DOCTOR 2020 | JU

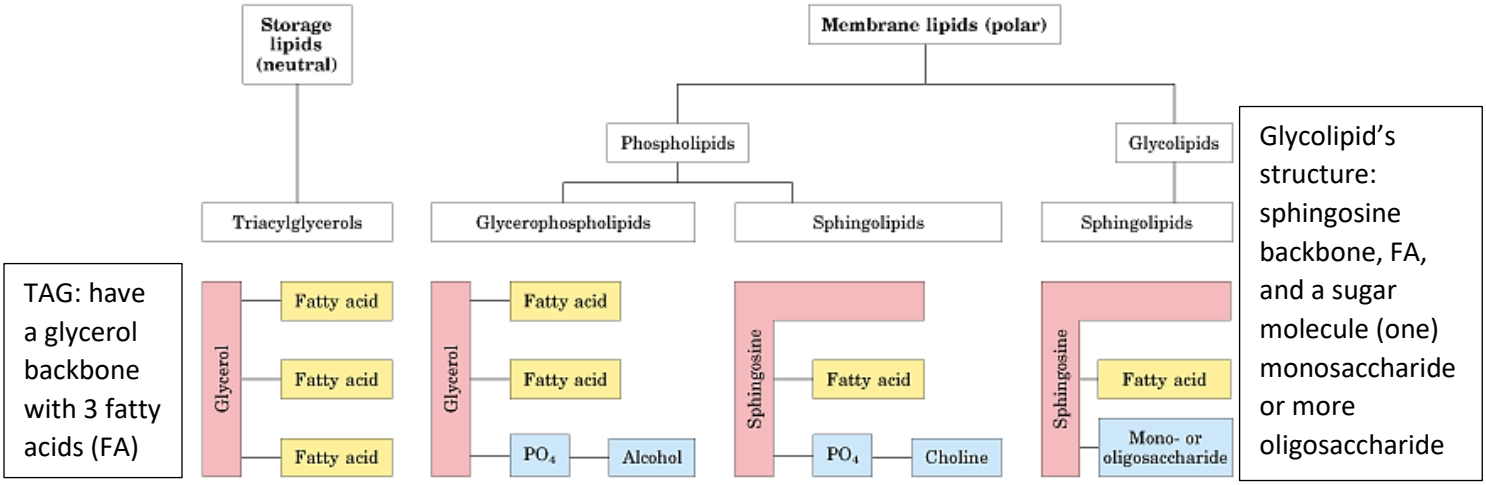
METABOLISM

WRITER : Hala Zaghloul

CORRECTOR : Ahmad Qatawneh

DOCTOR: Dr. Mamoun Ahram

Recall from previous lectures that lipids can be membrane associated like:
1) **Phospholipids** and 2) **Glycolipids**
OR stored as TAG droplets in adipose tissue



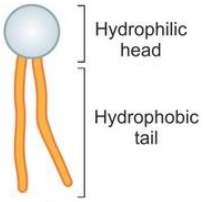
TAG: have a glycerol backbone with 3 fatty acids (FA)

Glycolipid's structure: sphingosine backbone, FA, and a sugar molecule (one) monosaccharide or more oligosaccharide

Phospholipids compose the majority of membrane lipids, classified into:
A) glycerophospholipids: **main phospholipids
Structure: a glycerol backbone, FA on carbon no.1 & no.2, phosphate group on carbon no.3 + head group (usually an alcohol) attached to the phosphate.

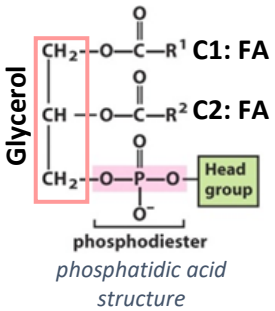
B) sphingolipids have a sphingosine backbone, FA on **C2**, PO_4 on C1 + Choline
this structural molecule is known as sphingomyelin the only existing phosphosphingolipid.

Side note: (not mentioned in the lecture)



Remember that phospholipids are amphipathic, and u can conclude that from their structure:
hydrophobic tail→ fatty acids hydrophilic head→ phosphate + alcohol

Glycerophospholipids metabolism & degradation is the main topic of this lecture



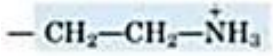
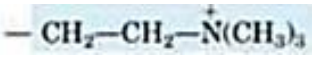
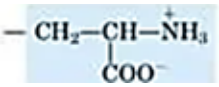
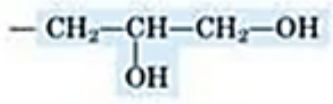
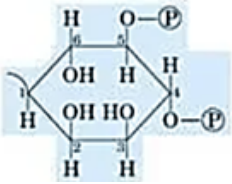
phosphatidic acid structure

Classification of Glycerophospholipids:

- **Phosphatidic acids**: the basic glycerophospholipid, the precursor to all glycerophospholipids.
  the Head group attached to the phosphate in phosphatidic acid is **-H**

-different **head groups** can attach to the phosphate group in phosphatidic acid as the following composing different type of glycerophospholipids:

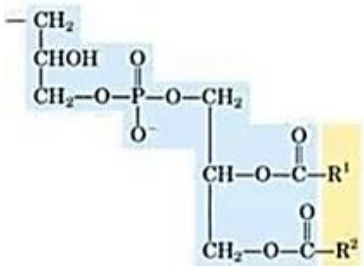
phosphatidic acid PA(base) + head group → different glycerophospholipids

Glycerophospholipids	**Head** group (alcohol)
Phosphatidylethanolamine (PE)	Ethanolamine 2 carbons (ethanol) + amino group 
Phosphatidylcholine PC (lecithin)	Choline 2 carbons + quaternary amine 
Phosphatidylserine (PS)	Serine 2 carbons + amino group + carboxyl group 
Phosphatidylglycerol (PG)	Glycerol 
Phosphatidylinositol (PI) Specifically, phosphatidyl inositol 4,5-bisphosphate	Myo-Inositol 4,5-bisphosphate Inositol + 2 phosphates a sugar molecule + 2P 

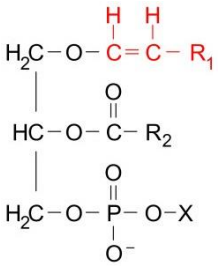
Other Glycerophospholipids:

- **Cardiolipin (Complex structure)**

Head: Phosphatidyl glycerol



- **Plasmalogens (ether phospholipids)**



Synthesis

- Location: smooth ER
  (except for ether lipids—discussed in page 9)
- synthesis of phospholipids requires activation by attaching CDP

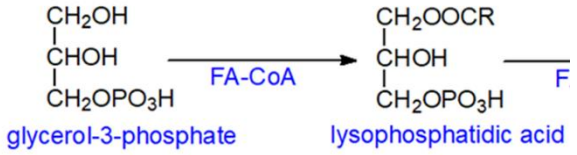
→Activation is attachment of a group that gives a molecule high energy, for example glucose-6P is an activated molecule because it has a phosphate group attached to it, same concept applies to UDP-glucose that's involved in glycogen metabolism.

- High energy molecules have specificity in their activation in biosynthetic reactions:

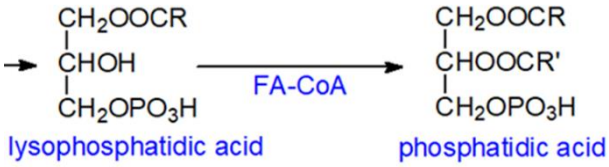
carbs→ activated by attachment to UDP-
Proteins→ activated by attachment to GDP-
lipids→activated by attachment to CDP-

Phosphatidic Acid Synthesis

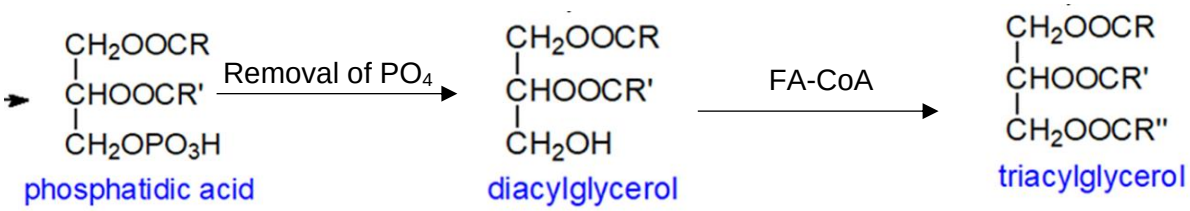
1) Formation of Lysophosphatidic acid by the attachment of the first fatty acid to carbon no.1 on G3P molecule (G3P is an activated molecule since phosphate Is attached to it)



2) Attachment of the 2nd fatty acid on carbon no.2 forming phosphatidic acid



TAG can be synthesized from PA by removing the phosphate group and attaching a third fatty acid

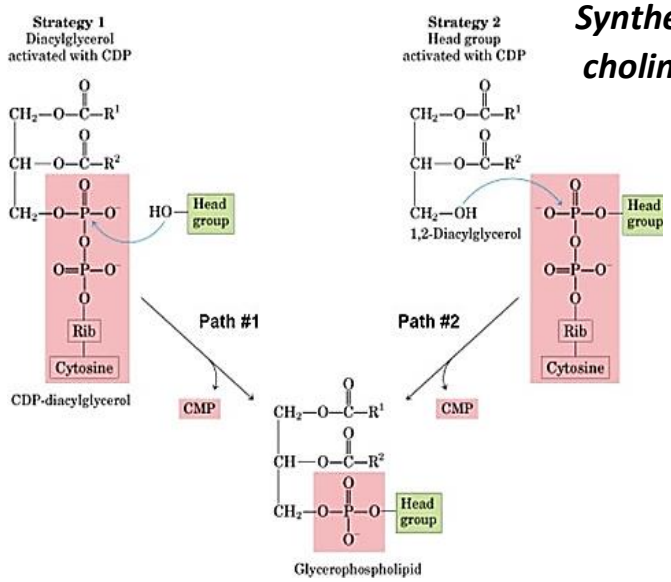


- since phosphatidic acid is the precursor for all other glycerophospholipids, it continues the reaction forming other glycerophospholipids

- the activated molecule used in lipids synthesis differs according to the type of lipid that's being synthesized as demonstrated in this figure:

Synthesis of phosphatidyl glycerol, serine, and inositol

the activated group in is the backbone (CDP-DAG)

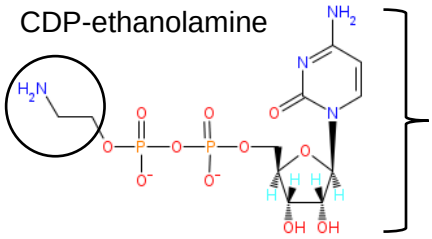


Synthesis of phosphatidyl choline & ethanolamine.

The head group (CDP-alcohol) is the activated group

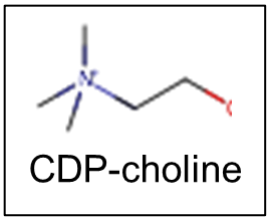
- A closer look at the structure of CDP ethanol amine

Head:
ethanol +
amine-group
2C + NH_3



the structure of CDP-choline is the similar

CDP + Choline
Head: 2C + NH_3 attached to $3CH_3$ (methyl)



synthesis of phosphatidyl choline and phosphatidyl ethanolamine

Sources of choline and ethanolamine:

A) Diet: phosphatidyl choline and ethanolamine exist in all plasma membranes, therefore they are essential molecules that we mainly obtain from diet because the body's demand is higher than the supply.

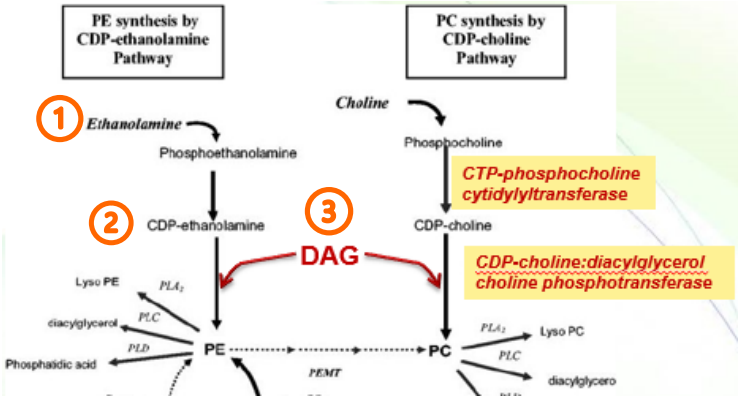
B) synthesis –primarily in the liver

C) recycled by turnover of preexisting glycerophospholipids

Steps of synthesis

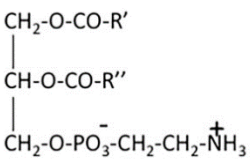
1) Ethanolamine and Choline are activated by phosphorylation through kinase activity forming phosphoethanolamine and phosphocholine.

2) The phosphate group is removed and replaced by CDP by the enzyme transferase forming the **activated** molecules CDP-ethanolamine & CDP-choline.



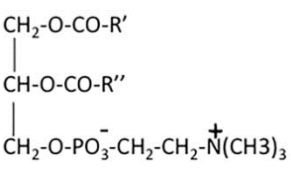
3) the activated molecule is added to DAG (diacylglycerol backbone) by phosphotransferase activity in which the CDP-group is removed from the activated molecule –released as CMP and phosphatidyl ethanolamine & phosphatidyl choline are obtained.

Structure of phosphatidylethanolamine



Phosphatidylethanolamine

Structure of phosphatidylcholine (Ph-choline)



Phosphatidylcholine

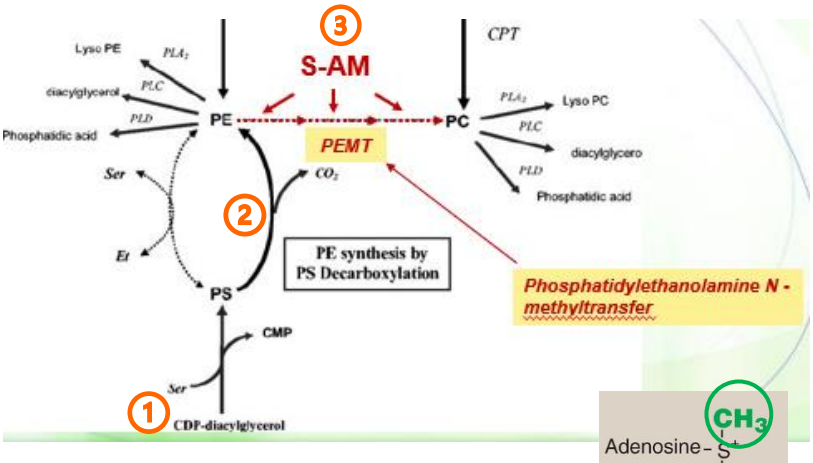
Synthesis of Ph-choline from Ph-serine

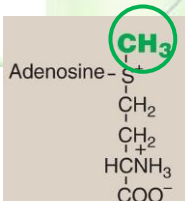
- the liver uses this mechanism to produce PC because it uses it for production of bile and other plasma lipoproteins
- another pathway for synthesizing phosphatidylcholine and phosphatidyl ethanolamine is decarboxylation of phosphatidyl serine. Unlike the previous pathway this one starts with an **activated backbone** CDP-diacylglycerol and proceeds as the following:

1) serine is attached is attached to CDP-diacylglycerol & CMP is released forming phosphatidyl serine.

2)PS gets decarboxylated, CO_2 is released from its head group forming ph-ethanolamine

- the enzyme catalyzing this step (PS decarboxylase) requires vitamin B1 (thiamine)—decarboxylation

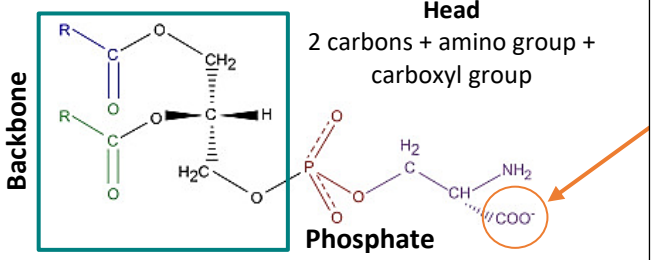




structure of S-Adenosyl methionine

3) three sequential methylation reactions take place in order to attach 3 methyl groups one at a time to the amino group on PE to formulate Ph-choline. the doner of the methyl groups is **S-Adenosyl methionine.** The reaction is catalyzed by **Phosphatidyl ethanolamine methyl transferase**

Structure of Phosphatidyl serine

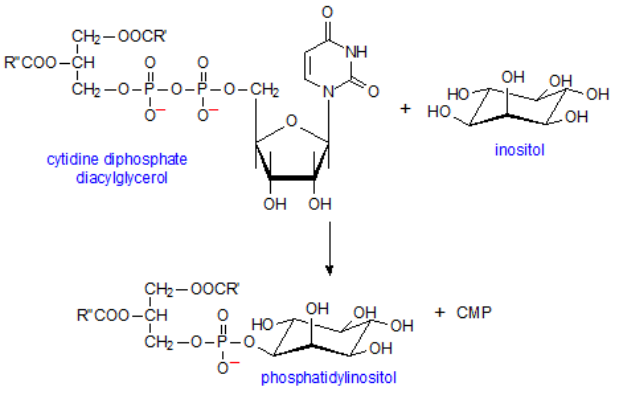


- **Altering the head structure of PS forms PE & PC** because they all share the same basic structure which is Phosphatidic acid PA.
- decarboxylation of serine includes the removal of this carboxyl group from the serine head. forming ph-ethanol amine (2 carbons + amino group) addition of 3 methyl groups the amino group would form phosphatidyl choline (2 carbons + quaternary amine $N(CH_3)_3$

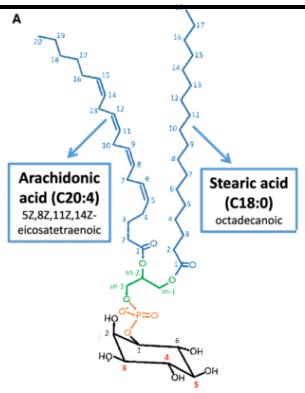
*go back to page 3 for structure references

Synthesis of Ph-Inositol

- inositol is added to the activated group CDP-DAG (activated backbone).
  Inositol + CDP-DAG → Phosphatidyl inositol + CMP

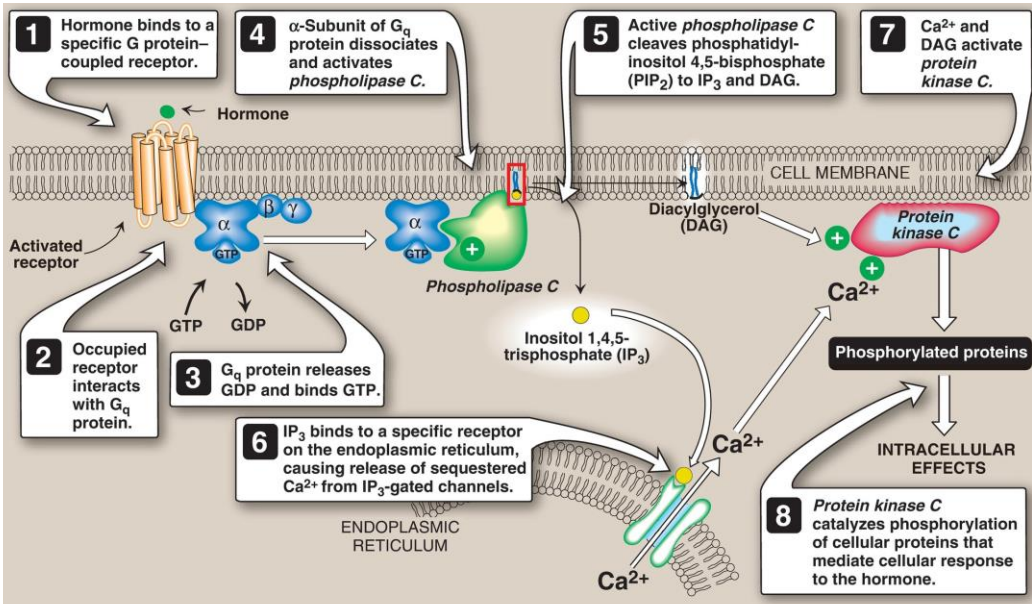


- stearic acid—an 18-carbon saturated fatty acid is attached to Carbon no.1 of Ph-inositol
- Arachidonic acid— is attached to Carbon no.2 of Ph-inositol; a 20-carbon polyunsaturated fatty acid with 4 double bonds & the precursor to the inflammatory molecules (Eicosanoids).
  which makes Ph-inositol a reservoir (storage) for the signaling molecule arachidonate

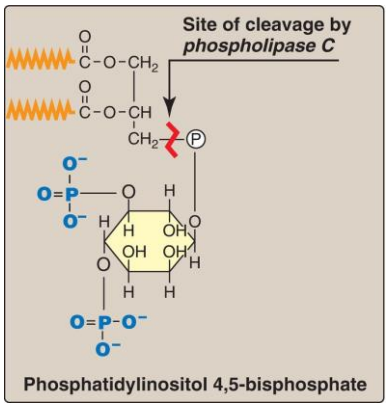


- the phosphorylated form of phosphatidyl inositol **PIP2** is a precursor of signaling molecules that are obtained by Phospholipase C cleavage.

Signaling by PIP2 products



PIP2

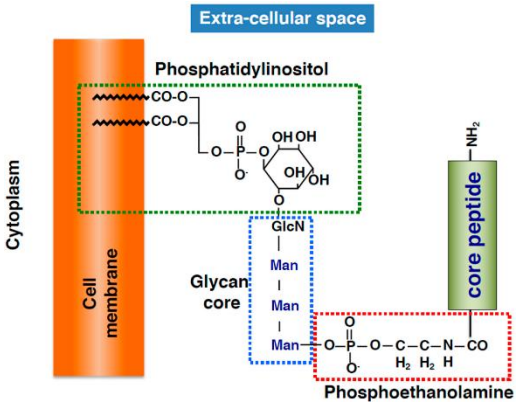


1) A hormone like epinephrine or glucagon binds to its GPCRs.
2) binding activates the receptor; the receptor consequently activates the associated G-protein—specifically **Gq** that is responsible for activating phospholipase C.
3) activated Gq releases the α_q subunit that interacts with phospholipase C activating it.
4) activated phospholipase C acts on membrane phosphatidyl inositol releasing two signaling molecules **IP3:** inositol 1,4,5-triphosphate & **DAG**: diacylglycerol.

- these two molecules have a common pathway even though they participate in signaling in different ways.

→**DAG** interacts with protein kinase C to activate it.
→**IP3** binds to Ca^{+2} channels on ER causing them to open and release calcium ions to the cytosol, Ca^{+2} ions bind to protein kinase C participating in its activation too.
→ **activated Protein kinase C** phosphorylates many and different proteins to emit a response.

- Phosphatidyl inositol combines with different sugars (e.g. glycosyl phosphatidylinositol GPI) to anchor different proteins to the plasma membrane either intra or extracellularly.
- the two fatty acids of PI attach to the membrane (hydrophobic anchor), while the sugar molecules (**glycan core**) bind to the inositol head to aid in protein anchoring

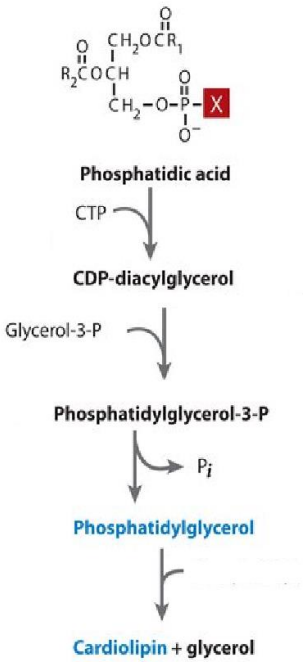


- Advantage of attaching proteins this way:
  lateral mobility of the attached proteins in the plasma membrane, free movement in 2 dimensions.
- lipid rafts are specialized regions within the plasma membrane the contain many signaling molecules that can gather and accumulate together in these rafts by being anchored to phosphatidyl inositol.

Example: **lipoproteins lipase** is anchored by GPI **extracellularly** into the plasma membrane of endothelial cells allowing them to do their function of extracting fatty acids from triacylglycerols and phospholipids that exist inside the chylomicrons as they move in the blood the released fatty acids enter peripheral tissues (muscles, adipocytes, etc..) using them for energy purposes or they can be utilized for storage.

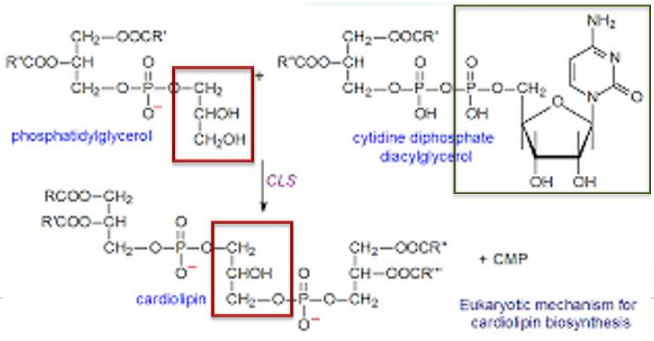
Phosphatidylglycerol and cardiolipin

- phosphatidylglycerol has the basic structure of phosphatidic acid (2 Fatty acids attached to a glycerol backbone) + phosphate group PO_4 attached to a glycerol head.
- **Phosphatidylglycerol** is synthesized from CDP-DAG and glycerol 3-phosphate:
  phosphatidic acid is activated by adding CTP forming CDP-DAG, glycerol 3-P reacts with CDP-DAG forming phosphatidyl glycerol 3-P, the phosphate is removed to form phosphatidyl glycerol



- Phosphatidylglycerol can react with CDP-DAG through the glycerol head synthesizing **Cardiolipin**, in which the DAG from CDP-DAG is added the glycerol head & CMP is released.

*Cardiolipin is also known as Diphosphatidylglycerol (2 phosphatidates + glycerol)



Ether glycerophospholipids

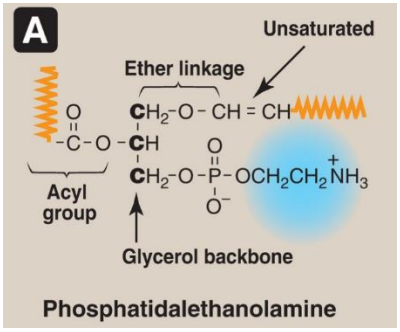
- these phospholipids have an alkyl group attached via ether bond on Carbon no.1 replacing the FA.
- Two types: **A) Plasmalogens** **B) Platelet-activating factor.**

A) Plasmalogens: (**tidal**→ refers to the ether group)

1) **Phosphatidal ethanolamine**: similar in structure to phosphatidylethanolamine, abundant in **nerve** tissue.

Structure:

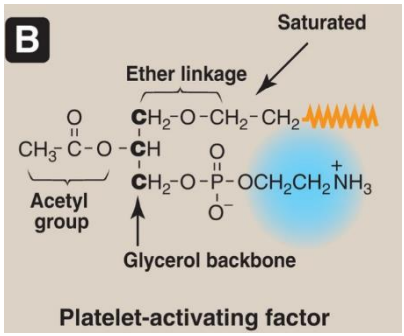
the ester group on C1 with FA that is present on the regular phosphatidyl ethanolamine is replaced by an ether group with an unsaturated alkyl group that has a double bond and on C2 there's an Acyl group with ester bonding



2)**Phosphatidal choline** is the other quantitatively significant ether lipid in mammals, abundant in **heart** muscle.

B) Platelet-activating factor.

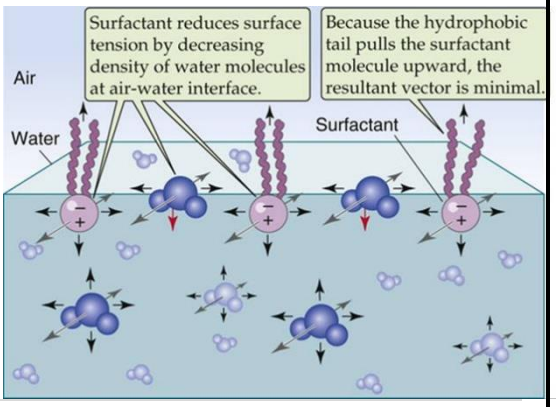
- Prothrombotic: induces thrombosis—clot formation
- inflammatory factor: induces inflammation
- Structure:
  has a **saturated** alkyl group in an ether link to carbon 1 and an **acetyl** residue at carbon 2 of the glycerol backbone.



Surfactants

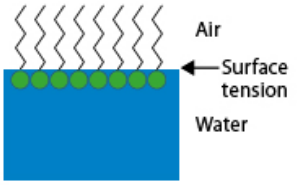
- are special, complex molecules that are mainly made of lipids (90%) and proteins (10%) and are secreted by type II pneumocytes in the lungs.
- they cover the lung lining of alveoli; the extracellular fluid layer lining the alveoli.
- The major lipid in surfactants is Dipalmitoylphosphatidylcholine (DPPC); phosphatidyl choline + 2 palmitate (di) on carbon no.1 + no.2
- **Function**: Surfactants **decrease** the surface tension of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis).

  water molecules usually interact with each other except on the surface they cluster due to surface tension where they are exposed to air.

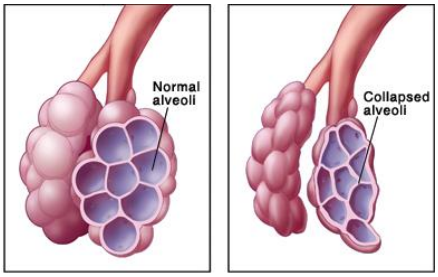


surfactants reduce surface tension by creating a layer between the hydrophilic surface of cells and the air preventing their shrinkage and, in this case, preventing lung from shrinking.

- Surface tension explains why a piece of paper doesn't sink but rather stays when put directly on the surface.
  water droplets when placed on surfaces like a balloon the surface would shrink due to surface tension as well.



- With surfactants alveoli are stretched out, but without surfactants and with the presence of surface tension alveoli would shrink and collapse on themselves.



- **Respiratory distress syndrome (RDS)** in preterm infants is associated with insufficient surfactant production and/or secretion.
  →Surfactants are produced in the body shortly before birth, premature babies don't have mature lungs and surfactants, their lungs would collapse, and they'd have a hard time breathing air which causes their death.
- **Treatment:** Prenatal administration of **glucocorticoids** shortly before delivery to induce expression of specific genes to produce surfactants in premature babies.

Degradation of Phospholipids by phospholipases

- **Phospholipase A_1** is responsible for releasing the FA attached to carbon no.1 present in many mammalian tissues.
- **Phospholipase A_2** released as a proenzyme (zymogen), activated by trypsin.
  is responsible for releasing the 2nd FA attached to carbon no.2
  and responsible for releasing the arachidonic acid from the phosphatidyl inositol PI.
  present in snakes and bee venoms: damages glycerophospholipids which causes cell damage like RBCs damage resulting in excessive bleeding which explains why snakes are fatal.
- **Phospholipase C** acts before the phosphate group, as mentioned previously PLC removes the phosphorylated inositol releasing IP3
- **Phospholipase D** acts after the phosphate group, would release the inositol molecule only from PI.