ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

1. Biosynthesis of fatty acids
2. Regulation of fatty acid degradation and synthesis
3. Assembly of fatty acids into triacylglycerol and phospholipids

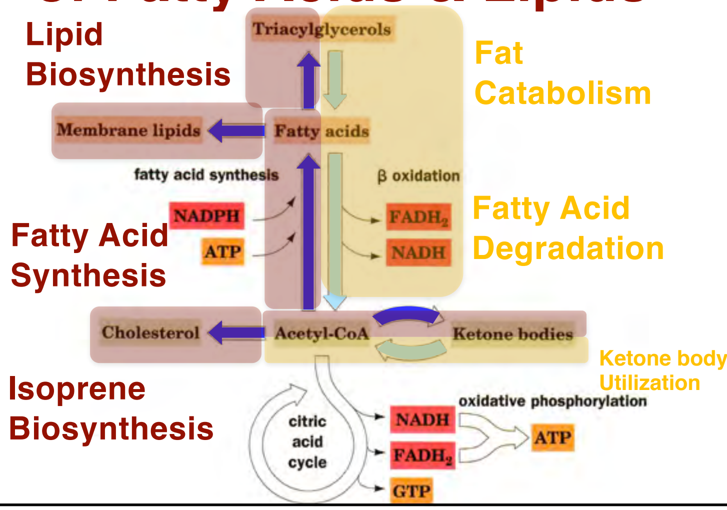
Exam 4

4. Metabolism of isoprenes

Exam 5

   a. Isoprene biosynthesis and ketone bodies
   b. Isoprene polymerization
      i. Cholesterol
      ii. Steroids & other molecules
      iii. Regulation
      iv. Role of cholesterol in human disease

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids



Fatty Acid Biosynthesis

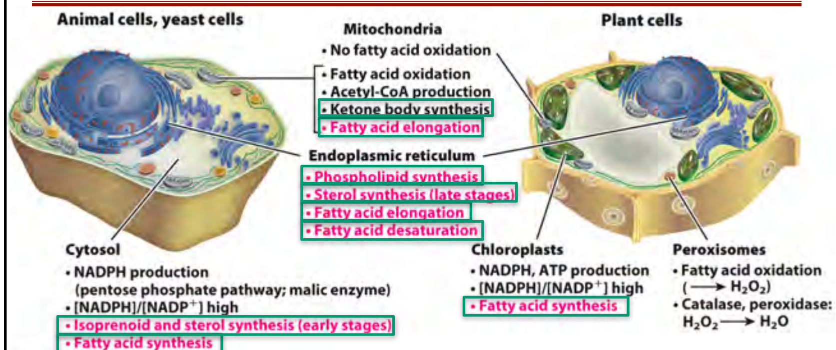
- Contrast with Sugars
  - Lipids have have hydro-carbons not carbo-hydrates
  - more reduced=more energy
  - Long-term storage vs short-term storage
  - Lipids are essential for structure in ALL organisms: membrane phospholipids
- Catabolism of fatty acids
  - *produces* acetyl-CoA
  - *produces* reducing power (NADH, $FADH_2$)
  - takes place in the *mitochondria*
- Anabolism of fatty acids
  - *requires* acetyl-CoA and sufficient carbohydrates
  - *requires* reducing power from NADPH
  - takes place in *cytosol* in animals, *chloroplast* in plants

Anabolism of fat will occur only when there is excess, carbon, electrons, and ΔG

Acetyl-CoA & carbohydrates → NADPH → ATP →

How is this monitored in the cell?

Fatty Acid Biosynthesis



Fatty Acid Synthesis

Cytosol for animals — *Chloroplast* for plants

Both of these compartments are where there are ample Sources of NADPH:

in adipocytes: pentose phosphate pathway and malic enzyme

NADPH made as malate converts to pyruvate + CO_2.

in hepatocytes and mammary gland: pentose phosphate pathway

NADPH made as glucose-6-phosphate converts to ribulose 6-phosphate.

in plants: photosynthesis

Fatty Acid Biosynthesis

EXAMPLE: Synthesis of Palmitate (16:0)

Where do the carbons come from? **Acetyl-CoA**

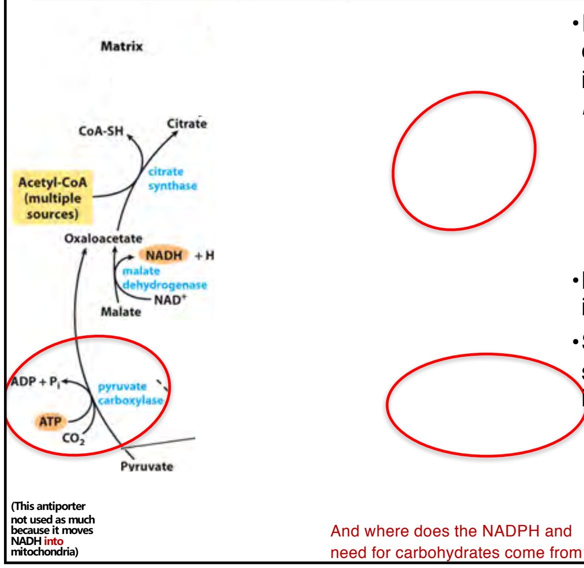
1. 8 acetyl-CoA x 2 carbons = 16 carbons (palmityl-CoA)
2. Longer fatty acids and desaturases use palmityl-CoA
3. 1 acetyl-CoA ”primes” the enzyme
   a. other “acetyl-CoA-derived units” are ACTIVATED by carboxylation (recall gluconeogenesis)
   b. Used to make 7 malonyl-CoAs… using? **ATP & CO_2**

7 acetyl-CoA + 7 CO_2 + 7 ATP → 7 malonyl-CoA + 7 ADP + 7 P_i ….more later

2. Seven cycles of condensation, reduction, dehydration, and reduction… using **NADPH** to reduce the β-keto group and trans-double bond

acetyl-CoA + 7 malonyl-CoA + 14 NADPH + 14 H^+ → palmitate (16:0) + 7 CO_2 + 8 CoA + 14 $NADP^+$ + 6 H_2O

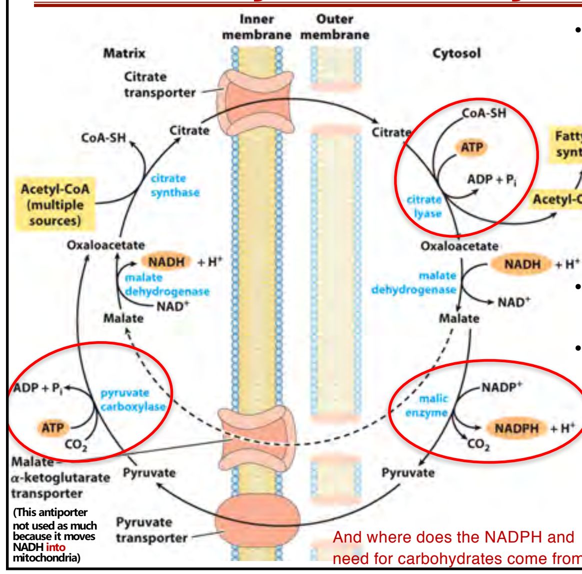
Fatty Acid Biosynthesis

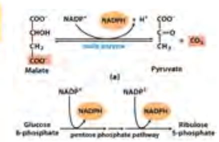


- In non-photosynthetic eukaryotes…Acetyl-CoA is made in the *mitochondria*
- But fatty acids are made in the *cytosol*
- So acetyl-CoA is smuggled (**transported)** into the cytosol
  - cost of 2 ATPs
  - Converted back to acetyl-CoA by citrate lyase
  - Therefore, cost of FA synthesis is 3 ATPs per 2-C unit….. Where is third?

And where does the NADPH and need for carbohydrates come from?

Fatty Acid Biosynthesis



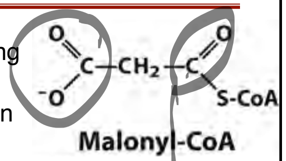


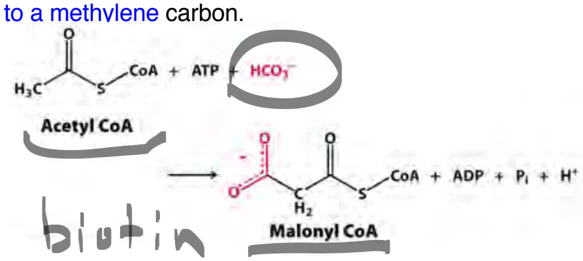
- In non-photosynthetic eukaryotes…Acetyl-CoA is made in the *mitochondria*
- But fatty acids are made in the *cytosol*
- So acetyl-CoA is smuggled (**transported)** into the cytosol
  - cost of 2 ATPs
  - Converted back to acetyl-CoA by citrate lyase
  - Therefore, cost of FA synthesis is 3 ATPs per 2-C unit ….. Where is third?

And where does the NADPH and need for carbohydrates come from?

Fatty Acid Biosynthesis

- Fatty acids are built in several passes, processing one acetate unit at a time.
- The acetate is coming from activated malonate in the form of malonyl-CoA.
- Each pass involves reduction of a carbonyl carbon to a methylene carbon.





- Making the Malonyl-CoA:
  - Reaction carboxylates acetyl-CoA
  - Catalyzed by *acetyl-CoA carboxylase*

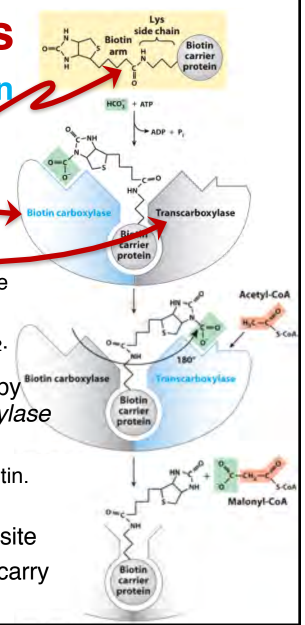
Fatty Acid Biosynthesis

Acetyl-CoA Carboxylase Reaction

–The enzyme has three subunits:
- One unit has biotin covalently linked to Lys.
- Another subunit is biotin carboxylase
- The third subunit is a transcarboxylase
- Biotin carries CO_2.
- In animals, all three subunits are on one polypeptide chain.

–HCO_3^- (bicarbonate) is the soluble source of CO_2.

– Two-step Rx similar to carboxylations catalyzed by *pyruvate carboxylase* and *propionyl-CoA carboxylase*
- CO_2 binds to biotin.
  - CO_2 is activated by attachment to N in ring of biotin.
  - Reaction with ATP produces carbamoyl.
- CO_2 attaches to acetyl-CoA and leaves active site
- Enzyme undergoes conformational change to carry carbamoyl to transcarboxylase site



Fatty Acid Biosynthesis

Fatty Acid Synthase (FAS)

- Catalyzes a repeating four-step sequence that elongates the fatty acyl chain by two carbons at each step
- NADPH as as the electron donor

- Condensation with acetate
  - β-ketoacyl-ACP synthase (KS)
- Reduction of carbonyl to hydroxyl
  - β-ketoacyl-ACP reductase (KR)
- Dehydration of alcohol to alkene
  - β-hydroxyacyl-ACP dehydratase (DH)
- Reduction of alkene to alkane
  - enoyl-ACP reductase (ER)
- Chain transfer/charging
  - malonyl/acetyl-CoA ACP transferase (M/AT)

- Overall goal: attach acetate unit (2-carbon) from malonyl-CoA to a growing chain and then reduce it.
- Reaction involves cycles of four enzyme-catalyzed steps:
  - condensation of the growing chain with activated acetate
  - reduction of carbonyl to hydroxyl
  - dehydration of alcohol to trans-alkene
  - reduction of alkene to alkane
- The growing chain is initially attached to the enzyme via a thioester linkage.

Fatty Acid Biosynthesis

FAS I vs. FAS II

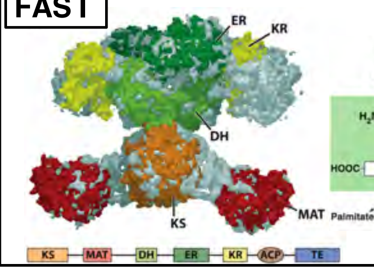
FAS I

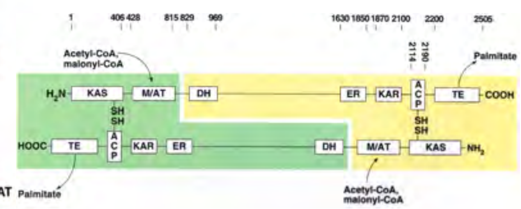
- Single polypeptide chain in vertebrates
- Leads to single product: palmitate 16:0
- C-15 and C-16 are from the acetyl-CoA used to prime the Rx
- FAS I in vertebrates and fungi

FAS II

- Made of separate, diffusible enzymes
- Makes many products (saturated, unsaturated, branched, many lengths, etc.)
- Mostly in plants and bacteria

FAS I



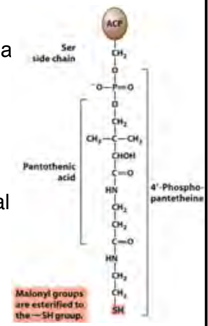


What you can't see is the ACP……

Fatty Acid Biosynthesis

Acyl Carrier Protein (ACP)

- The *E. coli* ACP is a small 77-residue protein with a a covalently attached prosthetic group, 4'-phosphopantetheine, at a Ser residue.
  - In vertebrate FAS, it's a domain with a flexible arm to tether the growing acyl chain
- Delivers acetate (in the first step) or malonate (in al the next steps) to the fatty acid synthase enzymes
- Shuttles the growing chain from one active site to another during the four-step reaction



Priming FAS

- Two thiols must be **charged with the correct acyl groups** before the condensation reaction can begin.
  - thiol from 4-phosphopantethine in ACP
  - thiol from Cys β-ketoacyl-ACP synthase (KS)
- The acetyl group of acetyl-CoA is transferred to ACP.
  - catalyzed by malonyl/acetyl-CoA transferase (MAT)
  - ACP passes this acetate to the Cys of the KS domain of FAS 1.
  - ACP –SH group is recharged with malonate from malonyl-CoA again catalyzed by MAT