BIO-212 - Lecture 4
Lipids

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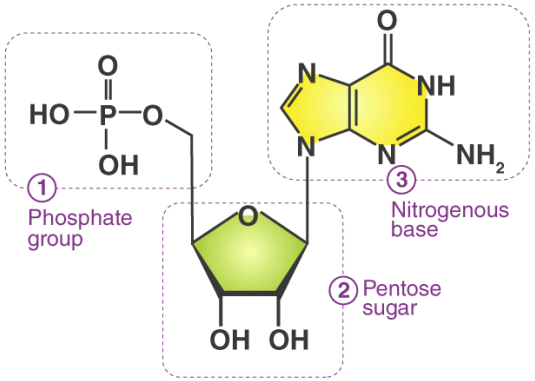
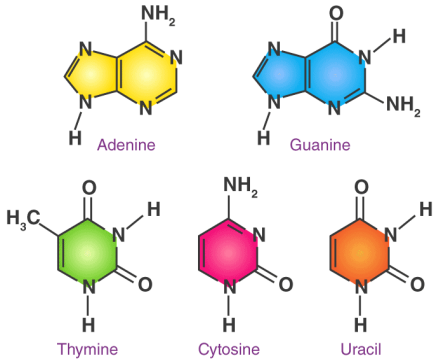
Lecture 3 – Quick Summary

• Nucleic Acid building blocks

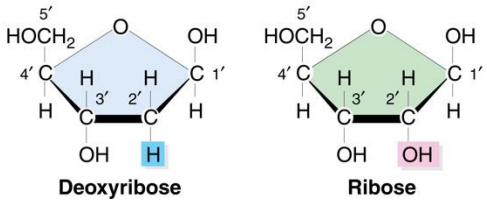
- 3 main components: **base, pentose, and phosphate**



- 5 base options



- 2 pentose options



- 2 x 4 sets of nuceotides to produce DNA and RNA

• Nucleic Acids (DNA and RNA)

- Linear **polymers of nucleotides**

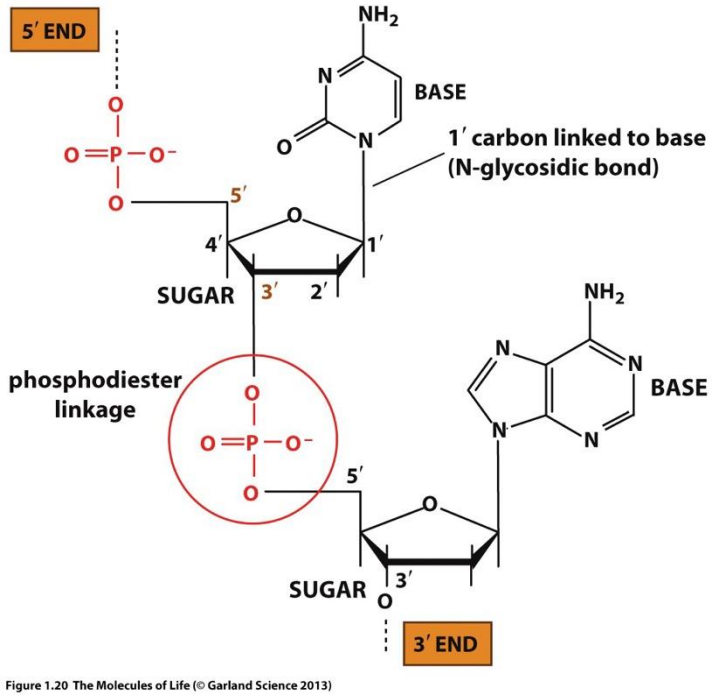


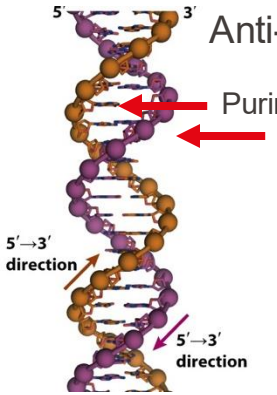
Figure 1.20 The Molecules of Life (© Garland Science 2013)

- 5'->3' directionality in addition of nucleotides
- Attachment via phosphodiester linkages

Lecture 2 – Quick Summary

• Nucleic Acid structure and assembly

- Double-stranded helical assembly of DNA (B form)

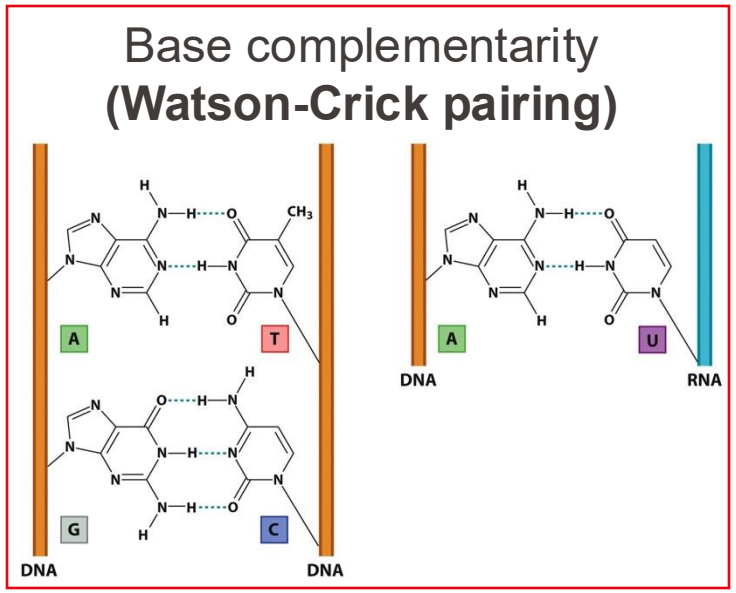


Anti-parallel complementary strands

Purine-Pyrimidine Base Pairs (inwards)

Phosphate-pentose backbone (outwards)

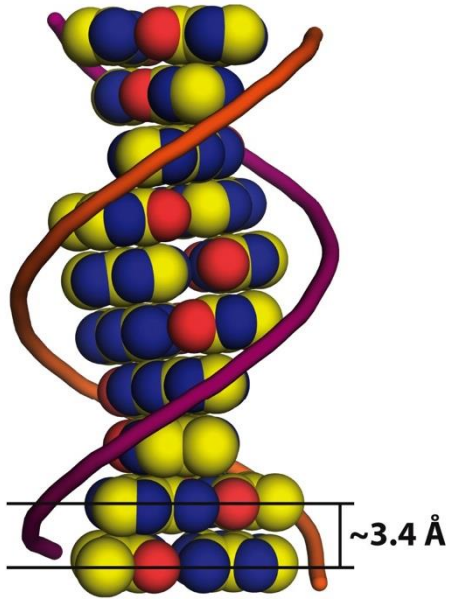
10 base pairs per helical turn



- RNA can be double- and single-stranded and features greater conformational and functional diversity

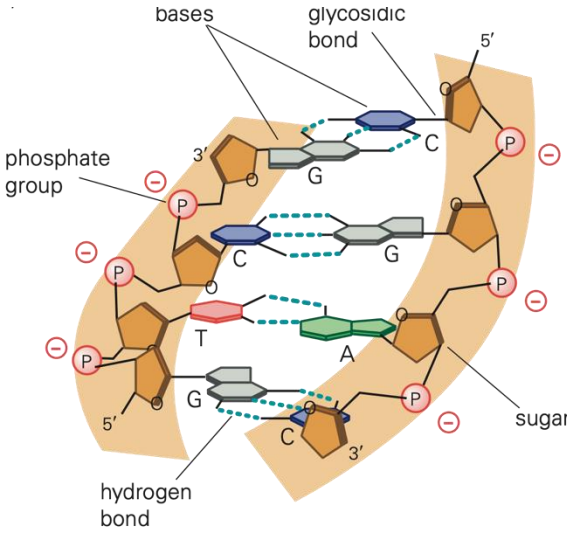
• Important non-covalent interactions

Van der Waals interactions (layered base stacking)



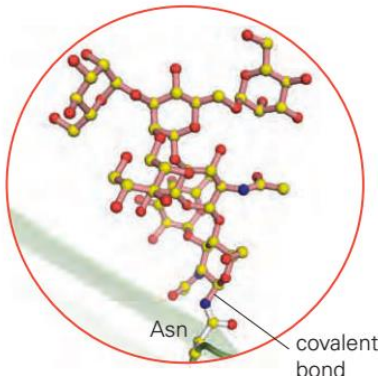
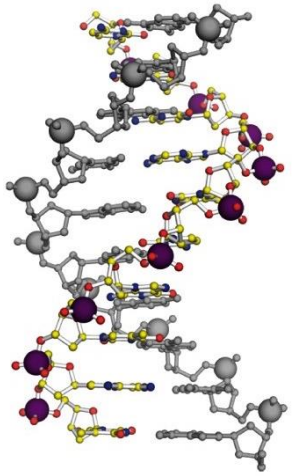
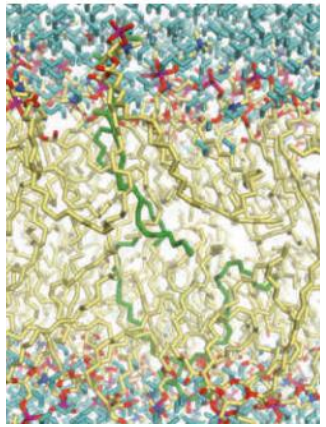
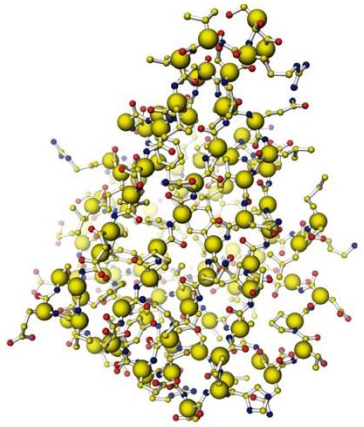
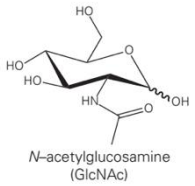
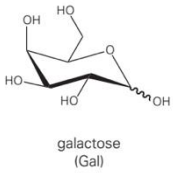
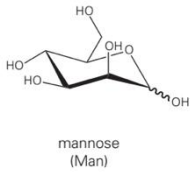
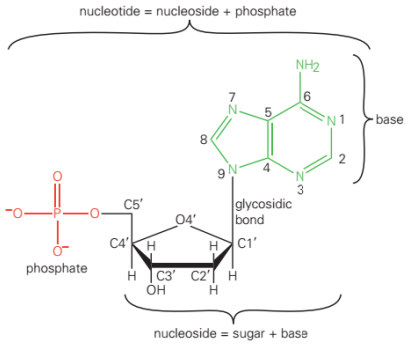
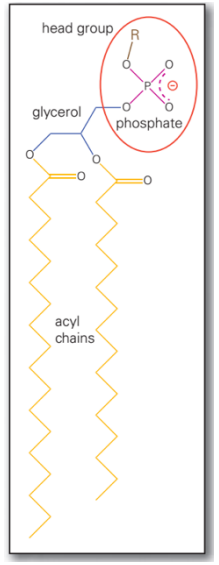
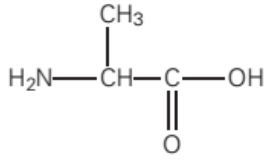
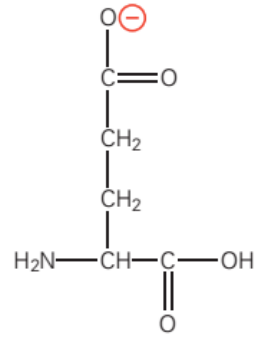
- Stacking of arromatic π-orbitals (π-π stacking)

Hydrogen-bond network (base pairing)



- Charged, polar backbone attracts water and positively charged ions

The molecules of Life

	Carbohydrates	Nucleic Acids	Lipids	Proteins
Macromolecular Structure				
Building Block	  			 

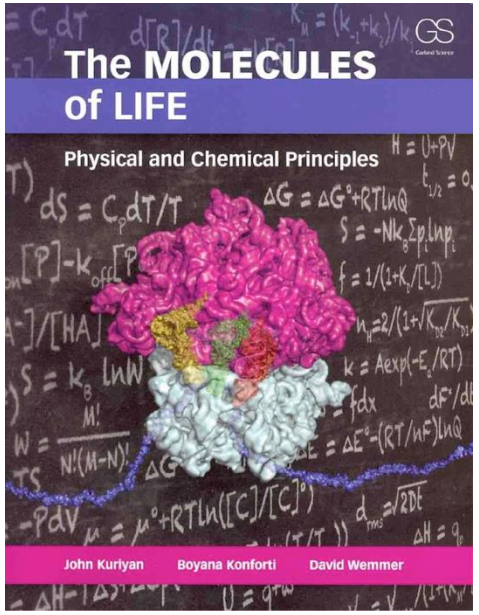
Lecture 4 - Outline

Today:

- Lipid composition and chemical assembly
- The main classes of lipids and their properties
- Biological functions

Reading suggestions:

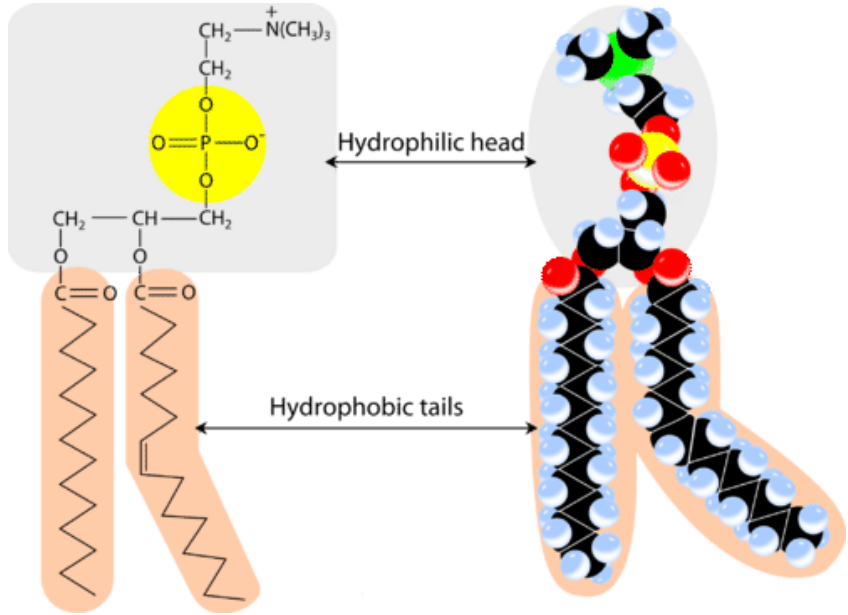
- The Molecules of Life (Chapter 3)



What is a Lipid?

• In biology and biochemistry, a **lipid** is a biomolecule that is soluble in non-polar solvents and does not readily dissolve in water.

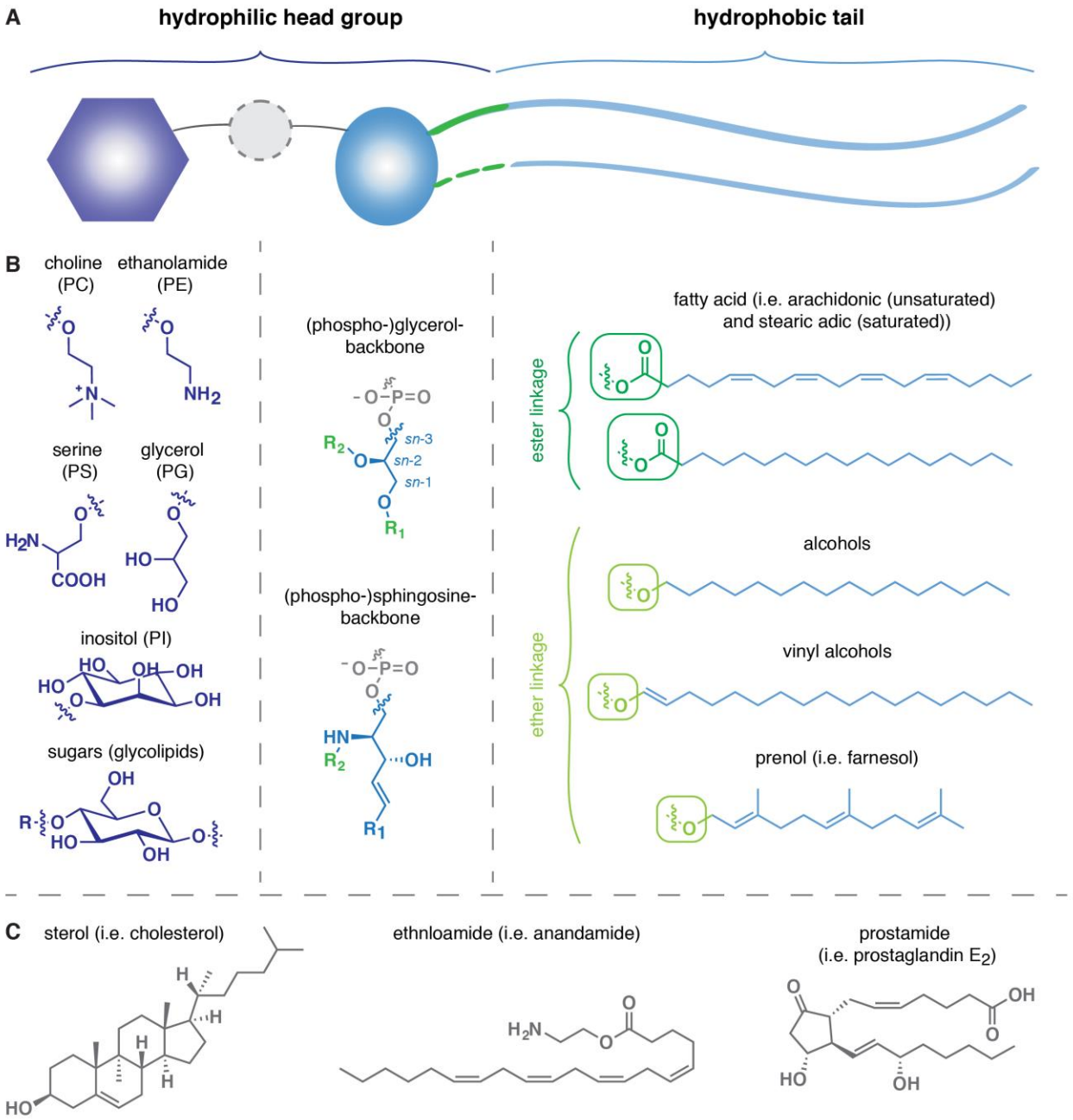
• They all contain hydrophobic moieties, and some contain a hydrophilic head group (“amphiphilic”)



• Three Classes of Lipids Based on Their Functions:

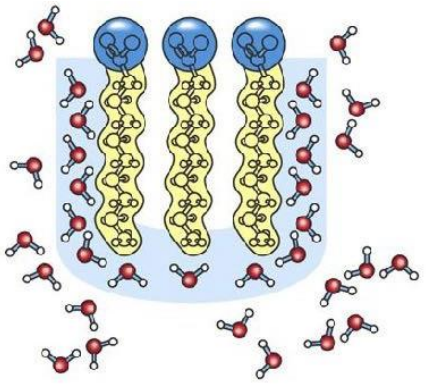
- **Storage lipids:** Used for bioenergetic purposes and thermal insulation.
- **Structural lipids:** Used to make membranes.
- **Bioactive lipids:** Used as hormones and second messengers in signal transduction

Membrane Lipids

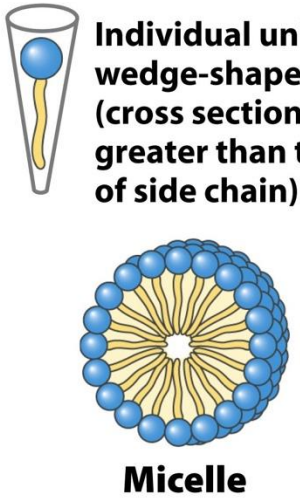


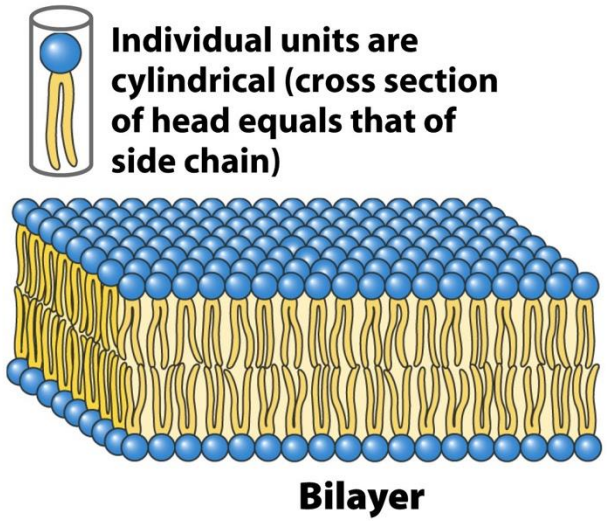
Membrane Lipids

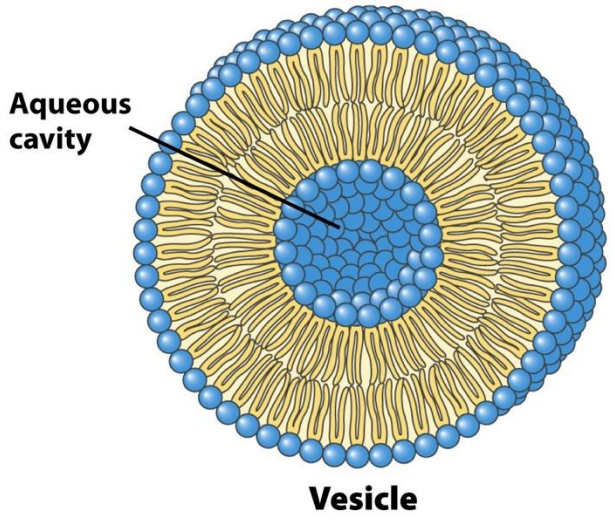
- Membrane lipids are **amphiphilic** and contain a hydrophilic head and a hydrophobic tail
- The hydrophobic interactions between **membrane lipids** and their hydrophilic interactions with water guide their arrangement into sheets known as membrane bilayers.



Hydrophobic groups pack and exclude water



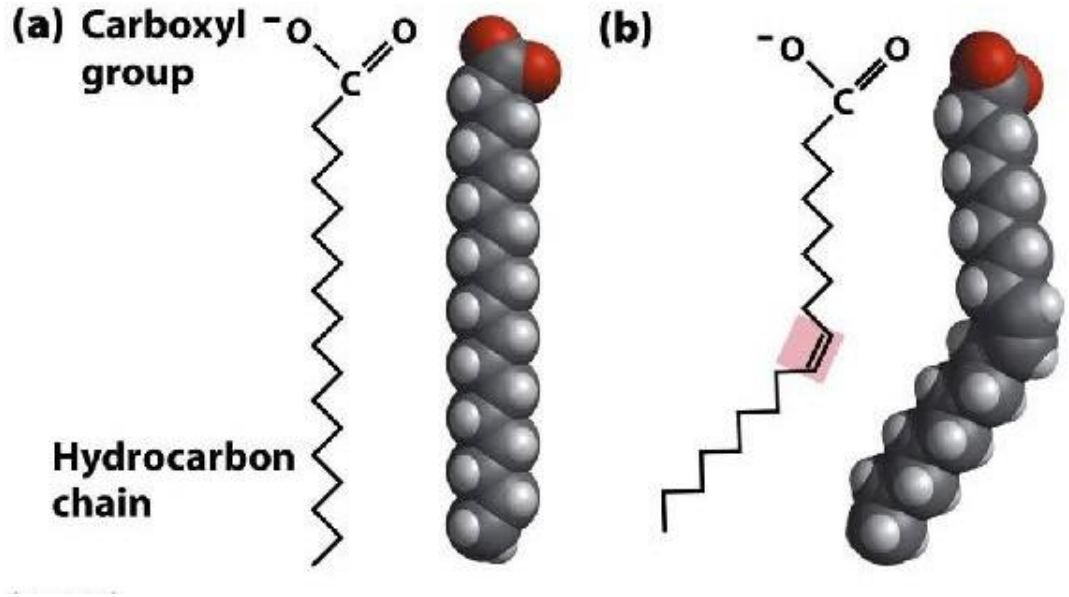




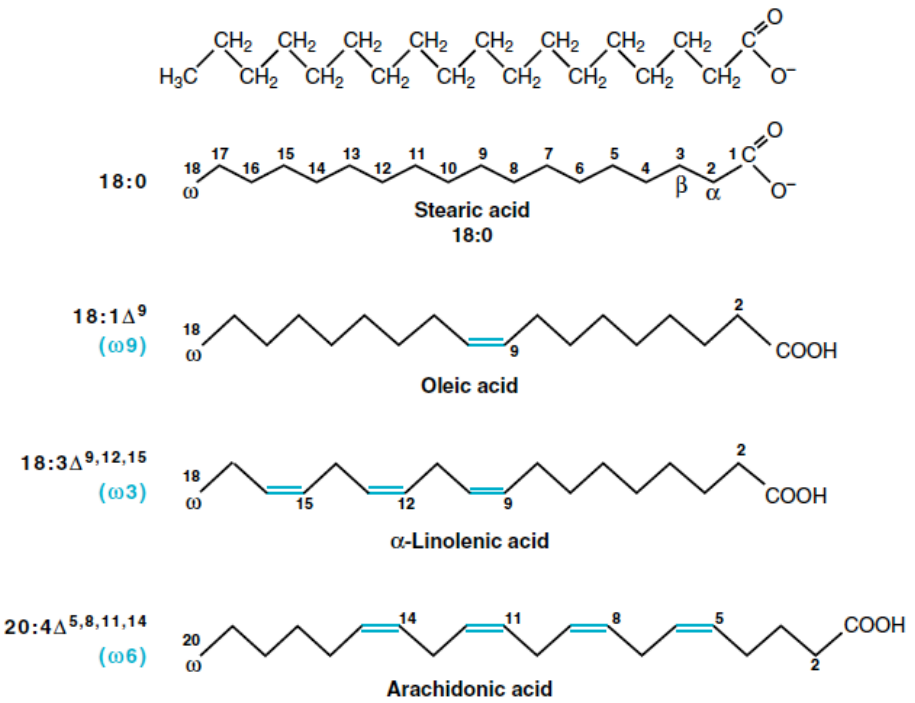
- Cell Membranes are the **barrier** and the **interface** between the cell and the environment. Membranes also define sub-cellular compartments.

Fatty acids

- Naturally occurring monocarboxylic acids



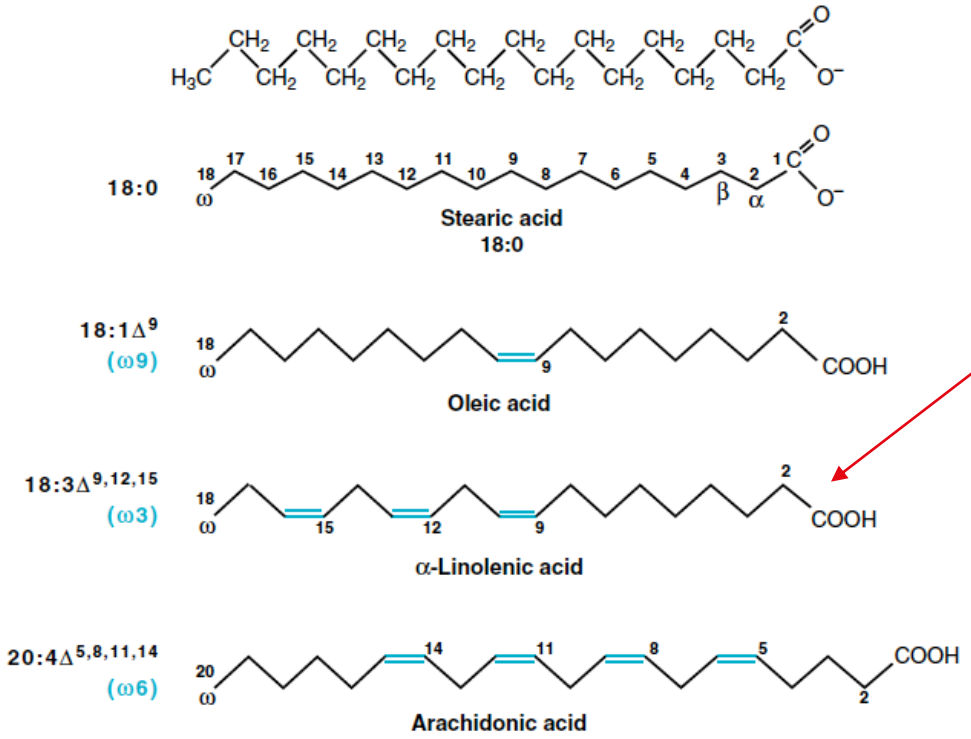
Examples:



- Components of all lipids except sterols
  - **Saturated** -> no double bonds.
  - **Unsaturated** -> one double bond.
  - **Polyunsaturated** (PUFAs) -> more double bonds.

Fatty acid naming convention

- Nomenclature includes the following format: “Number of carbons” : ”Number double bonds”
- Δ^{XYZ} indicates that the double bonds are located at carbon positions XYZ (starting at the carboxyl)
- ω indicates the location of the first double bond starting from the aliphatic (methyl) terminus



Alpha-Linoleic acid

Octadecatrienoic acid

18 : 3 $\Delta^{9,12,15}$ (ω3)

18 Carbons

3 double bonds

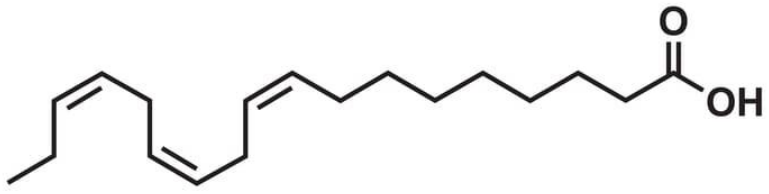
Double bond location

First unsaturated bond from the methyl terminus

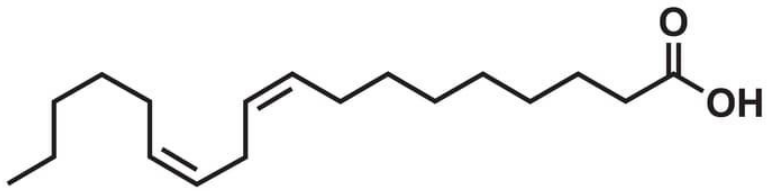
Most common: 16-20 carbons

Fatty acids and nutrition

• Essential vs Non-essential fatty acids



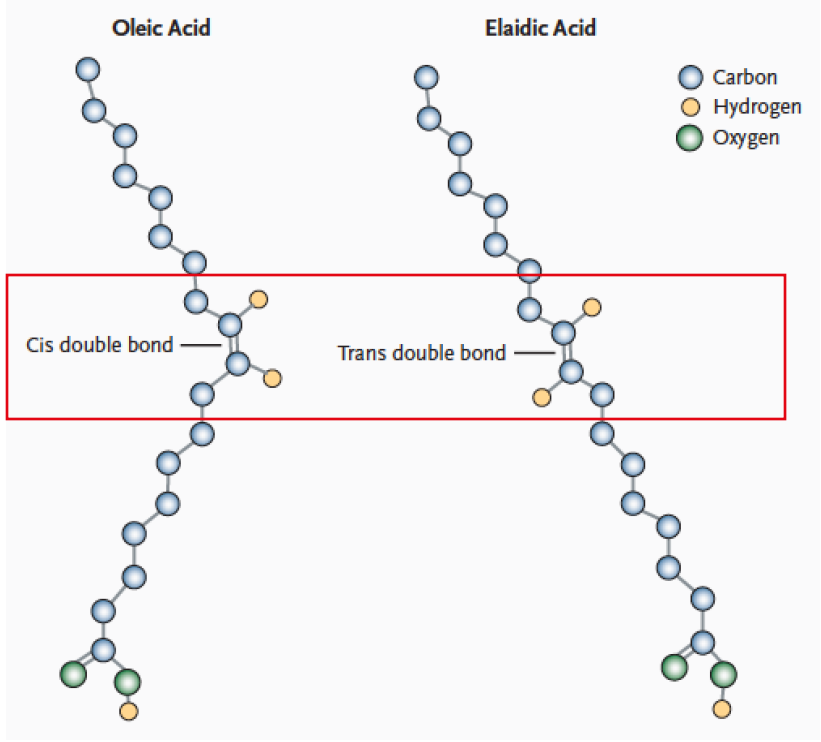
Linolenic Acid (Omega-3)



Linoleic Acid (Omega-6)

- Two essential fatty-acids that cannot be synthesized in humans or other animals: linoleic and linolenic acids
- Acquired through diet (“vitamin F”)
- Omega Fas are found in the membranes of the retina and brain and are important components of heart-healthy diets

• Cis vs Trans fatty acids



- Trans fats are thermodynamically favored but problematic to metabolize by human body
- Found in milk (3%) but largely produced by hydrogenation of vegetable oils for industrial purposes
- Also correlated with coronary diseases caused by low-density lipoprotein (LDL) cholesterol

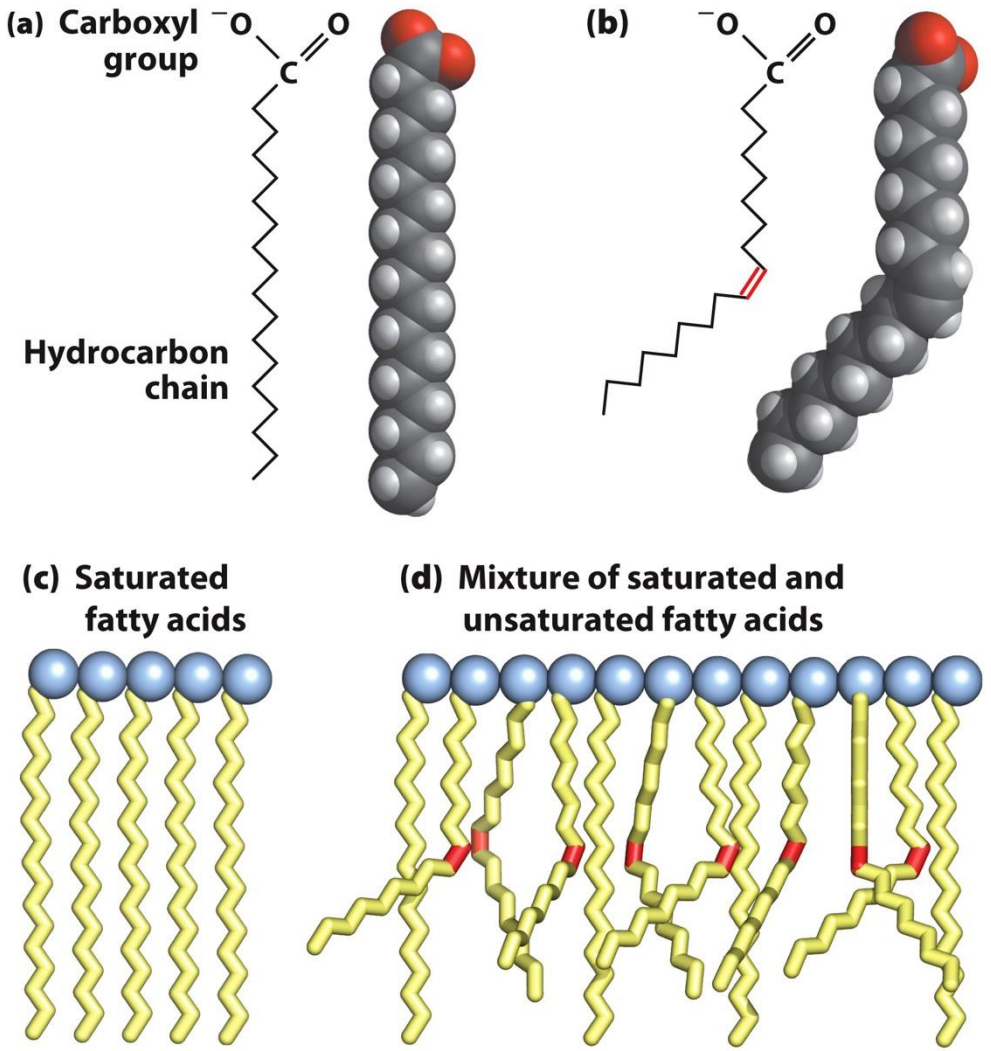
Physicochemical properties of fatty acids

- The hydrocarbon chain accounts for the poor solubility of fatty acids in water.

- Solubility decreases with the increasing chain length and saturation level

- Lauric acid (12:0) has a solubility of 0.063mg/g in water. In contrast, glucose (a carbohydrate) has a solubility of 1'100 mg/g in water **(~17'000-fold difference)**

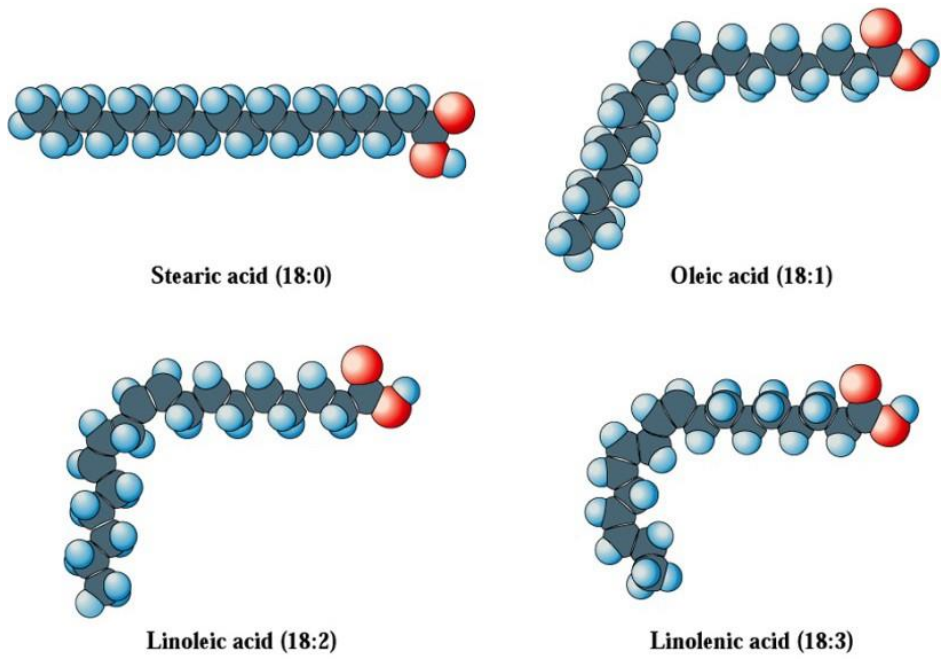
- Albumin in blood can bind and transport FAs

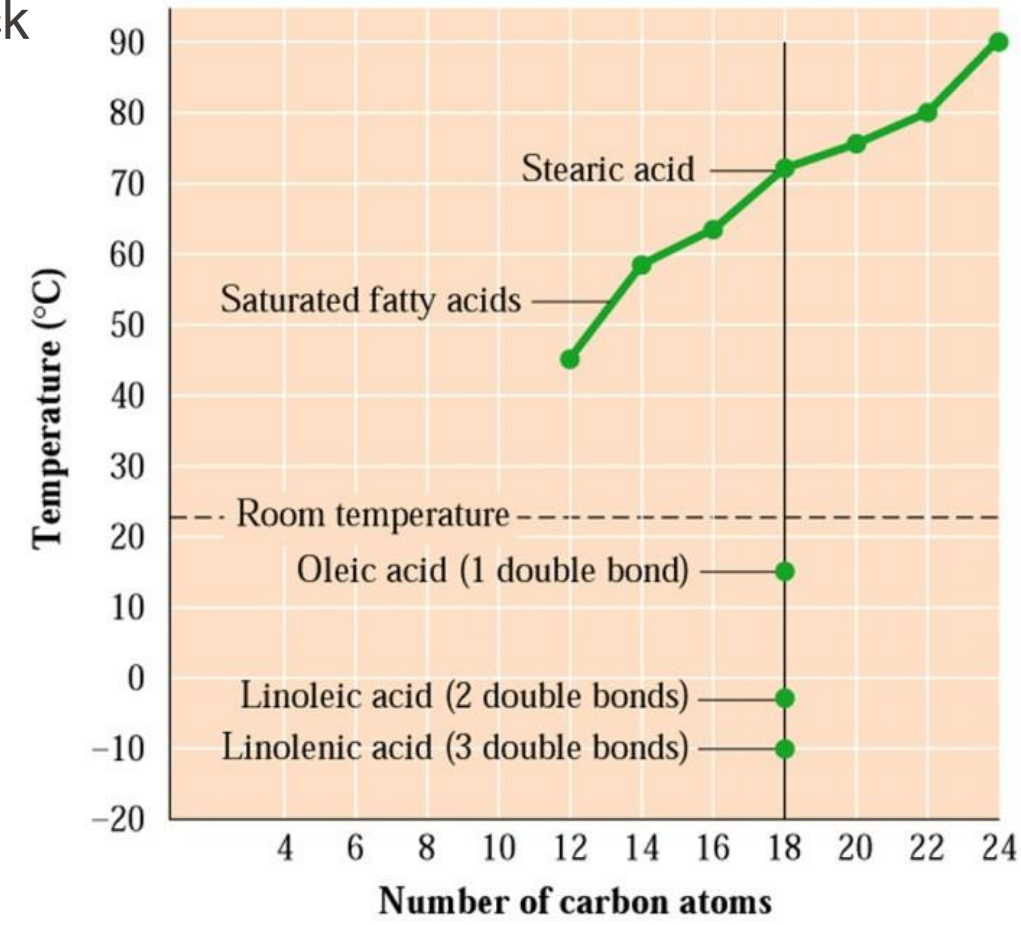


Physicochemical properties of fatty acids

- Melting points **increase with increasing molar mass** (due to van der Waals forces), meaning that the longer the carbon chain in a fatty acid, the higher its melting point.

- Cis-double bonds **lower the melting point** by causing the molecule to become bent and hard to pack with neighboring molecules (lower vdW interactions)

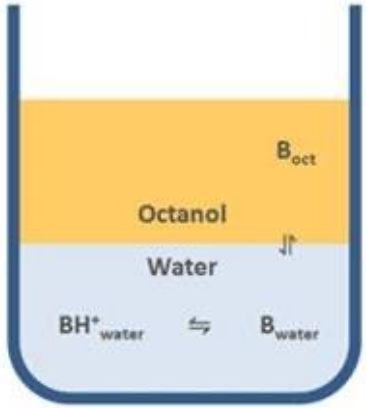




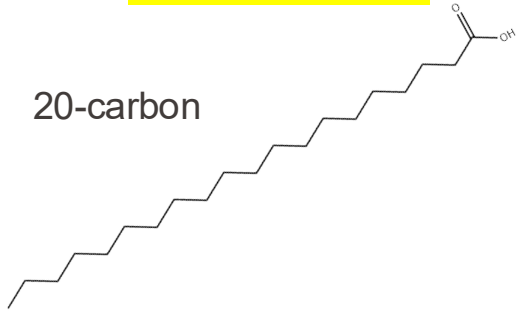
Measuring the relative hydrophobicity of a lipid

- The partition coefficient, P, is a measure of the differential solubility of a lipid in two immiscible solvents. The most commonly used solvent system is **octan-1-ol and water**.
- Higher LogP value -> More hydrophobic

$$\text{Log}P = \log_{10}(\text{Partition Coefficient}) \qquad \text{Partition Coefficient, } P = \frac{[\text{Compound}]_{\text{octanol}}}{[\text{Compound}]_{\text{water}}}$$

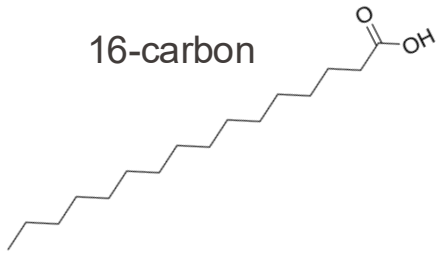


Arachidic Acid



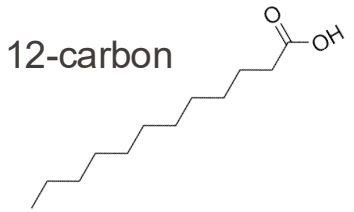
logP ≈ 7.5-9.5 *

Palmitic Acid



logP ≈ 5.5-6.5 *

Lauric Acid

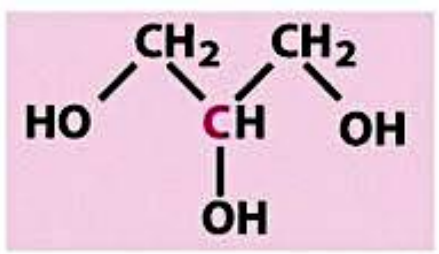


logP ≈ 4.5-5.2 *

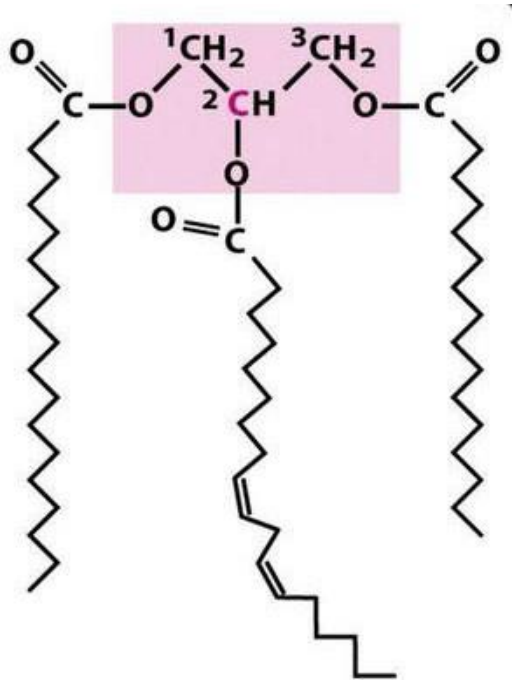
* - Value range is based on different literature souces

- The differing hydrophobicity of lipids can be used for their separation by chromatography methods (e.g., reverse phase chromatography)
- This parameter is also calculated for drugs and therapeutics as a measure of their bioavailability (more water soluble -> easier to traffic to different tissues)

Storage Lipids - Triacylglycerols



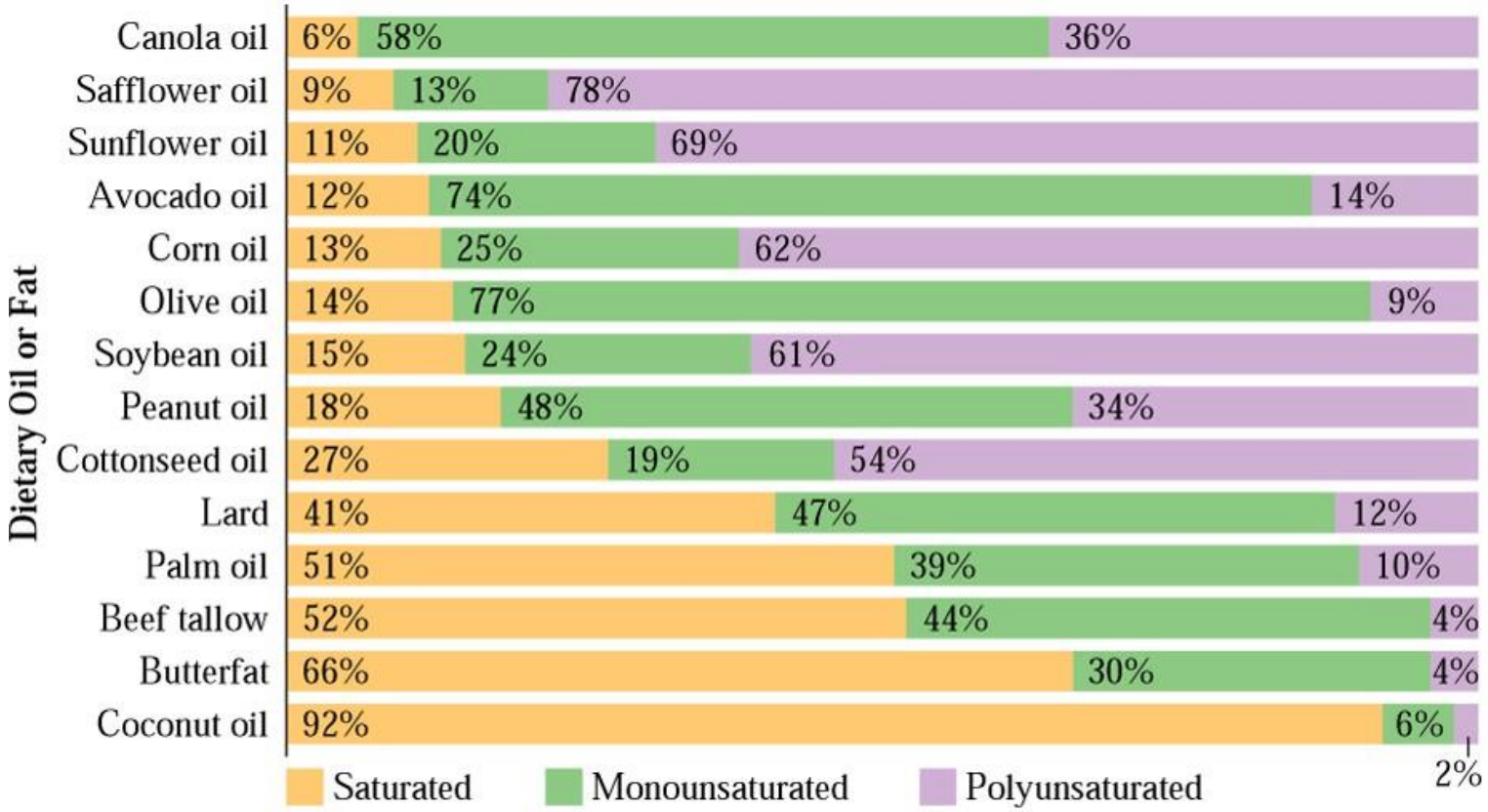
Glycerol

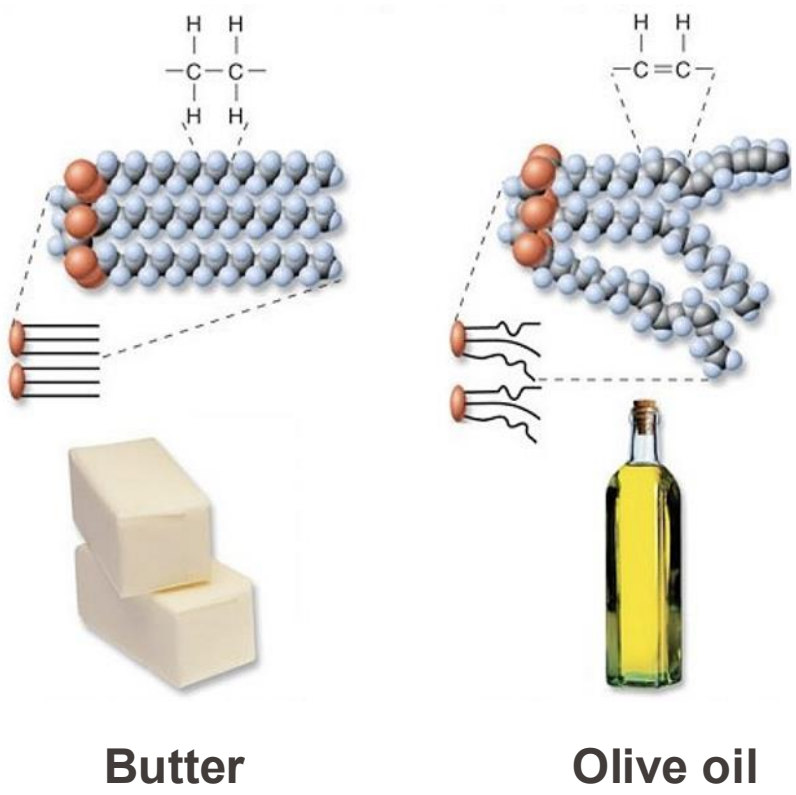


- Triacylglycerols are composed of **three fatty acids** each in **ester** linkage with **a single glycerol molecule**.
- Those containing the same kind of fatty acid in all three positions are called **simple triacylglycerols** and are named after the fatty acid they contain.
- Simple triacylglycerols of 16:0, 18:0, and 18:1(Δ^9) are called tripalmitin, tristearin, and triolein, respectively. Most naturally occurring triacylglycerols are **mixed** and contain two or more different fatty acids.

Storage Lipids - Triacylglycerols

- The content of unsaturated fatty acids regulates the melting point and the aggregate state of the resulting lipid at room temperature (i.e., solid or liquid)





Butter **Olive oil**

Storage Lipids - Triacylglycerols

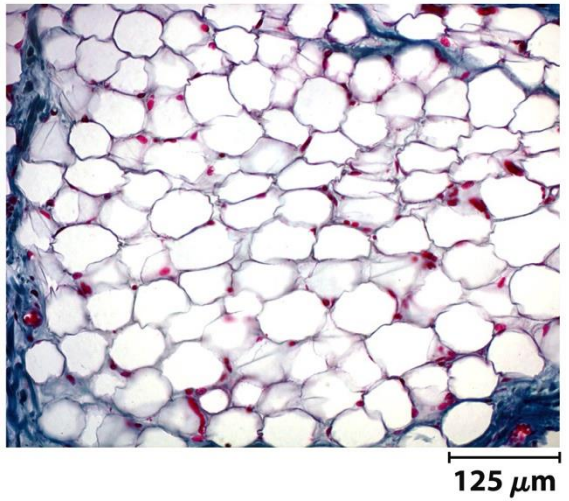
• In the cytosol of most eukaryotic cells, triacylglycerols form oily droplets that serve as **metabolic fuel**.

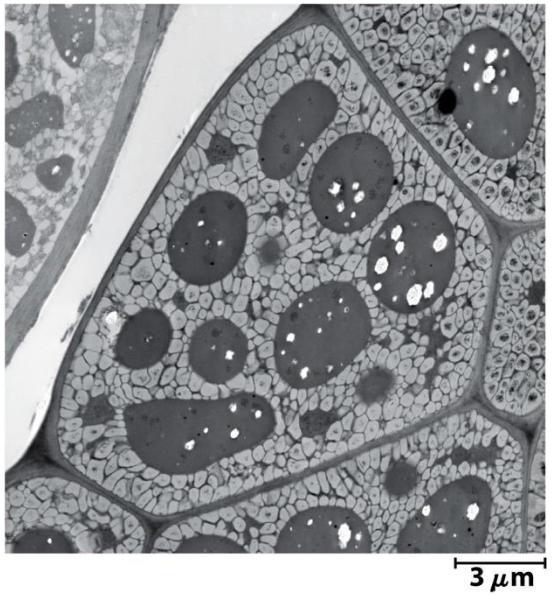
• In vertebrates, there are specialized cells called adipocytes (or fat cells) that store large amounts of these lipids

• Triacylglycerols contain **more energy per gram compared to carbohydrates**. Additionally, they are non-hydrated so there is no extra mass of water.

• In some animals (e.g., seals, penguins, bears) fat stored under the skin **serves as insulation against cold temperatures**

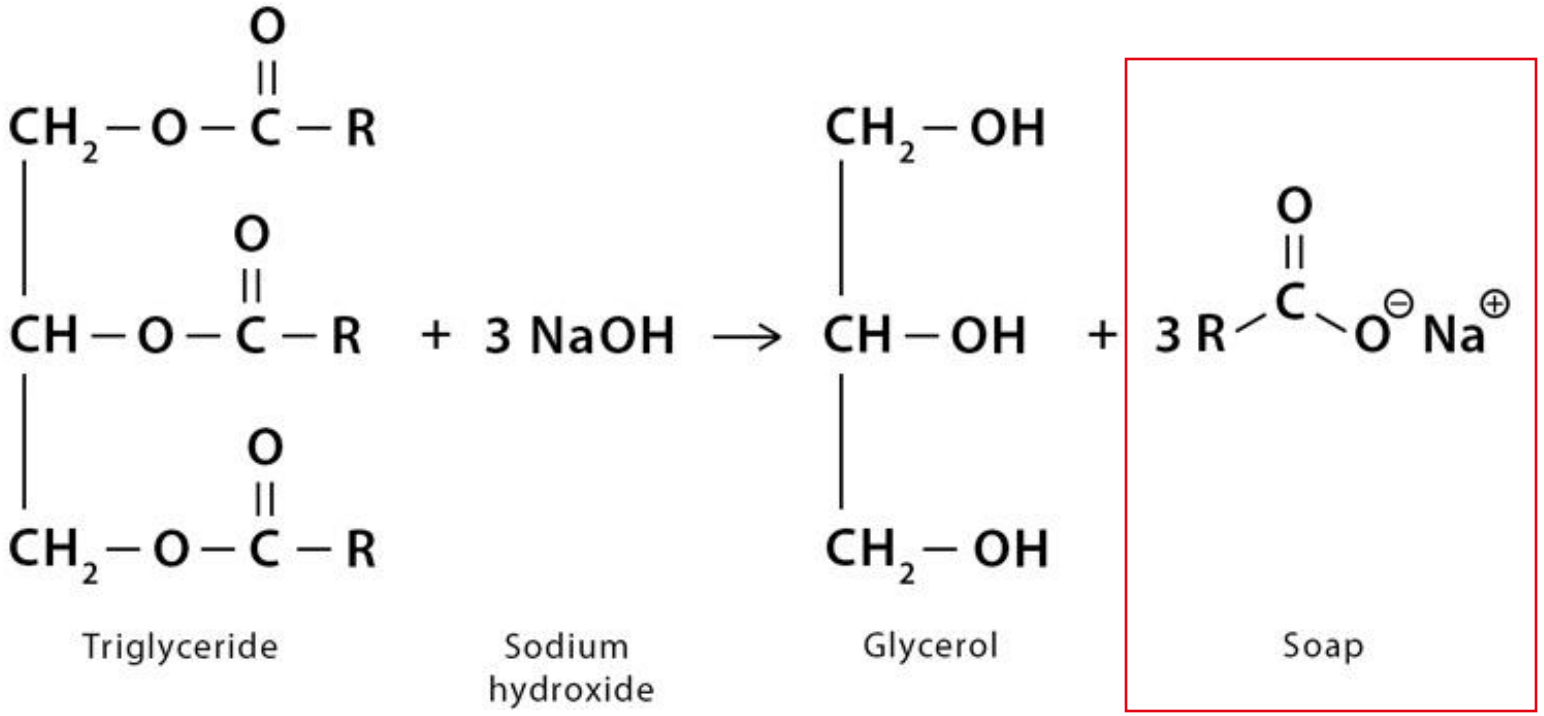
Adipocytes





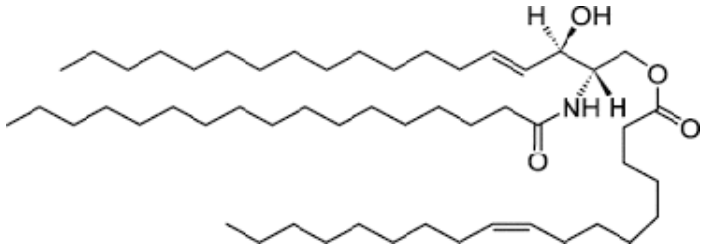
Triacylglycerol hydrolysis - Saponification

- Saponification is a process that involves the conversion of fats, oils, or lipids into soap and alcohol through the application of heat in the presence of an aqueous alkali (e.g., NaOH)

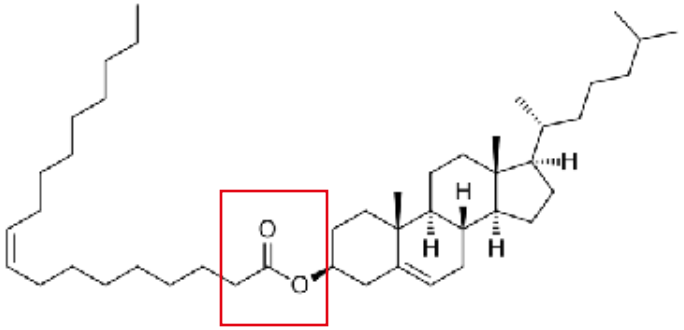


- Soaps are the salts of fatty acids which are monomers with long carbon chains

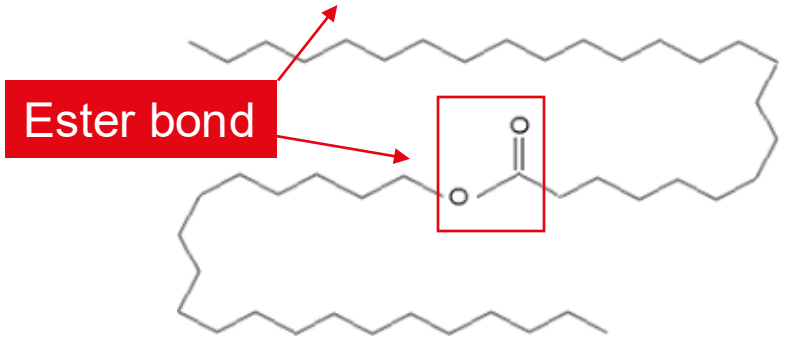
Other Storage Lipids



• **Acylceramides** -> ceramide can be metabolised into acylceramide and stored in lipid droplets



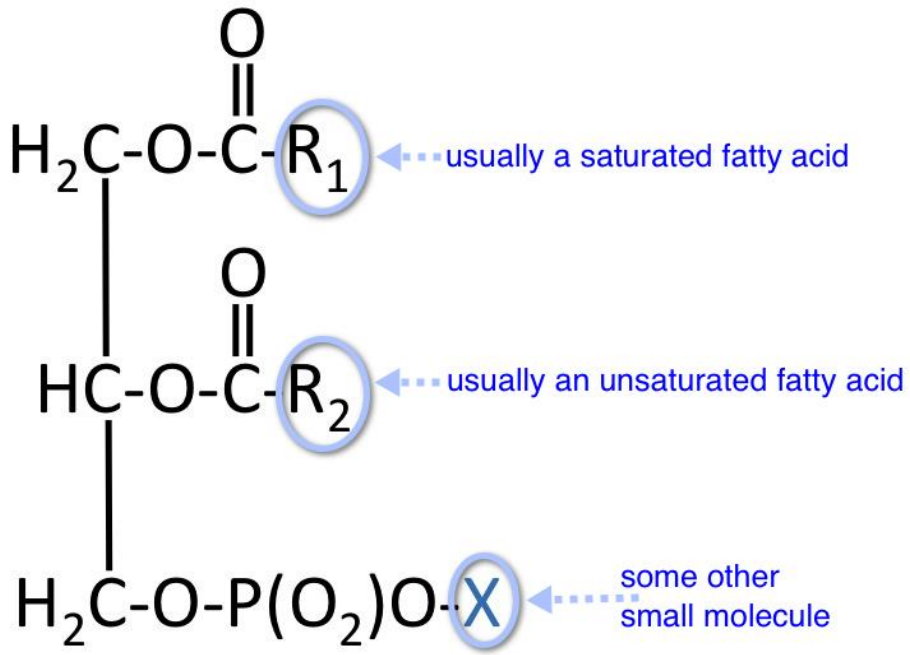
• **Cholesteryl esters** -> A cholesteryl ester is formed through the bonding of the carboxylate group of a fatty acid with the hydroxyl group of cholesterol.

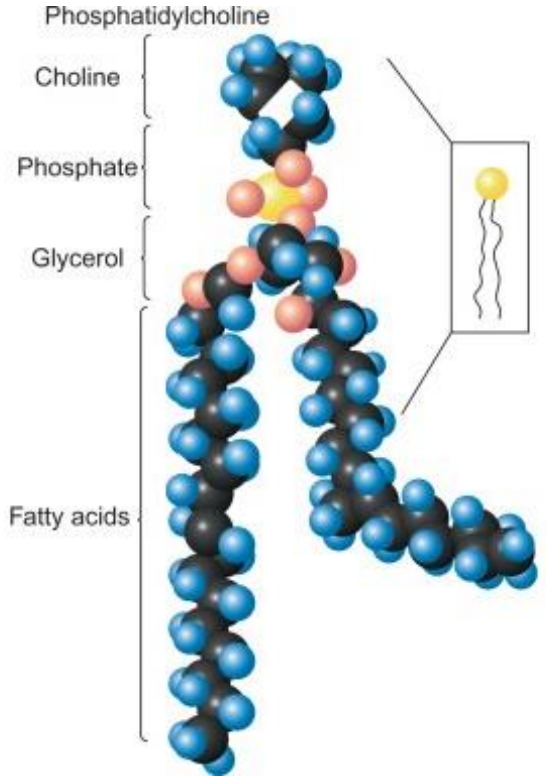


• **Waxes** -> waxes are esters formed by long-chain (C14 to C36) saturated and unsaturated fatty acids with long-chain (C16 to C30) alcohols.

Glycerophospholipids

• These lipids consist of **two fatty acids** attached via **ester linkage** to the **first and second carbons of glycerol**, with a **highly polar or charged group** attached through a phosphodiester linkage to the **third carbon**.

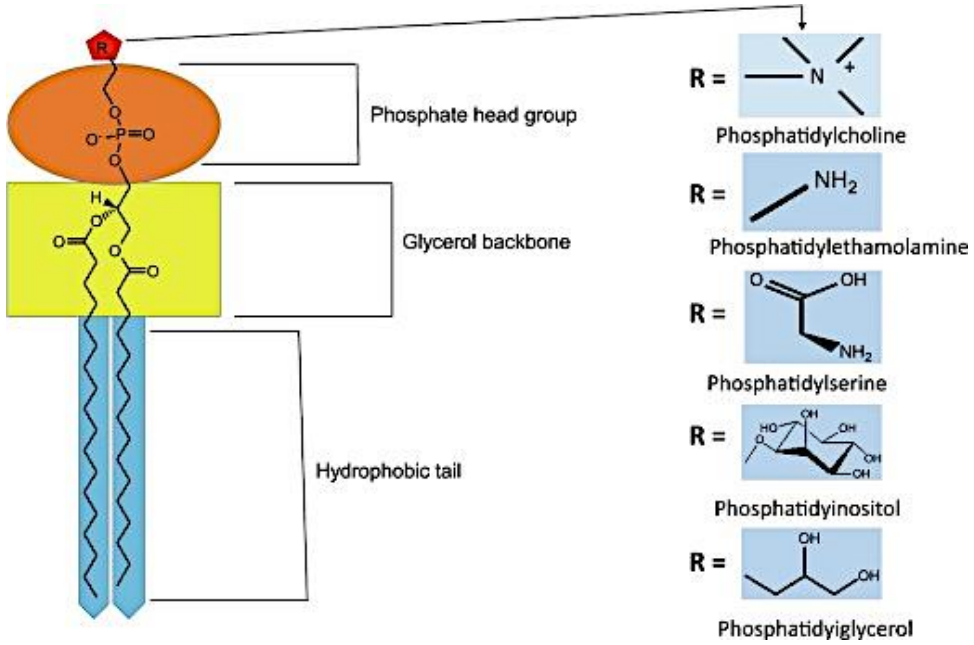




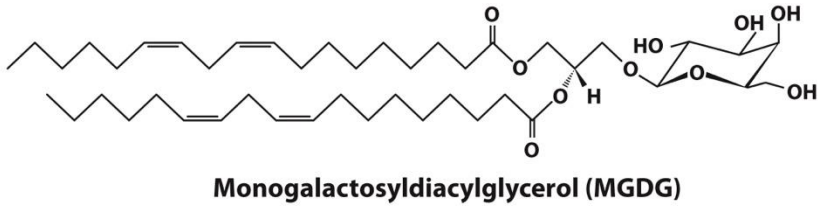
• They represent **the major constituent of cellular membranes, organelles and vesicles**

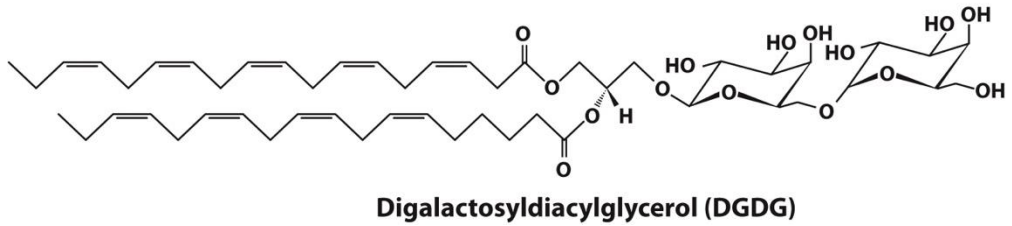
Glycerophospholipids

- Glycerophospholipids are named based on the **polar head group**
- The head group can be charged (positively or negatively) which plays a significant role in the **surface properties of the membrane**



Galactolipids

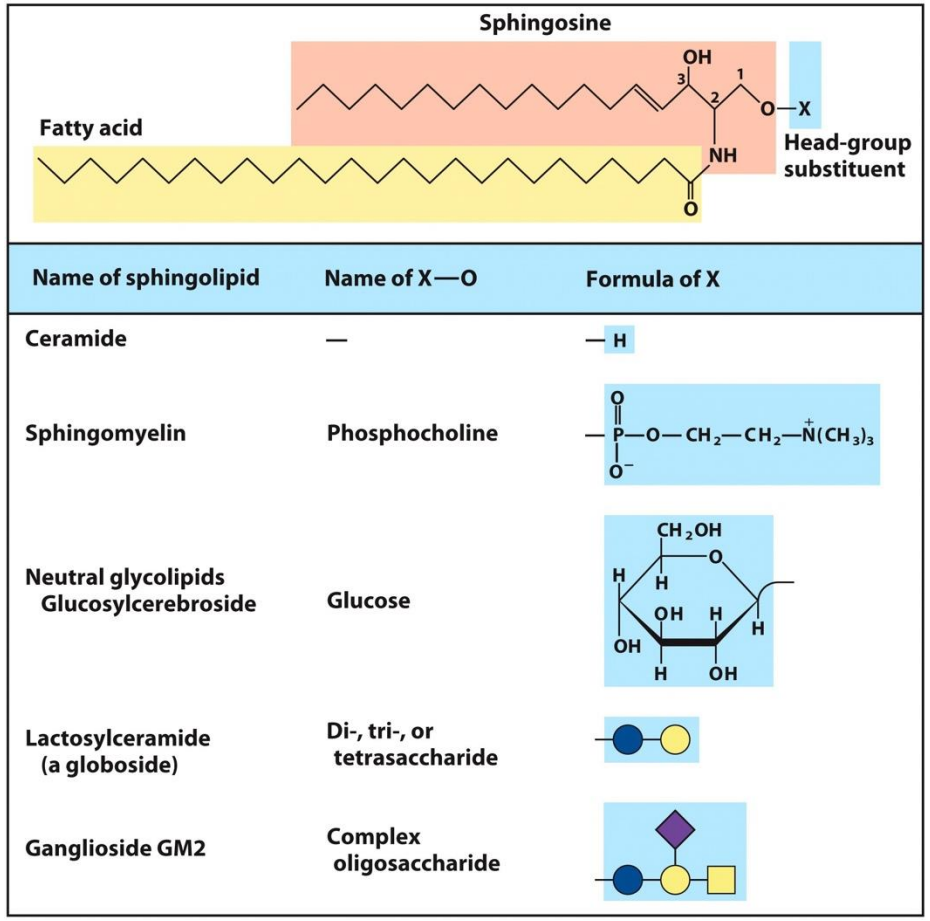




They constitute 70% to 80% of the total membrane lipids in vascular plants, making them **the most abundant membrane lipids in the biosphere.**

Sphingolipids

• Unlike glycerophospholipids, **sphingolipids** contain **no glycerol**. Instead, sphingolipids are composed of one molecule of the **long-chain base** (here sphingosine).



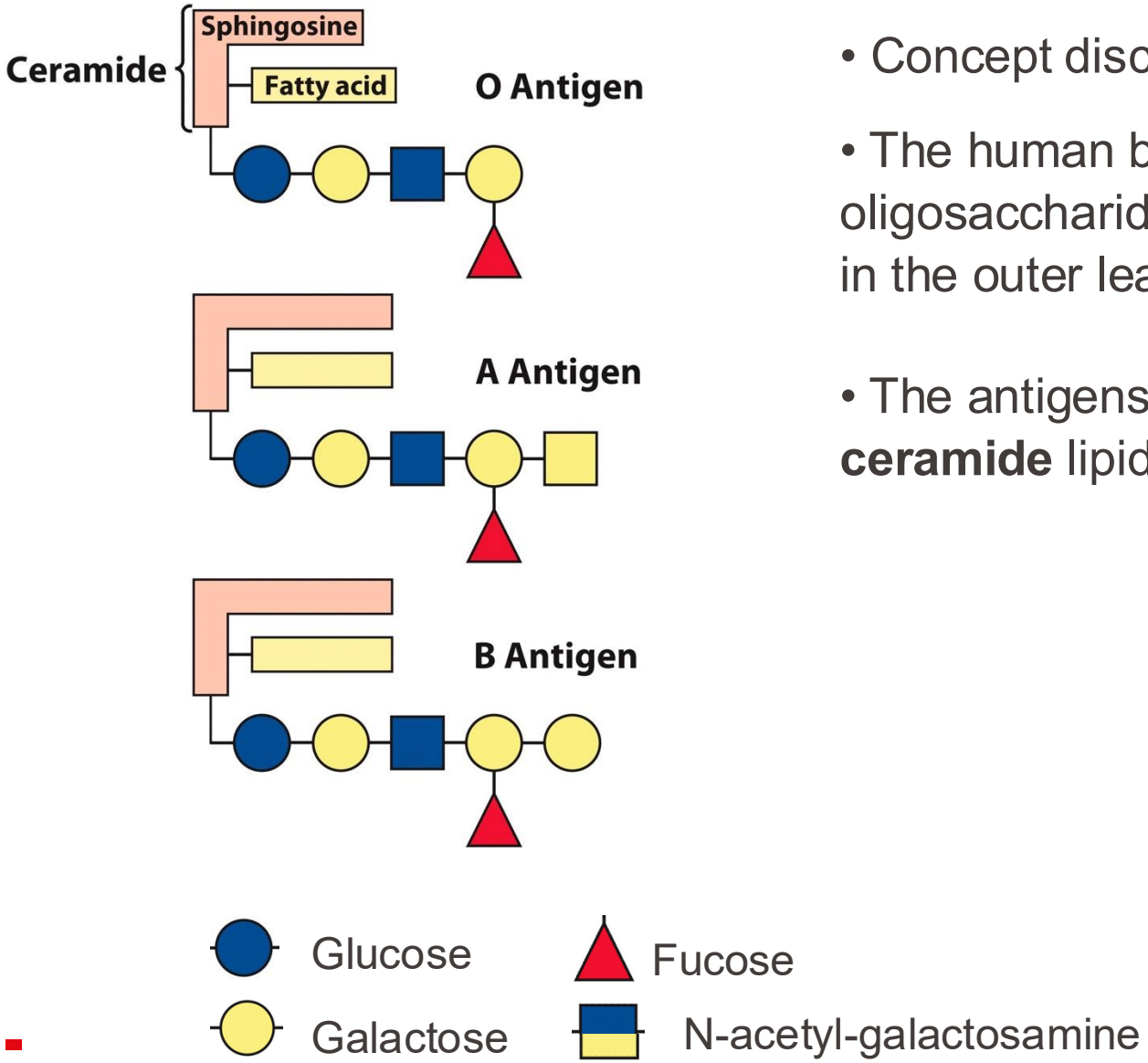
• Depending on the head group they are divided into subclasses (e.g., ceramide, sphingomyelins etc.)

• In addition to constituting cell membranes they play many functional roles, and feature specific tissue distribution

• Sphingomyelins are enriched in plasma membranes of animal cells, particularly in myelin, a membranous sheet that surrounds and insulates neuronal axons

• Glycosphingolipids are found in outer leaflet of cell membranes and play important roles in cell recognition (e.g., neuron development, ABO blood groups)

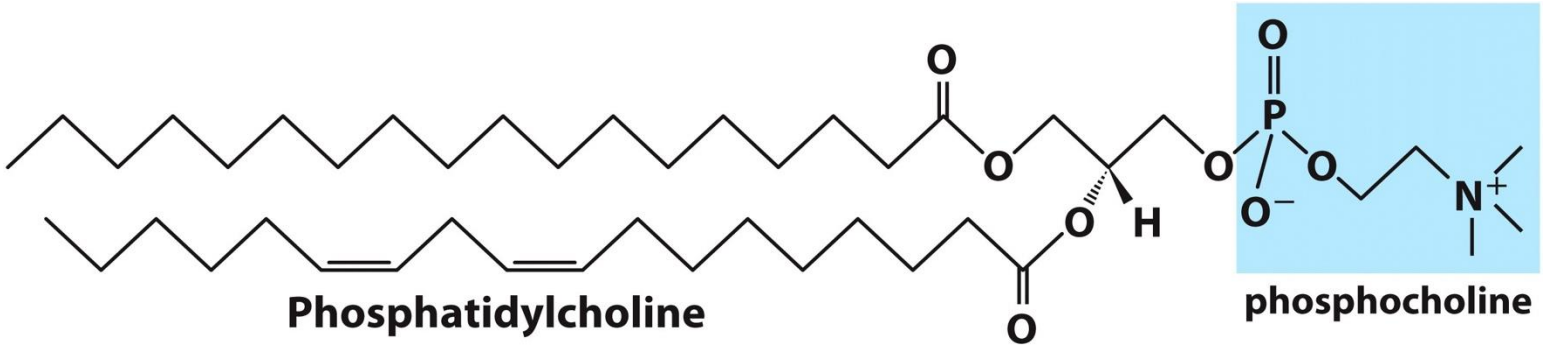
Blood group antigens determined by sphingolipids

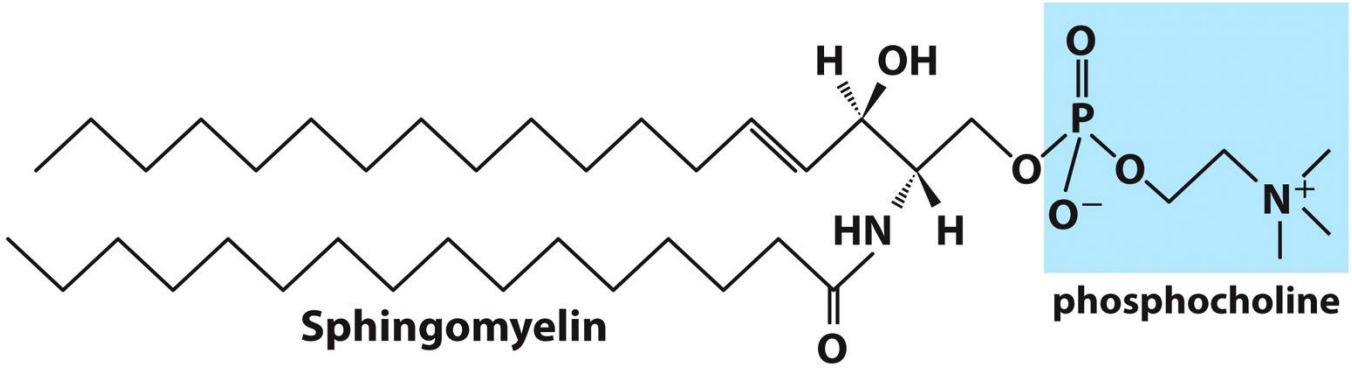


- Concept discussed in Lecture 2
- The human blood groups (ABO) are determined by the oligosaccharide head groups of glycosphingolipids present in the outer leaflet of the red blood cell membrane
- The antigens (O, A and B) are actually attached to **ceramide** lipid backbone

Sphingolipids vs Glycerophospholipids

- Structurally they are very similar, but they are synthesized differently and have diverse roles



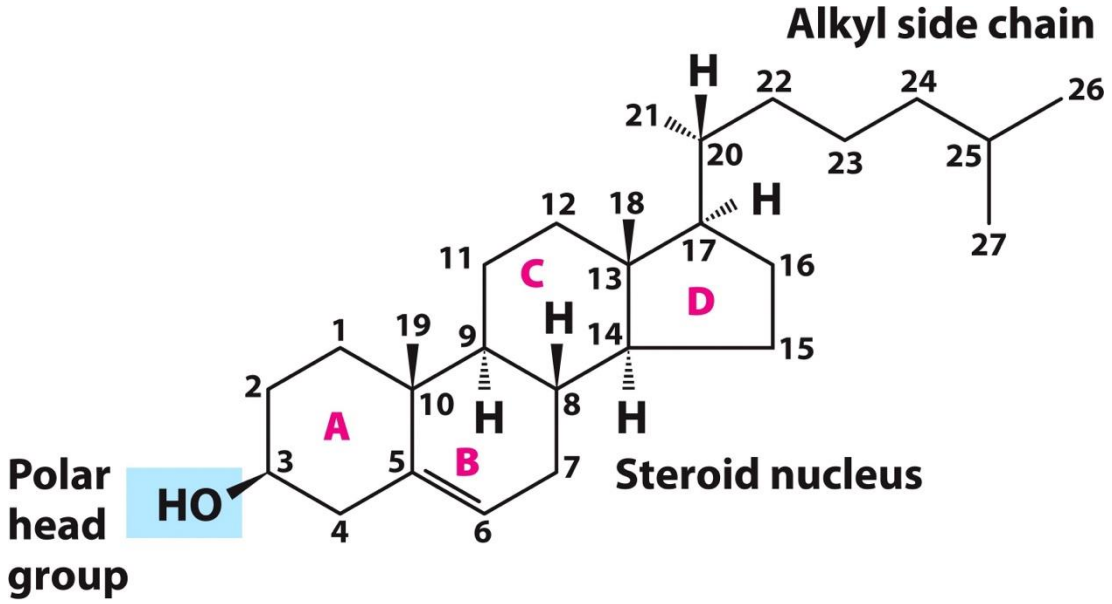


- Defects in sphingolipid metabolism can lead to neurodegenerative diseases (e.g., ALS, HSP) and, if genetic, brain development disorders (e.g., CerTra syndrome)

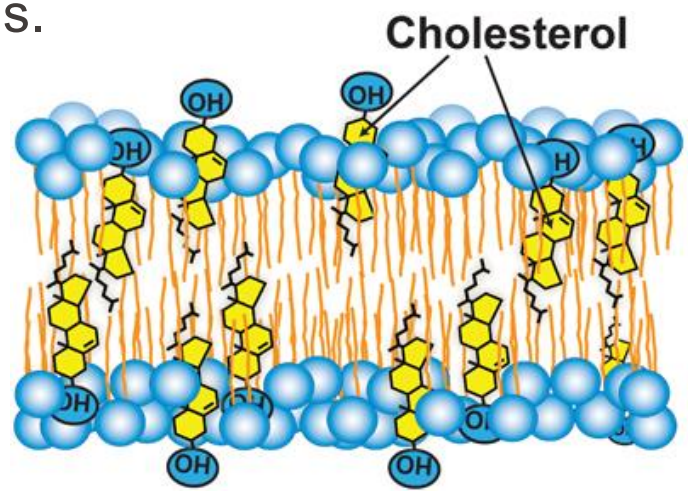
Sterols

• Sterols consist of a rigid steroid nucleus containing four fused rings, an alkyl side chain of 8 carbons, and a single hydrophilic hydroxyl group attached to C-3 of ring A.

• They are synthesized in humans but also acquired through diet, and they are present in the membranes of most eukaryotic cells.



• The steroid nucleus is nearly planar, and the molecule efficiently packs with the acyl chains of membrane glycerophospholipids and sphingolipids.



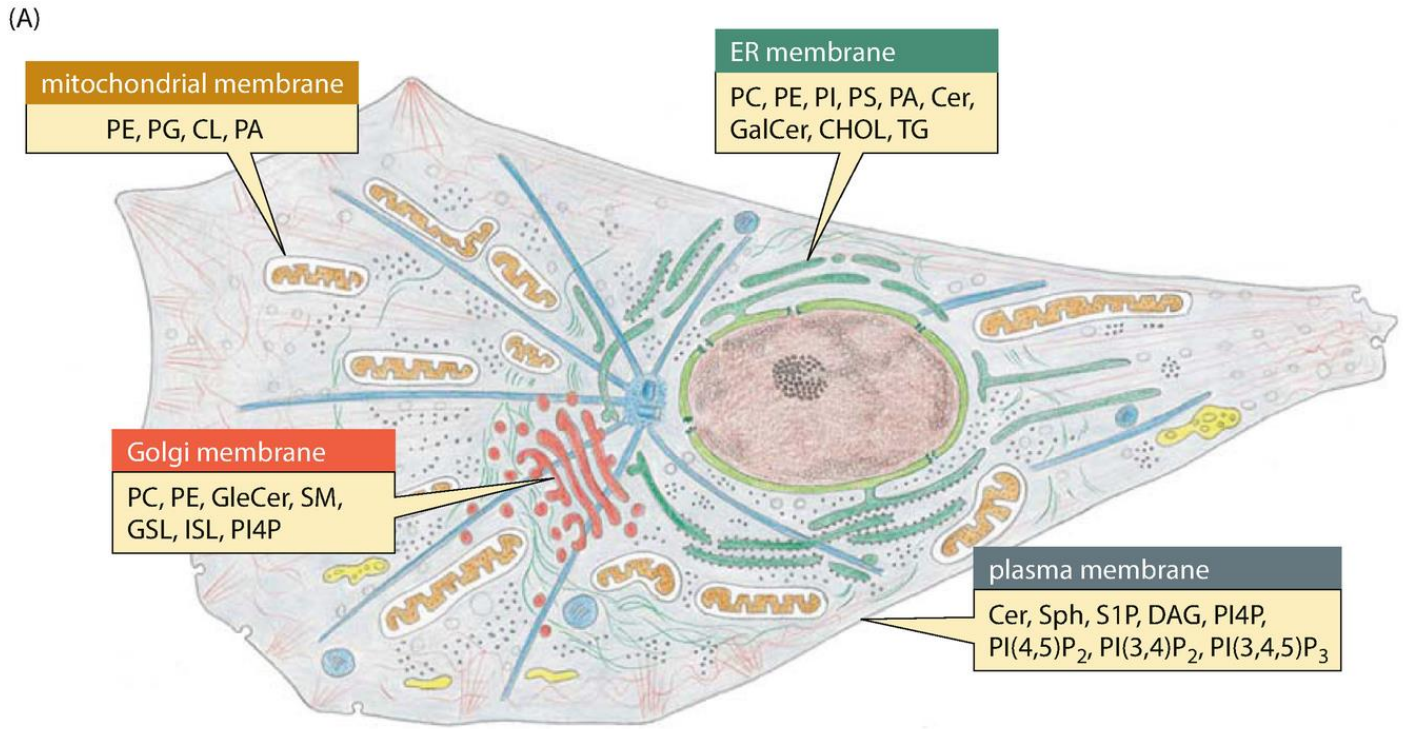
• Cholesterol impacts membrane rigidity/mobility

Lipid composition in different cell compartments

- Phospholipids (PE, PC, PI, PS) are relatively uniform across most membranes

- Sphingolipids (CER, GalCER, Sph) largely present on the plasma membrane but also Golgi and ER

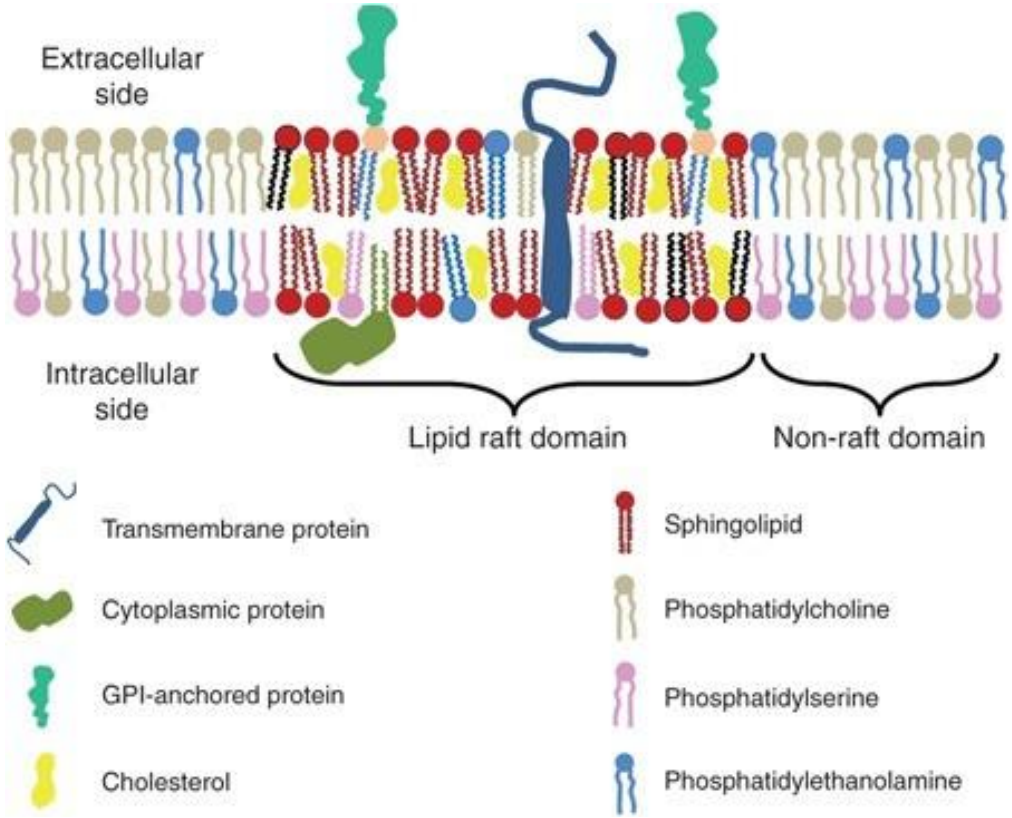
- Cholesterol comprises all membranes but is the highest at the cell membrane where it represents 40-50% of all lipids.



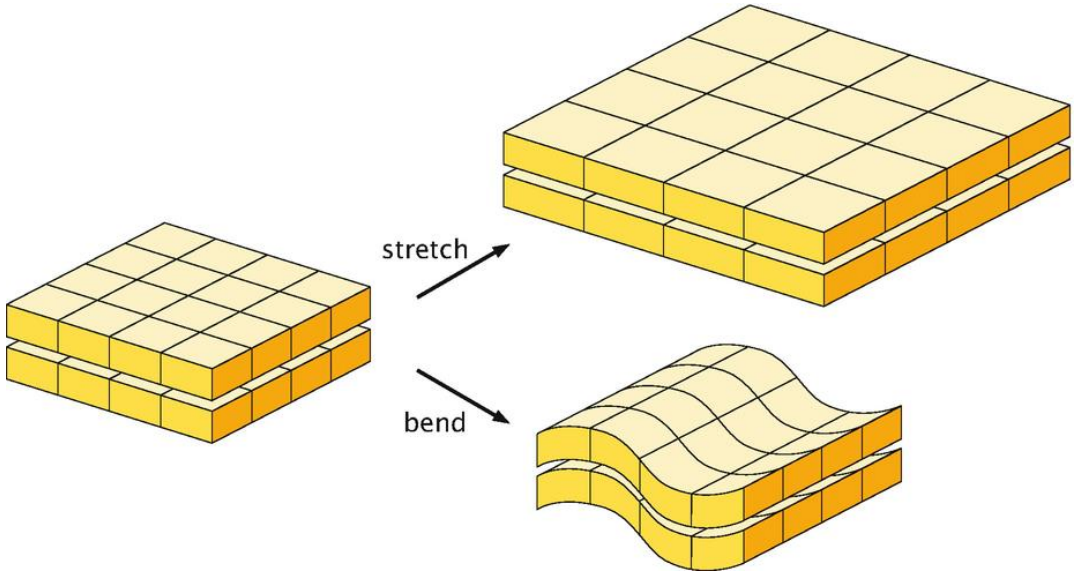
Cholesterol/Phospholipid ratio:

Membranes are asymmetric dynamic structures

- Inner and outer leaflet have different compositions



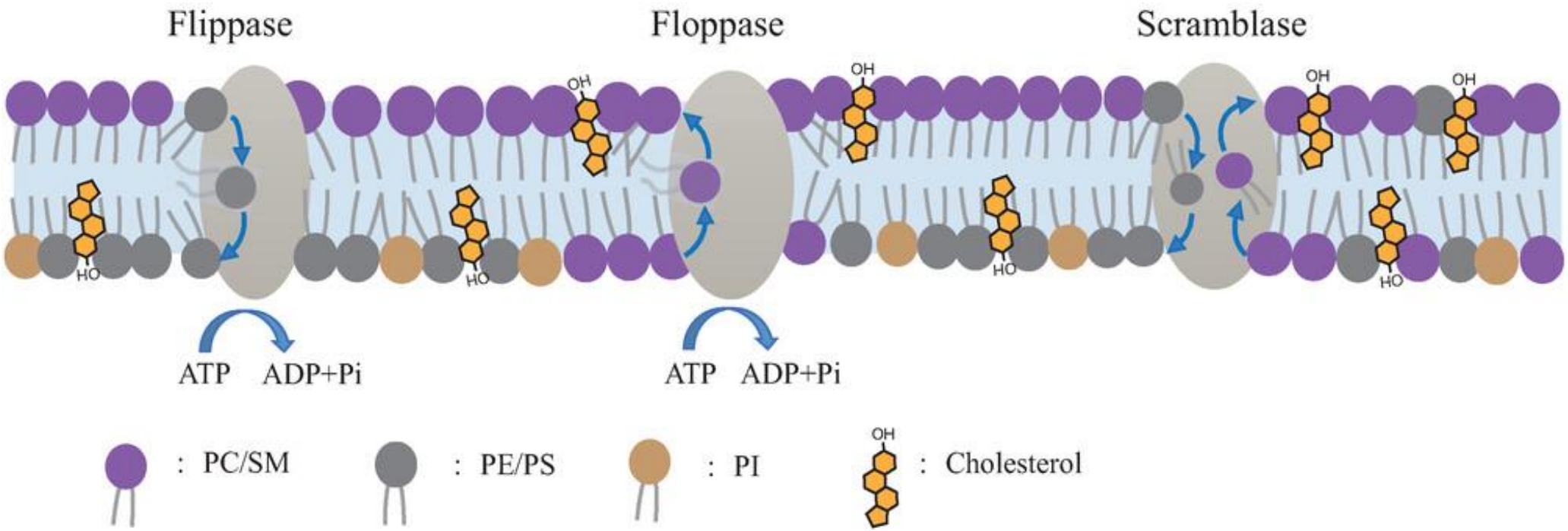
- Membranes are dynamic and pleomorphic



- **Flippases, Floppases** and **Scramblases** are transmembrane proteins that regulate transport of lipids between leaflets

- Membrane flexibility is determined by lipid composition and environmental factors (e.g., mechanical forces)

Fippasees, Floppases and Scramblases

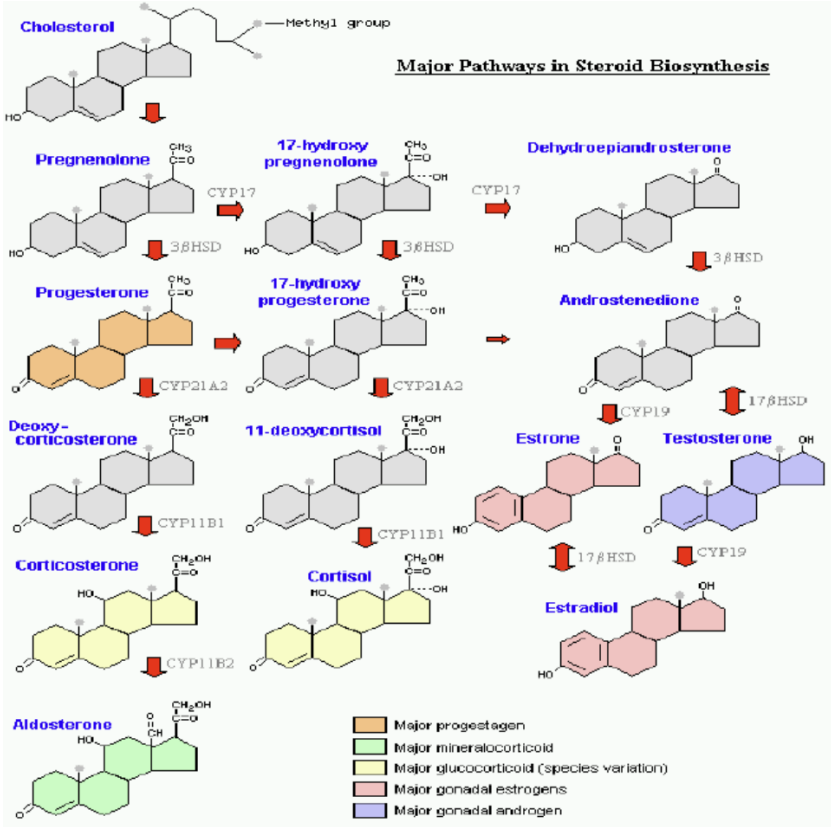


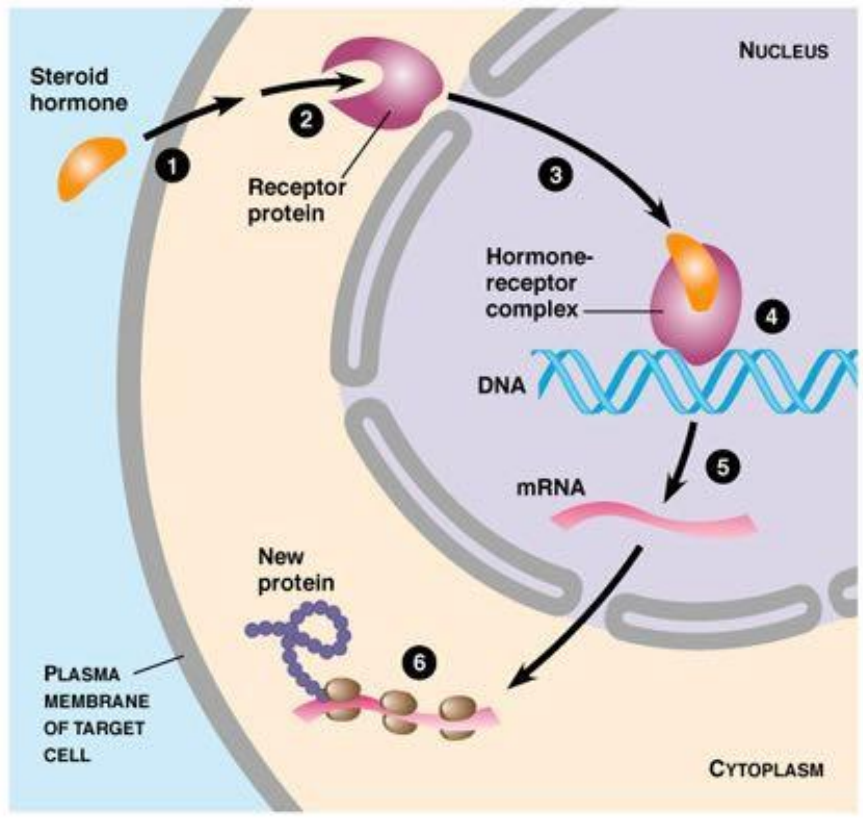
- **Flippases, Floppases** transport lipids against the gradient in an energy dependent manner (ATP consupmtion)
- **Scramblases** are independent of ATP and break lipid asymmetry

Tang, Dan, et al. "Scramblases and virus infection." *Bioessays* 44.12 (2022): 2100261.

Bioactive lipids – Steroid hormones

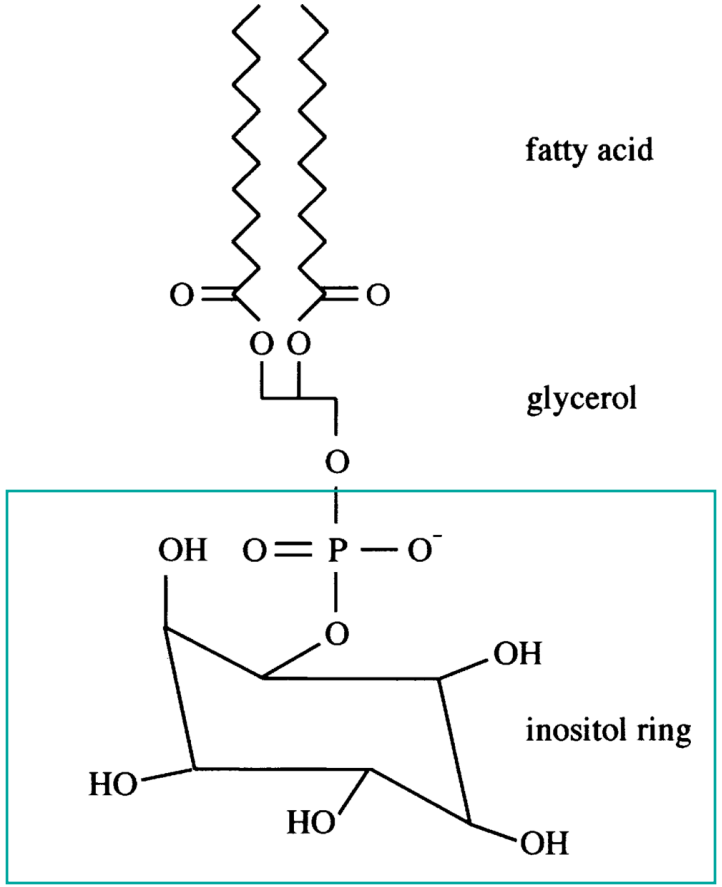
- Bioactive lipids affect cell function in a concentration dependent manner.
- Most commonly they serve as hormones and secondary messengers
- Sterols are precursors of steroid hormones and are therefore also considered bioactive lipids

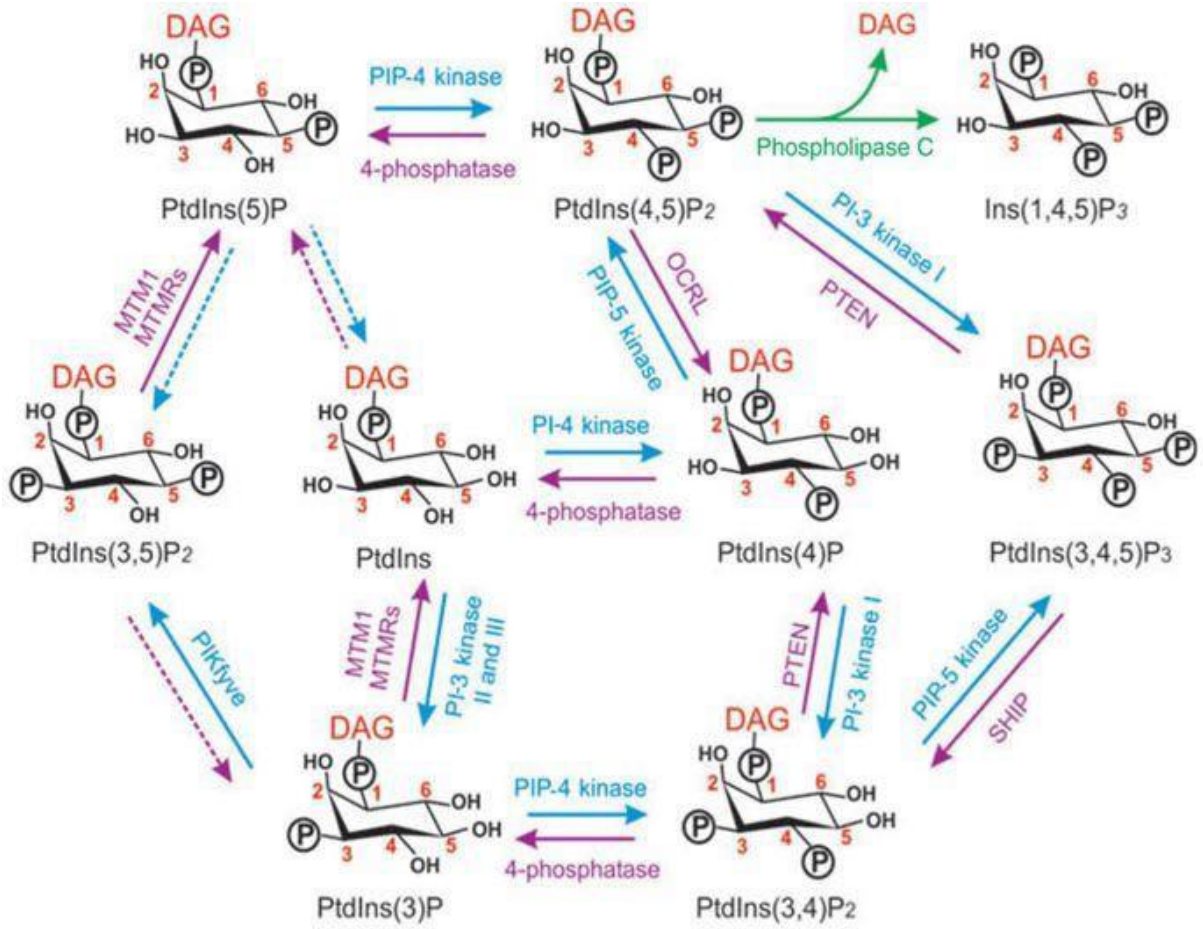




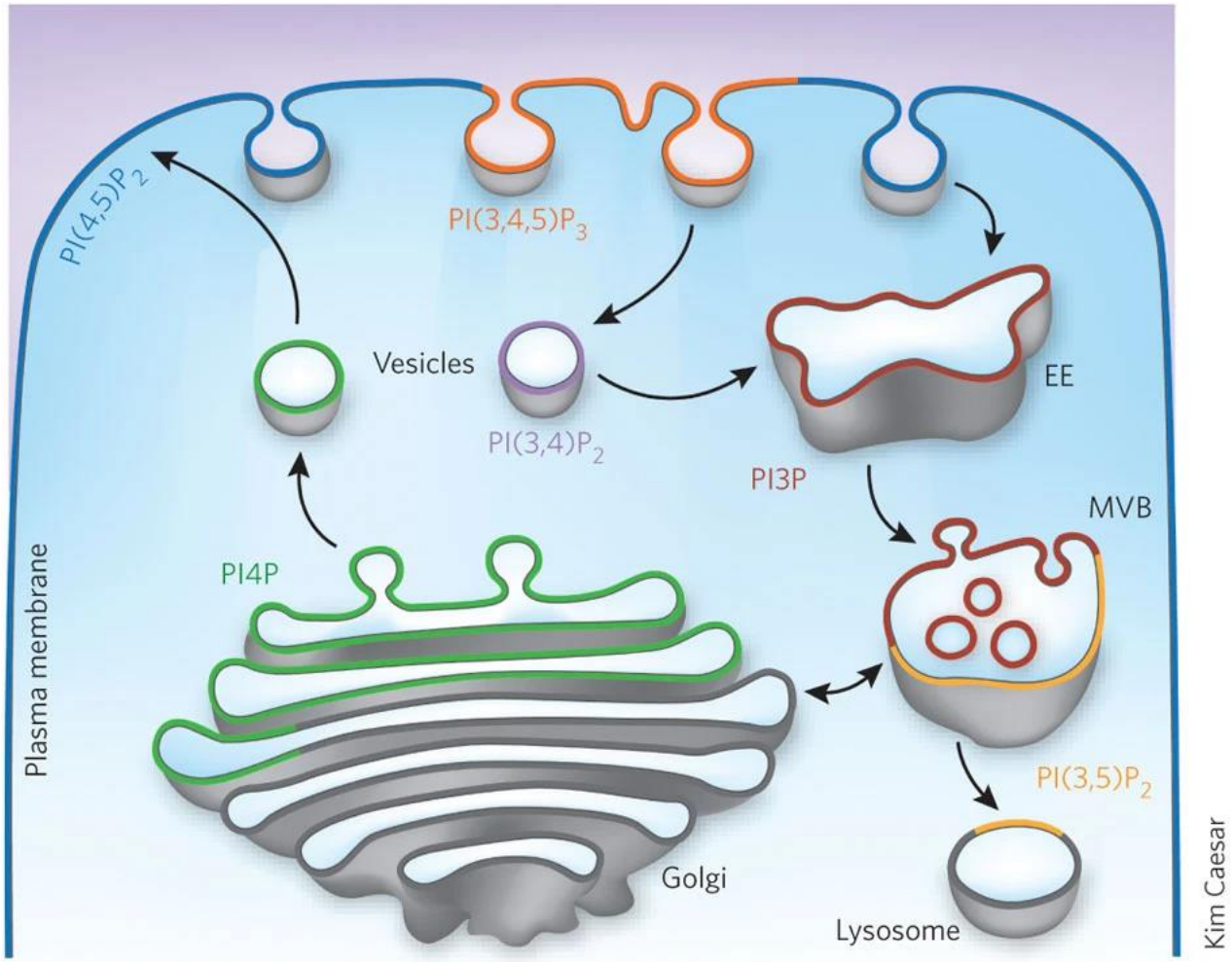
Bioactive lipids – Phosphoinositides (PI)

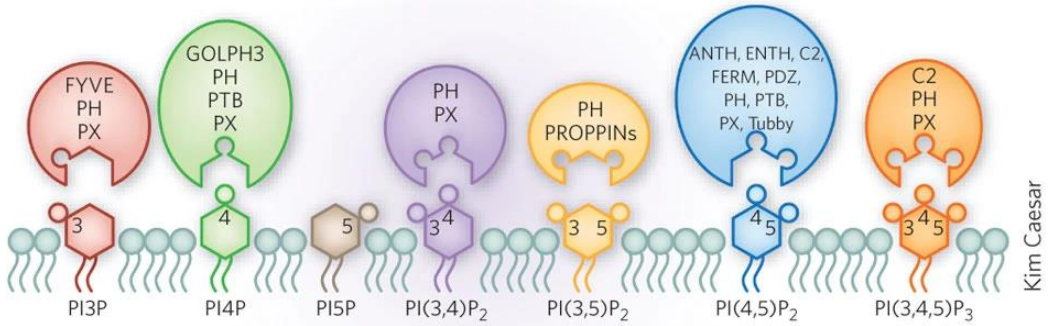
- Phosphoinositides are minority phospholipids on cellular membranes that have a phosphoglycerol backbone esterified with 2 fatty acids and inositol head group.
- Inositol group can be phosphorylated (P) at one or more sites in a reversible fashion (kinase – phosphatase)





Bioactive lipids – The “PIP”-code



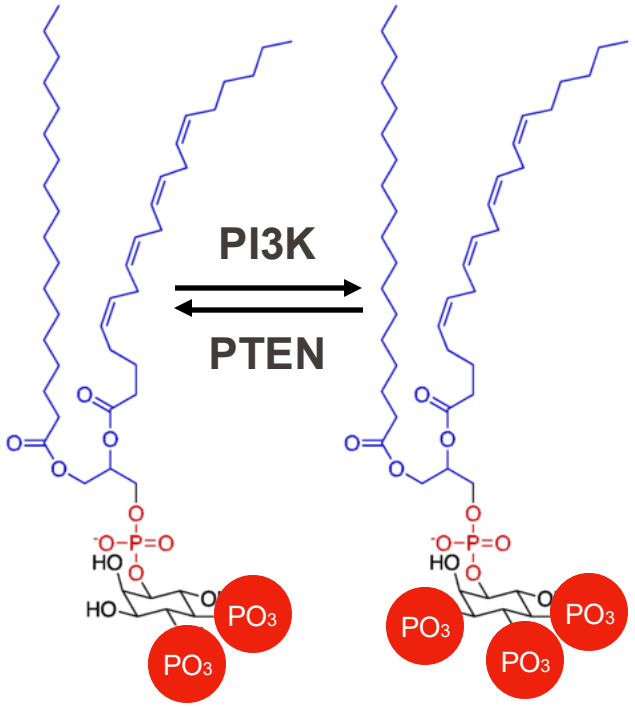


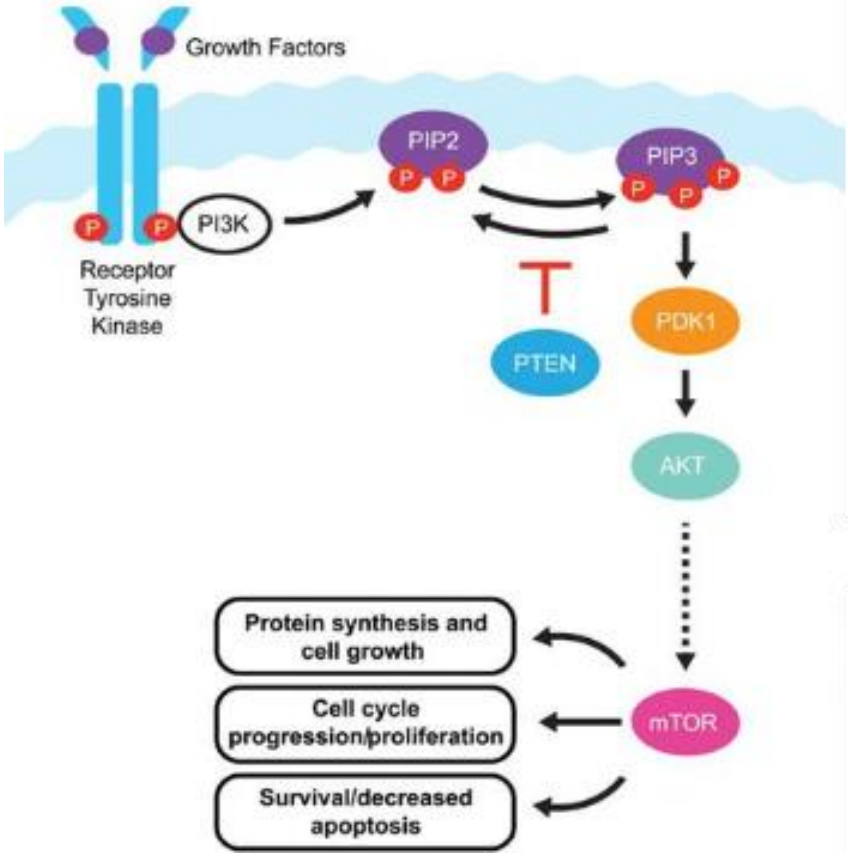
- **Different phosphorylation patterns** on the inositol ring (at positions 3, 4, and 5) generate distinct **phosphoinositides**
- These distinct PIPs act as **molecular “zip codes”** on membranes, recruiting specific effector proteins with domains that recognize particular phosphorylation patterns.
- The PIP code thereby defines **organelle identity, signaling pathways, and trafficking events**, enabling spatial and temporal regulation of membrane dynamics.

Kutateladze, Tatiana G. "Translation of the phosphoinositide code by PI effectors." *Nature chemical biology* 6.7 (2010): 507-513.

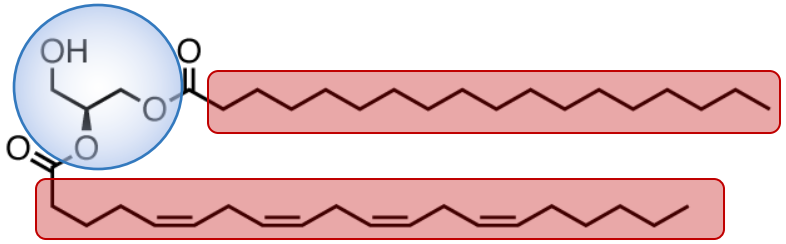
Bioactive lipids – PtdIns(3,4,5)P3

- Phosphorilation of PtdIns(3,4)P2 to PtdIns(3,4,5)P3 catalyzed by receptor typrosine kinase is recognized by PDK1 resulting in activation of the downstream signaling cascade and leading to different outcomes to the cell
- In this case, phosphoinositides serve as **secondary messengers**

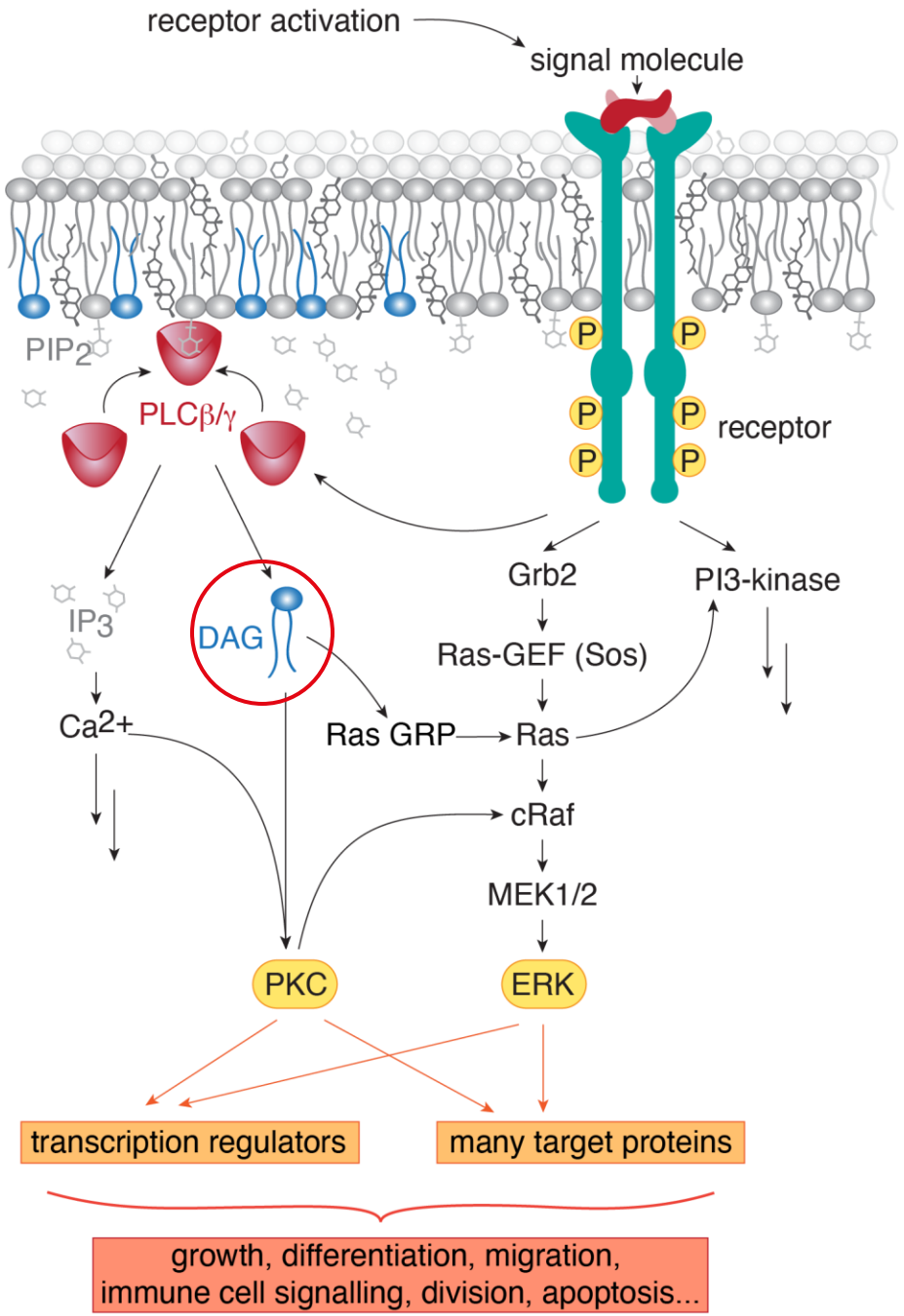




Bioactive lipids – DAGs



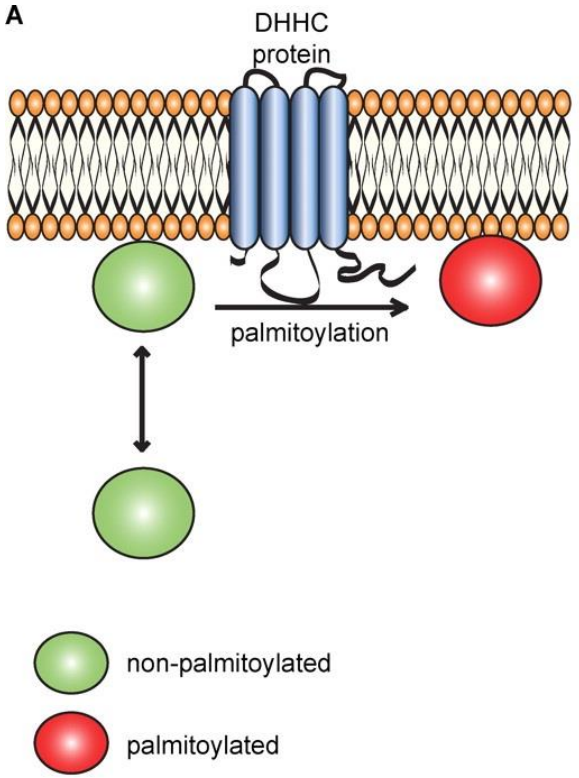
- Important class of second messenger signaling lipids
- Generated by PLC-mediated PIP_2 cleavage
- Involved in important processes: Signal transduction (PKC, PKD, Chimaerin), neurotransmitter release (Munc13) and Ca^{2+} signaling via TRP channels…



Lipids in bioengineering

- Conventional applications include food, cosmetics, soap, biofuel, chemical feedstock etc.

Protein lipidation

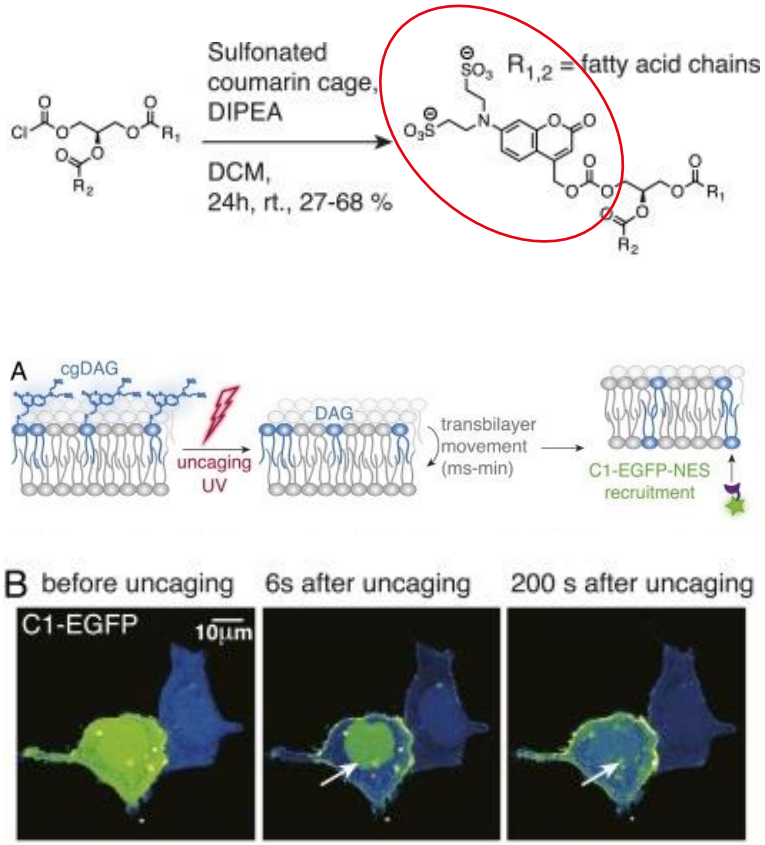


https://www.epfl.ch/labs/vdg/

Membrane development

https://www.epfl.ch/labs/dangelo-lab/

Chemical toolkit for biology



https://www.epfl.ch/labs/gr-schuhmacher/

Lipids – Take Home messages

- Lipids are amphiphilic constituents of living organisms
- Lipids may serve as energy stores and thermal insulators
- Lipids constitute the building blocks of biological membranes
- Lipids can serve as first and second messengers in signal transduction
- Lipids are structurally and functionally heterogeneous
- The three main classes of lipids in eukaryotes are glycerophospholipids, sphingolipids and sterols