Glycerolipids

Metabolismo y Enfermedades Metabólicas
Máster en Investigación Biomédica
Universidad de Valladolid

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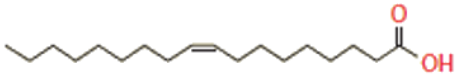
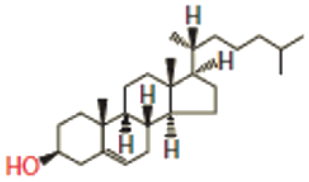
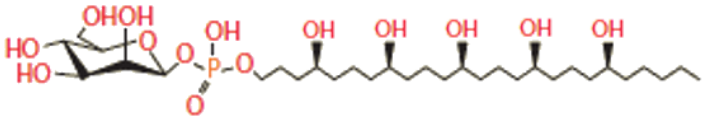
Lipid Categories



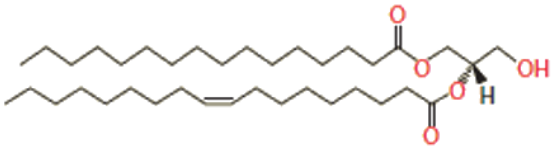
Fatty acyls
Fatty acids and conjugates
Eicosanoids
Docosanoids
Fatty Alcohols



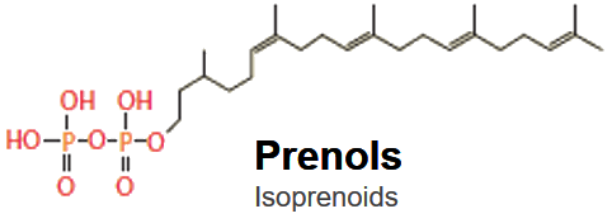
Sterols
Cholesterol and its esters
Steroid hormones



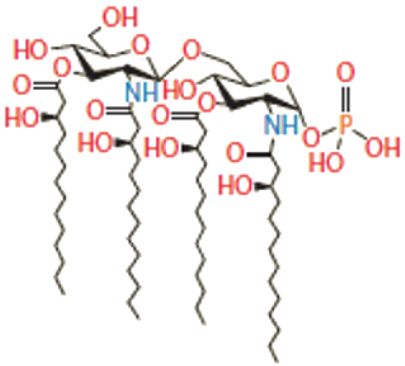
Polyketides
Linear Polyketides
Aflatoxins



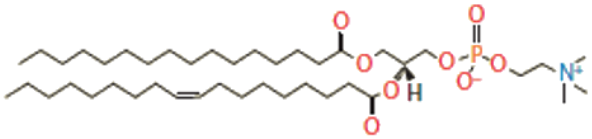
Glycerolipids
Monoradyglycerols
Diradylglycerols
Triradylglycerols



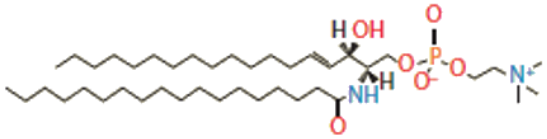
Prenols
Isoprenoids



Saccharolipids
Acylaminosugars



Glycerophospholipids
Glycerophosphocolines
Glycerophosphoethanolamines
Glycerophosphoinositols

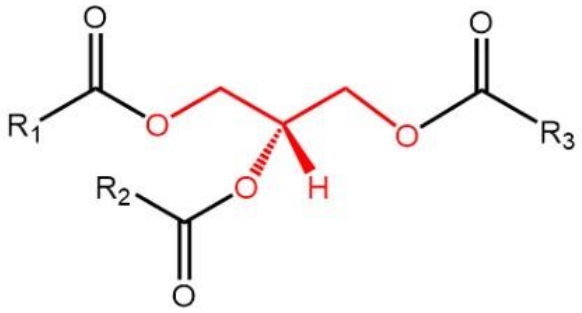


Sphingolipids
Sphingoid bases
Ceramides
Phosphosphingolipids
Glycosphingolipids

Definitions

Triacylglycerol = a lipid in which three fatty acids are esterified by a glycerol backbone.

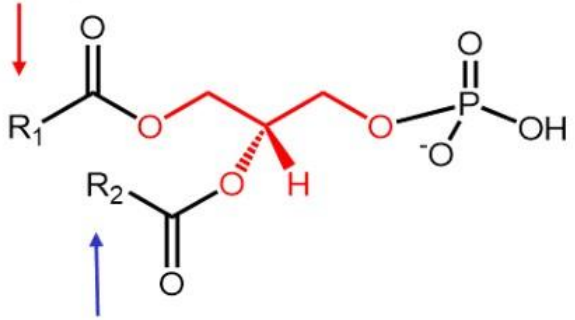
It is the major form of energy storage in humans. Also called a triglyceride.



Usually a saturated FA

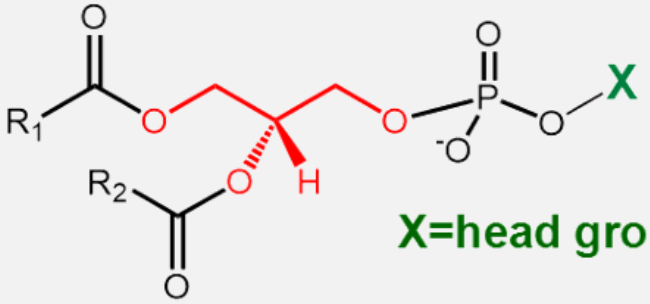
Phosphatidic acid = the simplest glycerophospholipid -the precursor to other phospholipids and to triacylglycerols.

Also called diacylglycerol-3-phosphate.



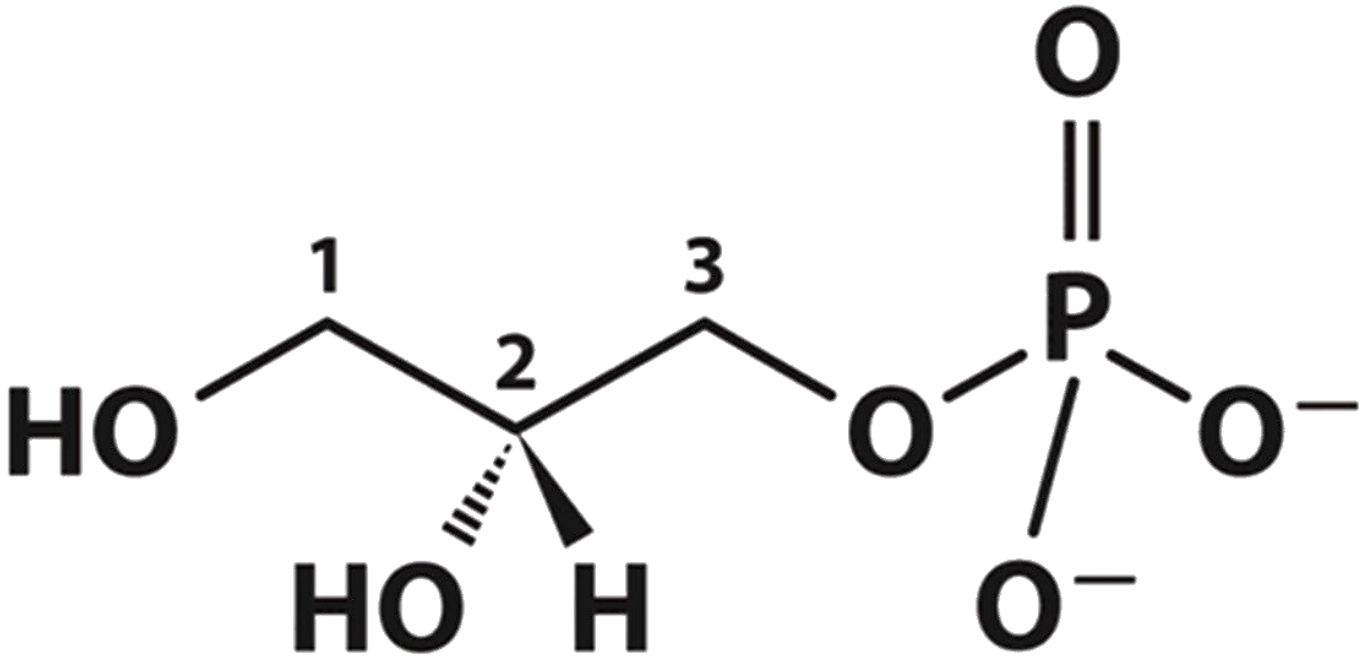
Usually an unsaturated FA

Glycerophospholipid = an amphipathic lipid in which two fatty acyl groups are attached to a glycerol-3-phosphate whose phosphate group is linked to a polar group



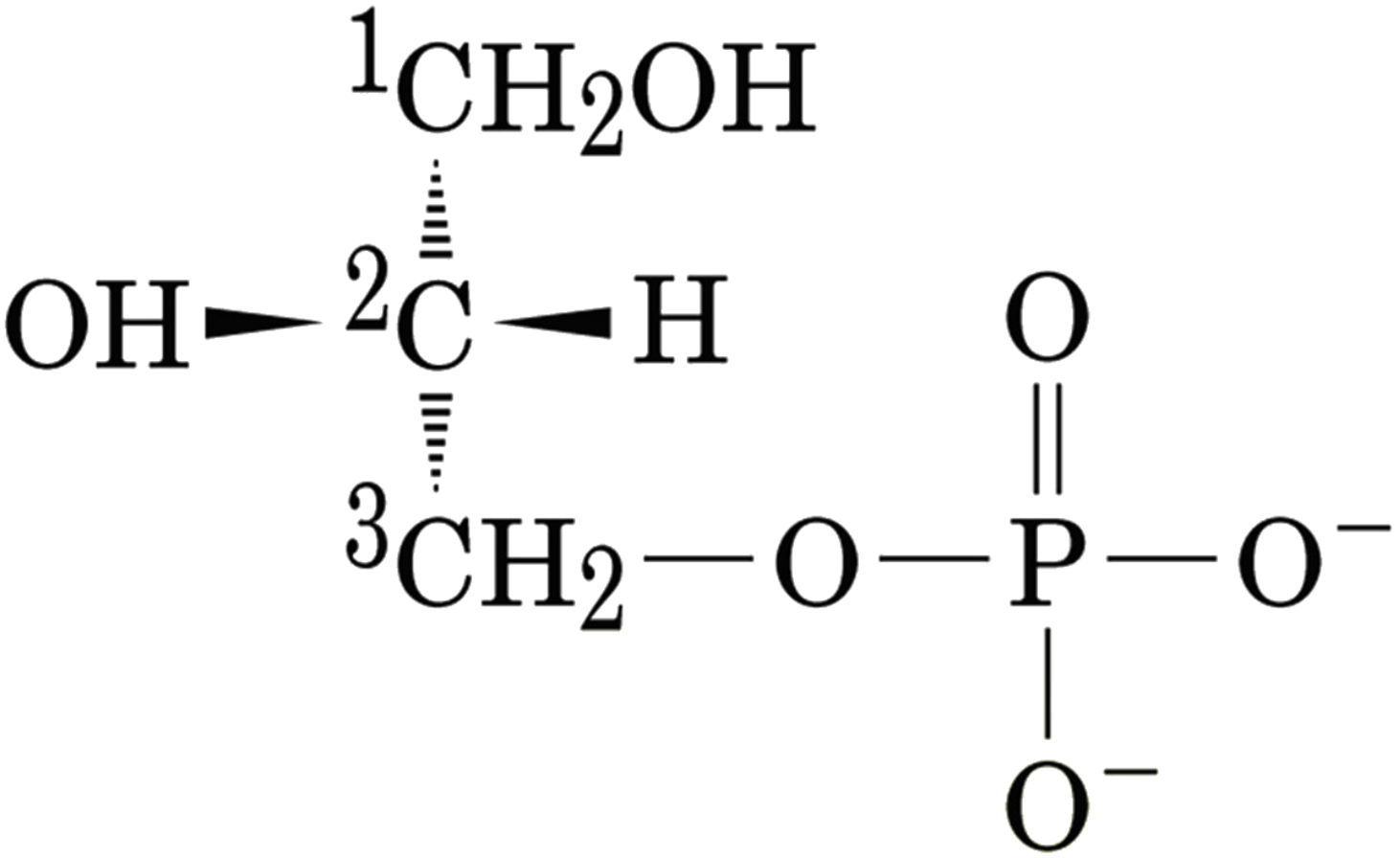
X=head group

Stereospecific Numbering



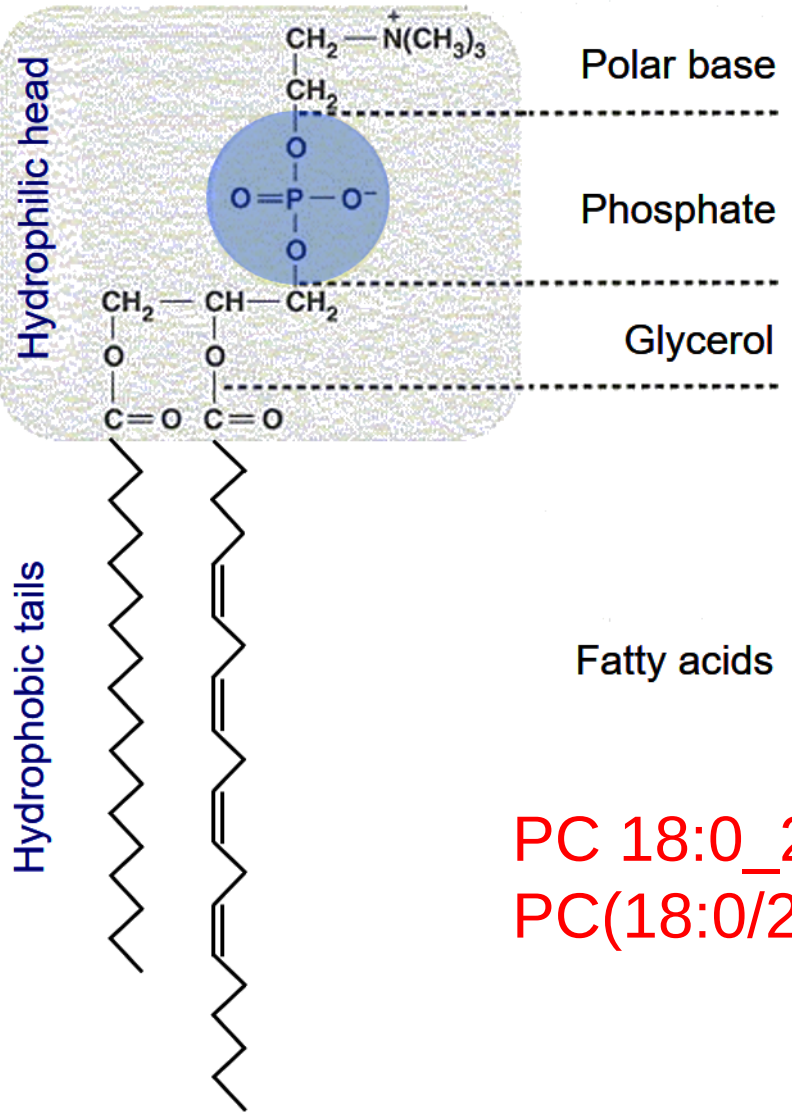
L-Glycerol-3-Phosphate or sn-Glycerol-3-Phosphate

Stereospecific Numbering



L-Glycerol-3-Phosphate or sn-Glycerol-3-Phosphate

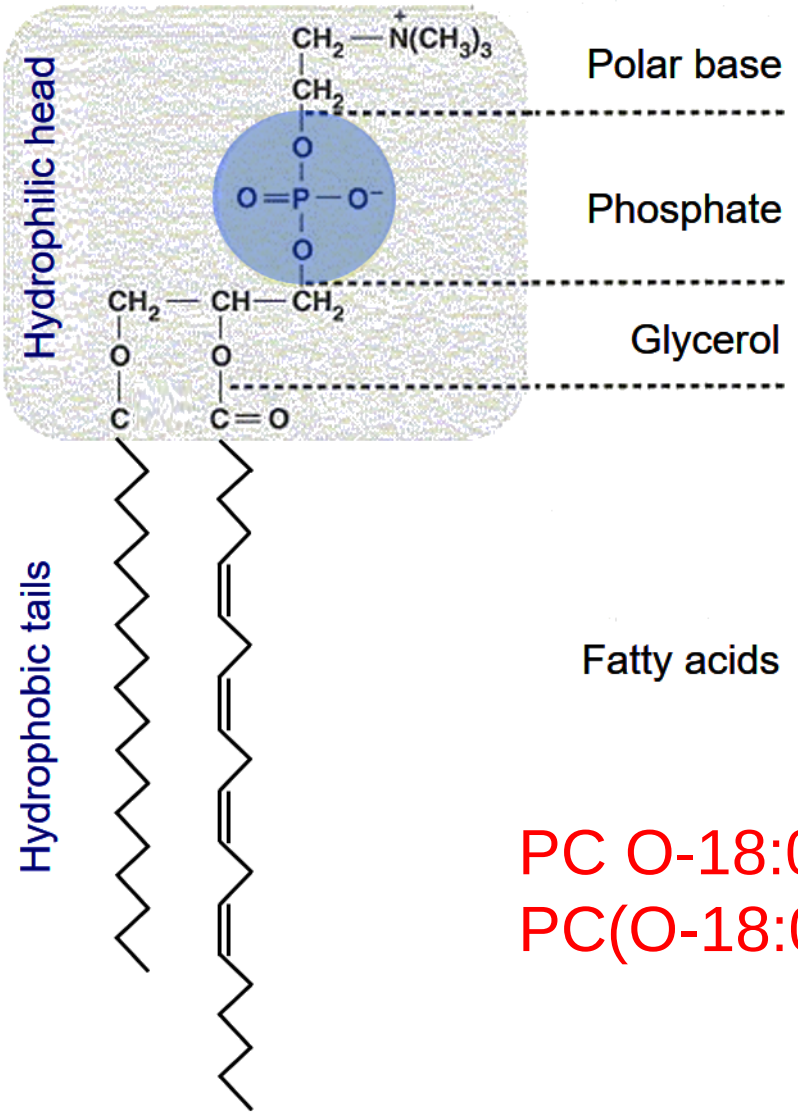
Naming Conventions



PC 18:0_20:4

PC(18:0/20:4)

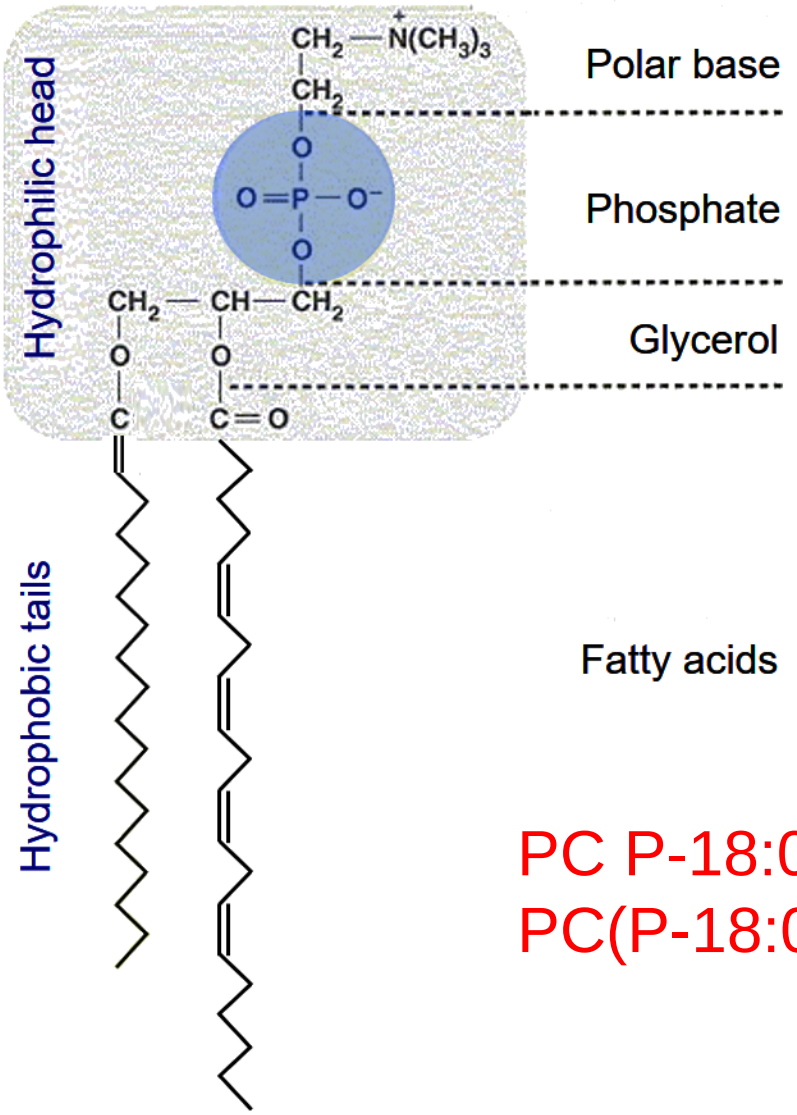
Naming Conventions



PC O-18:0_20:4

PC(O-18:0/20:4)

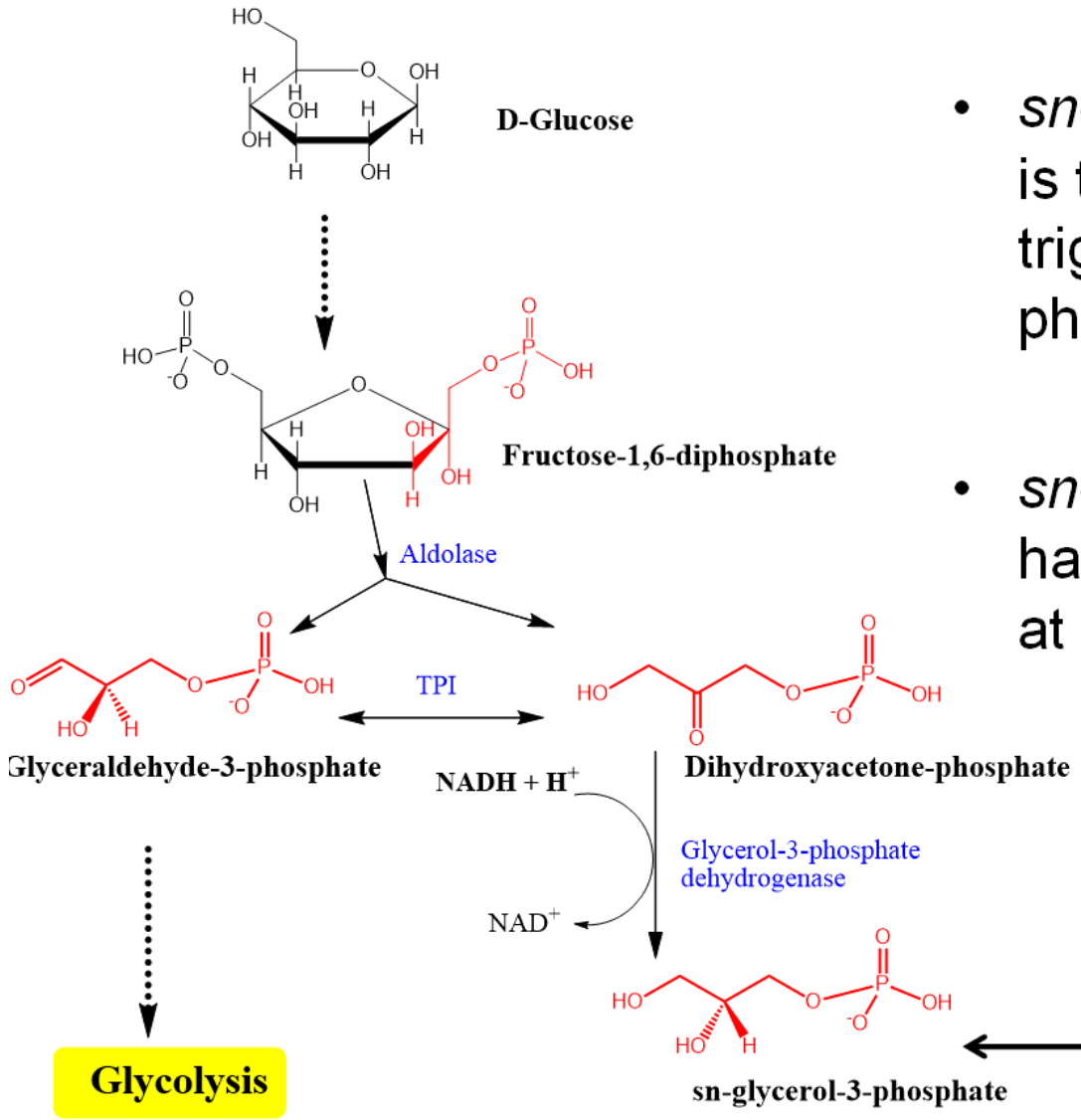
Naming Conventions



PC P-18:0_20:4

PC(P-18:0/20:4)

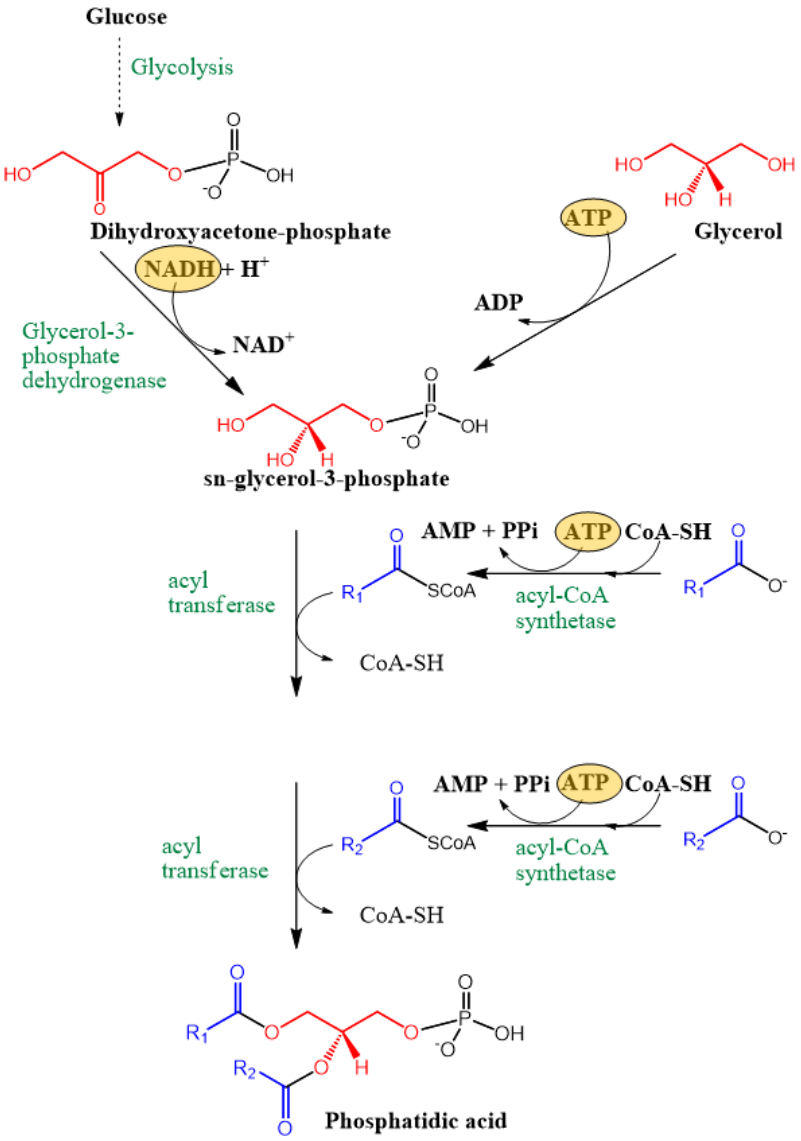
Glycerol-3-Phosphate Synthesis



- *sn*-glycerol-3-phosphate is the backbone of triglycerides and phospholipids
- *sn*-glycerol-3-phosphate has the R configuration at C2

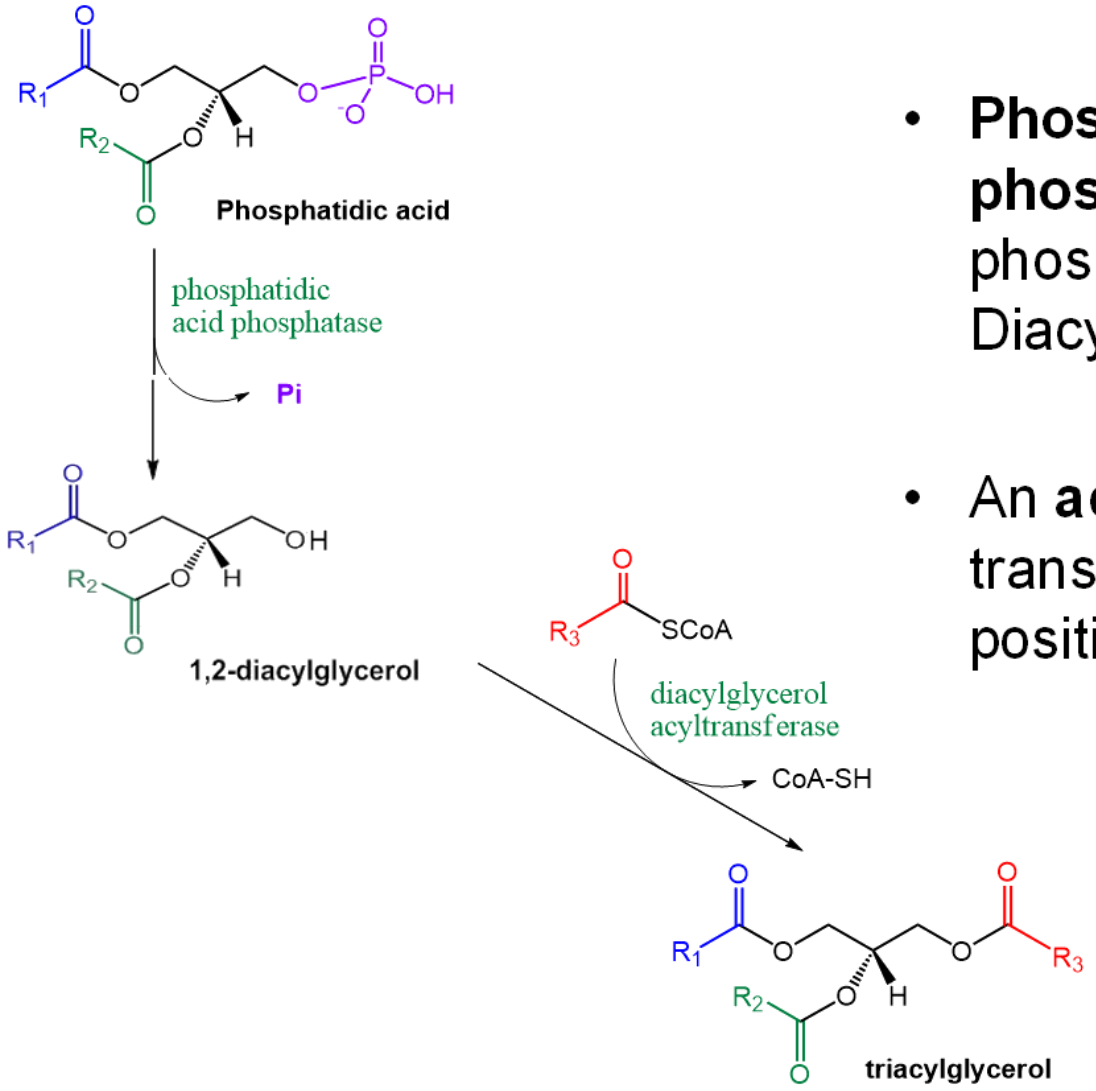
Backbone of phospholipids and triglycerides

Biosynthesis of Phosphatidic Acid



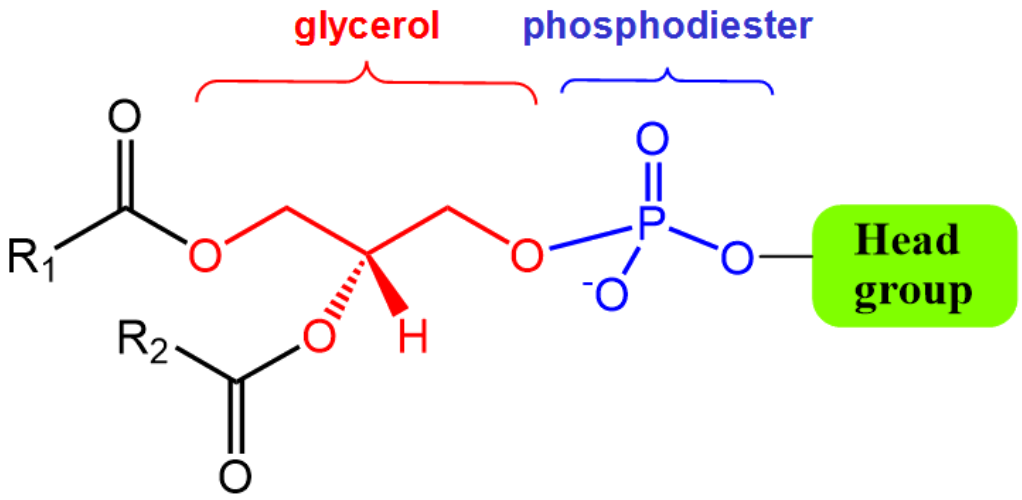
- **Precursors**
  - Fatty acids
  - *sn*-glycerol-3-phosphate
- ***sn*-glycerol-3-phosphate is produced from the**
  - Reduction of DHAP by glycerol phosphate dehydrogenase OR
  - Phosphorylation of glycerol by glycerol kinase and ATP
- **Acyl transferases** perform two successive esterifications with fatty acyl Co A to generate phosphatidic acid

Biosynthesis of Triacylglycerol



- **Phosphatidic acid phosphatase** removes the phosphate producing 1,2-Diacylglycerol
- An **acyl transferase** transfers an acyl CoA to position 3.

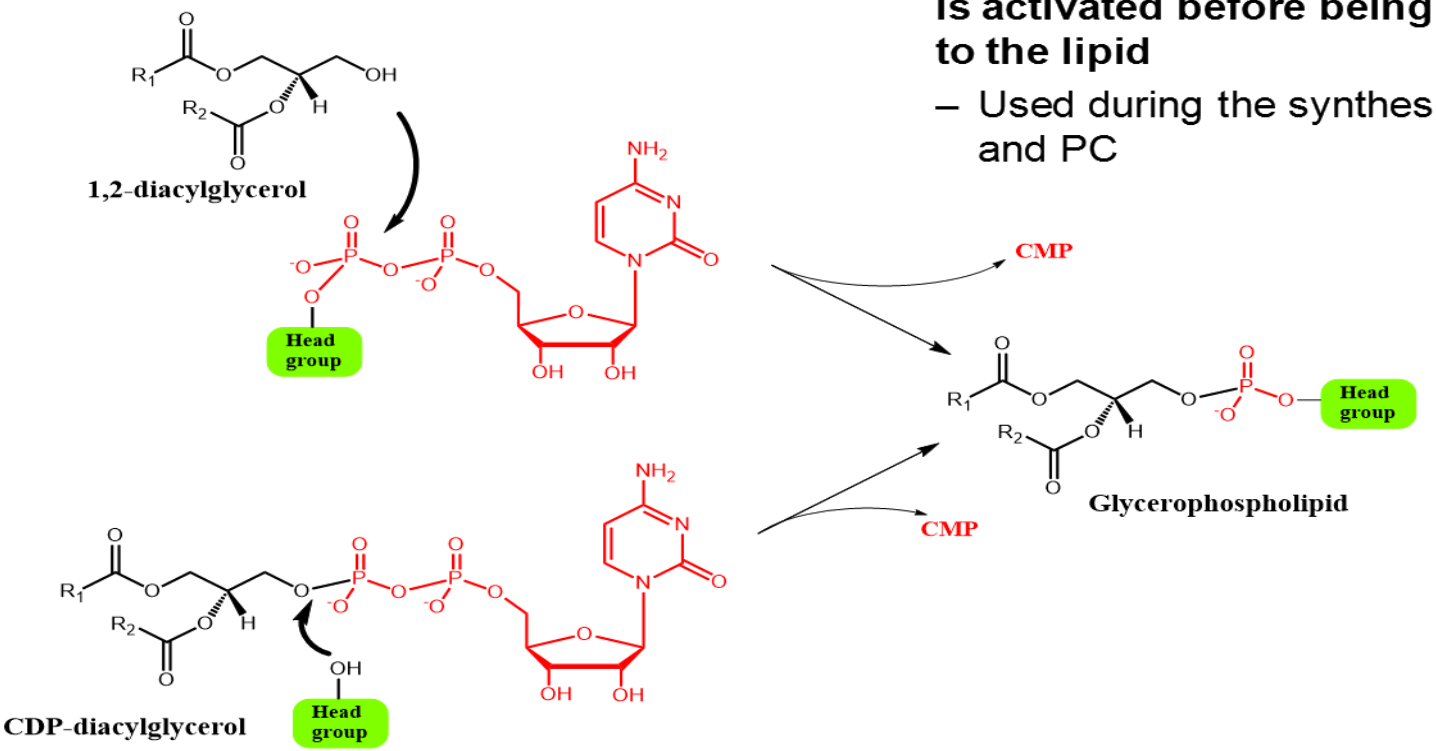
Biosynthesis of Glycerophospholipids



- Glycerophospholipids (or phospholipids) can be made from
  - Phosphatidic acid OR
  - Diacylglycerol
- There are many different head groups which can be linked to the C3 of glycerol by a phosphodiester bond
- Cytidine triphosphate (CTP) provides the synthetic energy in the synthesis of all PLs

Strategies for Phospholipid Synthesis

Strategy 1: Headgroup activated with CDP



Strategy 1: The polar head group is activated before being attached to the lipid

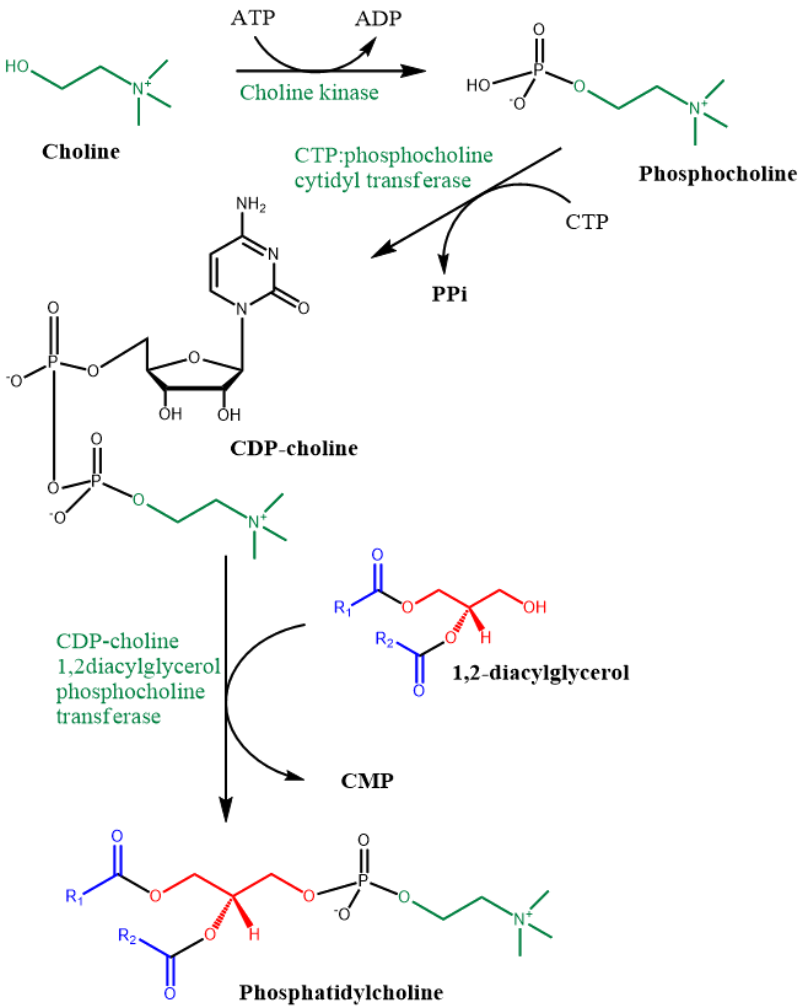
- Used during the synthesis of PE and PC

Strategy 2: Diacylglycerol activated with CDP

Strategy 2: The hydrophobic tail of diacylglycerol is activated rather than the polar head group

- Used during the synthesis of PI and PG

De novo Synthesis of PC (Phosphatidylcholine)

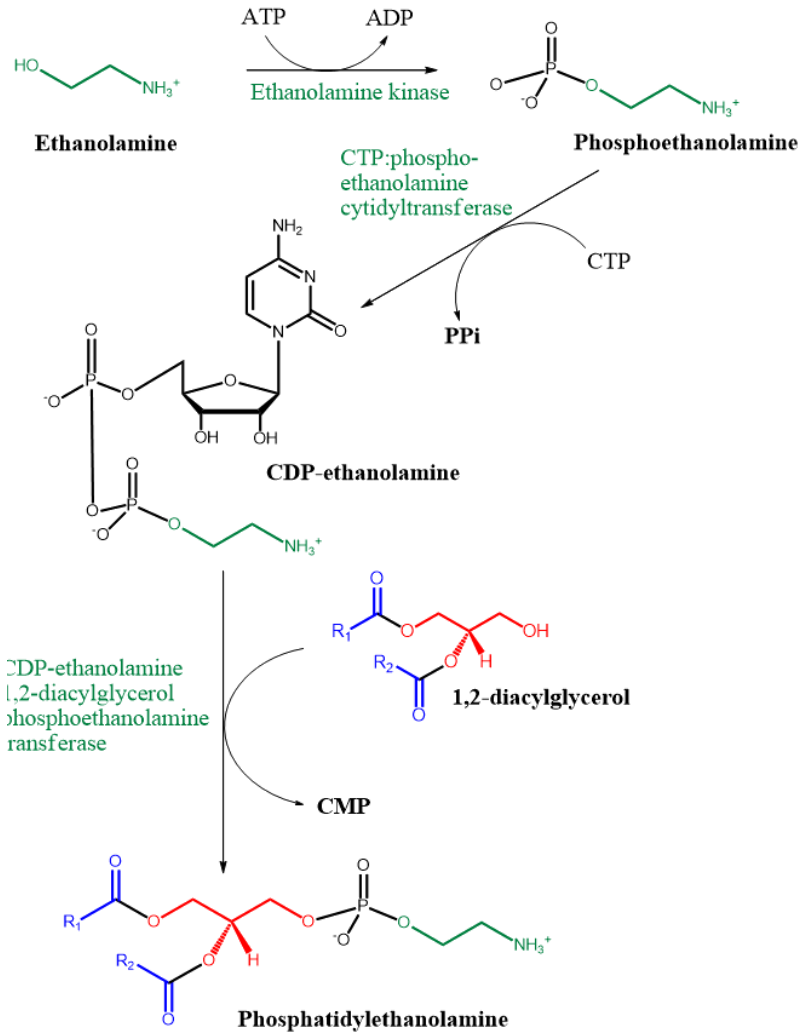


- PC is the most abundant phospholipid in eukaryotic cells
- PC is also known as lecithin

***De Novo* Synthesis**

- Choline is phosphorylated
- Cytidyltransferase makes CDP-choline
- C3 OH groups of DAG attacks the phosphoryl groups of the activated CDP-choline displacing CMP and yielding the glycerophospholipid

De novo Synthesis of PE (Phosphatidylethanolamine)

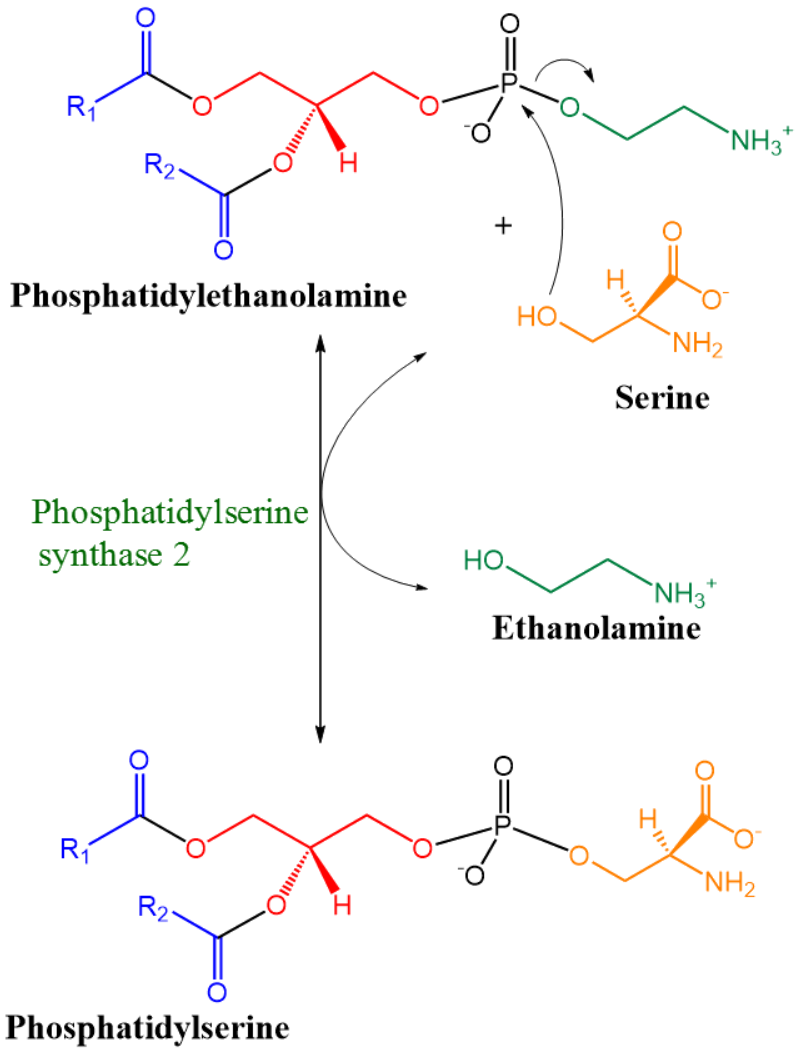


- PE is the second most abundant phospholipid in eukaryotic cells

***De Novo* Synthesis**

- Ethanolamine is phosphorylated
- Cytidyltransferase makes CDP-ethanolamine
- C3 OH groups of DAG attacks the phosphoryl groups of the activated CDP-ethanolamine or displacing CMP and yielding the glycerophospholipid

De novo Synthesis of PS (Phosphatidylserine)

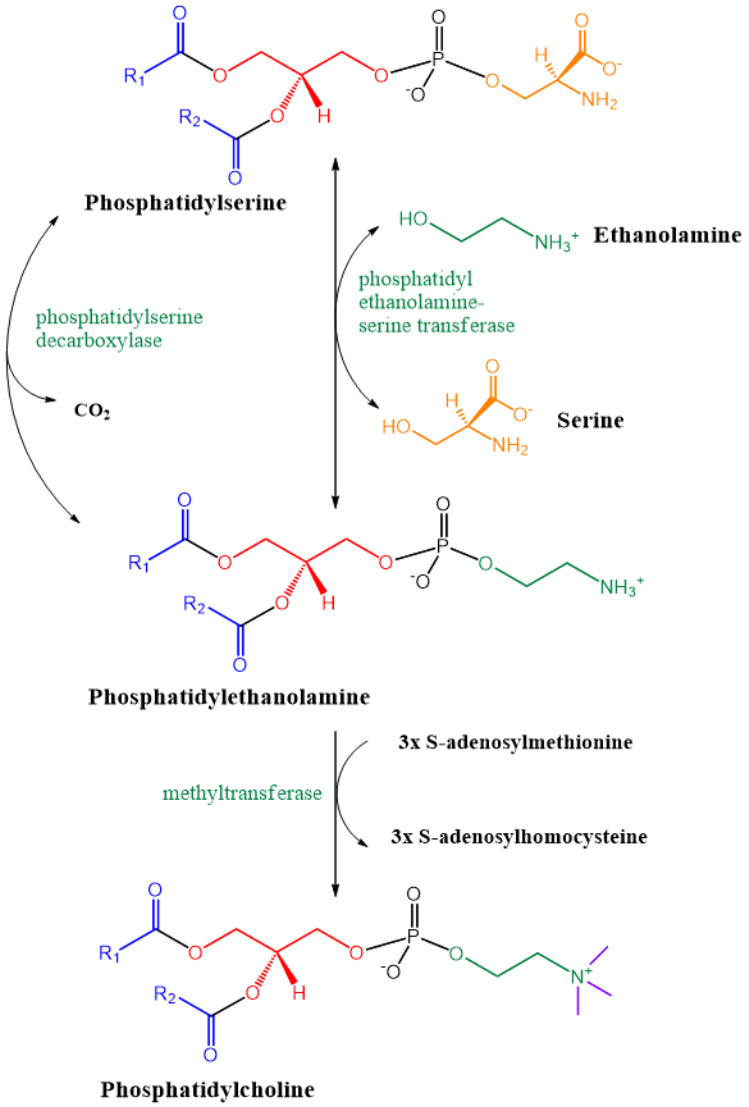


Phosphatidylserine (PS) is synthesized from PE by a head group exchange

Bacteria can make PS *de novo* because they have a PS synthase which adds serine to diacylglycerol- (Strategy 1 mechanism)

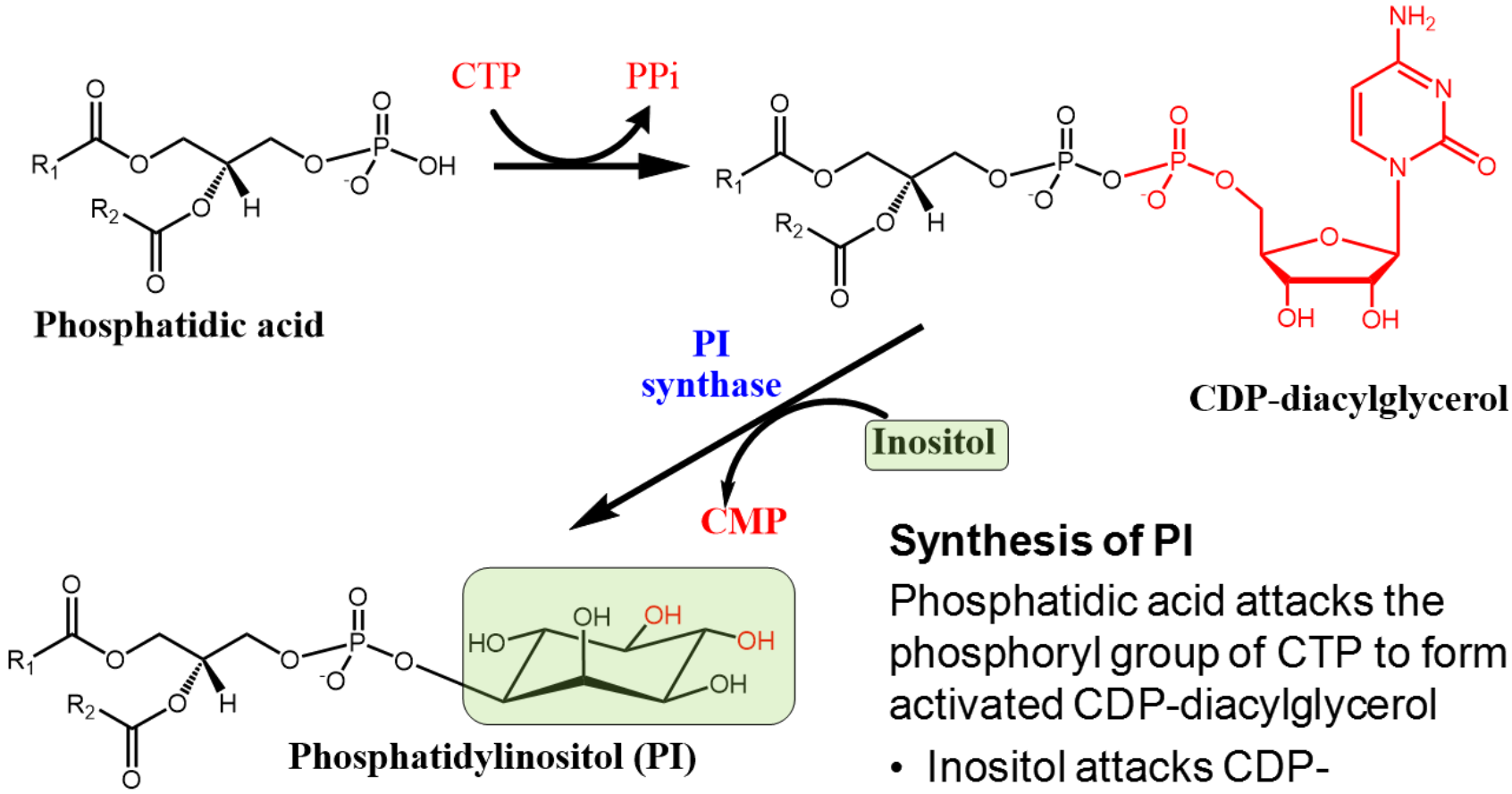
Mammals do not make PS de novo because they lack this type of PS synthase

Interconversions of PC, PE and PS



- PS decarboxylase in the mitochondria can convert PS to PE
  - Bacteria can do this too!
- A calcium-activated transferase can exchange ethanolamine for the serine of PS
  - This reaction occurs in the ER and Golgi
- In mammals, PE can undergo 3 successive methylations to yield PC
  - This reaction occurs in the ER of liver
  - S-adenosylmethionine is the methyl donor

De novo Synthesis of PI (Phosphatidylinositol)

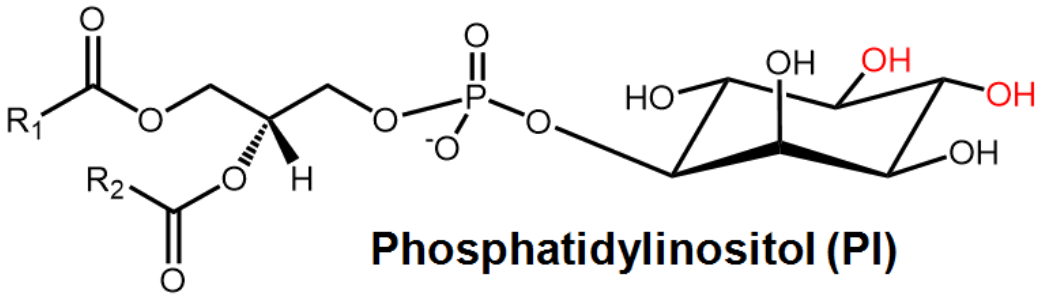


Synthesis of PI

Phosphatidic acid attacks the phosphoryl group of CTP to form activated CDP-diacylglycerol

- Inositol attacks CDP-diacylglycerol

PI Phosphorylation

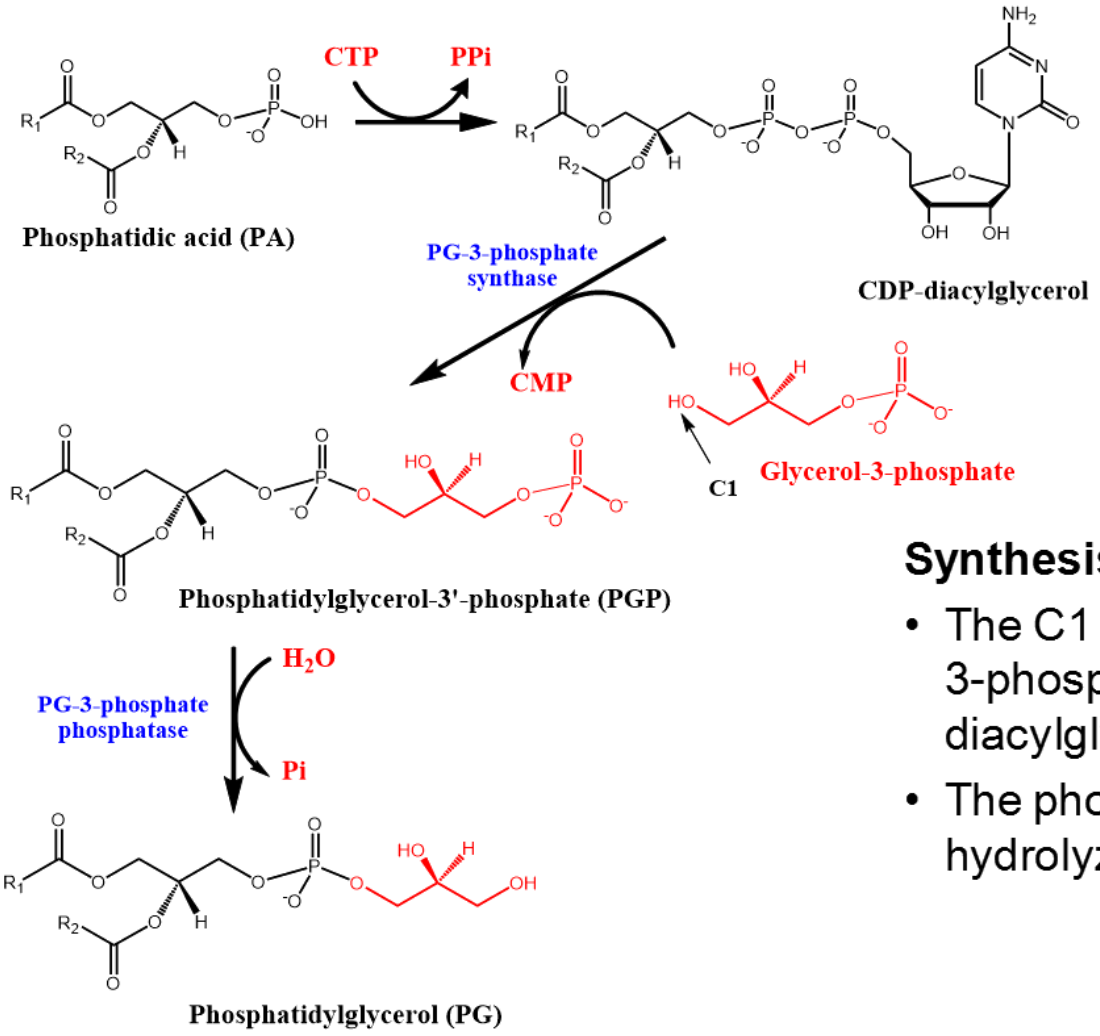


Phosphatidylinositol (PI)

These OH groups can also be esterified with PO_3^{2-}

- **PI can be phosphorylated to different degrees**
- **PIP_2 = phosphatidylinositol 4,5-bisphosphate is very important in signal transduction**
  - When a receptor G protein is activated it can mediate the cleavage of PIP_2 to DG and IP_3
  - DG activates protein kinase C which adds phosphates to certain proteins
  - IP3 mobilizes intracellular Ca and activates certain cell processes

De novo Synthesis of PG (Phosphatidylglycerol)

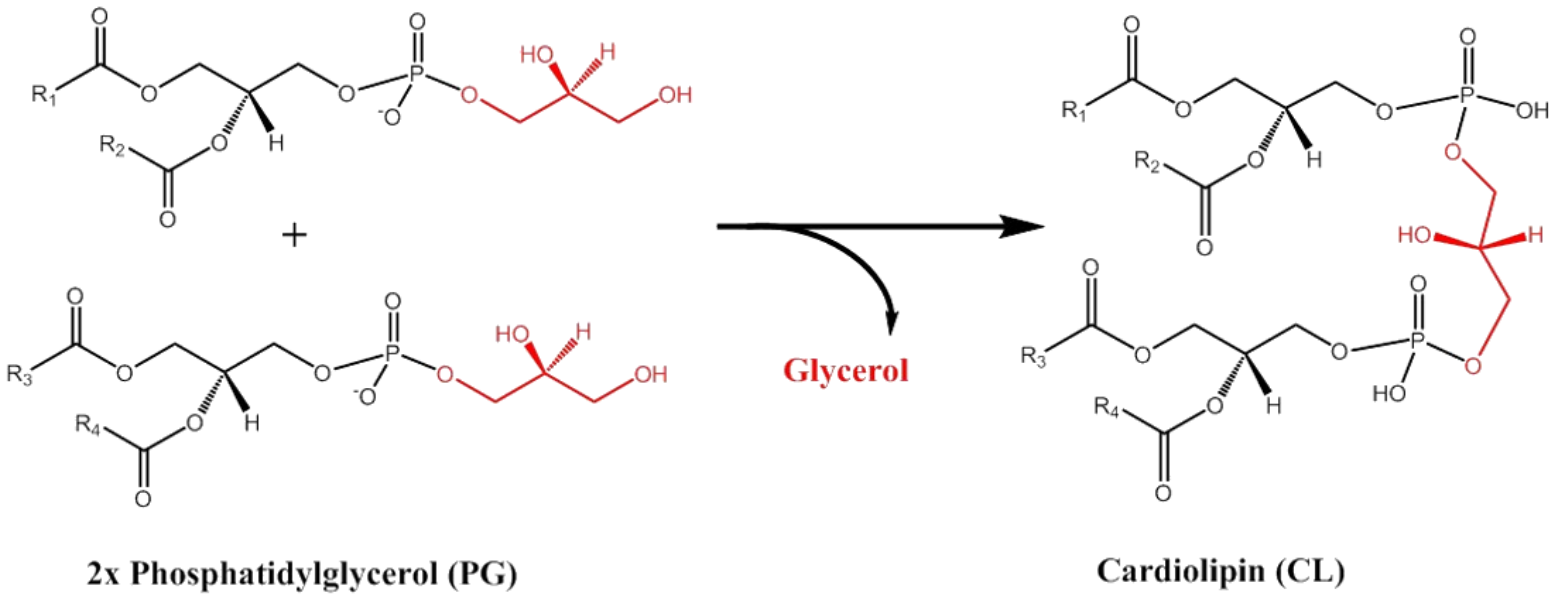


Synthesis of PG

- The C1 OH group of glycerol-3-phosphate attacks CDP-diacylglycerol
- The phosphoryl group is hydrolyzed to form PG

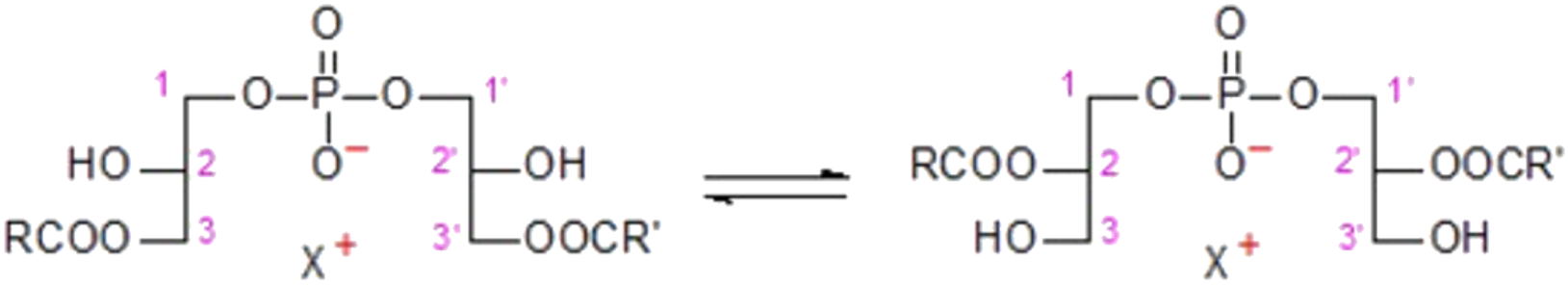
Cardiolipin

- Present in mitochondria only.
- Many autoimmune disorders, such as lupus, are associated with anti-cardiolipin antibodies



Bis(Monoacylglycero)Phosphate

- Also known as lyso bis-phosphatidic acid
- Highly enriched in lysosomes and ‘late’ endosomes
- Important for the degradation of sphingolipids

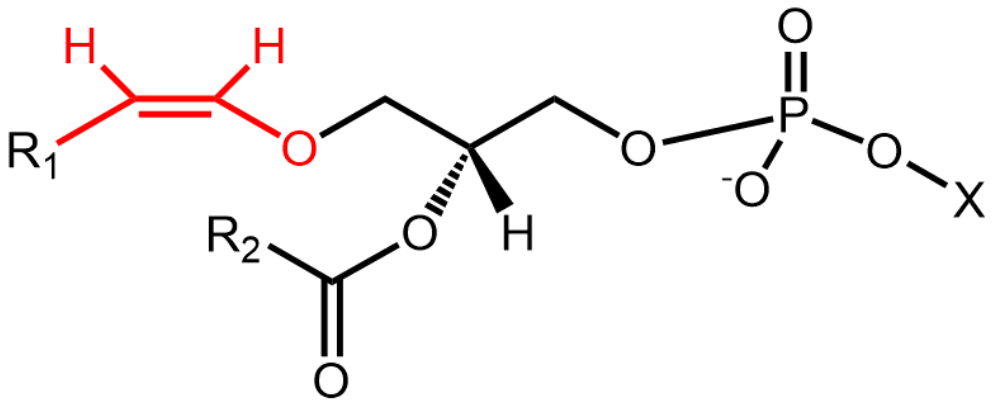


bis(monoacylglycero)phosphate

Note that both glycerol molecules are linked to the phosphate group via C1

Ether Phospholipids: The Plasmalogens

- About 20% of eukaryotic glycerophospholipids are plasmalogens. They are found in varying amounts in different tissues.
- Plasmalogens contain a hydrocarbon chain linked to glycerol C1 by a vinyl ether linkage.

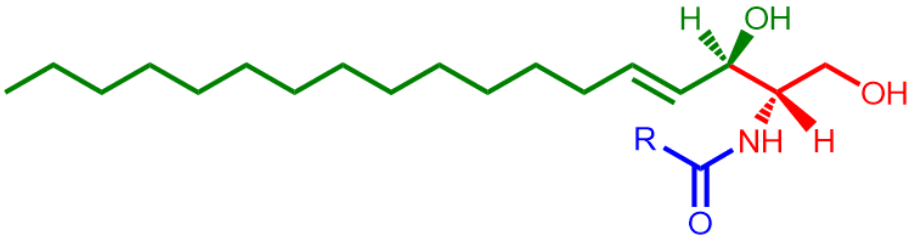


Most frequently, the polar headgroup is choline (C) or ethanolamine (E)

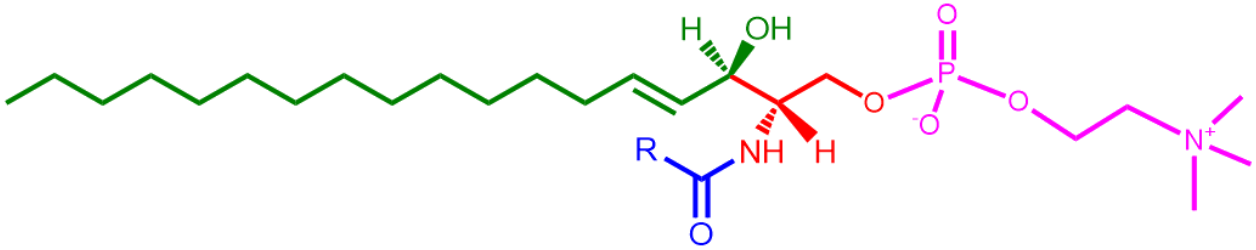
Sphingolipids

Sphingolipid Definitions

Sphingosine: a family of compounds, with the most common found in mammals being this 18-carbon amino alcohol with a trans double bond; the starting point for ceramides.

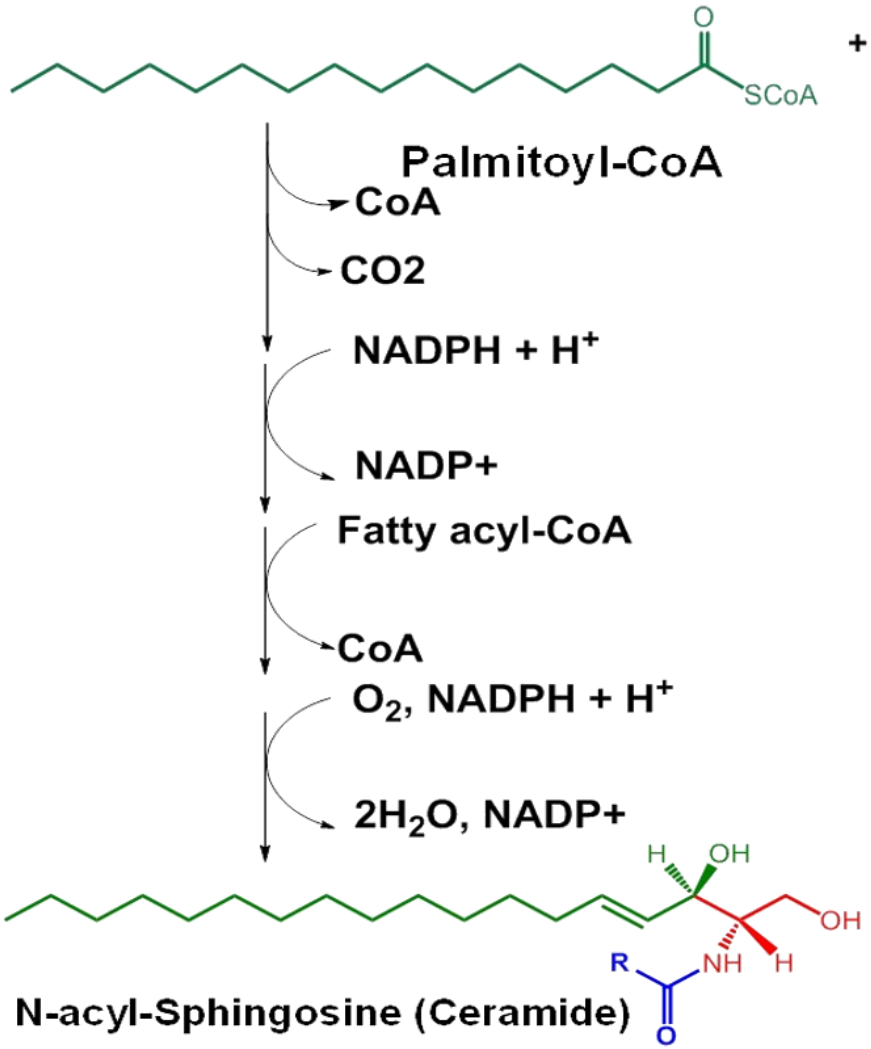


Ceramide: a sphingosine molecule connected to a fatty acid by an amide bond. Ceramides are the starting point for sphingomyelin, cerebrosides and gangliosides.



Sphingomyelin: a ceramide that has a phosphorylcholine head group in place of its hydroxyl. Present in most mammalian cells, and rich in myelin sheaths around nerves.

Biosynthesis of Sphingosine



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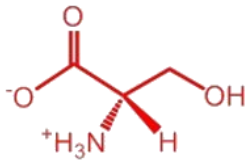
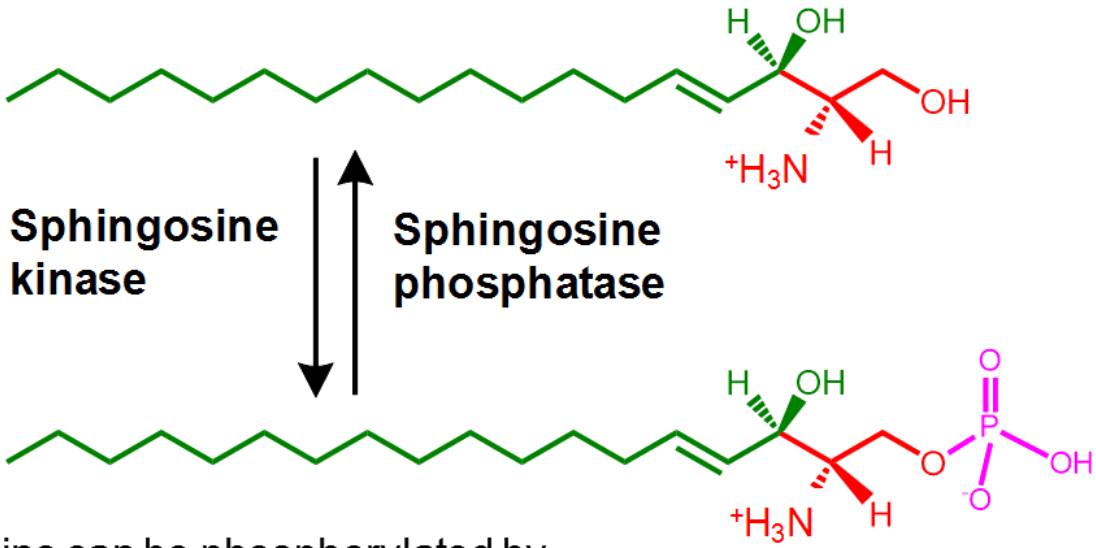


Serine

1. Serine donates 2 carbons and an amino group
2. Reduction of the carbonyl to a hydroxyl
3. Acyl group added to convert to a dihydroceramide
4. Then, oxidation to add a double bond

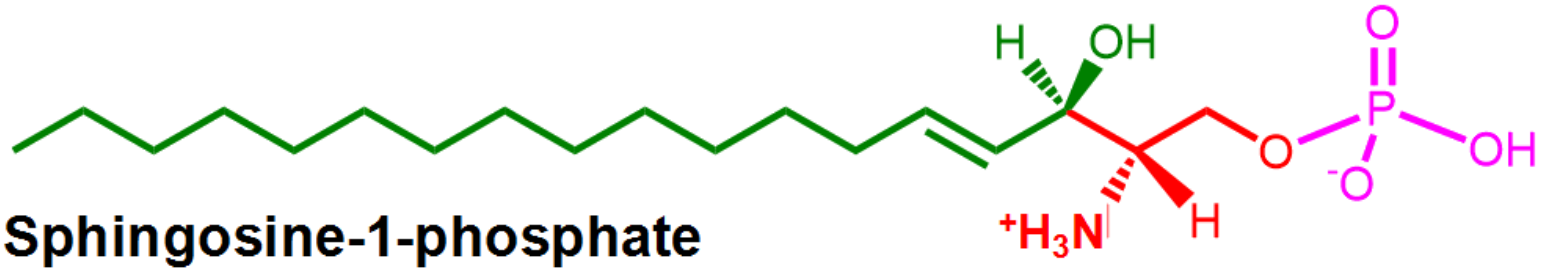
Sphingosine 1-Phosphate



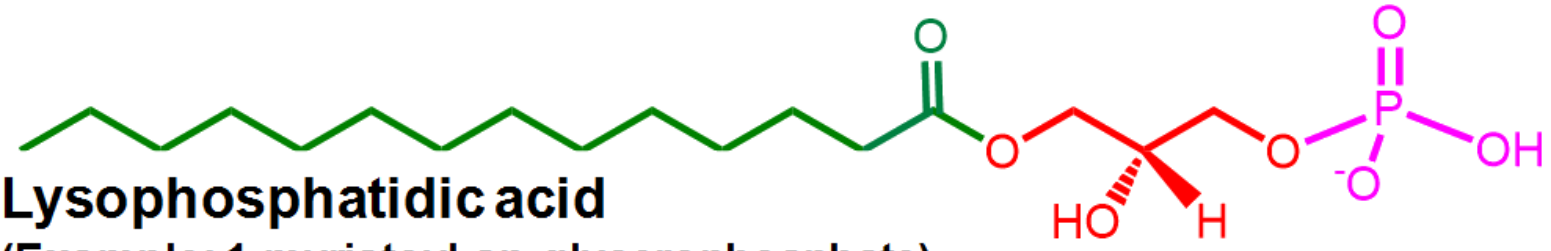
- Sphingosine can be phosphorylated by sphingosine kinases, ubiquitous enzymes in the cytosol, ER and nucleus to make **sphingosine-1-phosphate (S1P)**.
- Sphingosine-1-phosphate, a lysophospholipid, acts as a potent messenger molecule that operates both intra- and inter-cellularly.
- **Within the cell**, it promotes mitosis and inhibits apoptosis. It also regulates calcium mobilization and cell growth in response to a variety of extracellular stimuli.

- **Outside the cell**, S1P exerts many of its effects through interaction with five specific G protein-coupled receptors on cell surfaces. Different cells have different receptor profiles.
- **S1P is vital to the function of several immune cells**. It is a major regulator of T cell development, B and T cell recirculation, tissue homing patterns, and chemotactic responses to chemokines.

Comparison of S-1-P and LysoPA



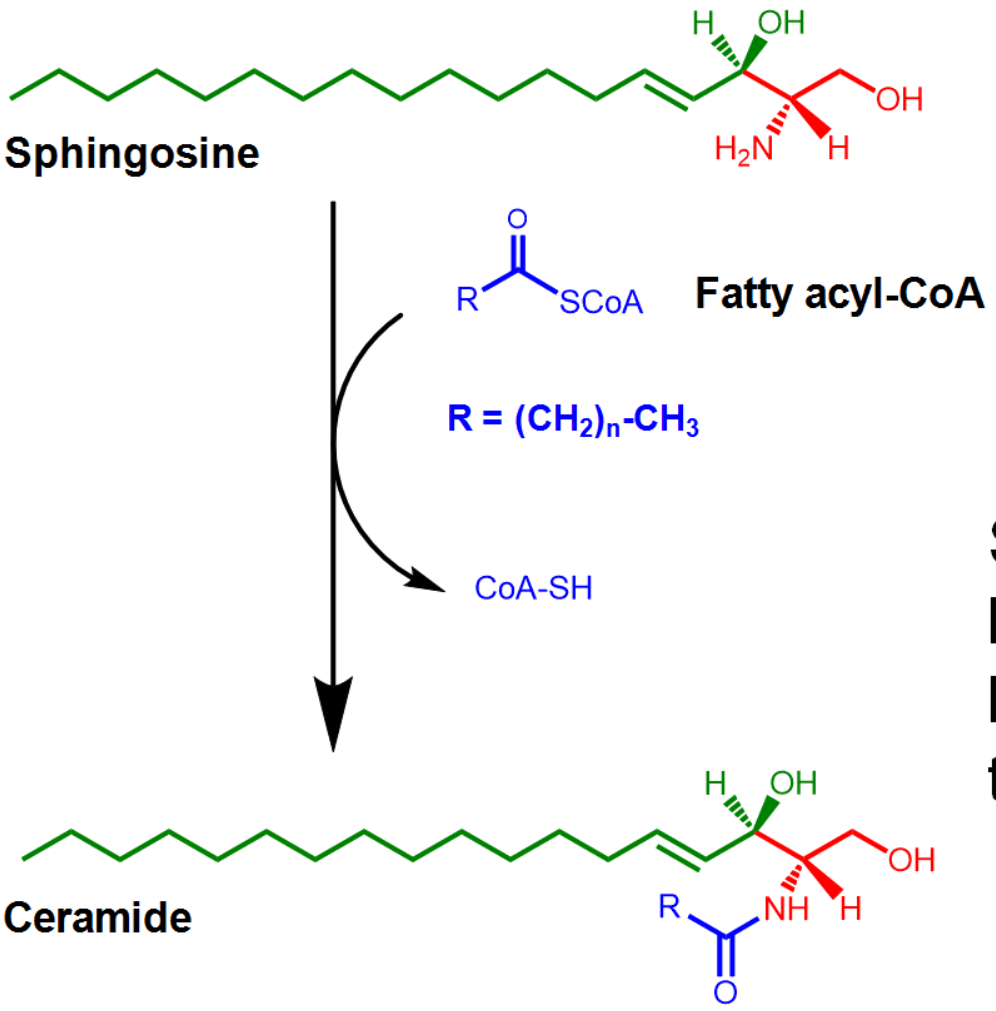
Sphingosine-1-phosphate
(neutral zwitterion; net charge 0)



Lysophosphatidic acid
(Example: 1-myristoyl-sn-glycerophosphate)

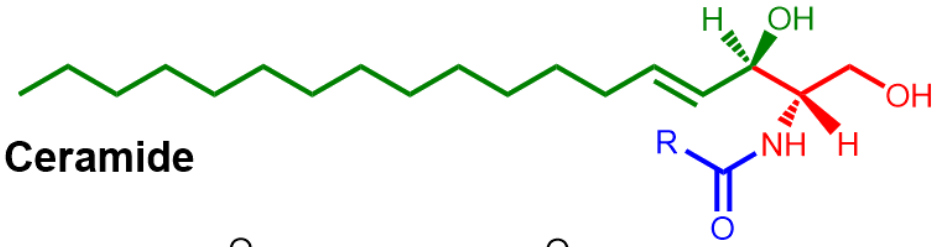
(net negative charge)

Biosynthesis of Ceramide

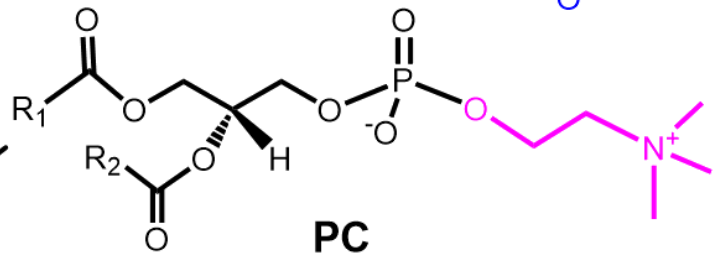


Simple acyl transfer, but to an amide bond instead of the typical ester

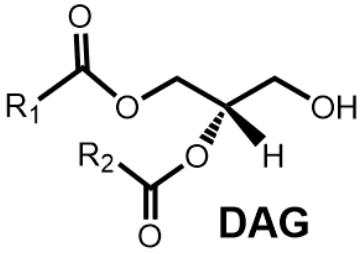
Biosynthesis of Sphingomyelin



Ceramide



PC

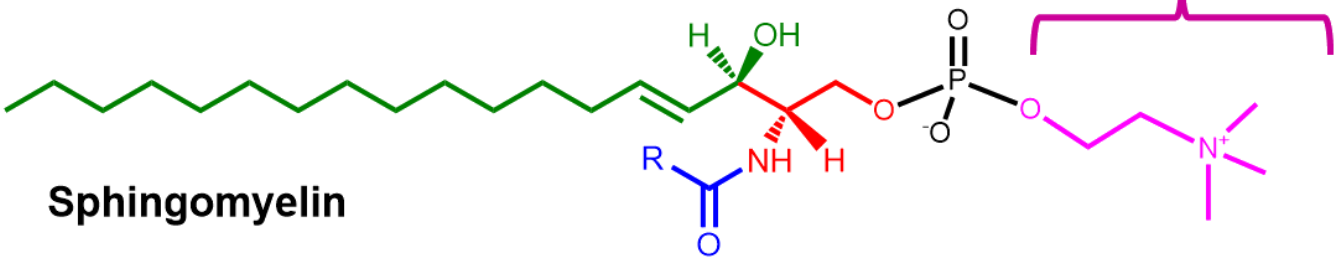


DAG

Phosphocholine head group gives sphingomyelin a hydrophilic end

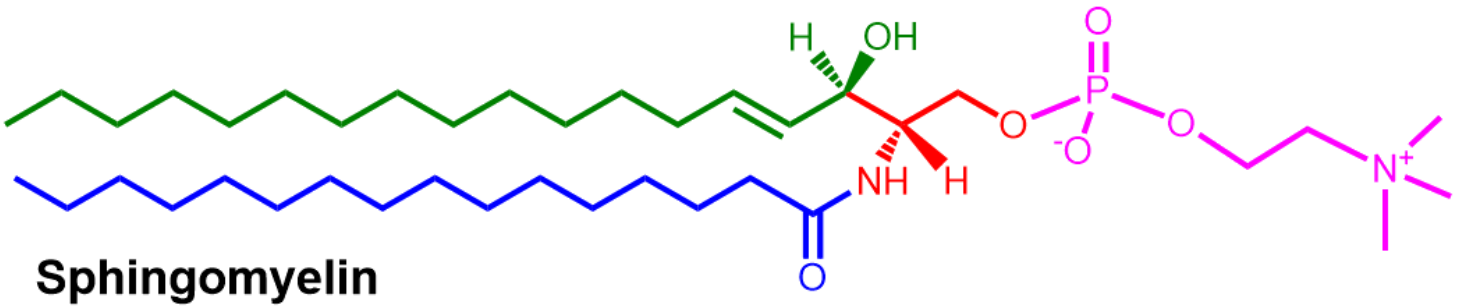
The phosphocholine headgroup is transferred to ceramide from PC

Choline

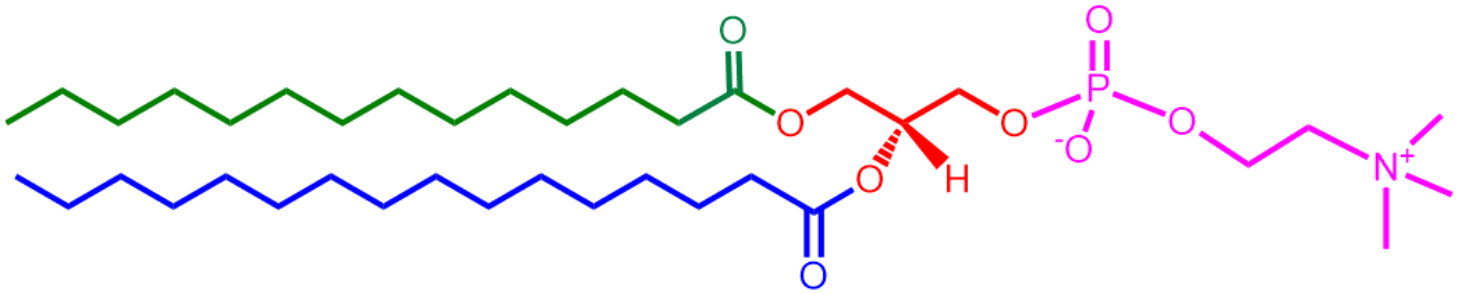


Sphingomyelin

Comparison Sphingomyelin and PC



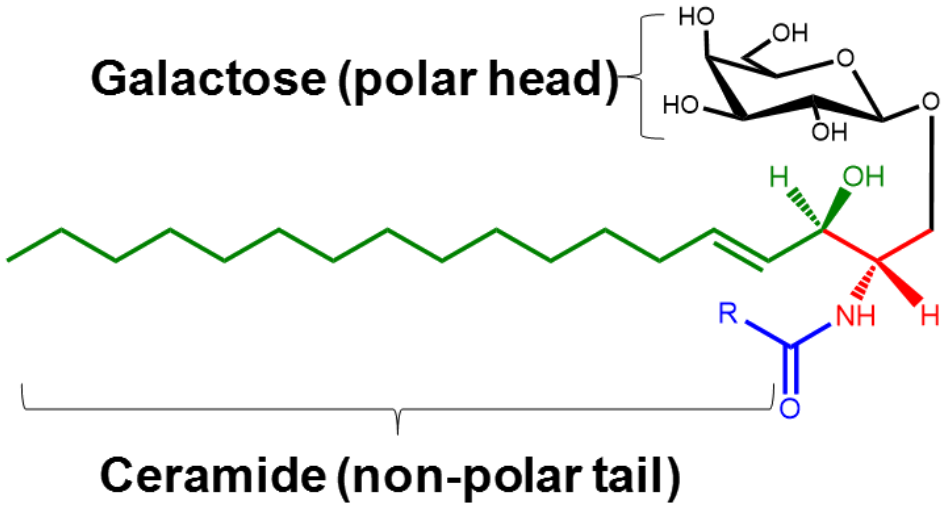
Sphingomyelin
(Example: N-palmitoyl- SM)



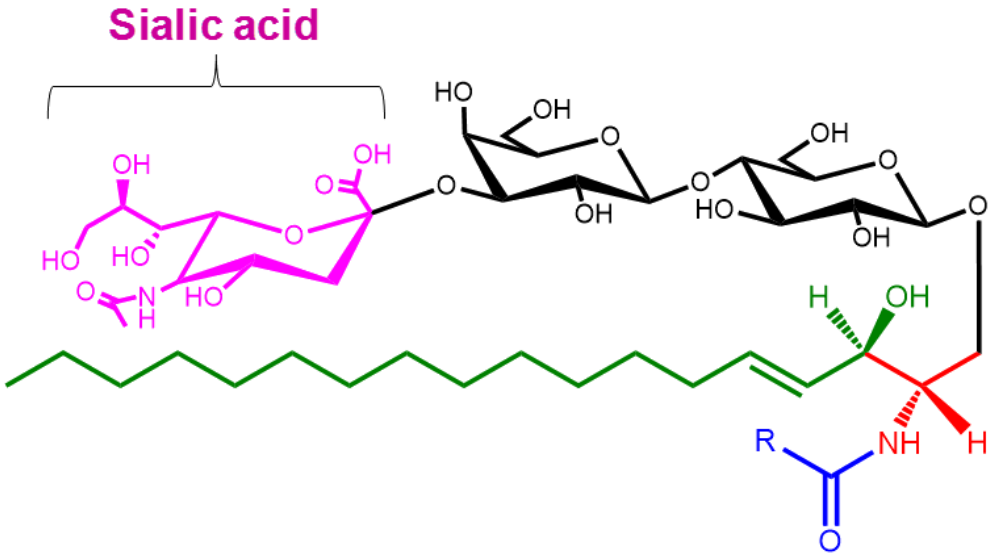
Phosphatidylcholine
(Example: 1-myristoyl-2-palmitoyl-sn-glycerophosphocholine)

At least one fatty acid of PC is usually unsaturated or polyunsaturated, whereas, SM is usually saturated or mono-unsaturated; therefore, SM rich membranes are less “fluid” than typical PC-rich membranes.

More Definitions



Cerebrosides: a ceramide that has a sugar added to the head group. Most commonly, the sugar is glucose (Glu) or galactose (Gal).

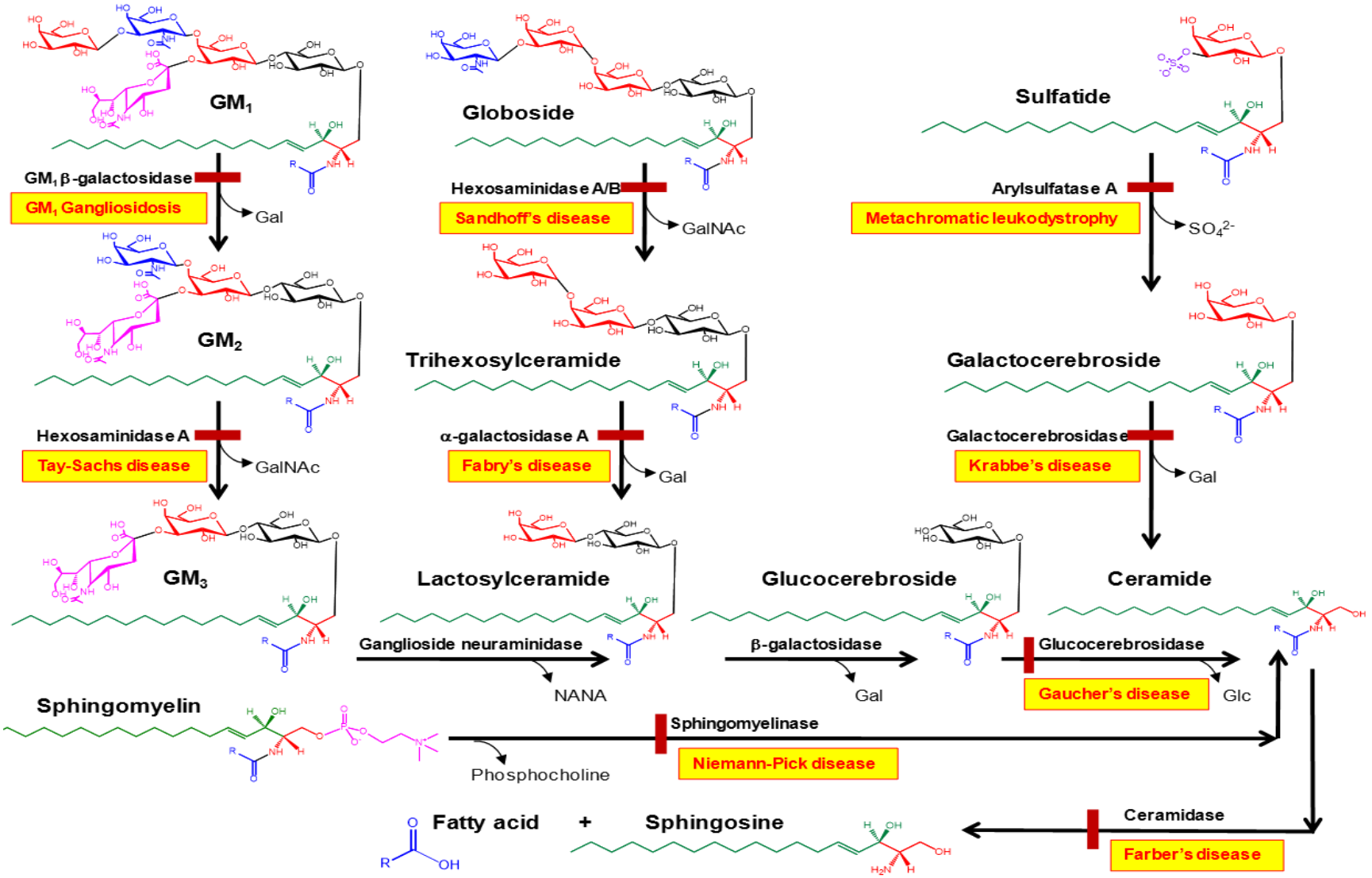


Gangliosides: a ceramide that has multiple sugars including at least 1 sialic acid residue added to the head group. Increased variety and complexity.

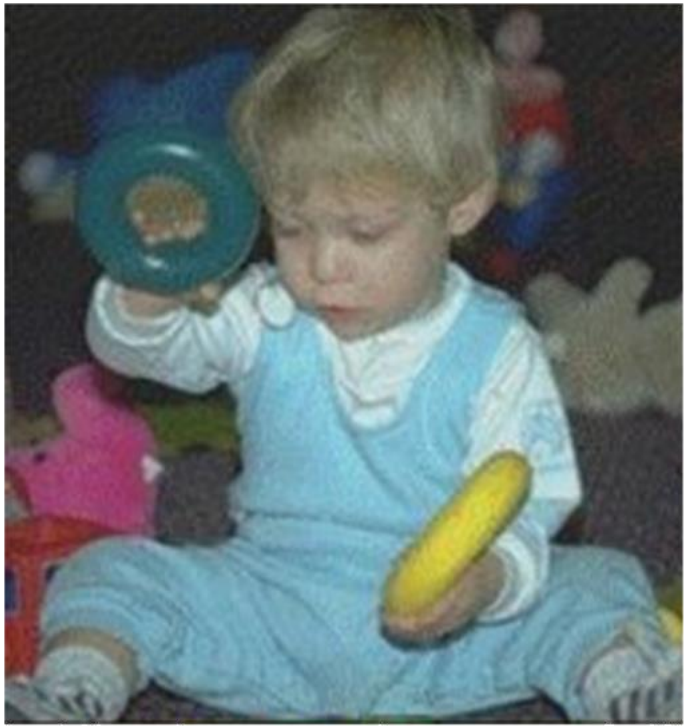
Degradation of Sphingolipids

- The amide bond of sphingolipids does not break down easily
  - which is why they make good membrane components
- Enzymatic degradation is used for turnover
  - LOTS of degradation enzymes exist
    - it's a long, complicated bunch of pathways
- Genetic defects in these enzymes cause a long list of diseases
  - all involve unhealthy accumulation of some sphingolipid
  - most are rare, but more common in specific ethnicities
  - key diseases: Gaucher's, Tay-Sachs', Fabry's and Niemann-Pick
  - Resources: (Online Mendelian Inheritance in Man)
    - OMIM Web site: www.ncbi.nih.gov/OMIM/searchomim.html

Degradation of Sphingolipids



Niemann-Pick Disease Type A



Patient with Niemann Pick Disease

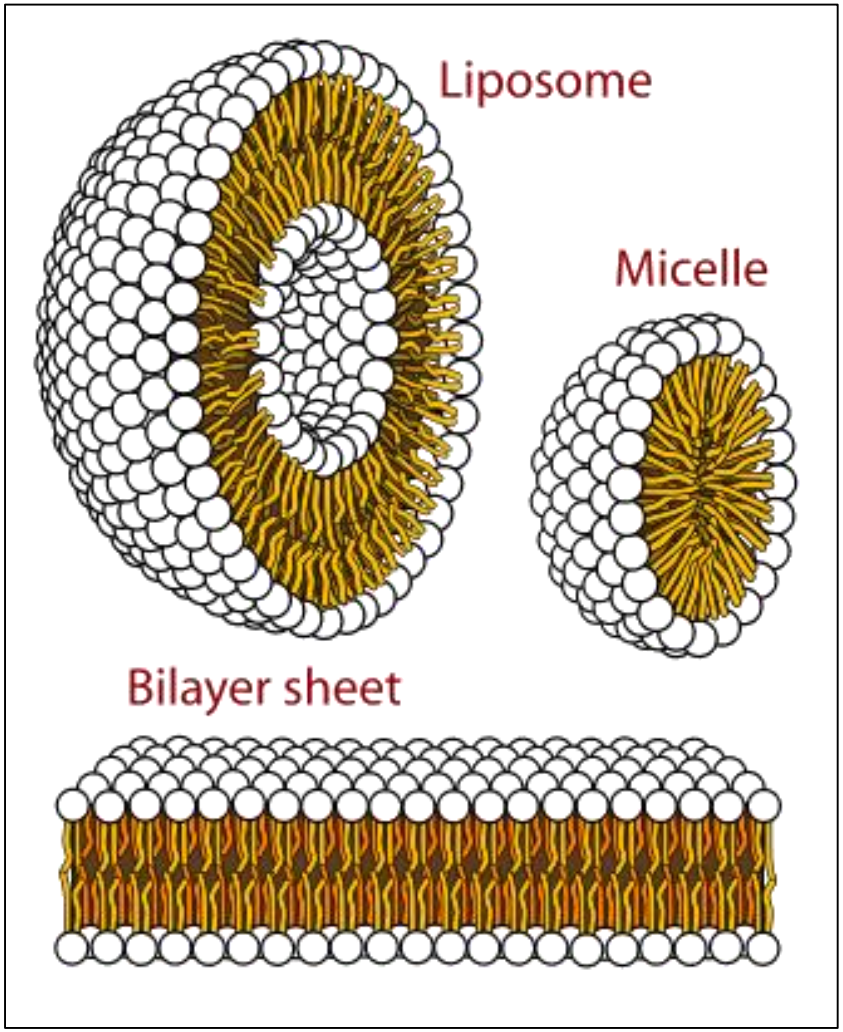
- **Incidence**: Type A is the most severe of the 5 subtypes of Niemann-Pick Disease
  - ~1:90 Ashkenazi Jews are carriers
- **Symptoms**: Neurodegenerative
  - Large abdomen within 3-6 mos. and jaundice
  - Progressive loss of early motor skills, progressive spasticity, developmental delay
  - Cherry red spot in the eye
  - (Generally) a very rapid decline leading to death by two to three years of age.
- **Mechanism**: Genetic
  - Lack of Sphingomyelinase
    - Auto recessive, OMIM #257200
  - Sphingomyelin
    - builds up in CNS, liver and lungs
- **Treatments**:
  - Supportive and symptomatic
  - Patients die by age 3
  - No effective therapy to date

What Are Glycerolipids and Phospholipids Good for?

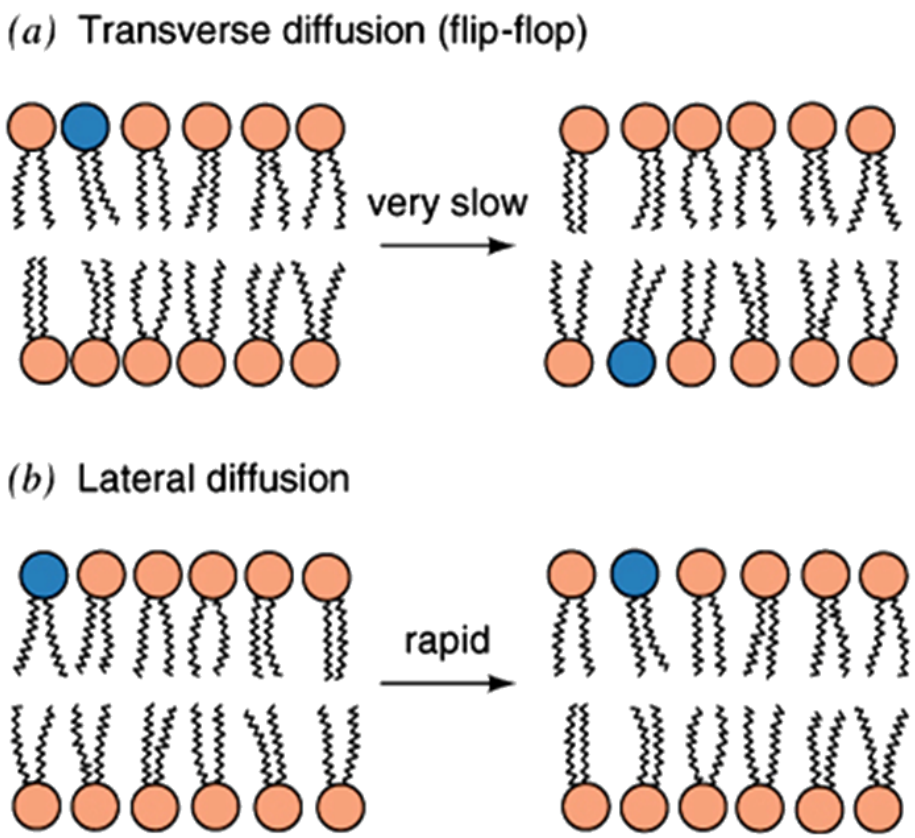
- Build Biological Membranes
- Energy Sources
- Signaling Pathways

Lipid Bilayers

- In aqueous solution, amphiphilic molecules form micelles to eliminate the contact of the hydrophobic tails with water, but allow the polar heads to be in contact with it.
- The diameter of the micelle depends upon the length of the tail.
- A suspension of PLs can form liposomes, closed, self-sealing solvent-filled vesicles, that have only a single bilayer.
- Liposomes serve as models of biological membranes.



Movement in Bilayers



Key Principle:

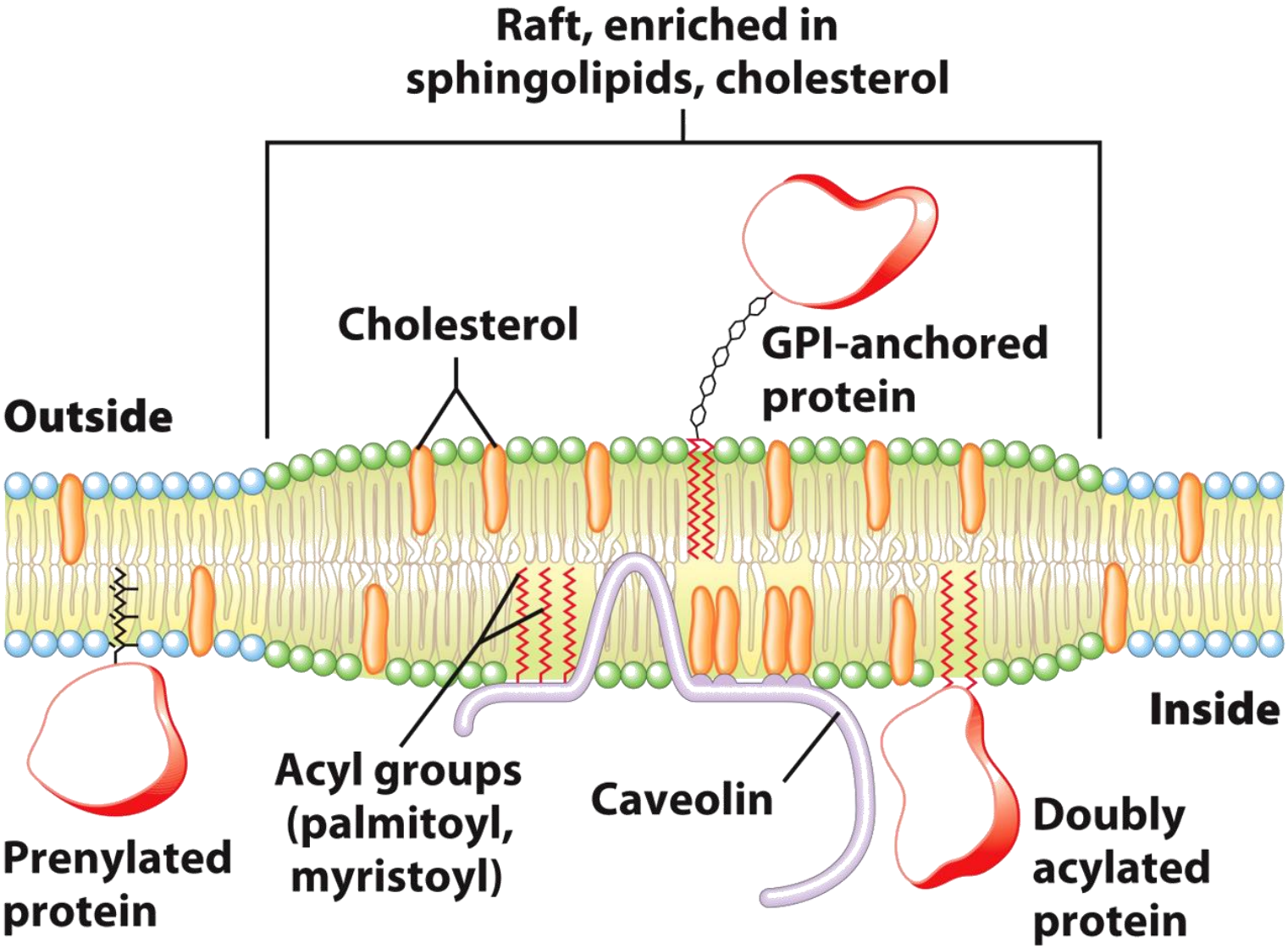
Things on one side tend to *stay* on that side…

…unless specifically moved by a carrier protein called a "flippase."

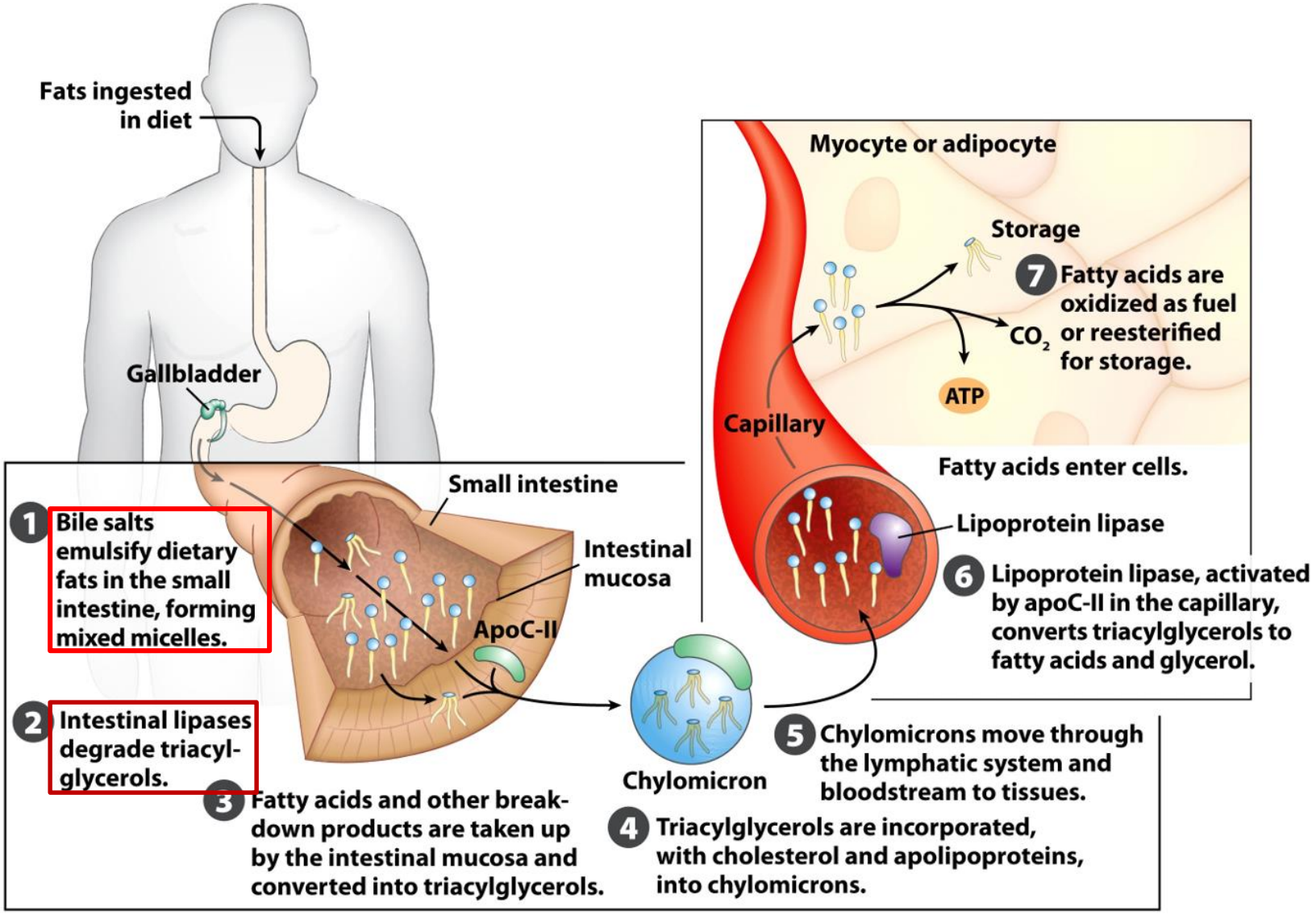
Some Implications:

- Lipid populations on each side can be different
- Receptors aim out
- Embedded/anchored enzymes localize reactions to only one side
- Ion pumps move the same ions the same direction
- Etc.

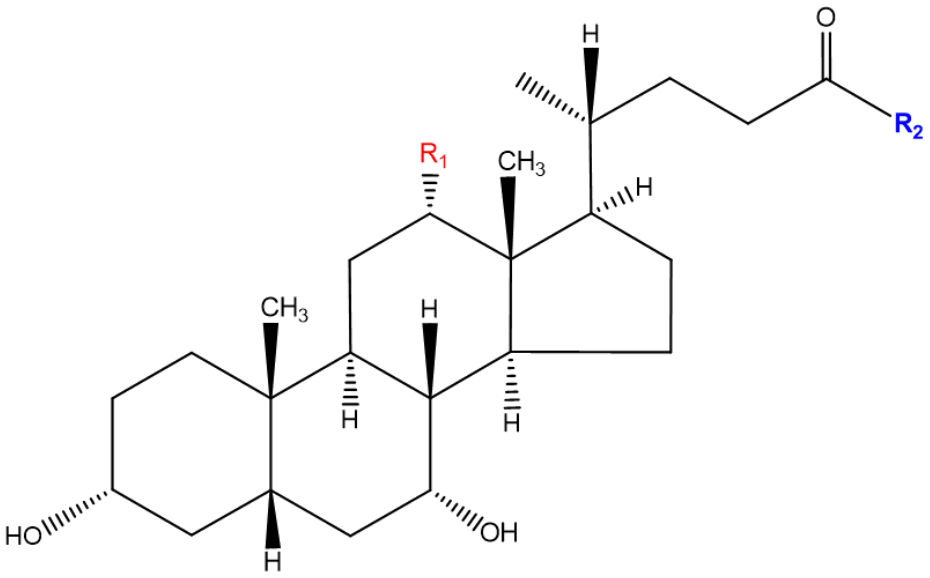
Lipid Rafts


Raft, enriched in sphingolipids, cholesterol
Cholesterol
GPI-anchored protein
Outside
Inside
Prenylated protein
Acyl groups (palmitoyl, myristoyl)
Caveolin
Doubly acylated protein

Digestion of Fats



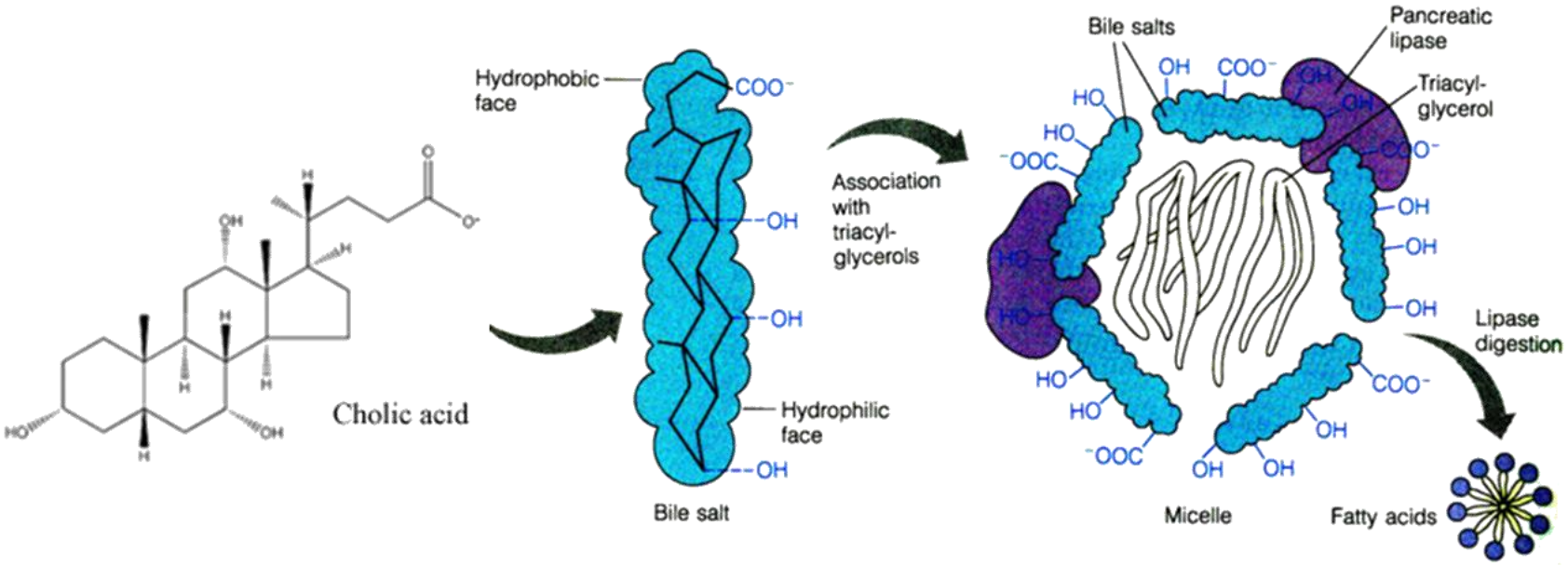
Bile Acids/Salts



	$R_1 = OH$	$R_1 = H$
$R_2 = OH$	Cholic acid	Chenodeoxycholic acid
$R_2 = NH - CH_2 - COOH$	Glycocholic acid	Glycochenodeoxycholic acid
$R_2 = NH - CH_2 - CH2 - SO_3H$	Taurocholic acid	Taurochenodeoxycholic acid

- Bile salts act as detergents in the digestive tract to emulsify triacylglycerols and phospholipids into micelles.
- Bile salts are highly oxidized derivatives of cholesterol.

Mixed Micelles

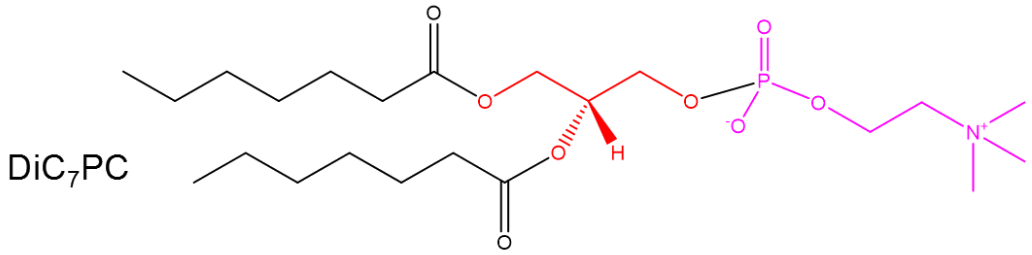


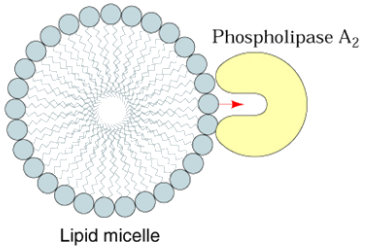
- The hydrophobic surface of the bile salt associates with TAGs, and a number of these aggregate to form a micelle

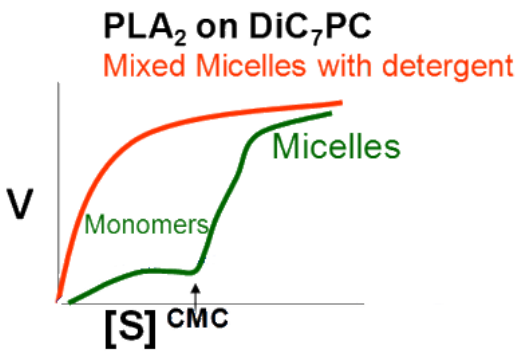
- This allows the association of pancreatic lipase, which liberates free fatty acids in smaller micelles that are absorbed through the mucose

Lipases and Phospholipases

- Lipases and phospholipases are unique enzymes because their substrates are lipids, not small molecules.
- Lipases and phospholipases work best on surfaces: Surface Activation







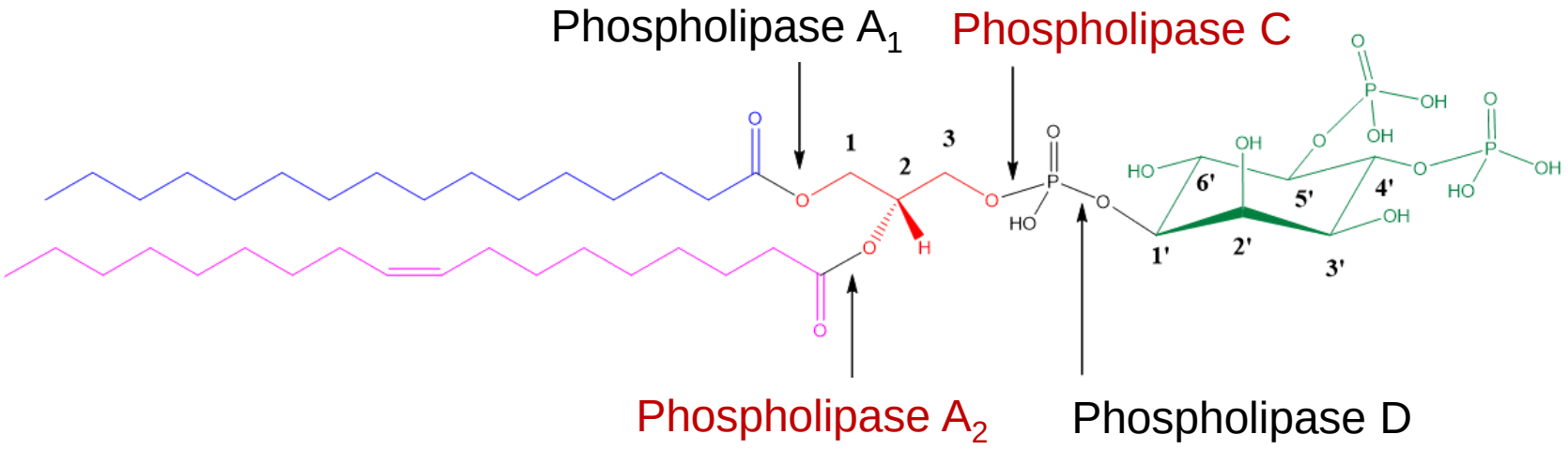
- At low concentrations, DiC7PC forms monomers.
- At higher concentrations, it forms micelles.
- The concentration at which micelles form is called critical micellar concentration (CMC).

Definitions

- **Lipases and phospholipases are esterases**
  - **Triacylglycerol Lipase** – the general term.
  - **Lingual Lipase**- found in saliva for pre-digestion.
  - **Pancreatic Lipase**- produced by the pancreas for digestion.
  - **Lipoprotein lipase**- found on capillary endothelial cells. It hydrolyzes TAG in chylomicrons and VLDLs.
  - **Desnutrin (ATGL) – Coupled to HSL** – generates FAs when energy is needed. Found in adipose tissue
  - **The Phospholipases**

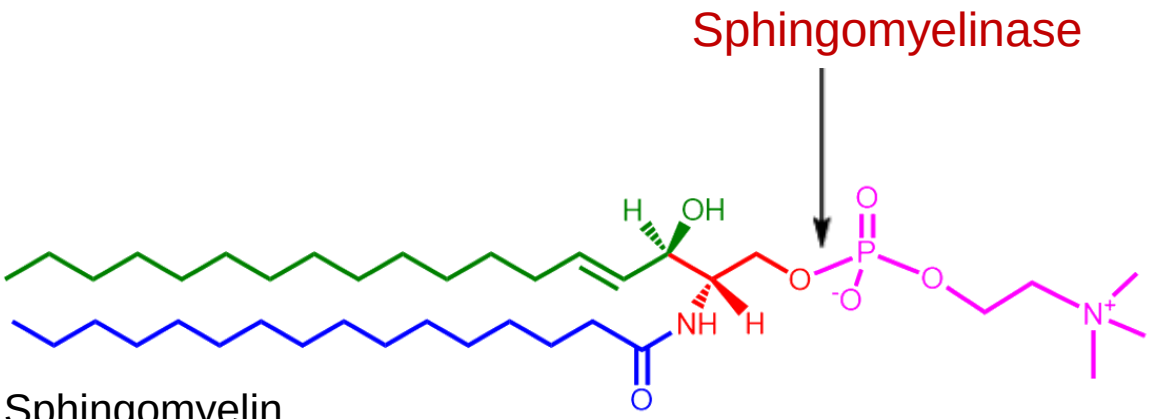
Lipid Signaling

Phospholipase Sites of Action

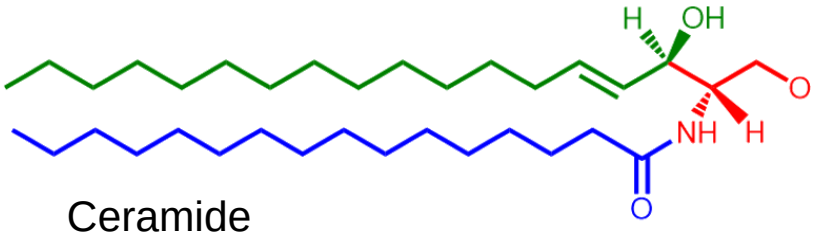


1-Palmitoyl-2-oleoyl-sn-glycerol-3-phosphoinositol 4',5' bisphosphate (PIP_2)

Phospholipase Sites of Action



Sphingomyelin



Ceramide

Sphingomyelinase is a sphingomyelin-specific phospholipase C

Phospholipids Are Key to Signaling