Acetyl-CoA and the Citric Acid Cycle

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Respiration

Conversion of nutrients into useful energy for the cell

- Carbohydrates - Sugars
- Proteins - Amino Acids
- Fats - Fatty Acids & Glycerol
Acetyl-CoA
Pyruvate Dehydrogenase

Mitochondrial Enzyme
Very large multimeric complex
Three subunits - E1, E2, E3

Pyruvate → Acetaldehyde → Acetyl-CoA

E1 Subunit of Pyruvate Dehydrogenase

Ethanol

CO₂
NAD⁺
NADH
No O₂

Acetate

O₂
NAD⁺
NADH

Animals

Bacteria & Yeast

NADH + CO₂
Acetaldehyde $\rightarrow$ Ethanol

Alcohol Dehydrogenase

NADH $\rightarrow$ NAD$^+$
Pyruvate → CO₂ → TPP-Acetaldehyde → Electron transfer to lipoamide-S-S → Acetyl-Lipoamide → Acetyl-CoA → Bacteria / Yeast (Mostly in low O₂) → Acetaldehyde
Pyruvate → TPP-Acetaldehyde

E1

Acetyl-Lipoamide

E2

Electron transfer to lipoamide-S-S

CoA-SH → Acetyl-CoA

Acetyl-CoA

E3

NAD⁺ → FADH₂ → FAD → NADH/H⁺
Lipoamide Oxidized/Reduced

Lipoic Acid Component Oxidized

Lipoic Acid Component Reduced

Lysine Side Chain
PD = Pyruvate Dehydrogenase
Phosphorylation Inactivates
Dephosphorylation Activates
PD Kinase Puts Phosphate on
PD Phosphatase Takes Phosphate off

Be careful not to confuse PD with the PD Phosphatase or the PD Kinase

These Hormones Inactivate PD
(Favor Phosphorylation)

These ions Activate
(Favor Dephosphorylation)
Figure 6.69 - The citric acid cycle

Image by Aleia Kim
Citrate Synthase

Very Negative $\Delta G^{\circ'}$

Acetyl-CoA + Oxaloacetate $\leftrightarrow$ Citrate + CoA-SH
Isocitrate + NAD⁺ → α-ketoglutarate + NADH + CO₂

First oxidative decarboxylation
α-ketoglutarate + NAD\(^+\) + CoA-SH

\[
\begin{align*}
α-ketoglutarate & \quad \downarrow \quad α-ketoglutarate \\
\text{dehydrogenase} & \\
Succinyl-CoA + NADH + CO_2
\end{align*}
\]

Second oxidative decarboxylation
Succinyl-CoA + GDP + P_i

\[ \text{Succinyl-CoA Synthetase} \]

\[ \text{Succinate} + \text{GTP} + \text{CoA-SH} \]

Symmetrical Product

Only Substrate Level Phosphorylation in Cycle
Succinyl-CoA Synthetase Mechanism

Succinyl CoA + CoA → Succinate + NDP
Succinate + FAD

\[
\text{Succinate dehydrogenase}
\]

\[
\text{Succinate} + \text{FAD} \quad \text{Fumarate} + \text{FADH}_2
\]

Third Oxidation of Cycle

\[
\text{Fumarate} + \text{FADH}_2
\]
Succinate Dehydrogenase

Enzyme is embedded in inner mitochondrial membrane
Only enzyme of Citric Acid Cycle not found in matrix
Electron Movement

Reaction
The fourth and final oxidation of the cycle is catalyzed by malate dehydrogenase.

Very positive $\Delta G^\circ$

Reaction pulled by citrate synthase reaction

Fourth and final oxidation of cycle
Figure 6.69 - The citric acid cycle

Image by Aleia Kim
Citric Acid Cycle Summary

Input 2 Carbons (1 Acetyl CoA)
Release 2 CO$_2$ Molecules
Four Oxidations
3 NADH, 1 FADH$_2$, 1 GTP Per Turn of Cycle
Each Citric Acid Cycle Intermediate Functions in Other Pathways

Citrate - Glyoxylate Cycle, Allosteric Effector, Shuttle System
Isocitrate - Glyoxylate Cycle
a-Ketoglutarate - Amino Acid/Nitrogen Metabolism
Succinyl-CoA - Heme Synthesis, Amino Acid Metabolism
Succinate - Glyoxylate Metabolism, Odd Chain Fatty Acid Metabolism
Fumarate - Nucleotide Metabolism
Malate - Shuttle System
Oxaloacetate - Gluconeogenesis, Amino Acid Metabolism
Anaplerotic / Cataplerotic
I love my citrate synthase
It really is first rate
Adds O-A-A to Ac-Co-A
Producing one citrate

Aconitase is picky
Binds substrates specially
Creating isocitrate
Which has no symmetry

Then CO₂ gets lost from it
Released in the next phase
The secret weapon - Isocitrato
Dehydrogenase

The alpha K-D-H is next
It gets my admiration
For clipping CO₂ in one more
Decarboxylation

Succ-CoA synthetase steps up
Reacting most absurd
It's named for a catalysis
That simply runs backward

Suc -CIN-ate de-hyd-ROG-en-ase
Pulls H from succinate
Creating FADH₂
As well as fumarate

The fumarate gains water
O-H configured L
The fumarase's product?
Some malate for the cell

With one last oxidation
Malate de-hyd-ROG-en-ase
Expels its two creations
N-A-D-H / O-A-A

Kevin Ahern
Arnon-Buchanan Cycle
Figure 6.74 - Overview of the glyoxylate cycle

Image by Aleia Kim
Two per turn of cycle
Isocitrate Lyase

Isocitrate → Succinate + Glyoxylate
Malate Synthase

$$\text{Acetyl-CoA} + \text{Glyoxylate} \rightarrow \text{L-Malate}$$
**Glyoxylate Cycle Summary**

Input 4 Carbons (2-Acetyl CoA)  
Releases 0 CO$_2$ Molecules  
Produces One Extra Oxaloacetate  
Two Oxidations  
1 NADH, 1 FADH$_2$, 1(extra ) Oxaloacetate Per Turn of Cycle  
Net Synthesis of Glucose from Acetyl-CoA

**Citric Acid Cycle Summary**

Input 2 Carbons (1 Acetyl CoA)  
Releases 2 CO$_2$ Molecules  
Four Oxidations  
3 NADH, 1 FADH$_2$, 1 GTP Per Turn of Cycle  
No Net Synthesis of Glucose from Acetyl-CoA
Figure 6.77 - Acetyl-CoA metabolism

Image by Aleia Kim
The Animals’ Dilemma

No net glucose synthesis from fat
Ketone Body Metabolism

2 Acetyl-CoA + H₂C\(\text{S-CoA}\) → Acetoacetyl-CoA

Thiolase

Acetoacetate

H₂C\(\text{S-CoA}\) → β-hydroxy-β-methylglutaryl-CoA (HMG-CoA)

HMG-CoA Synthase

β-hydroxybutyrate dehydrogenase

NADH + H⁺ → NAD⁺

Acetone

D-β-hydroxybutyrate