The image depicts the Citric acid cycle, a fundamental metabolic process in cellular respiration. It begins with the conversion of pyruvate to acetyl-CoA. Acetyl-CoA then reacts with oxaloacetate to form citrate, which undergoes a series of enzymatic reactions including the conversion of isocitrate to α-ketoglutarate, the reduction of α-ketoglutarate to succinate, and finally, the conversion of succinate to fumarate. Each reaction is catalyzed by specific enzymes and involves the transfer of electrons to co-factors such as NAD+ and FAD. The process is crucial for the production of ATP and the recycling of co-factors.
How is the oxidation of pyruvate regulated?
PDH complex is regulated by product inhibition and covalent modification

- **Product inhibition:**
  - Acetyl-CoA binds and inhibits $E_2$
  - NADH binds and inhibits $E_3$

- **Covalent modification (eukaryotes only):** reversible phosphorylation of $E_1$ Ser

![Diagram showing the regulation of PDH complex by product inhibition and covalent modification.](image)

- Phosphatase activated by insulin (high [glc]) and Ca$^{2+}$
- Kinase activated by NADH and acetyl-CoA
The slowest steps of the citric acid cycle have negative ΔG’s, and are regulated.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Enzyme</th>
<th>$\Delta G^\circ$ (kJ · mol$^{-1}$)</th>
<th>$\Delta G$ (kJ · mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Citrate synthase</td>
<td>$-31.5$</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Aconitase</td>
<td>$\sim 5$</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>3</td>
<td>Isocitrate dehydrogenase</td>
<td>$-21$</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>$\alpha$-Ketoglutarate dehydrogenase</td>
<td>$-33$</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Succinyl-CoA synthetase</td>
<td>$-2.1$</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>6</td>
<td>Succinate dehydrogenase</td>
<td>$+6$</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>7</td>
<td>Fumarase</td>
<td>$-3.4$</td>
<td>$\sim 0$</td>
</tr>
<tr>
<td>8</td>
<td>Malate dehydrogenase</td>
<td>$+29.7$</td>
<td>$\sim 0$</td>
</tr>
</tbody>
</table>
Compounds reflecting energy status and energy use are regulators of the TCA cycle

- **NADH**
  - Product inhibitor of NAD\(^+\)-using dehydrogenases
  - Inhibitor of citrate synthase

- **Pathway intermediates**
  - Citrate and succinyl-CoA act via product inhibition or competitive feedback inhibition
  - Levels of substrates OAA and acetyl-CoA determine activity of citrate synthase

- **Adenylates**
  - Allosteric inhibitors (ATP) or activators (ADP) of isocitrate DH

- **Ca\(^{2+}\) (muscle contraction)**
  - Allosteric activator of the dehydrogenases
TCA cycle intermediates are made and used in additional metabolic pathways

Cataplerotic reactions use cycle intermediates to make:
- Glucose
- Amino acids
- Lipids
- Cofactors

Anaplerotic reactions generate cycle intermediates from:
- Pyruvate
- Amino acids
- Odd-chain fatty acids
Amino acids and TCA cycle intermediates are readily inter-converted

Reactive amination:
\[
\begin{align*}
\text{CH}_2 - \text{COO}^- & \quad \text{CH}_2 - \text{COO}^- \\
\text{CH}_2 - \text{COO}^- + \text{NADH} + \text{H}^+ + \text{NH}_4^+ & \leftrightarrow \text{CH}_2 - \text{COO}^- + \text{NAD}^+ + \text{H}_2\text{O} \\
\text{C} = \text{O} & \quad \text{H} - \text{C} - \text{NH}_3^+ \\
\text{COO}^- & \quad \text{COO}^-
\end{align*}
\]

\(\alpha\)-Ketoglutarate \quad \text{Glutamate}

Transamination:
\[
\begin{align*}
\text{CH}_2 - \text{COO}^- & \quad \text{CH}_2 - \text{COO}^- \\
\text{C} = \text{O} & \quad \text{H}_3\text{N} - \text{C} - \text{H} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{COO}^- & \quad \text{COO}^-
\end{align*}
\]

\(\text{Oxaloacetate} \quad \text{Alanine} \quad \text{Aspartate} \quad \text{Pyruvate}\)
Production of pyruvate increases flux through TCA cycle by increasing [substrate]

- Action of PDH complex increases [acetyl-CoA] (as does FA oxidation), but [OAA] can limit flux
- Pyruvate carboxylase is activated by acetyl-CoA, and can generate more OAA to enhance flux
- Pyruvate can also act in transamination rxns, yielding α-KG (from Glu) or OAA (from Asp)
The oxidation of acetyl-CoA to CO$_2$ in the TCA cycle generates energy currencies.