

- Many proteins bind to PL head groups e.g. phosphoinositide-binding proteins in cytosol

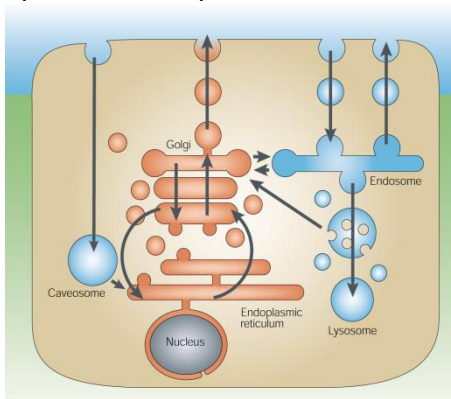
How are phospholipids synthesised?

- Each step is catalysed by enzymes in the ER membrane that have their active site facing the cytosol, where all of the required metabolites are found
- When the fatty acids arrive in the ER membrane, they are activated with CoA
- Glycerol-3-phosphate acyl transferases add a fatty acid to phosphoglycerol to make lysophosphatidate
- Glycerol-3-phosphate acyl transferase add a fatty acid to lysophosphatidate to make phosphatidate (phosphatidic acid) which is sufficiently insoluble to stay in the lipid bilayer, and it cannot be extracted from the bilayer by the fatty acid binding proteins.
- To make **phosphatidylcholine**:
 - Phosphatidase catalyses the removal of a phosphate group from phosphatidate to make diacylglycerol
 - Choline phosphotransferase catalyses the addition of CDP-choline to diacylglycerol to make phosphatidylcholine and CMP
- To make **phosphatidylserine**
 - CTP catalyses the conversion of phosphatidate to cytidine
 - Transferase catalyses the addition of serine to cytidine to make phosphatidylserine and CMP
- **Ceramide** is made by condensing the amino acid serine with a fatty acid to form the amino alcohol sphingosine – a second fatty acid is then added to form ceramide – exported to Golgi apparatus – precursor for synthesis of two types of lipid:
 - Oligosaccharide chains are added to form glycosphingolipids
 - Phosphocholine head groups are transferred from phosphatidylcholine to other ceramide molecules to form **sphingomyelin**
- Ceramide and sphingomyelin are both produced relatively late in the protein of membrane synthesis
- They are produced by enzymes exposed to the Golgi lumen – they are found exclusively in the non-cytosolic leaflet of the lipid bilayers that contain them

Where are lipids made?

Lipids are made in the ER and are inserted into the cytosolic leaflet of the ER membrane.

Lipids are transported via vesicular transport.



Energy-independent flippases

- It is driven by the concentration gradient between leaflets.

- They import most of their proteins from the cytosol
- They do not synthesise lipids *de novo* – their lipids are imported from the ER
- So how do lipids get from the ER to other organelles? By lipid transfer proteins

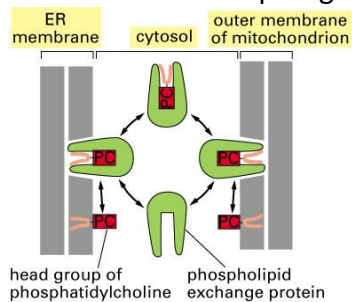
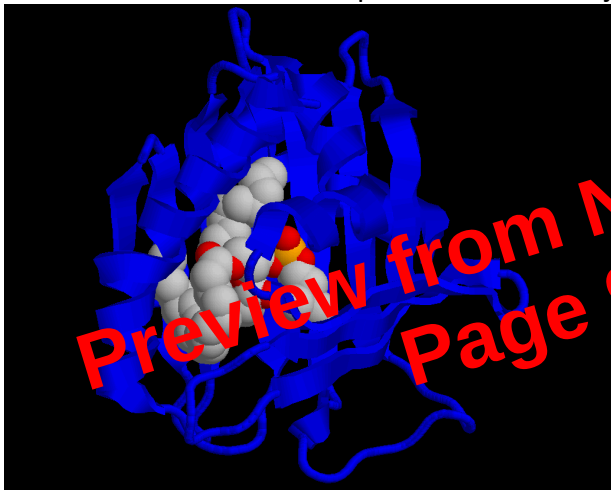


Figure 12-60. Molecular Biology of the Cell, 4th Edition.

Phospholipid exchange proteins

Lipids are insoluble in water and therefore require carrier proteins. PC high in ER, low in mitochondrial OM, therefore the transfer can occur without input of additional energy. Some mechanism for PS, PS can then be decarboxylated to PE (cf. bacteria). Lipids are shepherded from their sites of synthesis to the ER by a fatty acid binding protein in the cytosol. This enlarges the ER lipid bilayer. Mitochondria are also often seen in close juxtaposition to ER membranes in electron micrographs and there may be specific lipid transfer mechanisms that operate between adjacent membranes.



Summary

- Phospholipids are synthesised *de novo* in the ER cytoplasmic leaflet.
 - Require Acyl-CoA transferase to generate phosphatidate
 - Phosphatidate is **activated** by reacting with CTP to yield CDP-diacylglycerol
 - CDP can then react with head groups such as serine to yield phospholipids
 - Alternatively, they can dephosphorylate phosphatidate to yield diacylglycerol
 - DAG can then react with CDP-activated head group
- In ER, energy-independent flippase (scramblase) equilibrates phospholipids between lipids of the bilayer; therefore the ER membrane is **symmetric** with respect to lipids
- Can measure flipping by vectorially radiolabelling lipids and then modifying with TNBS
- Phospholipids can move via membrane containers to other compartments of the endomembrane system
- Ceramide produced in the **cytoplasmic** ER leaflet – flipped to inner leaflet and moved to Golgi