Session 15 - Chemical Interlude - Why did we have to use a thioester (FAcyl CoA)?

-- The reverse reaction (decarboxylation of β-keto acid) is VERY favorable.

\[
R-C=CH_2-S-\beta K\text{T}
\]

Cannot do this with a carboxylic acid - unfavorable

Recall how to make a thioester from an acid:

\[
R-CO_2^+ + ATP \rightarrow R-CO_2^+ + AMP + PP_i
\]

Step I Could phosphorylation work? - Probably. AMP (and phosphate) are good leaving groups

Special Case 1 - FA has a Cis-Double bond

-- Cis-Double bonds promote membrane plasticity
  -- trans-double bonds have a slight reduction in overall energy yield

-- But, Cis-double bonds present a biochemical challenge to digestion

-- For example, Oleic Acid (18:1)Δ9
  -- The word "oil" comes from oleic (olive oil = oleic)

\[
\begin{align*}
\text{Oleyl CoA} & \quad \text{Isomerase} \\
\text{trans-Δ}^2\text{ enoyl CoA} & \quad \text{Hydratase}
\end{align*}
\]

regular β-oxidation

Special Case 2 - Odd Chain FA: Introduction to Carboxylases

Pentadecanoic acid (15:0) = 1.2% of milk fat

\[
\begin{align*}
\text{Pentadecanoyl CoA} \quad & \text{HSCoA ATP} \\
\text{Acetyl CoA} \quad & \text{6 Acetyl CoA} \\
\text{6 rounds of β-oxidation} & \quad \text{6 rounds of β-oxidation}
\end{align*}
\]

Acetyl CoA (many)

-- Odd chain FA in diet \rightarrow Propionyl CoA (C-3)

Succinyl CoA (C-4)

"CO_2" inserted CH α-carbon; must activate CO_2 for it to add to Cα

-- They are anapleurotic (increase rate of TCA cycle)

-- They can be gluconeogenic (later) \Rightarrow can result in net synthesis of glucose from this part of the FA chain (the Acetyl CoA-derived units are typically not gluconeogenic unless glyoxylate cycle (later) is operative)

-- The carboxylase family does much more than metabolize odd chain FA
More General View of Carboxylases

- Require biotin (Vit. B7), CO₂ and ATP
- Increase size of molecule by one carbon (as "CO₂")
- This is a kind of carbon fixation
- Play a role in:
  
  (a) **Odd chain FA metabolism**
      Example: Propionyl CoA Carboxylase
      "We'll look at this in detail later (this is also anapleurotic)"
  
  (b) **FA biosynthesis**
      Example: Acetyl CoA Carboxylase
  
  (c) **Anapleurosis and Gluconeogenesis**
      Example: Pyruvate Carboxylase

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Start with (c) - Pyruvate Carboxylase (PC)

Role: To ↑ [Oxaloacetate] in mitochondrion
always limiting

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"CO₂"
Steps (most are common to all carboxylases)

1.) Synthesis of Bicarbonate via Carbonic Anhydrase (CA)

\[
\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{HCO}_3^- \quad \text{via CA}
\]

“Hydrated CO2”

not very soluble in water

very soluble

2.) Biotin Carboxylase (BC) Reaction of Pyruvate Carboxylase (PC)

\[
\text{CO}_2 + \text{ATP} \rightarrow \text{ADP} + \text{CO}_2 \text{carbonyl (or carboxy) phosphate}
\]

2 cont.) Biotin Carboxylase Reaction of Pyruvate Carboxylase (PC)

We use a high Energy bond to “dehydrate” bicarbonate in active site of enzyme

Biotin will hold CO2 temporarily

Substrate (pyruvate)

Pyruvate enolate

3.) Carboxytransferase (CT) Reaction of PC

(from above)
How to Visualize Carboxylase Chemistry

-- CT and BC are ~55 Å apart
-- swinging arm does the "CO₂" transfer

Example (b) - Acetyl CoA Carboxylase

-- Exactly the same chemistry, but acetyl CoA receives the CO₂

Example (c) - Propionyl CoA Carboxylase - followed by synthesis of Succinyl CoA (2 more steps)