Biology 5357: Chemistry & Physics of Biomolecules
Fall 2021

Lecture 2: Chemical Composition of the Cell Membrane

Janice L. Robertson
Dept. of Biochemistry & Molecular Biophysics
McDonnell Sciences Building 223A (Lab 225)
janine.robertson@wustl.edu
Reading for this week:

Required reading:


Figure 1: An electron micrograph of an E. coli cell highlighting the width of the cell inner and outer membranes and the cell wall. Zoom in: a schematic of the lipid bilayer. The red circle denotes the hydrophilic head consisting of a polar phosphoglycerol group and the pink lines represent the hydrocarbon chains forming a tight hydrophobic barrier excluding water as well as polar or charged compounds. Two tails are drawn per head but there could also be three or four. (Electron microscopy image adapted from A. Briegel et al. Proc. Nat. Acad. Sci., 106:17181, 2009.)
A molecular understanding of the lipid bilayer
Biology requires fluid membranes

Biological membranes contain many different types of lipids.
Cell membranes have infinite chemical composition

Polar solvent across the kingdoms of life

Water 100%
(Prokaryotes, Archaea & Eukaryotes)

Prokaryotes e.g. Escherichia coli
PE 58%  PG 15%  cardiolipin 10%

Archaia e.g. Sulfolobus solfataricus
Cardarchaeol 95%

Solfatarea crater, Italy
pH 2-3, 75-80 °C

Eukaryotes e.g. brain
PI 2%

PE 17%  PS 11%  PC 10%

Non-polar solvents across the kingdoms of life

cholesterol 40%
Lipid subclasses

- Fatty acids
  - Eicosanoids
  - Triacylglycerols
  - Waxes
  - Sphingolipids

- Steroids
- Lipid vitamins
  - Isoprenoids
- Terpenes

- Glycerophospholipids
  - Plasmalogens
  - Phosphatidates
  - Sphingomyelins
    - Phosphatidyl-ethanolamines
    - Phosphatidyl-serines
    - Phosphatidyl-cholines
    - Phosphatidyl-inositol
    - Other phospholipids

- Ceramides
  - Cerebrosides
    - Gangliosides
    - Other glycosphingolipids
  - Glycosphingolipids
Lipid subclasses

glycerolphospholipid
glycerolipid
sphingolipid
fatty acyl
polyketide
prenol lipid
sterol lipid

saccharolipid
Glycerophospholipid structures

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138
Fatty acid-glycerol linkage

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138
Fatty acid-glycerol linkage

https://employees.csbsju.edu/hjakubowski/classes/ch331/lipidstruct/LS_1A3_Glycero_Sphingo.html
Headgroups

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138

Aktas et al., 2014; https://doi.org/10.3389/fpls.2014.00109

Cardiolipin (CL)
Ionization state depends on conditions

Phosphatidylserine
Percent Ionization as a Function of pH
Ionic Strength = 0.1 (NaCl)
Data from CRC Handbook of Lipid Bilayers, Derek Marsh (1990) CRC Press, Boca Raton

pKa = 2.6
pKa = 5.5
pKa = 11.55

https://avantilipids.com/tech-support/physical-properties/ionization-constants
Glycerophospholipid tail structures

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138

### Impact of tail modifications on fluidity

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Structure</th>
<th>Effect on membrane fluidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>C16:0</td>
<td><img src="image1" alt="structure" /></td>
<td>Decreases membrane fluidity</td>
</tr>
<tr>
<td>C18:1 cis-11</td>
<td><img src="image2" alt="structure" /></td>
<td>Increases membrane fluidity</td>
</tr>
<tr>
<td>Iso-C17:0</td>
<td><img src="image3" alt="structure" /></td>
<td>Decreases membrane fluidity compared with anteiso-chains</td>
</tr>
<tr>
<td>Anteiso-C17:0</td>
<td><img src="image4" alt="structure" /></td>
<td>Increases membrane fluidity compared with iso-chains</td>
</tr>
<tr>
<td>Cyclopropane-C17:0</td>
<td><img src="image5" alt="structure" /></td>
<td>Mimics unsaturated fatty acids and increases stability to acid stress</td>
</tr>
<tr>
<td>Trans-11-C18:1</td>
<td><img src="image6" alt="structure" /></td>
<td>Mimics saturated fatty acids, and provides resistance to solvents and increases in growth temperature</td>
</tr>
</tbody>
</table>

**Table 1 | Chemical structures of membrane phospholipid fatty acids**
Glycerolipids

Diacylglycerol
Fatty acids

- arachidic
- stearic
- palmitic
- erucic
- oleic
- arachidonic
- linoleic
- linolenic
Sphingolipid structures

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138
Glycosphingolipid structures

Cerebroside (both a sphingolipid and a glycolipid)
Saccharolipids

- e.g. lipid A in bacterial outer membranes
- Different from glycolipids, as glycolipids have sugar bound by glycosidic linkage to the fatty acid
Polyketides

Biosynthesis of orsellinic acid from a polyketide intermediate

https://www.lipidmaps.org/resources/tutorials/lipid_tutorial#PK
prenol lipids

(a) $C_5$ isoprenoids: isopentenyl pyrophosphate; 3-methylbut-3-enyl pyrophosphate

(b) $C_{10}$ isoprenoids: 2E-geraniol

(c) $C_{15}$ isoprenoids: 2E,6E-farnesol

(d) $C_{20}$ isoprenoids: retinol; vitamin A

(e) $C_{40}$ isoprenoids: β-carotene
Sterol lipids

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138

Ergosterol

Beta-sitosterol

Hopanoids

Harayama & Riezman, 2018; https://doi.org/10.1038/nrm.2017.138
Sterol lipids

Cholesterol oleate

Nature Reviews | Microbiology

Lipid composition varies with cell type

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>MITOCHONDRION (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>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>7</td>
<td>18</td>
<td>15</td>
<td>25</td>
<td>17</td>
<td>70</td>
</tr>
<tr>
<td>Phosphatidyserine</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>39</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>21</td>
<td>27</td>
<td>30</td>
</tr>
</tbody>
</table>

From: The Lipid Bilayer


NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.
Locations of synthesis and composition of different membranes

(A)

- **mitochondrial membrane**: PE, PG, CL, PA
- **ER membrane**: PC, PE, PI, PS, PA, Cer, GalCer, CHOL, TG
- **Golgi membrane**: PC, PE, GlcCer, SM, GSL, ISL, PI4P
- **plasma membrane**: Cer, Sph, S1P, DAG, PI4P, PI(4,5)P2, PI(3,4)P2, PI(3,4,5)P3

(B)

- **ER**: CHOL/PL = 0.15
- **plasma membrane**: CHOL/PL = 1.0
- **mitochondria**: CHOL/PL = 0.1
- **Golgi**: CHOL/PL = 0.2

Sterol lipids

budding yeast lipidome

mol% of sample

lipid class

CL  Erg  IPC  MIPC  MII(P)2C  PA  PC  PE  PI  PS  TAG  DAG  LysopA  LysopC  LysopE  Lysopi

OD = 6.0
OD = 3.5
OD = 1.0

stationary

time (h)

mol %
molecules per cell (×10^9)

PC 100-16:0  PC 120-16:0  PC 120:16:1  PC 140-16:1  PC 140-16:0  PC 160:16:0  PC 161:16:1  PC 160:18:1  PC 161:18:1  PC 180:18:0

0  1  2  3  4  5  6

0  15  30  45  60
Distribution of lipids across the bilayer

**a Compositional diversity of PtdCho**

- **Brain**
- **Lung**
- **Liver**
- **Heart**

Legend: 
- 16:0-16:0
- 16:0-18:1
- 16:0-18:2
- 16:0-20:4
- 16:0-22:6

**b Acyl incorporation**

- Lyso-PtdA
- In precursor PtdA
- PtdA
- Precursor synthesis
  - Tissues with higher preference for 18:2 and/or 22:6
- Enrichment of 18:2 and/or 22:6 in precursor PtdA
- PtdCho inherits fatty acid enrichment

**c Head group conversion**

- PtdEtn
- Methyltransferase
- Preference for PtdEtn with 22:6
- High 16:0-22:6 PtdCho in liver

**Lyso-PtdCho**

- By remodelling
  - LPCATs
  - Tissues with higher preference for 16:0 and/or 18:1
  - Tissues high in 16:0-18:0 PtdCho
  - Tissues high in 16:0-18:1 PtdCho

**PtdCho synthesis**

- Tissues high in 16:0-18:2 PtdCho
- Tissues high in 16:0-20:4 PtdCho
- (except for liver)
Phospholipid compositions observed for various strains of *E. coli*, as measured at various growth phases or following culturing in unusual media. Example 1 is wild type strain SD12 during exponential growth. Example 2 contains an interrupted allele of PS synthase in strain AH930 during exponential growth. Example 3 is strain SD10, which contains a temperature sensitive PS synthase, during exponential growth. Example 4 is strain SD10 grown at stationary phase. Example 5 is a double mutant of strain SD312 containing a mutated phosphatidyglycerophosphate synthase and a defective CL synthase during exponential growth. Example 6 is strain CB64-CLI with a knockout of CL synthase during exponential growth. Example 7 is strain SD9 containing a temperature sensitive PS synthase and a defective CL synthase during exponential growth. Example 8 is strain SD10 (see example 3) grown under high D-mannitol conditions during exponential growth. Example 9 is strain SD10 grown under high mannitol conditions during stationary phase. Abbreviations: phosphatidylethanolamine (PE), phosphatidylglycerol (PG), cardiolipin (CL), phosphatidylmethionine (PM), diacylglycerophosphoethanolamine (DPEM), others.
Distribution of lipids across the bilayer

**Figure 10-5** The distribution of specific erythrocyte membrane lipids between the inner and outer face is asymmetric

Lipid extraction & analysis

**Bligh Dyer:** chloroform/methanol/water 2:2:1.8 (v/v/v)

**Folch:** chloroform/methanol/water in a volumetric ratio of 8:4:3 (v/v/v)
Thin layer chromatography
Mass Spectrometry
Homework & Journal Club Assignment


2. Identify 2 new hypotheses presented in the fluid mosaic model (note, there are many)

3. Describe the rationale and experimental evidence supporting the fluid mosaic model in contrast to previous hypothesized models

4. Identify a limitation in their logic and propose an experiment that could test their hypothesis further.

5. Come prepared to discuss your reading and rationale on Thursday.

Email me if you have questions :) 
janice.robertson@wustl.edu