Membrane and Neutral Lipid Biosynthesis

Biochemistry in Health and Disease
Professor Edward A. Dennis
Types of Biological Lipids

• Simple Lipids
  – Fatty acids
  – Prostaglandins

• Mixtures
  – Lipoproteins

• Other Lipids
  – Wax esters
  – Terpenes
  – Fat Soluble Vitamins

• Complex Lipids
  – Neutral
  – Phospholipids
  – Sphingolipids
  – Steroids and XOL

Today’s Topic
Definitions

**Phosphatidic acid** = precursor to both phospholipids and to triacylglycerols. Also called diacylglycerol-3-phosphate.

**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.

**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.

\[ \text{Phosphatidic acid} = \text{diacylglycerol-3-phosphate} \]
\[ \text{Triacylglycerol} = \text{triglyceride} \]
\[ \text{Glycerophospholipid} = \text{an amphipathic lipid} \]
Glycerol-3-Phosphate Synthesis

- L-Glycerol-3-phosphate is the backbone of triglycerides and phospholipids
- D-glycerol-1-phosphate is the same molecule as L-glycerol-3-phosphate
Biosynthesis of Phosphatidic Acid

- **Precursors**
  - Fatty acids
  - Glycerol-3-phosphate

- **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
Synthesis of Triacylglycerol

- **Phosphatidic acid phosphatase** removes the phosphate producing 1,2-Diacylglycerol

- **An acyl transferase** transfers an acyl CoA to position 3.
Biosynthesis of Phospholipids

- Phospholipids (PL) 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**: The hydrophobic tail of diacylglycerol is activated rather than the polar head group
  - Used during the synthesis of PI and PG
- **Strategy 2**: The polar head group is activated before being attached to the lipid.
  - Used during the synthesis of PE and PC
De Novo Synthesis of PC

- 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

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
Synthesis of PS

- Phosphatidylserine (PS) is synthesized from PE by a head group exchange.
- Bacteria can make PS de novo because they have PS synthase - Strategy 1 mechanism.
- Mammals do not make PS de novo because they lack PS synthase.
Interconversion of PS, PE and PC

- 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
Neutral Lipids and PLs: What to Know...

- Diagram and Explain
  - Synthesis of triglycerides
  - Synthesis of PE and PC
  - Synthesis of PS
  - Interconversion of PE, PC, and PS