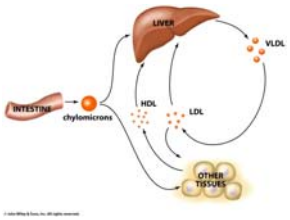
Fatty Acid Synthesis

Chapter 28, Stryer Short Course

Lipoprotein Metabolism

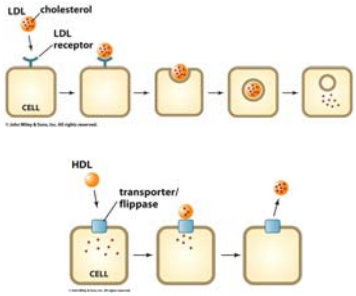


- Liver is the packaging center
- VLDL are sent out of liver
- Constant cycling of LDL in blood
- Genetic cholesterol problem: no LDL receptors in non-liver cells
- HDLs are “good cholesterol”

[TABLE 17-1] Characteristics of Lipoproteins

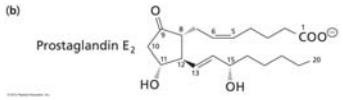
Lipoprotein	Diameter (Å)	Density ($g \cdot cm^{-3}$)	% Protein	% Triacylglycerol	% Cholesterol and Cholesteryl Ester
Chylomicrons	1000–5000	<0.95	1–2	85–90	4–8
VLDL	300–800	0.95–1.006	5–10	50–65	15–25
IDL	250–350	1.006–1.019	10–20	20–30	40–45
LDL	180–250	1.019–1.063	20–25	7–15	45–50
HDL	50–120	1.063–1.210	40–55	3–10	15–20

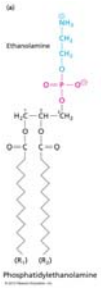
Role of LDL and HDL



Biosynthesis of Lipids

- Triacylglyerides as fuels
- Glycerophospholipids in membrane
- Prostaglandins as signal molecules
- Cholesterol and derivatives

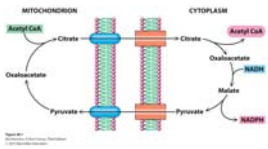




Fatty Acid Synthesis

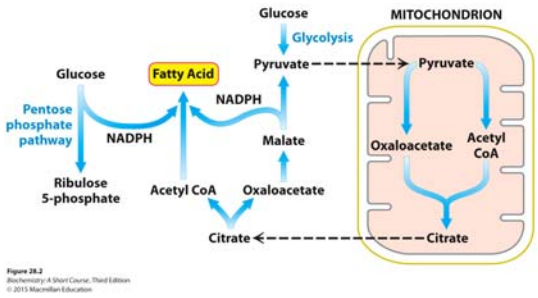
- Opposite of beta oxidation in the sense that 2-carbon acetate units are linked to form even-chain, saturated fatty acids
- Differs from Fatty acid degradation
  - In cytoplasm, not matrix
  - Acyl carrier protein rather than CoA
  - Enzymes linked in a complex
  - Utilizes NADPH
  - Energetically linked to ATP hydrolysis

Transport to Cytoplasm



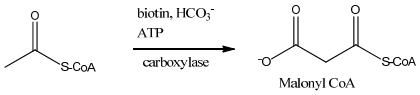
- Acetyl CoA takes the oxaloacetate taxi out of the matrix
- Recycling transforms NADH into NADPH, which is reducing power needed for fatty acid synthesis

Integration of Pathways



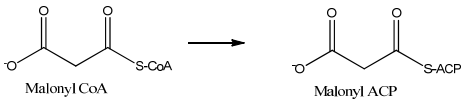
Activation of Acetyl Group

- Acetyl CoA carboxylase (analogous to pyruvate carboxylase of gluconeogenesis)
- Requires biotin, ATP
- A regulation step—shifts fuel away from CAC

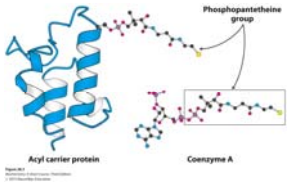


Malonyl CoA

Transfer to Acyl Carrier Protein

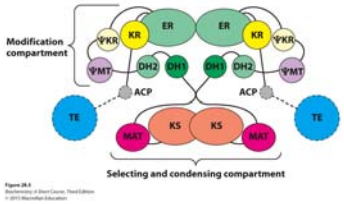


- Acyl carrier protein is 77 residues
- Scaffold for building
- "macro CoA"



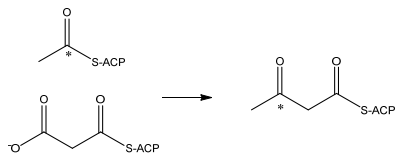
Four Step Elongation

- Enzyme complex coordinates synthesis
- Coordination of enzyme activity
- Makes palmitate (16 C)

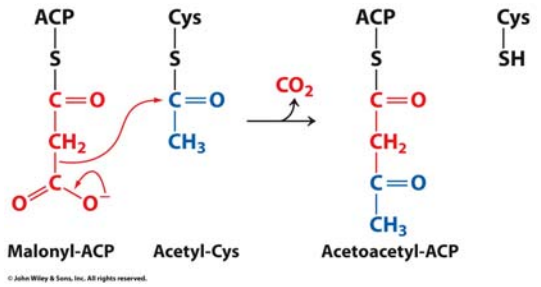


Step 1: Condensation

– Opposite of thiolase
– Loss of CO_2 drives reaction to completion

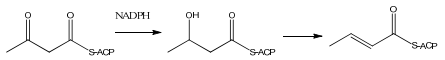


Rough Mechanism

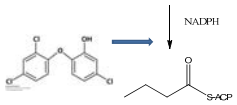


Steps 2-4: Opposite of beta Oxidation

- Input of 2 NADPH
- Major use of PPP



- Triclosan: broad spectrum antibiotic



Synthesis of Palmitate

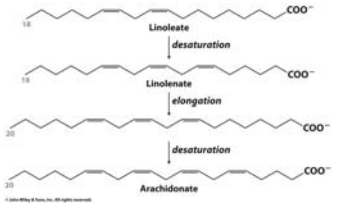
Acetyl CoA + 7 Malonyl CoA + 14 NADPH + 20 $H^{\oplus}$ ⟶

Palmitate + 7 CO_2 + 14 $NADP^{\oplus}$ + 8 HS–CoA + 6 H_2O

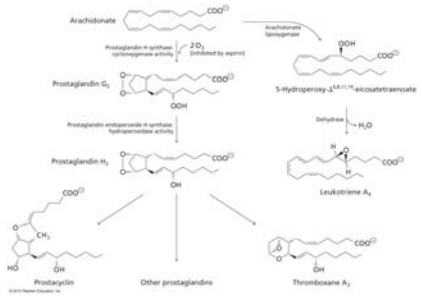
- 16-carbon fatty acid produced in major synthesis complex
- **Problem 31:** What is the ATP cost of synthesizing palmitate from acetyl-CoA?

Post-synthesis Modification

- Elongations possible with other enzymes
- Many organisms can make odd-chain fatty acids
- Essential Fatty acids

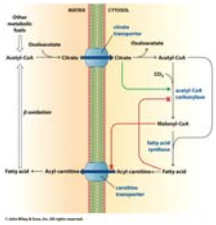


Prostaglandins and COX Inhibitors



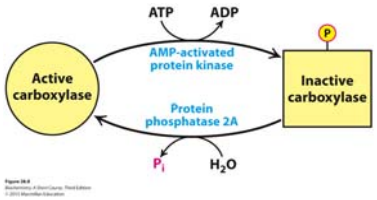
Regulation

- Carnitine Transporter
  - Matrix malonyl CoA
    - Error in this picture
    - Actually produced by acetyl CoA carboxylase isozyme in matrix
- Acetyl CoA carboxylase
  - Local
    - AMP level
    - Citrate and Fatty Acids
  - Hormones



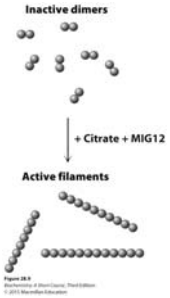
AMP level

- AMP-activated protein kinase
  - Fuel sensor
  - Inactivates acetyl CoA carboxylase under low energy conditions in cell



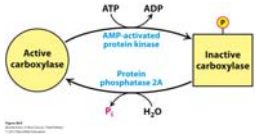
Citrate and Fatty Acids

- [Citrate] high in well fed state
  - Lots of OAA and acetyl CoA
- Carboxylase forms active filaments
  - If [fatty acids] is high, no need to synthesize
  - Fatty acids break down filaments



Hormone-level control

- Glucagon and epinephrine
  - Suppress acetyl CoA carboxylase by keeping it phosphorylated
- Insulin—activates storage
  - Leads to dephosphorylation of carboxylase



Metabolism of Ethanol

- Liver damage
  - Too much NADH and acetyl CoA
  - Shuts down citric acid cycle
  - Fatty acid synthesis upregulated
    - "fatty liver"
  - Ketone bodies form
    - acidosis