingomyelin are homogeneous. Right: liposomes made from 1:1:1 phosphatidylcholine, spingomyelin and cholesterol form immiscible phases. The dye preferentially partitions into one of the phases.

Figure 10-13 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Biological Membranes are Not Homogeneous: Lipid Rafts

Lipid raft areas are thicker than the rest of the bilayer, as they are made of cholesterol and spingomyelin. An AFM image shows the surface of the rafts. Yellow is protein molecules, which rafts are thought to concentrate.
Biological Membranes are Inhomogeneous: Lipid Rafts

Owen et al., Bioessays 2012
Phospholipids in the Cells: Visualizing Cellular Membranes
Tomography of cellular membranes
Using Tomography to Determine How Reticulons Shape the ER

From: West et al., 2011 JCB: A 3D analysis of yeast ER structure reveals how ER domains are organized by membrane curvature
Tomography of WT ER

QuickTime™ and a decompressor are needed to see this picture.

From: West et al., 2011 JCB
Tomography of Cells Lacking ER-shaping Proteins

QuickTime™ and a H.264 decompressor are needed to see this picture.

From: West et al., 2011 JCB
Triacylglycerides in the Cell: Lipid Storage
Using Fats Stores

Adipocytes are professional fat storage cells, and lipid droplets can occupy the majority of the cytoplasm.
Triacylglycerols are Stored in Lipid Droplets

Figure 2-81a Molecular Biology of the Cell 5/e (© Garland Science 2008)
Lipid droplets:
- Store energy in the form of triacylglycerides.
- Are a repository for the building blocks of biological membranes.
- Compartmentalize lipids to buffer cells from the toxic effects of excessive lipids.
What’s in a lipid droplet?

- Polar lipids at the surface (phospholipids and sterols)
- Neutral lipids at the core
- Proteins on the surface including perilipin, lipid synthesizing enzymes, membrane-trafficking proteins and lipases

From Farese and Walther, Cell, 2009
Outline:

1) Classification and Properties of Lipids
2) Biological Functions of Lipids
3) Lipids in Bioscience
Artificial membrane systems

For biochemical studies of membranes/membrane proteins, membrane mimetics include:
- nanodiscs
- bicelles
- micelles
- unilaminar vesicles
Artificial membrane systems: Nanodiscs

Nanodiscs allow incorporation of a membrane protein into an artificial lipid bilayer of defined size.

Jath et al., JBC 2007
Artificial Membrane Systems: Nanodiscs

Applications of Nanodics: Anthrax Toxin Translocon

The protective antigen (PA) component of anthrax toxin forms a pore that delivers the two enzymatic components of the toxin to the cytosol of cells. Here, they solve a 16 Å structure of the whole pore containing one of the enzymatic factors (Lethal factor N) using cryo-Em of nanodisc embedded PA.

Gogol et. al., Protein Science 2013
Artificial Membrane Systems: Bicelles (Bilayered Micelles)

Bicelles: they are discoidal lipid aggregates composed of long-chain phospholipid and either detergent or short-chain phospholipid. They are useful for NMR studies and as substrates for lipolytic enzymes.

Whiles et. al., Bioinorganic Chemistry 2002
Biochem society transactions
Artificial membrane systems: unilaminar vesicles

Unilaminar Vesicles

Small unilaminar vesicle: 20 to 40 nm
Medium unilaminar vesicle: 40 to 80 nm
Large unilaminar vesicle: 100 to 1000 nm
Giant unilaminar vesicle: >1000 nm

Useful for: chemical microreactors, delivery vehicles for pharmaceuticals, and platforms for synthetic biological systems

Multilaminar Vesicle
Microfluidics for Unilaminar Vesicles

Stachowiak et al., Proc Natl Acad Sci U S A. 2008
Microfluidics for Unilaminar Vesicles

QuickTime™ and a Animation decompressor are needed to see this picture.
For Wednesday:

Download UCSF Chimera
http://www.cgl.ucsf.edu/chimera/download.html
or Pymol if you haven’t already

Download PDB file 1RH5

Read Van den Berg et al., Nature 2003