CHAPTER 28:
Fatty Acid Synthesis
Problems: 2-4, 6-7, 10, 13-14, 21-24

28.1 Stages of FA Synthesis

1. Transfer of acetyl-CoA from mitochondria to cytosol.
2. Activation of acetyl-CoA; synthesis of malonyl-CoA.
3. Five step elongation cycle of FA synthesis via ACP intermediates.
Transport of Acetyl-CoA from Mitochondria to Cytoplasm

- Acetyl CoA
- Citrate synthase
- Oxaloacetate
- Pyruvate carboxylase
- Pyruvate
- Citrate
- ATP-citrate lyase
- Oxaloacetate
- Malate dehydrogenase
- Malate
- Malic enzyme
- NADH
- NADPH

Figure 28.1
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Sources of NADPH for FA Synthesis
Formation of Malonyl-CoA: Committed Step

Acetyl-CoA Carboxylase

\[
\begin{align*}
\text{HCO}_3^- + \text{ATP} & \rightarrow \text{Enz-Biotin} \\
\text{ADP} + P_i & \rightarrow \text{Enz-Biotin-COO}^- \\
\Theta \text{OOC} & \rightarrow \text{CH}_2 - \text{C} - \text{S-CoA} \\
\text{H}_3\text{C} & \rightarrow \text{C} - \text{S-CoA} \\
\text{Malonyl CoA} & \rightarrow \text{Acetyl CoA}
\end{align*}
\]
Fatty Acid Synthesis

- FA are synthesized by the repetitive condensation of two-carbon units derived from malonyl CoA

*Loading* of precursors via thioester derivatives, followed by chain *elongation*:

1. Condensation of the precursors
2. Reduction
3. Dehydration
4. Reduction
Loading Stage of FA Synthesis

\[
\text{OOC} - \text{CH}_2 - \text{C} - \text{S-CoA} \\
\text{Malonyl CoA}
\]

\[
\text{OOC} - \text{CH}_2 - \text{C} - \text{S-ACP} \\
\text{Malonyl ACP}
\]

\[
\text{H}_3\text{C} - \text{C} - \text{S-CoA} \\
\text{Acetyl CoA}
\]

\[
\text{H}_3\text{C} - \text{C} - \text{S-ACP} \\
\text{Acetyl ACP}
\]

Malonyl CoA:ACP transacylase → HS-ACP → HS-CoA

Acetyl CoA:ACP transacylase → HS-ACP → HS-CoA

Phosphopantetheine group

-Acyl carrier protein  
-Coenzyme A

-SH
The synthesis of palmitic acid requires 7 ATPs and 8 NADPHs: Can you account for these ATPs and NADPHs?
Fatty Acid Activation

Different synthetases:
- Short (<C6)
- Medium (C6 – C12)
- Long (>C12)
- Very long (>C16)

\[ R-\text{COO}^- + \text{HS-CoA} \rightarrow \text{Fatty acid} \]

\[ \text{ATP} \rightarrow \text{AMP + PP}_i \]

\[ \text{Acyl-CoA synthetase} \]

\[ R-C-S-CoA \]

Acyl CoA
28.2 Elongation and Desaturation

C16:0 to C18:n – C20:n

Elongation occurs with enzymes on the cytosolic face of the ER membrane. This is done by elongases that use malonyl-CoA to add the 2-carbon subunits.

oxidase

Mammals

C18:0-CoA $\rightarrow$ C18:1$^\Delta^9$-CoA $\times$ C18:2$^\Delta^9,12$-CoA

Stearoyl CoA  Oleoyl CoA  linolenoyl CoA

Dietary source
Longer Chain and Unsaturated Fatty Acids
In Eukaryotes

Linoleoyl CoA (18:2 cis,cis-\(\Delta^{9,12}\))

\[ \text{O}_2 \xrightarrow{\Delta^\Delta-\text{Desaturase}} \text{NADH} + \text{H}^+ \xrightarrow{2 \text{H}_2\text{O}} \text{NAD}^+ \]

\(\gamma\)-Linolenoyl CoA (18:3 all cis-\(\Delta^{6,9,12}\))

\[ \text{OOC} - \text{CH}_2 - \text{C} - \text{S-CoA} \]

\[ \text{Malonyl CoA} \]

\[ \text{CO}_2 + \text{HS-CoA} + \text{Elongase} \]

Eicosatrienoyl CoA (20:3 all cis-\(\Delta^{6,11,14}\))

\[ \text{O}_2 \xrightarrow{\Delta^\Delta-\text{Desaturase}} \text{NADH} + \text{H}^+ \xrightarrow{2 \text{H}_2\text{O}} \text{NAD}^+ \]

Arachidonoyl CoA (20:4 all cis-\(\Delta^{5,8,11,14}\))

Essential for the synthesis of prostaglandins

Figure 16-7 Principles of Biochemistry, 4/e
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28.3 Acetyl CoA Carboxylase and Regulation of FA Metabolism

**Acetyl-CoA Carboxylase**

- High ATP OFF
- Low ATP ON
- High Citrate ON
- High C16:0-CoA OFF
- Malonyl CoA inhibits carnitine acyl transferase I. How does this affect FA metabolism?
Hormonal Regulation of Acetyl CoA Carboxylase

- Insulin activates
- Glucagon & epinephrine deactivate

**Glucagon & epinephrine** deactivate via enhancing acetyl CoA carboxylase inhibition through the activity of AMP-dependent kinase.

**Insulin** stimulates FA synthesis by stimulating protein phosphatase that activates acetyl CoA carboxylase.

28.4 Ethanol Metabolism and FA Synthesis