Pyruvate Dehydrogenase Complex and Tricarboxylic Acid-cycle

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Recall from Glycolysis

• Glycolysis is the first step of aerobic cellular respiration.

• The end product of glycolysis is **pyruvate**.

• Glycolysis takes place in the **cytosol** of cells where all the enzymes are present.

• Pyruvate enters the mitochondrion to be metabolized further.
Mitochondrial Compartments

Matrix

Cristae

Inner membrane

Outer membrane

Cytoplasm
Pyruvate dehydrogenase is a large complex containing many copies of each of three enzymes:
- **Pyruvate Dehydrogenase (PDH)**
- **Dihydrolipoyl Transacetylase (DALT)**
- **Dihydrolipoyl Dehydrogenase (DLD)**

Has five cofactors:
- **TPP**
- **Lipoic acid**
- **FAD**
- **NAD+**
- **CoA-SH**
Oxidative Decarboxylation of Pyruvate

Pyruvate \( \rightarrow \) Acetyl CoA

Decarboxylation

\[ \text{NAD}^+ \rightarrow \text{NADH} + H^+ \]

Oxidation

\[ 2e^- \]
Oxidative Decarboxylation of Pyruvate

Pyruvate $\rightarrow$ TPP $\rightarrow$ Acyl-TPP $\rightarrow$ Acyl-lipoate $\rightarrow$ CoASH $\rightarrow$ Acetyl-CoA

$\rightarrow$ NAD$^+$ Dehydrogenase $\rightarrow$ FADH$_2$ $\rightarrow$ Lip-$S$ $\rightarrow$ Lip-$SH$ $\rightarrow$ NADH + H$^+$

$\rightarrow$ CO$_2$ Pyruvate Dehydrogenase $\rightarrow$ Acyl-lipoate Dihydrolipoyl Transacetylase $\rightarrow$ CoASH

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(Catalytic)
What is the Net Result of PDHc Reactions?

Pyruvate + CoA + NAD$^+$ $\rightarrow$ CO$_2$ + acetyl-CoA + NADH + H$^+$
Acetyl CoA: A Common Meeting Point

• Acetyl-CoA is an important molecule in metabolism.

• In chemical structure, acetyl-CoA is the thioester between coenzyme A (a thiol) and acetic acid (an acyl group carrier).

\[
\begin{array}{c}
\text{O} \\
\text{CH}_3-C-S-\text{CoA}
\end{array}
\]

• Several metabolic pathways converge to Acetyl-CoA including:
  1. Fatty acid metabolism
  2. Amino acid metabolism
  3. Carbohydrate metabolism
Acetyl CoA: A Common Meeting Point

Metabolism Summary

- **Proteins**: amino acids
- **Carbohydrates**: glucose, fructose, galactose
- **Fats and Lipids**: fatty acid, glycerol
- **Nitrogen Pool**: tissue protein
- **Glycogen**: glycogen synthesis
- **Glucose-6-Phosphate**: glycogenolysis, gluconeogenesis
- **Pyruvic Acid**: glycolysis
- **Lactic Acid**:
- **Urea Cycle**: ammonia (NH₃), urea
- **Citric Acid Cycle**: 2 CO₂, 2H⁺, 2e⁻, ADP, ATP
- **Electron Transport Chain**: ADP, ATP, O₂, H₂O
- **Lipogenesis**: fatty acid spiral

synthesis of the neurotransmitter **acetylcholine**
Tricarboxylic Acid Cycle (TCA-cycle)

• Also known as citric acid cycle and Krebs cycle.

Nobel Prize in Medicine (1953), which he shared with Fritz Lipmann.

Hans Adolf Krebs (1900-1981)

Harvests chemical energy from biological fuel in the form of electrons in NADH and FADH$_2$.

Consists of a series of eight reactions.

Converts acetyl-CoA to two CO$_2$ while conserving the free energy for ATP production.

- The energy is stored as: three NADHs, one FADH$_2$, and one GTP.

Intermediates from the TCA-cycle can be used to synthesize molecules such as amino acids and fatty acids.
The final product of glycolysis is **pyruvate**. It is located in the **cytosol**.

In order to enter the TCA-cycle pyruvate has to be **converted** to **acetyl-CoA**, releasing CO₂.

This is achieved by **pyruvate dehydrogenase complex** (PDHc), which consists of **three** enzymes and is located in the **mitochondrial matrix**.
The primary function of the TCA-cycle is oxidation of acetyl CoA to two CO₂.

The energy from these oxidation reactions is captured as:
- NADH
- FADH₂
TCA-cycle in Detail

Total of eight reactions
**Reaction 1: Condensation Reaction**

\[
\text{Acetyl CoA} + \text{Oxaloacetate} \rightarrow \text{Citrate}
\]

\[\Delta G^\circ = -32.2 \text{ kJ/mol}\]
Reaction 2: Rearrangement Reaction

Citrate

\[ \Delta G^\circ = 13.3 \text{ kJ/mol} \]
Reaction 3: First Oxidative decarboxylation

\[ \text{Isocitrate dehydrogenase} \]

\[ \text{Isocitrate} \rightarrow \text{α-ketoglutarate} \]

\[ \Delta G^\circ = -20.9 \text{ kJ/mol} \]

The only irreversible reaction.
Reaction 4: Second Oxidative Decarboxylation

\[
\text{α-ketoglutarate} \\ \\
\text{dehydrogenase} \\ \\
\text{ΔG°' = -33.5 kJ/mol}
\]

Back to four carbon molecule
Reaction 5: Oxidation Reaction

Succinyl CoA

Succinyl CoA synthetase

\[
\Delta G^\circ = -2.9 \text{ kJ/mol}
\]
Summary

• In terms of carbons:

  A two carbon acetyl group has been linked to oxaloacetate and two $CO_2$ molecules have been liberated.

• In terms of energy captured:

  Two $NAD^+$ have been reduced to NADH + $H^+$. One ATP produced.

  Leaving us with a molecule of succinate
Reaction 6: Oxidation Reaction

\[ \text{Succinate} \rightarrow \text{Fumarate} \]

\[ \Delta G^\circ = 0 \text{ kJ/mol} \]
Reaction 7: Hydration Reaction

Fumarate

\[ \text{Fumarase} \]

\[ \Delta G^\circ = -3.8 \text{ kJ/mol} \]
Reaction 8: Final Oxidation Reaction
Regeneration of Oxaloacetate

\[
\text{Malate dehydrogenase} \rightarrow \text{NAD}^+ \rightarrow \text{NADH} + H^+
\]

\[
\Delta G^\circ = 29.7 \text{ kJ/mol}
\]
Regenerated VS Starting Oxaloacetate

\[
\begin{align*}
\text{Oxaloacetate} & : & \text{Oxaloacetate} \\
\end{align*}
\]
TCA-cycle: In Terms of Carbon # of the Different Steps

http://www.uic.edu/classes/bios/bios100/summer2002/lect10.htm
• We saw how the acetyl-CoA made from glucose, fat, or protein burnt and energy captured as NADH and FADH$_2$.

• Next lecture we will see how this captured energy is used to make ATP via oxidative phosphorylation.
THE END

More questions??
Please email me @
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